Appeal No. 2017-2508

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ATHENA DIAGNOSTICS, INC.; OXFORD UNIVERSITY INNOVATION LTD.; MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V.,

Plaintiffs-Appellants,

v.

MAYO COLLABORATIVE SERVICES, LLC, d/b/a Mayo Medical Laboratories; MAYO CLINIC,

Defendants-Appellees.

Appeal from the United States District Court for the District of Massachusetts in
Case No. 1:15-cv-40075-IT
Indira Talwani, United States District Judge

JOINT APPENDIX

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March 22, 2018

Athena Diagnostics, Inc., et al. v. Mayo Collaborative Servs. LLC, et al., 2017-2508 (Fed. Cir.)

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UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ATHENA DIAGONISTICS, INC., ISIS INNOVATION LIMITED, and MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN e.V.,	*	
Plaintiffs,	*	
v.	*	Civil Action No: 15-cv-40075-IT
MAYO COLLABORATIVE SERVICES, LLC, d/b/a MAYO MEDICAL LABORATORIES, and MAYO CLINIC,	*	
Defendants.	*	

MEMORANDUM & ORDER

August 4, 2017

TALWANI, D.J.

Plaintiffs Athena Diagnostics, Inc., Isis Innovation Limited, and Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V., allege that two tests developed by Defendants Mayo Collaborative Services, LLC, and Mayo Clinic, infringe on Plaintiffs' patent, U.S. Patent No. 7,267,820 (the "'820 Patent"). Third Am. Compl. ("Complaint") [#92]. Defendants moved to dismiss Plaintiffs' complaint arguing that the '820 patent is invalid under 35 U.S.C. § 101 because the claimed method applies routine and conventional techniques to a law of nature. Defs.' Rule 12(b)(6) Mot. Dismiss ("Defs.' Mot. Dismiss") [#25]. The court was unable to determine on the papers before it whether the patent used standard techniques in the art, or whether it was sufficiently inventive to be patentable under § 101, and denied the motion. Mem. & Order 10 [#103]. At a subsequent hearing, Plaintiffs' counsel agreed that a statement in

the patent specification (that "[i]odination and immunoprecipitation are standard techniques in the art") was undisputed. See '820 Patent col. 4 l. 10-11; Tr. Oral Argument, at 17-18, Athena Diagnostics, Inc. v. Mayo Collaborative Servs., Inc., No. 15-cv-40075 (D. Mass. Oct. 6, 2016). Based on that statement, the court allowed Defendants the opportunity to renew their motion to dismiss, and allowed additional briefing by the parties. For the following reasons, the Renewed Motion to Dismiss [#131] is ALLOWED.

I. Facts

A. The '820 Patent

The '820 patent allows for the diagnosis of a form of Myasthenia Gravis, a chronic autoimmune disorder. '820 Patent col. 1 l. 13-14. Patients with Myasthenia Gravis experience waning muscle strength throughout the day, and symptoms include eye weakness (drooping eyelids, double vision), leg weakness, dysphagia (difficulty swallowing), and slurred or nasal speech. Id. col. 1 l. 15-23. In 1960, it was discovered that in 80% of patients with Myasthenia Gravis, antibodies attack the acetyle choline receptor (AChR) (a neurotransmitter). Id. col. 1 l. 24-26, 34-36. In those patients, diagnosis is achieved through tests which detect the presence of AChR autoantibodies. See id. col. 1 l. 34-36. Autoantibodies "are naturally occurring antibodies directed to an antigen which an individual's immune response recognizes as foreign even though that antigen actually originated in the individual." Id. col. 1 l. 42-45. However, 20% of Myasthenia Gravis patients do not have the AChR autoantibodies despite experiencing the same symptoms and responding to the same therapies. Id. col. 1 l. 36-40. For the 20% of Myasthenia Gravis patients who do not have the AChR autoantibodies, the '820 patent inventors discovered that they had IgG antibodies that attack the N-terminal domains of muscle specific tyrosine

kinase ("MuSK"), a receptor that is located on the surface of neuromuscular junctions. Id. col. 1 l. 55-61.

The patent describes the method for a more accurate and speedy diagnosis of these patients. Id. col. 3 l. 4-7. Specifically, the patent describes a method for diagnosing Myasthenia Gravis in which a radioactive label is attached to MuSK (or a fragment thereof) and is then introduced to a sample of bodily fluid. Id. col. 3 l. 66-67, col. 4 l. 1-10. The method specifies that ^{125}I be used as the radioactive label. Id. col. 4 l. 9-10. When ^{125}I-MuSK is introduced into the sample of bodily fluid, the MuSK autoantibodies, if present, attach to the labeled fragment. Id. col. 4 l. 2-9. After the bodily fluid is immunoprecipitated, the presence of the radioactive label on any antibody indicates that the person is suffering from Myasthenia Gravis. Id. col. 4 l. 8-10.

B. Infringement Allegations

Athena's test, "FMUSK," uses the patented method to diagnose neurotransmission or developmental disorders related to MuSK. Compl. ¶ 16 [#92]; '820 Patent Claim 1. Plaintiffs allege that "Defendants, with specific knowledge of the '820 patent and the method it covers, surreptitiously and purposefully designed an alternate test to avoid paying Athena for Athena's licensed FMUSK test." Compl. ¶ 20 [#92]. Plaintiffs allege that Defendants availed themselves of the technology disclosed in the '820 patent, and developed two tests for diagnosing Myasthenia Gravis patients. Id. ¶ 18. Plaintiffs argue that Defendants' actions directly or indirectly, and literally or under the doctrine of equivalents, infringe the '820 patent. Id. ¶ 24. The claims at issue are those listed in Claims 6-9 of the '820 patent. Pls.' Mem. Opp'n Defs.' Mot. Dismiss. 24 [#37]. Plaintiffs concede that they will not pursue infringement claims against Defendants based on the other claims in the patent. Id. at 8.

II. Motion to Dismiss

Defendants moved to dismiss the complaint on the ground that the patent seeks to patent a law of nature, and it uses techniques standard in the art. Defs.' Mem. Supp. Mot. Dismiss 5-6 [#26]; Defs.' Renewed Mem. Supp. Mot. Dismiss 4-5 [#132]. Plaintiffs argue that the patent is not directed at a law of nature because the patent requires the production and use of ^{125}I-MuSK, a non-naturally occurring protein. Pls.' Mem. Opp'n Defs.' Mot. Dismiss 17 [#37]. Plaintiffs also argue that applying various known types of procedures to a non-naturally occurring protein transforms the claim and makes it patent eligible. Id. at 13-14.

A. Standard of Review under 35 U.S.C. § 101

In applying § 101 at the pleading stage, the court construes the patent claims in a manner most favorable to the non-moving party. See Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat'l Ass'n, 776 F.3d 1343, 1349 (Fed. Cir. 2014). As a threshold requirement for patent protection, the subject matter of a patent must be patentable under § 101; otherwise, the patent is invalid. § 101 states that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. The Supreme Court has held that this section contains an implicit exception: "[l]aws of nature, natural phenomena, and abstract ideas are not patentable." Alice Corp. Pty. Ltd. v. CLS Bank Intern., 134 S. Ct. 2347, 2354 (2014) (quoting Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2116 (2013)). Although "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas," these three patent-ineligible exceptions prevent "monopolization" of the "basic tools of scientific and

technological work" and the impeding of innovation. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 71 (2012).

To distinguish between patents that claim laws of nature, natural phenomena, and abstract ideas from patent-eligible inventions, the court must first determine whether the claims at issue are directed to one of those patent-ineligible concepts. Alice, 134 S. Ct. at 2355. If the concept is patent ineligible, the court then considers the elements of each claim both "individually and 'as an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application." Id. at 2355 (quoting Mayo, 566 U.S. at 78-79). "We have described step two of this analysis as a search for an 'inventive concept' – i.e., an element or combination of elements that is 'sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.'" Id. at 2355 (quoting Mayo, 566 U.S. at 72-73). At step two, more is required than well-understood, routine, conventional activity already engaged in by the scientific community. Rapid Litig. Mgmt., Ltd. v. CellzDirect, Inc., 827 F.3d 1042, 1047 (Fed. Cir. 2016).

B. Step One: Are Claims Directed to a Patent Ineligible Concept?

Defendants argue that the '820 patent is directed at a law of nature: that the bodily fluid of some people with Myasthenia Gravis have autoantibodies to MuSK. Defs.' Renewed Mem. Supp. Mot. Dismiss 4-5 [#132]. Plaintiffs argue that the patent method uses a man-made, patent eligible molecule, and uses that chemical complex in an innovative and transformative manner. Pls.' Surreply Opp'n Mot. Dismiss 4 [#46]. Per Plaintiffs, "the claims are not directed to MuSK . . . [i]nstead, the claims recite using a man-made chemically-modified version of MuSK to form a specific complex that does not occur in nature," and are therefore patent eligible. Id. at 5.

The patent describes a method in which ^{125}I-MuSK is put into a sample of bodily fluid, and then the bodily fluid is filtered so that autoantibodies attached to the ^{125}I-MuSK are detected. '820 Patent col. 3 l. 66-67, col. 4 l. 1-9. The presence of the ^{125}I-MuSK autoantibodies indicates the person suffers from Myasthenia Gravis. Id. The relevant portion of the patent states:

> The invention claimed is:
>
> **1.** A method for diagnosing neurotransmission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK).
>
> **2.** A method according to claim 1 wherein said method comprises the steps of:
> a) contacting said bodily fluid with muscle specific tyrosine kinase (MuSK) or an antigenic determinant thereof: and
> b) detecting any antibody-antigen complexes formed between said receptor tyrosine kinase or an antigenic fragment thereof and antibodies present in said bodily fluid, wherein the presence of said complexes is indicative of said mammal suffering from said neurotransmission or development disorders.
>
> **3.** A method according to Claim 2 wherein said antibody-antigen complex is detected using an anti-IgG antibody tagged or labeled with a reporter molecule.
> . . .
> **6.** A method according to claim 3 whereby the intensity of the signal from the anti-human IgG antibody is indicative of the relative amount of the anti-MuSK autoantibody in the bodily fluid when compared to a positive and negative control reading.
>
> **7.** A method according to claim 1, comprising contacting MuSK or an epitope or antigenic determinant thereof having a suitable label thereon, with said bodily fluid, immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid and monitoring for said label on any of said antibody/MuSK complex or antibody/MuSK epitope or antigen determinant complex, wherein the presence of said label is indicative of said mammal is suffering from said neurotransmission or developmental disorder related to muscle specific tyrosine kinase (MuSK).
>
> **8.** A method according to claim 7 wherein said label is a radioactive label.
>
> **9.** A method according to claim 8 wherein said label is 125I.

'820 Patent Claims 1-9. Plaintiffs argue that because ^{125}I-MuSK is not naturally occurring, the claim is patent eligible under § 101. Pls.' Mem. Opp'n Defs.' Mot. Dismiss. 11 [#37] ("Those antibody/MuSK complexes are created in the laboratory and result from the use of a non-naturally-occurring laboratory-created molecule, ^{125}I-MuSK, and therefore, the antibody/MuSK complexes formed and detected by claim 9 are not found in nature.").

While ^{125}I-MuSK and the antibody/MuSK complexes are not found in nature, this does not transform the patent at issue here to a patent eligible concept. Contrary to Plaintiffs' argument, the '820 patent is not a composition patent directed at the creation of the ^{125}I-MuSK auto-antibody complex. Rather, the patent is directed at a method for the diagnosis of a disease. '820 Patent col. 1 l. 9-11 ("The present invention is concerned with neurotransmission disorders and, in particular, with a method of diagnosing such disorders in mammals."). Although the patented method uses man-made ^{125}I-MuSK, the use of a man-made complex does not transform the subject matter of the patent. The focus of the claims of the invention is the interaction of the ^{125}I-MuSK and the bodily fluid, an interaction which is naturally occurring. The purpose of the patent is to detect whether any antibody-antigen complexes are formed between the ^{125}I-MuSK receptor and the antibodies "present in said bodily fluid." Id. Claim 2. Counter to Plaintiffs' argument, because the patent focuses on this natural occurrence, it is directed to a patent-ineligible concept. See Elec. Power Grp., LLC v. Alstom S.A., 830 F.3d. 1350, 1353 (Fed. Cir. 2016) (quoting Enfish, LLC v. Microsoft Corp., 822 F.3d 1327, 1335-36 (Fed. Cir. 2016)) ("[W]e have described the first-stage inquiry as looking at the 'focus' of the claims, their 'character as a whole.'").

Athena's patent is similar to the patent invalidated by the Supreme Court in Mayo. In Mayo, the Supreme Court invalidated the patent of a diagnostic test which measured how well a

person metabolized thiopurine drugs. 566 U.S. at 74. The patent claimed a method in which the drug 6-thioguanine was given to a person, after which the level of 6-thioguanine in the person's blood stream was measured. Id. The Court held that the patent method was directed to observing a law of nature. "'Prometheus' patents set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of thiopurine drug will prove ineffective or cause harm." Id. at 77. While the Court acknowledged that it took human action (the administration of a thiopurine drug) to trigger the desired reaction, the reaction itself happened apart from any human action. Id. at 78. The Court found the claim invalid because the method sought to measure how well a person metabolizes the drug, which the Court described as "entirely natural processes." Id. at 77. Likewise, Plaintiffs' method seeks to measure autoantibodies that have attached to a receptor protein, an interaction which is a similarly natural process. In Mayo, a man-made substance was administered to a person, and the by-product of the metabolization of that man-made substance was observed. Id.; see also Genetic Techs. Ltd. v. Merial LLC, 818 F.3d 1369, 1376 (Fed. Cir. 2016) (finding that when the patent claim focuses on a newly discovered fact about human biology, the claim is directed to unpatentable subject matter). Here, a man-made substance (^{125}I-MuSK) is administered to a sample of bodily fluid, and the by-product (^{125}I-MuSK autoantibodies) is observed.

Further support can be found in Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1372 (Fed. Cir. 2015). That case involved the patent for a method using fetal DNA for the diagnosis of certain conditions. The inventors discovered that cell-free fetal DNA ("cffDNA") was present in maternal plasma and serum. By implementing a method for detecting the small fraction of paternal cffDNA in the maternal plasma or serum, the inventors were able to determine certain inherited characteristics. Id. at 1373. The patent method isolated and amplified

cffDNA, allowing for greater efficiency in diagnosis of genetic defects. As the court noted, "[t]he only subject matter new and useful as of the date of the application was the discovery of the presence of cffDNA in maternal plasma or serum . . ." Id. at 1377. Likewise, what is new and useful here is the discovery that some patients with Myasthenia Gravis have MuSK autoantibodies in their bodily fluid.

Relying on CellzDirect, 827 F.3d at 1042, Plaintiffs seek to distinguish the '820 patent from Ariosa and Mayo by arguing that the '820 patent is focused on the steps required by the claimed method, rather than on the outcome of the diagnostic test. In CellzDirect, patent inventors discovered that hepatocytes, special liver cells that are used for testing, diagnostic, and treatment purposes, could be refrozen. Id. at 1045. Refreezing of hepatocytes was a breakthrough because the cells naturally have a short life span, and can only be harvested from a limited number of people. Id. Prior to the discovery, hepatocytes could only be frozen one time, which limited their utility. Id. The patented method importantly allowed for multi-donor hepatocyte pools, a useful research tool that allows the study of a drug's impact on a representative population. Id. The Federal Circuit found the "end result of the '929 patent claims is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze thaw cycles. Rather, the claims are directed to a new and useful method of preserving hepatocyte cells." Id. at 1048. The court found that the process' "desired outcome" was a method to produce something useful, and therefore was not directed at a patent ineligible concept. Id. at 1048-49. The method allowed for refrozen hepatocyte cells to be used in a myriad of ways. Conversely, the desired outcome of the Plaintiffs' method is the detection of MuSK autoantibodies. It does not produce something useful beyond that diagnosis.

Plaintiffs' argument that the patent is transformed by the use of a man-made molecule is

unavailing. The stated purpose of the patent is to diagnose Myasthenia Gravis, and the method is directed to a patent ineligible law of nature under § 101.

C. Step Two: Does the Inventiveness of the Claim make it Patent Eligible?

While the patent is directed to a patent ineligible concept under § 101, the patent can still be upheld if the method contains an "inventive concept." See Alice, 134 S. Ct. at 2355; Genetic Techs. Ltd., 818 F.3d at 1376 ("[T]he application must provide something inventive beyond mere 'well-understood, routine, conventional activity.'"). The Supreme Court has "described step two of this analysis as a search for an 'inventive concept' – i.e., an element or combination of elements that is 'sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.'" Alice, 134 S. Ct. at 2355 (quoting Mayo, 566 U.S. at 72-73). At step two the claims are examined "in light of the written description," Amdocs (Israel) Ltd. V. Openet Telecom, Inc., 841 F.3d 1288, 1299 (Fed. Cir. 2016), and "more is required than well-understood, routine, conventional activity already engaged in by the scientific community." CellzDirect, 827 F.3d at 1047 (internal quotations omitted).

Defendants argue that Plaintiffs' patent fails step two of § 101 analysis because it uses well-known techniques for identifying the presence of autoantibodies to MuSK and therefore does not contain an "inventive concept." Defs.' Mem. Supp. Mot. Dismiss 14 [#26] ("[P]rocess steps that recite techniques scientists would have already known to use in conjunction with the newfound natural law cannot supply the inventive concept."). Defendants cite to the patent specification which states that "[i]ondination and immunoprecipitation are standard techniques in the art, the details of which can be found in references (4 and 6)." Id. at 10; '820 Patent col. 4 l. 9-12. Defendants note that the two publications referenced in the specification date from 1976 and 1985, and according to Defendants the publications "describe (1) the introduction of a ^{125}I-

labeled antigen (AChR) into a bodily fluid sample, (2) immunoprecipitation, and (3) detecting the radioactive label." Defs.' Mem. Supp. Mot. Dismiss 10 [#26]. Defendants argue that the publications show that the methods described in the patent are commonly used by researchers in the field, and thus the claims do not pass step two of the analysis under § 101.

Plaintiffs argue that at the time the invention was made, the step of "detecting" autoantibodies was neither well understood nor routine, and that the step of contacting MuSK or a MuSK epitope with a suitable label was novel. Pls.' Memo. Opp'n Defs.' Renew Mot. Dismiss 8 [#136]. Plaintiffs admit that the specification states "[i]odination and immunoprecipitation are standard techniques in the art," but Plaintiffs argue that none of those steps are routine when applied to proteins. According to Plaintiffs, proteins are complex, and getting known iodination methods to work with proteins is not routine. Id. at 11.

Plaintiffs' argument is unavailing. Patent applications are required to provide the precise description of the manner and process of making the invention. 35 U.S.C. § 112(a) ("The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention."); see also In re TLI Commc'ns LLC Patent Litig., 823 F.3d 607, 613-614 (Fed. Cir. 2016) ("[W]e must be mindful of extraneous fact finding outside the record, particularly at the motion to dismiss stage, here we need to only look to the specification . . . ."). None of the complexity to which Plaintiffs cite is described or claimed in the patent. While Plaintiffs argue that "Production of 'MuSK or an epitope or antigenic determinant thereof having a suitable label thereon' required several steps that were neither well-known, not standard, nor

conventional for MuSK," Pls.' Mem. Opp'n Defs.' Renewed Mot. Dismiss 15 [#136], this statement directly contradicts the language in the specification. In the specification, the inventors simply state that the "suitable label" is ^{125}I or the like, and that iodination of the label is a standard technique in the art. '820 Patent col. 4 l. 9-12. Furthermore, complexity alone does not make their method patentable. See Myriad, 133 S. Ct. at 2117 ("Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry.").

Plaintiff also argues that the use of a man-made molecule necessarily makes the claims patent eligible. Plaintiffs' claim that "[a] process that requires the use of a novel non-naturally-occurring patent-eligible element is necessarily a patent-eligible process." Pls.' Mem. Law. Opp'n Defs.'s Renewed Mot. Dismiss 8 [#136]. However, the patent specification itself states that the "present invention is concerned with neurotransmission disorders and, in particular with a method of diagnosing such disorders in mammals." '820 Patent col.1 l.9-11. The patent claims it is "for diagnosing neurotransimission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal compromising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK)." Id. Claim 1. On its face, the patent claims a process for detecting autoantibodies, not a process for creating the ^{125}I-MuSK. See Myriad, 133 S. Ct. at 2119 ("Had Myriad created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could have possibly sought a method patent.").

III. Conclusion

For the foregoing reasons, Defendants' Renewed Motion to Dismiss [#131] is GRANTED.

Date: August 4, 2017

/s/ Indira Talwani
United States District Court

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

ATHENA DIAGNOSTICS, INC., ISIS INNOVATION LIMITED, and MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN e.V.,	*	
Plaintiffs,	*	
v.	*	Civil Action No. 15-cv-40075-IT
MAYO COLLABORATIVE SERVICES, LLC, d/b/a/ MAYO MEDICAL LABORATORIES, and MAYO CLINIC,	*	
Defendants.	*	

ORDER OF DISMISSAL

August 4, 2017

TALWANI, D.J.

Having allowed Defendants' motion to dismiss the claims against them pursuant to 12(b)(6) of the Federal Rules of Civil Procedure, this matter is dismissed. The clerk shall close the case.

IT IS SO ORDERED.

/s/ Indira Talwani
United States District Judge

APPEAL,PATENT

United States District Court
District of Massachusetts (Boston)
CIVIL DOCKET FOR CASE #: 1:15-cv-40075-IT

Athena Diagnostics, Inc. v Mayo Collaborative Services, et al.
Assigned to: Judge Indira Talwani
Case in other court: USCA for the Federal Circuit, 17-02508
Cause: 35:271 Patent Infringement

Date Filed: 06/02/2015
Date Terminated: 08/04/2017
Jury Demand: Both
Nature of Suit: 830 Patent
Jurisdiction: Federal Question

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Defendant

Mayo Clinic represented by **Phillip Goter**
(See above for address)
LEAD ATTORNEY
PRO HAC VICE
ATTORNEY TO BE NOTICED

Adam J. Kessel
(See above for address)
ATTORNEY TO BE NOTICED

Elizabeth M. Flanagan
(See above for address)
PRO HAC VICE
ATTORNEY TO BE NOTICED

John C. Adkisson
(See above for address)
PRO HAC VICE
ATTORNEY TO BE NOTICED

Jonathan E. Singer
(See above for address)
PRO HAC VICE
ATTORNEY TO BE NOTICED

Kelly Allenspach Del Dotto
(See above for address)
PRO HAC VICE
ATTORNEY TO BE NOTICED

Counter Claimant

Mayo Collaborative Services, LLC represented by **Adam J. Kessel**
(See above for address)
ATTORNEY TO BE NOTICED

Elizabeth M. Flanagan
(See above for address)
ATTORNEY TO BE NOTICED

John C. Adkisson

(See above for address)
ATTORNEY TO BE NOTICED

Jonathan E. Singer
(See above for address)
ATTORNEY TO BE NOTICED

Kelly Allenspach Del Dotto
(See above for address)
ATTORNEY TO BE NOTICED

Counter Claimant

Mayo Clinic represented by **Adam J. Kessel**
(See above for address)
ATTORNEY TO BE NOTICED

Elizabeth M. Flanagan
(See above for address)
ATTORNEY TO BE NOTICED

John C. Adkisson
(See above for address)
ATTORNEY TO BE NOTICED

Jonathan E. Singer
(See above for address)
ATTORNEY TO BE NOTICED

Kelly Allenspach Del Dotto
(See above for address)
ATTORNEY TO BE NOTICED

V.

Counter Defendant

Athena Diagnostics, Inc. represented by **Manleen K. Singh**
(See above for address)
LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Andrew J. Kabat
(See above for address)
ATTORNEY TO BE NOTICED

Emmett J. McMahon
(See above for address)
ATTORNEY TO BE NOTICED

Lisa A. Furnald
(See above for address)
ATTORNEY TO BE NOTICED

Matthew Bowen McFarlane

(See above for address)
ATTORNEY TO BE NOTICED

Tara S.G. Sharp
(See above for address)
TERMINATED: 03/07/2016
ATTORNEY TO BE NOTICED

Counter Defendant

Isis Innovation Limited represented by **Manleen K. Singh**
(See above for address)
LEAD ATTORNEY

Andrew J. Kabat
(See above for address)
ATTORNEY TO BE NOTICED

Emmett J. McMahon
(See above for address)
ATTORNEY TO BE NOTICED

Lisa A. Furnald
(See above for address)
ATTORNEY TO BE NOTICED

Matthew Bowen McFarlane
(See above for address)
ATTORNEY TO BE NOTICED

Tara S.G. Sharp
(See above for address)
TERMINATED: 03/07/2016
ATTORNEY TO BE NOTICED

Counter Defendant

Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V. represented by **Manleen K. Singh**
(See above for address)
LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Andrew J. Kabat
(See above for address)
ATTORNEY TO BE NOTICED

Emmett J. McMahon
(See above for address)
ATTORNEY TO BE NOTICED

Matthew Bowen McFarlane
(See above for address)
ATTORNEY TO BE NOTICED

Date Filed	#	Docket Text

06/02/2015	1	COMPLAINT against Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories, Mayo Clinic Filing fee: $ 400, receipt number 0101-5584163 (Fee Status: Filing Fee paid), filed by Athena Diagnostics, Inc.. (Attachments: # 1 Civil Cover Sheet JS044, # 2 Civil Cover Sheet Local civil category form, # 3 Civil Cover Sheet AO120) (Singh, Manleen) (Attachment 1 replaced on 6/3/2015) (Jones, Sherry). (Attachment 2 replaced on 6/3/2015) (Jones, Sherry). (Attachment 3 replaced on 6/3/2015) (Jones, Sherry). (Entered: 06/02/2015)
06/02/2015	2	CORPORATE DISCLOSURE STATEMENT by Athena Diagnostics, Inc. identifying Corporate Parent Quest Diagnostics Incorporated for Athena Diagnostics, Inc... (Singh, Manleen) (Entered: 06/02/2015)
06/03/2015	3	REPORT ON THE FILING OF AN ACTION REGARDING PATENT. (Jones, Sherry) (Entered: 06/03/2015)
06/03/2015	4	ELECTRONIC NOTICE of Case Assignment. District Judge Timothy S Hillman assigned to case. If the trial Judge issues an Order of Reference of any matter in this case to a Magistrate Judge, the matter will be transmitted to Magistrate Judge David H. Hennessy. (Abaid, Kimberly) (Entered: 06/03/2015)
06/03/2015	5	Summons Issued as to Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. **Counsel receiving this notice electronically should download this summons, complete one for each defendant and serve it in accordance with Fed.R.Civ.P. 4 and LR 4.1. Summons will be mailed to plaintiff(s) not receiving notice electronically for completion of service.** (Jones, Sherry) (Entered: 06/03/2015)
07/24/2015	6	AMENDED COMPLAINT against All Defendants, filed by Athena Diagnostics, Inc.. (Singh, Manleen) (Entered: 07/24/2015)
08/05/2015	7	MOTION for Extension of Time to September 15, 2015 to File Answer re 6 Amended Complaint by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories.(Kessel, Adam) (Entered: 08/05/2015)
08/06/2015	8	District Judge Timothy S Hillman: ELECTRONIC ORDER entered granting 7 Motion for Extension of Time to Answer Mayo Clinic answer due 9/15/2015; Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories answer due 9/15/2015. (Jones, Sherry) (Entered: 08/06/2015)
08/14/2015	9	MOTION for Leave to File *Second Amended Complaint (Unopposed) and Motion to Transfer this Case to the Eastern Division* by Athena Diagnostics, Inc.. (Attachments: # 1 Affidavit, # 2 Exhibit Exhibit A to McFarlane Declaration)(Singh, Manleen). Added MOTION to Transfer Case on 8/17/2015 (Jones, Sherry). (Entered: 08/14/2015)
08/17/2015	10	District Judge Timothy S Hillman: ELECTRONIC ORDER entered: The motion to amend is allowed. The Plaintiff shall file a second amended complaint. Upon the filing of the amended complaint, the case shall be transfered to the Eastern Division. granting 9 Motion for Leave to File Document ; Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. Counsel must include - Leave to file granted on (date of order)- in the caption of the document.; granting 9 Motion to Transfer Case (Jones, Sherry) (Entered: 08/17/2015)
08/17/2015	11	AMENDED COMPLAINT *(SECOND)* against All Defendants, filed by Athena Diagnostics, Inc..(Singh, Manleen) (Entered: 08/17/2015)
08/18/2015	12	Case transferred to Eastern Division (Boston) (Jones, Sherry) (Entered: 08/18/2015)
08/18/2015	13	ELECTRONIC NOTICE of Reassignment. Judge Indira Talwani added. District Judge

		Timothy S Hillman no longer assigned to case. (Abaid, Kimberly) (Entered: 08/18/2015)
08/18/2015	14	If the trial Judge issues an Order of Reference of any matter in this case to a Magistrate Judge, the matter will be transmitted to Magistrate Judge M. Page Kelley. (Abaid, Kimberly) (Entered: 08/18/2015)
08/18/2015	15	Case transferred in from Central Division (Worcester) on 08/18/2015 Case Number 4:15-cv-40075. (Abaid, Kimberly) (Entered: 08/18/2015)
08/27/2015	16	NOTICE of Appearance by Matthew Bowen McFarlane on behalf of Athena Diagnostics, Inc., Isis Innovation Limited (McFarlane, Matthew) (Entered: 08/27/2015)
08/27/2015	17	NOTICE of Appearance by Manleen K. Singh on behalf of Isis Innovation Limited (Singh, Manleen) (Entered: 08/27/2015)
08/28/2015	18	MOTION for Leave to Appear Pro Hac Vice for admission of Emmett McMahon Filing fee: $ 100, receipt number 0101-5721769 by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Affidavit)(Singh, Manleen) (Entered: 08/28/2015)
08/28/2015	19	MOTION for Leave to Appear Pro Hac Vice for admission of Tara S.G. Sharp Filing fee: $ 100, receipt number 0101-5721786 by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Affidavit)(Singh, Manleen) (Entered: 08/28/2015)
08/28/2015	20	MOTION for Leave to Appear Pro Hac Vice for admission of Andrew J. Kabat Filing fee: $ 100, receipt number 0101-5721795 by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Affidavit)(Singh, Manleen) (Entered: 08/28/2015)
09/02/2015	21	MOTION for Leave to Appear Pro Hac Vice for admission of Jonathan E. Singer Filing fee: $ 100, receipt number 0101-5727795 by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Attachments: # 1 Exhibit Certification)(Kessel, Adam) (Entered: 09/02/2015)
09/02/2015	22	MOTION for Leave to Appear Pro Hac Vice for admission of John C. Adkisson Filing fee: $ 100, receipt number 0101-5727841 by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Attachments: # 1 Exhibit Certification)(Kessel, Adam) (Entered: 09/02/2015)
09/02/2015	23	MOTION for Leave to Appear Pro Hac Vice for admission of Elizabeth M. Flanagan Filing fee: $ 100, receipt number 0101-5727846 by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Attachments: # 1 Exhibit Certification) (Kessel, Adam) (Entered: 09/02/2015)
09/02/2015	24	MOTION for Leave to Appear Pro Hac Vice for admission of Kelly Allenspach Del Dotto Filing fee: $ 100, receipt number 0101-5727857 by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Attachments: # 1 Exhibit Certification)(Kessel, Adam) (Entered: 09/02/2015)
09/15/2015	25	MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6)* by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Kessel, Adam) (Entered: 09/15/2015)
09/15/2015	26	MEMORANDUM in Support re 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6)* filed by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Kessel, Adam) (Entered: 09/15/2015)
09/15/2015	27	DECLARATION re 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6)* by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C)(Kessel, Adam) (Entered: 09/15/2015)

09/21/2015	28	MOTION for Extension of Time to October 13, 2015 to Respond to Defendant's Motion to Dismiss *the Second Amended Complaint* by Athena Diagnostics, Inc., Isis Innovation Limited.(Singh, Manleen) (Entered: 09/21/2015)
09/23/2015	29	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 18 Motion for Leave to Appear Pro Hac Vice Added Emmett McMahon. **Attorneys admitted Pro Hac Vice must register for electronic filing if the attorney does not already have an ECF account in this district. To register go to the Court website at www.mad.uscourts.gov. Select Case Information, then Electronic Filing (CM/ECF) and go to the CM/ECF Registration Form.** (DaSilva, Carolina) (Entered: 09/23/2015)
09/23/2015	30	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 19 Motion for Leave to Appear Pro Hac Vice Added Tara S.G. Sharp. **Attorneys admitted Pro Hac Vice must register for electronic filing if the attorney does not already have an ECF account in this district. To register go to the Court website at www.mad.uscourts.gov. Select Case Information, then Electronic Filing (CM/ECF) and go to the CM/ECF Registration Form.** (DaSilva, Carolina) (Entered: 09/23/2015)
09/23/2015	31	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 20 Motion for Leave to Appear Pro Hac Vice Added Andrew J. Kabat. **Attorneys admitted Pro Hac Vice must register for electronic filing if the attorney does not already have an ECF account in this district. To register go to the Court website at www.mad.uscourts.gov. Select Case Information, then Electronic Filing (CM/ECF) and go to the CM/ECF Registration Form.** (DaSilva, Carolina) (Entered: 09/23/2015)
09/23/2015	32	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 21 Motion for Leave to Appear Pro Hac Vice Added Jonathan E. Singer. **Attorneys admitted Pro Hac Vice must register for electronic filing if the attorney does not already have an ECF account in this district. To register go to the Court website at www.mad.uscourts.gov. Select Case Information, then Electronic Filing (CM/ECF) and go to the CM/ECF Registration Form.** (DaSilva, Carolina) (Entered: 09/23/2015)
09/23/2015	33	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 22 Motion for Leave to Appear Pro Hac Vice Added John C. Adkisson. **Attorneys admitted Pro Hac Vice must register for electronic filing if the attorney does not already have an ECF account in this district. To register go to the Court website at www.mad.uscourts.gov. Select Case Information, then Electronic Filing (CM/ECF) and go to the CM/ECF Registration Form.** (DaSilva, Carolina) (Entered: 09/23/2015)
09/23/2015	34	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 23 Motion for Leave to Appear Pro Hac Vice Added Elizabeth M. Flanagan. **Attorneys admitted Pro Hac Vice must register for electronic filing if the attorney does not already have an ECF account in this district. To register go to the Court website at www.mad.uscourts.gov. Select Case Information, then Electronic Filing (CM/ECF) and go to the CM/ECF Registration Form.** (DaSilva, Carolina) (Entered: 09/23/2015)
09/23/2015	35	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 24 Motion for Leave to Appear Pro Hac Vice Added Kelly Allenspach Del Dotto. **Attorneys admitted Pro Hac Vice must register for electronic filing if the attorney does not already have an ECF account in this district. To register go to the Court website at www.mad.uscourts.gov. Select Case Information, then Electronic Filing (CM/ECF) and go to the CM/ECF Registration Form.** (DaSilva, Carolina) (Entered: 09/23/2015)
09/23/2015	36	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 28 MOTION for Extension of Time to October 13, 2015 to Respond to Defendant's Motion to Dismiss the Second Amended Complaint. (DaSilva, Carolina) (Entered: 09/23/2015)

10/13/2015	37	Opposition re 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6)* filed by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Affidavit Declaration of Emmett McMahon)(McMahon, Emmett) (Entered: 10/13/2015)
11/09/2015	38	MOTION for Leave to File *a Reply Brief in Support of Their Motions to Dismiss the Second Amended Complaint* by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Attachments: # 1 [Proposed] Reply Brief)(Kessel, Adam) (Entered: 11/09/2015)
11/10/2015	39	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 38 Motion for Leave to File Document ; Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. **Counsel must include** - Leave to file granted on (date of order)- in the caption of the document. (DaSilva, Carolina) (Entered: 11/10/2015)
11/10/2015	40	REPLY to Response to 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6)* filed by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Kessel, Adam) (Entered: 11/10/2015)
11/17/2015	41	SUR-REPLY to Motion re 38 MOTION for Leave to File *a Reply Brief in Support of Their Motions to Dismiss the Second Amended Complaint* filed by Athena Diagnostics, Inc., Isis Innovation Limited. (Singh, Manleen) (Entered: 11/17/2015)
11/17/2015	42	Judge Indira Talwani: ELECTRONIC ORDER entered: The Sur-Reply to Motion 41 filed by Isis Innovation Limited, Athena Diagnostics, Inc. having been filed without leave of court, it is hereby STRUCK. SO ORDERED. (MacDonald, Gail) (Entered: 11/17/2015)
11/17/2015	43	NOTICE of Scheduling Conference Scheduling Conference set for 1/7/2016 03:00 PM in Courtroom 9 before Judge Indira Talwani. See attached. (MacDonald, Gail) (Entered: 11/17/2015)
11/17/2015	44	MOTION for Leave to File *a Surreply Brief Opposing Defendants' Motion to Dismiss the Second Amended Complaint* by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 [Proposed] Surreply Brief)(Singh, Manleen) (Entered: 11/17/2015)
11/18/2015	45	Judge Indira Talwani: ELECTRONIC ORDER entered granting 44 Motion for Leave to File Document ; Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. Counsel must include - Leave to file granted on (date of order)- in the caption of the document. (MacDonald, Gail) (Entered: 11/18/2015)
11/18/2015	46	SUR-REPLY to Motion re 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6)* filed by Athena Diagnostics, Inc., Isis Innovation Limited. (Singh, Manleen) (Entered: 11/18/2015)
12/29/2015	47	JOINT STATEMENT re scheduling conference . (Attachments: # 1 Exhibit The Parties proposed Pretrial Schedule)(McMahon, Emmett) (Entered: 12/29/2015)
12/30/2015	48	CERTIFICATION pursuant to Local Rule 16.1 *of Plaintiff Athena Diagnostics, Inc.*. (McMahon, Emmett) (Entered: 12/30/2015)
12/30/2015	49	CERTIFICATION pursuant to Local Rule 16.1 *of Plaintiff Isis Innovation Limited*. (McMahon, Emmett) (Entered: 12/30/2015)
12/30/2015	50	CERTIFICATION pursuant to Local Rule 16.1 *of Defendants*. (Kessel, Adam) (Entered: 12/30/2015)
01/07/2016	51	Electronic Clerk's Notes for proceedings held before Judge Indira Talwani: Scheduling Conference held on 1/7/2016. Parties agreed that plaintiffs' will provide to defendants a

		preliminary production of documents due by 1/14/2016. Should defendants intend to file a motion regarding subject matter jurisdiction they will do so as soon as possible thereafter. The parties agreed to submit a revised pretrial schedule that will be based on the court's disposition of defendants' motion to dismiss. (Court Reporter: Cheryl Dahlstrom at cheryldahlstrom@comcast.net.)(Attorneys present: Singh, McMahon for Plaintiff.Kessel, Flanagan, and Singer for Defendant. (Geraldino-Karasek, Clarilde) (Entered: 01/07/2016)
01/26/2016	52	Transcript of Scheduling Conference held on January 7, 2016, before Judge Indira Talwani. The Transcript may be purchased through the Court Reporter, viewed at the public terminal, or viewed through PACER after it is released. Court Reporter Name and Contact Information: Cheryl Dahlstrom at cheryldahlstrom@comcast.net Redaction Request due 2/16/2016. Redacted Transcript Deadline set for 2/26/2016. Release of Transcript Restriction set for 4/25/2016. (Scalfani, Deborah) (Entered: 01/26/2016)
01/26/2016	53	NOTICE is hereby given that an official transcript of a proceeding has been filed by the court reporter in the above-captioned matter. Counsel are referred to the Court's Transcript Redaction Policy, available on the court website at http://www.mad.uscourts.gov/attorneys/general-info.htm (Scalfani, Deborah) (Entered: 01/26/2016)
02/24/2016	54	Letter/request (non-motion) from Mayo Collaborative Services, LLC and Mayo Clinic *to update Court on subject matter jurisdiction issue*. (Kessel, Adam) (Entered: 02/24/2016)
03/04/2016	55	MOTION to Withdraw as Attorney *Tara S.G. Sharp* by Athena Diagnostics, Inc., Isis Innovation Limited.(Singh, Manleen) (Entered: 03/04/2016)
03/07/2016	56	Judge Indira Talwani: ELECTRONIC ORDER entered granting 55 Motion to Withdraw as Attorney. Attorney Tara S.G. Sharp terminated (MacDonald, Gail) (Entered: 03/07/2016)
03/11/2016	57	MOTION for Leave to File *Third Amended Complaint* by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Exhibit Proposed Third Amended Complaint) (Singh, Manleen) (Entered: 03/11/2016)
03/11/2016	58	MEMORANDUM in Support re 57 MOTION for Leave to File *Third Amended Complaint* filed by Athena Diagnostics, Inc., Isis Innovation Limited. (Singh, Manleen) (Entered: 03/11/2016)
03/11/2016	59	DECLARATION re 58 Memorandum in Support of Motion, 57 MOTION for Leave to File *Third Amended Complaint* by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H, # 9 Exhibit I, # 10 Exhibit J)(Singh, Manleen) (Entered: 03/11/2016)
03/18/2016	60	RESPONSE to Motion re 57 MOTION for Leave to File *Third Amended Complaint Adding Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften E.V. as an Involuntary Plaintiff* filed by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Kessel, Adam) (Entered: 03/18/2016)
03/22/2016	61	MOTION for Leave to File *Notice of Decision* by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Exhibit Proposed Notice of Decision, # 2 Exhibit Exhibit A to Proposed Notice of Decision)(Singh, Manleen) (Entered: 03/22/2016)
03/23/2016	62	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 61 MOTION for Leave to File Notice of Decision ; Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. **Counsel must include** - Leave to file granted

		on (date of order)- in the caption of the document. (DaSilva, Carolina) (Entered: 03/23/2016)
03/23/2016	63	Notice of Supplemental Authorities re 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6)* filed by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Exhibit A)(Singh, Manleen) (Entered: 03/23/2016)
04/13/2016	64	Judge Indira Talwani: ELECTRONIC ORDER entered. ORDER Setting Hearing on Motion 57 MOTION for Leave to File *Third Amended Complaint* : Motion Hearing set for 5/5/2016 10:45 AM in Courtroom 9 before Judge Indira Talwani.(MacDonald, Gail) (Entered: 04/13/2016)
04/14/2016	65	MOTION for Leave to File *Notice of Supplemental Authority* by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Attachments: # 1 Defendants' Notice of Supplemental Authority, # 2 Exhibit A to Defendants' Notice of Supplemental Authority, # 3 Exhibit B to Defendants' Notice of Supplemental Authority) (Kessel, Adam) (Entered: 04/14/2016)
04/21/2016	66	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 65 MOTION for Leave to File Notice of Supplemental Authority; Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. **Counsel must include** - Leave to file granted on (date of order)- in the caption of the document. (DaSilva, Carolina) (Entered: 04/21/2016)
04/22/2016	67	Notice of Supplemental Authorities re 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6) (Leave to File Granted April 21, 2016)* (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Kessel, Adam) (Entered: 04/22/2016)
05/03/2016	68	Amended JOINT SUBMISSION pursuant to Local Rule 16.1 *[Proposed] Pretrial Schedule* by Athena Diagnostics, Inc., Isis Innovation Limited.(Kabat, Andrew J.) (Entered: 05/03/2016)
05/05/2016	69	Electronic Clerk's Notes for proceedings held before Judge Indira Talwani: Motion Hearing held on 5/5/2016 re 57 MOTION for Leave to File *Third Amended Complaint* filed by Isis Innovation Limited, Athena Diagnostics, Inc. Case called. Court hears argument from counsel. Additional briefing re: involuntary plaintiff issue and proposed schedule to be submitted. Further hearing to be set. (Court Reporter: Cheryl Dahlstrom at cheryldahlstrom@comcast.net.)(Attorneys present: McMahon, Kessel, Adkisson) (MacDonald, Gail) (Entered: 05/09/2016)
05/12/2016	70	Transcript of Hearing on Motion to Amend the Complaint held on May 5, 2016, before Judge Indira Talwani. The Transcript may be purchased through the Court Reporter, viewed at the public terminal, or viewed through PACER after it is released. Court Reporter Name and Contact Information: Cheryl Dahlstrom at cheryldahlstrom@comcast.net Redaction Request due 6/2/2016. Redacted Transcript Deadline set for 6/13/2016. Release of Transcript Restriction set for 8/10/2016. (Scalfani, Deborah) (Entered: 05/12/2016)
05/12/2016	71	NOTICE is hereby given that an official transcript of a proceeding has been filed by the court reporter in the above-captioned matter. Counsel are referred to the Court's Transcript Redaction Policy, available on the court website at http://www.mad.uscourts.gov/attorneys/general-info.htm (Scalfani, Deborah) (Entered: 05/12/2016)
05/18/2016	72	STIPULATION *by the Parties' Regarding Schedule for Briefing on Standing and Joinder Issues* by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Kessel, Adam) (Entered: 05/18/2016)

05/18/2016	73	Judge Indira Talwani: ELECTRONIC ORDER entered **ADOPTING** 72 STIPULATION by the Parties' Regarding Schedule for Briefing on Standing and Joinder Issues. (DaSilva, Carolina) (Entered: 05/18/2016)
05/24/2016	74	STIPULATION *by the Parties Regarding Schedule for Briefing on Standing And Joinder Issues* by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Kessel, Adam) (Entered: 05/24/2016)
05/25/2016	75	Judge Indira Talwani: ELECTRONIC ORDER entered ADOPTING Amended Joint 74 STIPULATION by the Parties Regarding Schedule for Briefing on Standing And Joinder Issues. (DaSilva, Carolina) (Entered: 05/25/2016)
05/31/2016	76	STIPULATION *by the Parties Regarding Schedule for Briefing on Standing And Joinder Issues (Second Amended)* by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Kessel, Adam) (Entered: 05/31/2016)
05/31/2016	77	Judge Indira Talwani: ELECTRONIC ORDER entered ADOPTING 76 Stipulation filed by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories: June 2, 2016 Defendants file a motion to dismiss for lack of standing June 16, 2016 Plaintiffs respond to Defendants motion, and may file a cross-motion for joinder under Rule 19 June 27, 2016 Defendants may file a reply brief in response to Plaintiffs response to their motion to dismiss, and may file a response to any cross-motion for joinder by Plaintiffs July 5, 2016 Plaintiffs may file a reply brief in support of their cross-motion for joinder(MacDonald, Gail) (Entered: 06/01/2016)
06/02/2016	78	MOTION to Seal *Mayo's Memorandum in Support of its Motion to Dismiss and Exhibits 1, 4, 5, and 7 to Declaration of Adam J. Kessel* by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories.(Kessel, Adam) (Entered: 06/02/2016)
06/02/2016	79	MOTION to Dismiss *the Second Amended Complaint* by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories.(Kessel, Adam) (Entered: 06/02/2016)
06/02/2016	80	DECLARATION re 79 MOTION to Dismiss *the Second Amended Complaint* by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Attachments: # 1 Exhibit 1 - SEALED, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4 - SEALED, # 5 Exhibit 5 - SEALED, # 6 Exhibit 6, # 7 Exhibit 7 - SEALED, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10, # 11 Exhibit 11, # 12 Exhibit 12, # 13 Exhibit 13, # 14 Exhibit 14, # 15 Exhibit 15, # 16 Exhibit 16)(Kessel, Adam) (Entered: 06/02/2016)
06/07/2016	81	ELECTRONIC NOTICE issued requesting **TWO** courtesy copies of 80 Declaration. Counsel who filed the document are requested to submit a courtesy copy to the Clerk's Office by June 10, 2016. **These documents must be clearly marked as a Courtesy Copy, contain appropriate (number/letter) tabs, reflect the document number assigned by CM/ECF, and be placed in a 3-ring binder.** (DaSilva, Carolina) (Entered: 06/07/2016)
06/10/2016	82	REDACTION *Defendants' Memorandum of Law in Support of Defendants' Rule 12(B)(1) Motion to Dismiss the Second Amended Complaint* byMayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Kessel, Adam) (Entered: 06/10/2016)
06/16/2016	83	Opposition re 79 MOTION to Dismiss *the Second Amended Complaint* filed by Athena Diagnostics, Inc., Isis Innovation Limited. (Singh, Manleen) (Entered: 06/16/2016)
06/16/2016	84	MOTION for Leave to File *Third Amended Complaint* by Athena Diagnostics, Inc., Isis Innovation Limited.(Singh, Manleen) (Entered: 06/16/2016)

06/16/2016	85	MEMORANDUM in Support re 84 MOTION for Leave to File *Third Amended Complaint* filed by Athena Diagnostics, Inc., Isis Innovation Limited. (Singh, Manleen) (Entered: 06/16/2016)
06/16/2016	86	DECLARATION re 84 MOTION for Leave to File *Third Amended Complaint , of M. McFarlane,* by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D)(Singh, Manleen) (Entered: 06/16/2016)
06/27/2016	87	RESPONSE to Motion re 79 MOTION to Dismiss *the Second Amended Complaint*, 84 MOTION for Leave to File *Third Amended Complaint* filed by Mayo Clinic, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories. (Kessel, Adam) (Entered: 06/27/2016)
06/30/2016	88	MOTION for Hearing by Athena Diagnostics, Inc., Isis Innovation Limited.(Kabat, Andrew J.) (Main Document 88 replaced on 6/30/2016 with correct 7.1) (DaSilva, Carolina). (Entered: 06/30/2016)
06/30/2016	89	DECLARATION re 88 MOTION for Hearing by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Kabat, Andrew J.) (Entered: 06/30/2016)
07/06/2016	90	Judge Indira Talwani: ORDER entered finding as moot 79 Motion to Dismiss; granting 84 Motion for Leave to File Document ; Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. Counsel must include - Leave to file granted on (date of order)- in the caption of the document.; granting 88 Motion for Hearing. SEE attached Order. (MacDonald, Gail) Modified date filed on 7/8/2016 date filed (DaSilva, Carolina). (Entered: 07/08/2016)
07/08/2016	91	Judge Indira Talwani: ELECTRONIC ORDER entered. ORDER Setting Hearing on Motion 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6)* : Motion Hearing set for 8/2/2016 10:30 AM in Courtroom 9 before Judge Indira Talwani.(MacDonald, Gail) (Entered: 07/08/2016)
07/08/2016	92	AMENDED COMPLAINT *(Third)* against Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories, Mayo Clinic, filed by Athena Diagnostics, Inc., Isis Innovation Limited.(Singh, Manleen) (Entered: 07/08/2016)
07/08/2016	93	Judge Indira Talwani: ELECTRONIC ORDER entered. Defendants' 78 Motion to Impound is DENIED as moot without prejudice. Defendants shall not file the proposed sealed documents. (DaSilva, Carolina) (Entered: 07/08/2016)
07/26/2016	94	Joint MOTION for Leave to File *Notice of Decision* by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (Attachments: # 1 Exhibit Proposed Notice of Decision, # 2 Exhibit A)(McMahon, Emmett) (Entered: 07/26/2016)
07/27/2016	95	Judge Indira Talwani: ELECTRONIC ORDER entered granting 94 Motion for Leave to File Document ; Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. Counsel must include - Leave to file granted on (date of order)- in the caption of the document. (MacDonald, Gail) (Entered: 07/27/2016)
07/27/2016	96	NOTICE of Decision Relevant to 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6) of Decision* by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.

		(Attachments: # 1 Exhibit A)(McMahon, Emmett) Modified docket text on 7/28/2016 (DaSilva, Carolina). (Entered: 07/27/2016)
08/02/2016	97	Electronic Clerk's Notes for proceedings held before Judge Indira Talwani: Motion Hearing held on 8/2/2016 re 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6)* filed by Mayo Collaborative Services, LLC, Mayo Clinic. Case called. Court hears argument from counsel. Order to follow. (Court Reporter: Cheryl Dahlstrom at cheryldahlstrom@comcast.net.)(Attorneys present: Singh, McMahon, Kessel, Kabat) (MacDonald, Gail) (Entered: 08/04/2016)
08/08/2016	98	Transcript of Hearing on Motion to Dismiss the Second Amended Complaint held on August 2, 2016, before Judge Indira Talwani. The Transcript may be purchased through the Court Reporter, viewed at the public terminal, or viewed through PACER after it is released. Court Reporter Name and Contact Information: Cheryl Dahlstrom at cheryldahlstrom@comcast.net Redaction Request due 8/29/2016. Redacted Transcript Deadline set for 9/8/2016. Release of Transcript Restriction set for 11/7/2016. (Scalfani, Deborah) (Entered: 08/08/2016)
08/08/2016	99	NOTICE is hereby given that an official transcript of a proceeding has been filed by the court reporter in the above-captioned matter. Counsel are referred to the Court's Transcript Redaction Policy, available on the court website at http://www.mad.uscourts.gov/attorneys/general-info.htm (Scalfani, Deborah) (Entered: 08/08/2016)
08/18/2016	100	MOTION for Leave to File *Brief Containing Additional Points and Supplemental Authorities Regarding Decisions Relevant to Defendants' Motion to Dismiss (Dkt. No. 25)* by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (Attachments: # 1 Plaintiffs' (Proposed) Brief Containing Additional Points and Supplemental Authorities, # 2 Exhibit A to Plaintiffs' (Proposed) Brief Containing Additional Points and Supplemental Authorities, # 3 Exhibit B to Plaintiffs' (Proposed) Brief Containing Additional Points and Supplemental Authorities)(McMahon, Emmett) (Entered: 08/18/2016)
08/19/2016	101	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING IN PART and DENYING IN PART 100 MOTION for Leave to File Brief Containing Additional Points and Supplemental Authorities Regarding Decisions Relevant to Defendants' Motion to Dismiss (Dkt. No. 25). Plaintiff is **GRANTED** leave to file supplemental authorities. Plaintiff is **DENIED** leave to file the supplemental brief. Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. **Counsel must include** - Leave to file granted on (date of order)- in the caption of the document. (DaSilva, Carolina) (Entered: 08/19/2016)
08/19/2016	102	Notice of Supplemental Authorities re 25 MOTION to Dismiss *the Second Amended Complaint Pursuant to Rule 12(B)(6)* (Attachments: # 1 Exhibit A, # 2 Exhibit B) (McMahon, Emmett) (Entered: 08/19/2016)
08/25/2016	103	Judge Indira Talwani: ORDER entered. MEMORANDUM AND ORDER DENYING 25 MOTION to Dismiss the Second Amended Complaint Pursuant to Rule 12(B)(6). (DaSilva, Carolina) (Entered: 08/25/2016)
09/06/2016	104	Letter/request (non-motion) from Adam J. Kessel *Regarding Discovery and Request for Status Conference*. (Kessel, Adam) (Entered: 09/06/2016)
09/07/2016	105	Letter/request (non-motion) from Emmett J. McMahon *Regarding Defendants' Request*

		for Status Conference. (McMahon, Emmett) (Entered: 09/07/2016)
09/07/2016	106	ELECTRONIC NOTICE of Hearing. Status Conference set for 10/4/2016 11:00 AM in Courtroom 9 before Judge Indira Talwani. The parties shall simultaneously file a submission not longer than three pages outlining their discovery proposal by end of business Friday, 9/30/16. (MacDonald, Gail) (Entered: 09/07/2016)
09/08/2016	107	ANSWER to 92 Amended Complaint *Third*, COUNTERCLAIM against Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V. by Mayo Collaborative Services, LLC, Mayo Clinic.(Kessel, Adam) (Entered: 09/08/2016)
09/14/2016	108	MOTION to Compel *Interrogatory Responses, Production of Documents, and Preliminary Disclosures* by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Text of Proposed Order)(McMahon, Emmett) (Entered: 09/14/2016)
09/14/2016	109	MEMORANDUM in Support re 108 MOTION to Compel *Interrogatory Responses, Production of Documents, and Preliminary Disclosures* filed by Athena Diagnostics, Inc., Isis Innovation Limited. (McMahon, Emmett) (Entered: 09/14/2016)
09/14/2016	110	DECLARATION re 108 MOTION to Compel *Interrogatory Responses, Production of Documents, and Preliminary Disclosures* by Athena Diagnostics, Inc., Isis Innovation Limited. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C)(McMahon, Emmett) (Entered: 09/14/2016)
09/16/2016	111	MOTION to Continue Status Conference Date to October 6 or October 7 by Mayo Clinic, Mayo Collaborative Services, LLC.(Kessel, Adam) (Entered: 09/16/2016)
09/16/2016	112	Judge Indira Talwani: ELECTRONIC ORDER entered granting 111 Motion to Continue Status Conference set for 10/4/16 is RESET to 10/6/2016 10:00 AM in Courtroom 9 before Judge Indira Talwani. (MacDonald, Gail) (Entered: 09/16/2016)
09/16/2016	113	Judge Indira Talwani: ELECTRONIC ORDER entered. ORDER Setting Hearing on Motion 108 MOTION to Compel *Interrogatory Responses, Production of Documents, and Preliminary Disclosures* : Motion Hearing set for 10/6/2016 10:15 AM in Courtroom 9 before Judge Indira Talwani.(MacDonald, Gail) (Entered: 09/16/2016)
09/28/2016	114	Assented to MOTION for Leave to Appear Pro Hac Vice for admission of Phillip W. Goter Filing fee: $ 100, receipt number 0101-6310204 by Mayo Clinic. (Attachments: # 1 Exhibit 1)(Kessel, Adam) (Entered: 09/28/2016)
09/28/2016	115	Opposition re 108 MOTION to Compel *Interrogatory Responses, Production of Documents, and Preliminary Disclosures* filed by Mayo Clinic. (Kessel, Adam) (Entered: 09/28/2016)
09/28/2016	116	DECLARATION re 115 Opposition to Motion *to Compel Interrogatory Responses, Production of Documents, and Preliminary Disclosures* by Mayo Clinic. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9)(Kessel, Adam) (Entered: 09/28/2016)
09/29/2016	117	ANSWER to Counterclaim by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V..(McFarlane, Matthew) (Entered: 09/29/2016)
09/30/2016	118	NOTICE by Mayo Clinic *Discovery Proposal* (Kessel, Adam) (Entered: 09/30/2016)
09/30/2016	119	NOTICE by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V. *Plaintiffs' Submission for a Discovery Proposal* (McMahon, Emmett) (Entered: 09/30/2016)

10/03/2016	120	Judge Indira Talwani: ELECTRONIC ORDER entered ALLOWING 114 Motion for Leave to Appear Pro Hac Vice Added Phillip W. Goter. **Attorneys admitted Pro Hac Vice must register for electronic filing if the attorney does not already have an ECF account in this district. To register go to the Court website at www.mad.uscourts.gov. Select Case Information, then Electronic Filing (CM/ECF) and go to the CM/ECF Registration Form.** (DaSilva, Carolina) (Entered: 10/03/2016)
10/04/2016	121	MOTION for Leave to File *Reply in Support of Plaintiffs' Motion to Compel Interrogatory Responses, Production of Documents, and Preliminary Disclosures* by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (Attachments: # 1 Exhibit A)(McMahon, Emmett) (Entered: 10/04/2016)
10/05/2016	122	Assented to MOTION for Leave to Appear Pro Hac Vice for admission of Vicki G. Norton Filing fee: $ 100, receipt number 0101-6320922 by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (Attachments: # 1 Affidavit)(Singh, Manleen) (Entered: 10/05/2016)
10/05/2016	123	Judge Indira Talwani: ELECTRONIC ORDER entered granting 122 Motion for Leave to Appear Pro Hac Vice. Added Vicki G. Norton. **Attorneys admitted Pro Hac Vice must register for electronic filing if the attorney does not already have an ECF account in this district. To register go to the Court website at www.mad.uscourts.gov. Select Case Information, then Electronic Filing (CM/ECF) and go to the CM/ECF Registration Form.** (MacDonald, Gail) (Entered: 10/05/2016)
10/05/2016	124	Copy re 123 Order on Motion for Leave to Appear, mailed to Vicki G. Norton (MacDonald, Gail) (Entered: 10/05/2016)
10/05/2016	125	Judge Indira Talwani: ELECTRONIC ORDER entered granting 121 Motion for Leave to File Document ; Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. Counsel must include - Leave to file granted on (date of order)- in the caption of the document. (Talwani, Indira) (Entered: 10/05/2016)
10/05/2016	126	REPLY to Response to 108 MOTION to Compel *Interrogatory Responses, Production of Documents, and Preliminary Disclosures (Leave to File Granted Oct. 5, 2016)* filed by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (McFarlane, Matthew) (Entered: 10/05/2016)
10/06/2016	127	Electronic Clerk's Notes for proceedings held before Judge Indira Talwani: Status Conference and Motion Hearing held on 10/6/2016: Case called. Court has colloquy with counsel and hears argument on the motion. Plaintiffs' 108 Motion to Compel denied in open court. Defendant may refile Motion to Dismiss in two weeks. (Court Reporter: James Gibbons at jmsgibbons@yahoo.com.)(Attorneys present: McMahon, McFarlane, Norton, Kessel, Singer) (MacDonald, Gail) Modified on 10/20/2016 to correct attorneys' names (MacDonald, Gail). (Entered: 10/12/2016)
10/14/2016	128	Transcript of Motion to Compel Hearing held on October 6, 2016, before Judge Indira Talwani. The Transcript may be purchased through the Court Reporter, viewed at the public terminal, or viewed through PACER after it is released. Court Reporter Name and Contact Information: James Gibbons at jmsgibbons@yahoo.com Redaction Request due 11/4/2016. Redacted Transcript Deadline set for 11/14/2016. Release of Transcript Restriction set for 1/12/2017. (Scalfani, Deborah) (Entered: 10/14/2016)
10/14/2016	129	NOTICE is hereby given that an official transcript of a proceeding has been filed by the court reporter in the above-captioned matter. Counsel are referred to the Court's Transcript Redaction Policy, available on the court website at

		http://www.mad.uscourts.gov/attorneys/general-info.htm (Scalfani, Deborah) (Entered: 10/14/2016)
10/19/2016	130	STIPULATION *Jointly Regarding Schedule for Briefing Defendants' Renewed Rule 12(B)(6) Motion to Dismiss the Third Amended Complaint* by Mayo Clinic, Mayo Collaborative Services, LLC. (Kessel, Adam) (Entered: 10/19/2016)
10/20/2016	131	MOTION to Dismiss *the Third Amended Complaint* by Mayo Clinic, Mayo Collaborative Services, LLC.(Kessel, Adam) (Entered: 10/20/2016)
10/20/2016	132	MEMORANDUM in Support re 131 MOTION to Dismiss *the Third Amended Complaint* filed by Mayo Clinic, Mayo Collaborative Services, LLC. (Kessel, Adam) (Entered: 10/20/2016)
10/20/2016	133	DECLARATION re 131 MOTION to Dismiss *the Third Amended Complaint* by Mayo Clinic, Mayo Collaborative Services, LLC. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E)(Kessel, Adam) (Entered: 10/20/2016)
11/11/2016	134	MOTION for Leave to File *an Overlength Memorandum of Law in Opposition to Defendants' Renewed Motion to Dismiss (D.I. 131)* by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (McMahon, Emmett) (Entered: 11/11/2016)
11/14/2016	135	Judge Indira Talwani: ELECTRONIC ORDER entered granting 134 Motion for Leave to File file overlength memorandum of law; Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. Counsel must include - Leave to file granted on (date of order)- in the caption of the document. (MacDonald, Gail) (Entered: 11/14/2016)
11/14/2016	136	MEMORANDUM in Opposition re 131 MOTION to Dismiss *the Third Amended Complaint* filed by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (McFarlane, Matthew) (Entered: 11/14/2016)
11/14/2016	137	Statement of Material Facts L.R. 56.1 re 131 MOTION to Dismiss *the Third Amended Complaint in Support of Plaintiffs' Opposition* filed by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (McFarlane, Matthew) (Entered: 11/14/2016)
11/14/2016	138	AFFIDAVIT in Opposition re 131 MOTION to Dismiss *the Third Amended Complaint -- Expert Declaration of Anthony W. De Tomaso, Ph.D.* filed by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (Attachments: # 1 Exhibit Exhibit A -- Curriculum Vitae, # 2 Exhibit Exhibit B -- Materials Considered)(McFarlane, Matthew) (Entered: 11/14/2016)
11/14/2016	139	AFFIDAVIT in Opposition re 131 MOTION to Dismiss *the Third Amended Complaint -- Declaration of Matthew B. McFarlane in Support of Plaintiffs' Opposition,* filed by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H, # 9 Exhibit I, # 10 Exhibit J, # 11 Exhibit K, # 12 Exhibit L, # 13 Exhibit M, # 14 Exhibit N, # 15 Exhibit O, # 16 Exhibit P, # 17 Exhibit Q)(McFarlane, Matthew) (Entered: 11/14/2016)
11/21/2016	140	MOTION for Extension of Time to December 9, 2016 to File Response/Reply as to 131 MOTION to Dismiss *the Third Amended Complaint* by Mayo Clinic, Mayo Collaborative Services, LLC.(Kessel, Adam) (Entered: 11/21/2016)

11/22/2016	141	Judge Indira Talwani: ELECTRONIC ORDER entered granting 140 Motion for Extension of Time to File Response/Reply re 140 MOTION for Extension of Time to December 9, 2016 to File Response/Reply as to 131 MOTION to Dismiss *the Third Amended Complaint* Responses due by 12/9/2016 (MacDonald, Gail) (Entered: 11/22/2016)
12/08/2016	142	NOTICE of Appearance by Lisa A. Furnald on behalf of Athena Diagnostics, Inc., Isis Innovation Limited (Furnald, Lisa) (Entered: 12/08/2016)
12/09/2016	143	REPLY to Response to 131 MOTION to Dismiss *the Third Amended Complaint Mayo's Reply Brief in Support of its Renewed Rule 12(B)(6) Motion to Dismiss the Third Amended Complaint* filed by Mayo Collaborative Services, LLC. (Kessel, Adam) (Entered: 12/09/2016)
12/09/2016	144	Statement of Material Facts L.R. 56.1 re 131 MOTION to Dismiss *the Third Amended Complaint Mayo's Response to Plaintiffs' Local Rule 56.1 Statement of Material Facts Beyond Reasonable Dispute* filed by Mayo Collaborative Services, LLC. (Kessel, Adam) (Entered: 12/09/2016)
12/20/2016	145	MOTION for Leave to File *Surreply Brief in Opposition to Defendants' Renewed Rule 12(b)(6) Motion to Dismiss* by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.. (Attachments: # 1 [Proposed] Surreply Brief in Opposition to Defendants' Renewed Motion to Dismiss) (McFarlane, Matthew) (Entered: 12/20/2016)
12/22/2016	146	Judge Indira Talwani: ELECTRONIC ORDER entered denying 145 Motion for Leave to File Document. The court will request additional briefing if needed. (MacDonald, Gail) (Entered: 12/22/2016)
12/22/2016	147	NOTICE issued to Attorney Vicki G. Norton Duane Morris LLP 750 B Street Suite 2900 San Diego, CA 92101 regarding mandatory use of ECF in compliance with Local Rule 5.4. Failure to comply may result in the imposition of sanctions. (MacDonald, Gail) (Entered: 12/22/2016)
07/05/2017	148	MOTION for Leave to File *Notice of Supplemental Authority* by Mayo Clinic, Mayo Collaborative Services, LLC. (Attachments: # 1 Proposed Notice of Supplemental Authority, # 2 Exhibit A to Notice of Supplemental Authority)(Kessel, Adam) (Entered: 07/05/2017)
07/06/2017	149	Judge Indira Talwani: ELECTRONIC ORDER entered granting 148 Motion for Leave to File Document ; Counsel using the Electronic Case Filing System should now file the document for which leave to file has been granted in accordance with the CM/ECF Administrative Procedures. Counsel must include - Leave to file granted on (date of order)- in the caption of the document. (MacDonald, Gail) (Entered: 07/06/2017)
07/06/2017	150	Notice of Supplemental Authorities re 131 MOTION to Dismiss *the Third Amended Complaint (Leave to File Granted on July 6, 2017)* (Attachments: # 1 Exhibit A)(Kessel, Adam) (Entered: 07/06/2017)
07/26/2017	151	NOTICE by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V. re 131 MOTION to Dismiss *the Third Amended Complaint regarding Esoterix v. Qiagen* (Attachments: # 1 Exhibit A, # 2 Exhibit B) (Singh, Manleen) (Entered: 07/26/2017)
08/04/2017	152	Judge Indira Talwani: ORDER entered. MEMORANDUM AND ORDER **GRANTING** 131 MOTION to Dismiss the Third Amended Complaint. (DaSilva, Carolina) (Entered: 08/04/2017)
08/04/2017	153	Judge Indira Talwani: ORDER entered. ORDER DISMISSING CASE(DaSilva,

		Carolina) (Entered: 08/04/2017)
08/18/2017	154	NOTICE OF APPEAL to the Federal Circuit as to 153 Order Dismissing Case, 152 Memorandum & ORDER by Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V. Filing fee: $ 505, receipt number 0101-6758415 Fee Status: Filing Fee paid. US District Court Clerk to deliver official record to Court of Appeals by 9/7/2017. (Singh, Manleen) (Entered: 08/18/2017)
09/05/2017	155	Certified and Transmitted Abbreviated Electronic Record on Appeal to US Court of Appeals for the Federal Circuit re 154 Notice of Appeal to the Federal Circuit. (Paine, Matthew) (Entered: 09/05/2017)
09/06/2017	156	USCA Case Number 17-2508 for 154 Notice of Appeal to the Federal Circuit, filed by Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V., Isis Innovation Limited, Athena Diagnostics, Inc.. (Paine, Matthew) (Entered: 09/06/2017)

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PACER Login:	wc0022:2660236:3941772	**Client Code:**	11853470002
Description:	Docket Report	**Search Criteria:**	1:15-cv-40075-IT
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US007267820B2

(12) **United States Patent**
Vincent et al.

(10) **Patent No.: US 7,267,820 B2**
(45) **Date of Patent: Sep. 11, 2007**

(54) **NEUROTRANSMISSION DISORDERS**

(75) Inventors: **Angela Vincent**, Oxford (GB); **Werner Hoch**, Houston, TX (US)

(73) Assignees: **Isis Innovation Limited**, Oxford (GB); **Max-Planck Gesellschaft zur Foerderung der Wissenschaften e.V.**, Munich (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 506 days.

(21) Appl. No.: **10/311,575**

(22) PCT Filed: **Jun. 15, 2001**

(86) PCT No.: **PCT/GB01/02661**

§ 371 (c)(1),
(2), (4) Date: **Jun. 6, 2003**

(87) PCT Pub. No.: **WO01/96601**

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(65) **Prior Publication Data**

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(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
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A61K 39/00 (2006.01)
A61K 38/00 (2006.01)
C07K 14/00 (2006.01)

(52) **U.S. Cl.** **424/130.1**; 424/184.1; 424/178.1; 514/2; 530/350

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

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(74) *Attorney, Agent, or Firm*—Hamilton, Brook, Smith & Reynolds, P.C.

(57) **ABSTRACT**

There is disclosed a method for diagnosing neurotransmission or developmental disorders in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of the muscle specific tyrosine kinase (MuSK). One such method comprises a) contacting said bodily fluid with said MuSK or an antigenic determinant thereof; and b) detecting any antibody-antigen complexes formed between said receptor tyrosine kinase or an antigenic fragment thereof and antibodies present in said bodily fluid, wherein the presence of said complexes is indicative of said mammal suffering from said neurotransmission or developmental disorders. Also disclosed are kits for use in the diagnosis of neurotransmission and subsequent developmental disorders.

12 Claims, 6 Drawing Sheets

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FIG. 1.

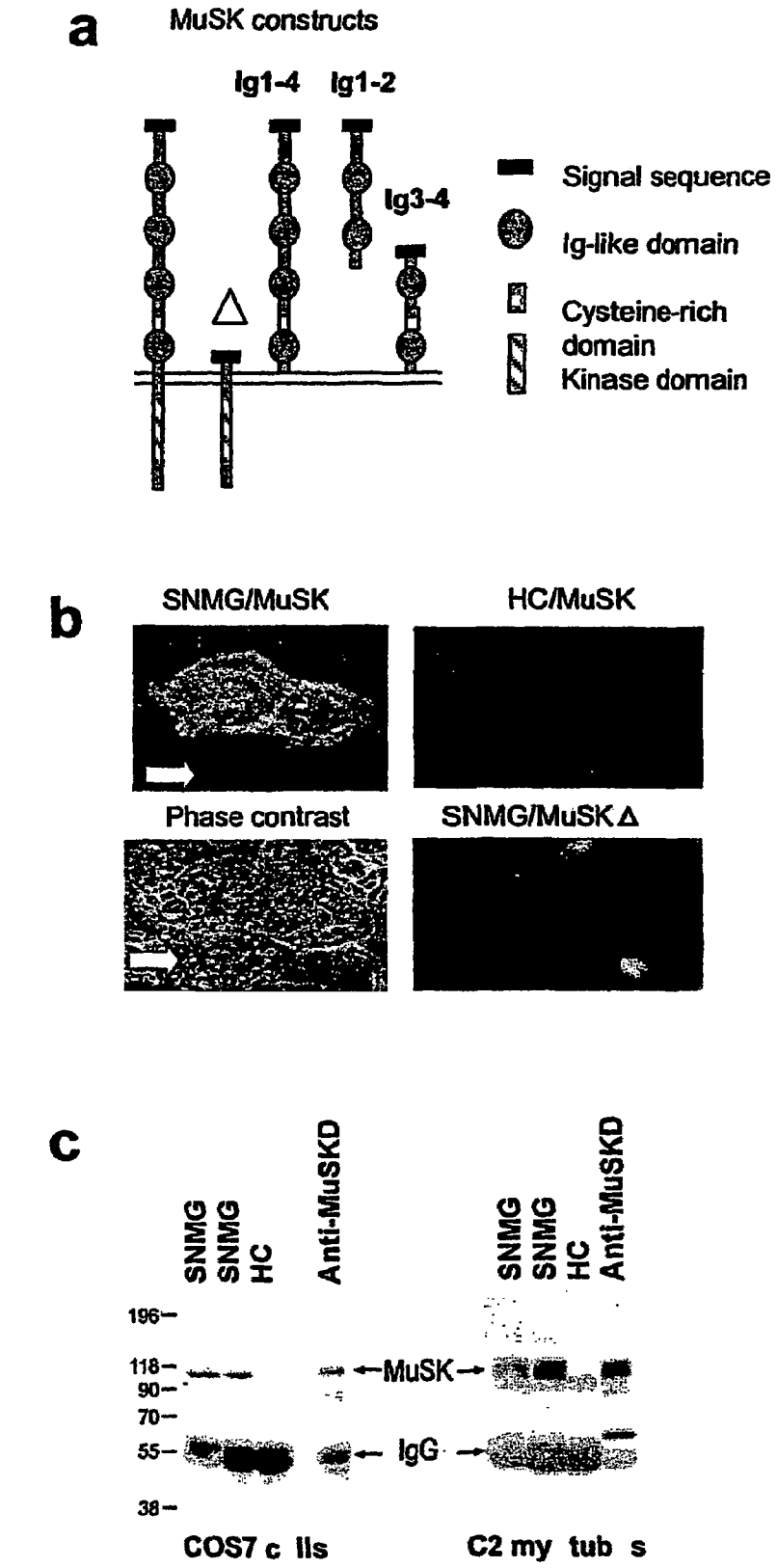

a
MuSK constructs
Ig1-4
Ig1-2
Ig3-4
Signal sequence
Ig-like domain
Cysteine-rich domain
Kinase domain
b
SNMG/MuSK
HC/MuSK
Phase contrast
SNMG/MuSKΔ
c
SNMG
SNMG
HC
Anti-MuSKD
SNMG
SNMG
HC
Anti-MuSKD
196
118
90
70
55
38
MuSK
IgG
COS7 c lls
C2 my tub s

FIG. 2.

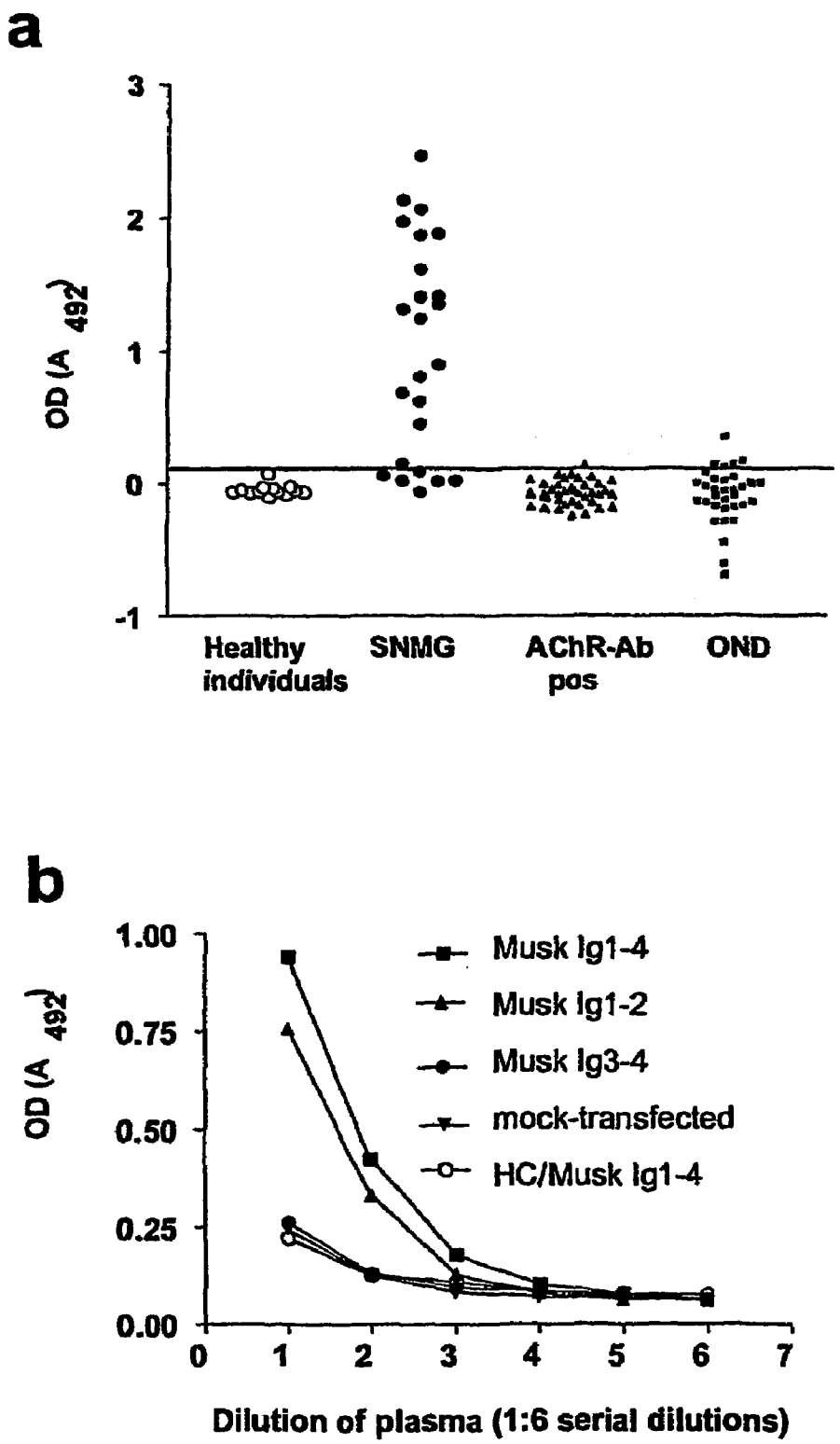

a
OD (A 492)
3
2
1
0
-1
Healthy individuals
SNMG
AChR-Ab pos
OND
b
OD (A 492)
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
Musk Ig1-4
Musk Ig1-2
Musk Ig3-4
mock-transfected
HC/Musk Ig1-4
Dilution of plasma (1:6 serial dilutions)

FIG. 3.

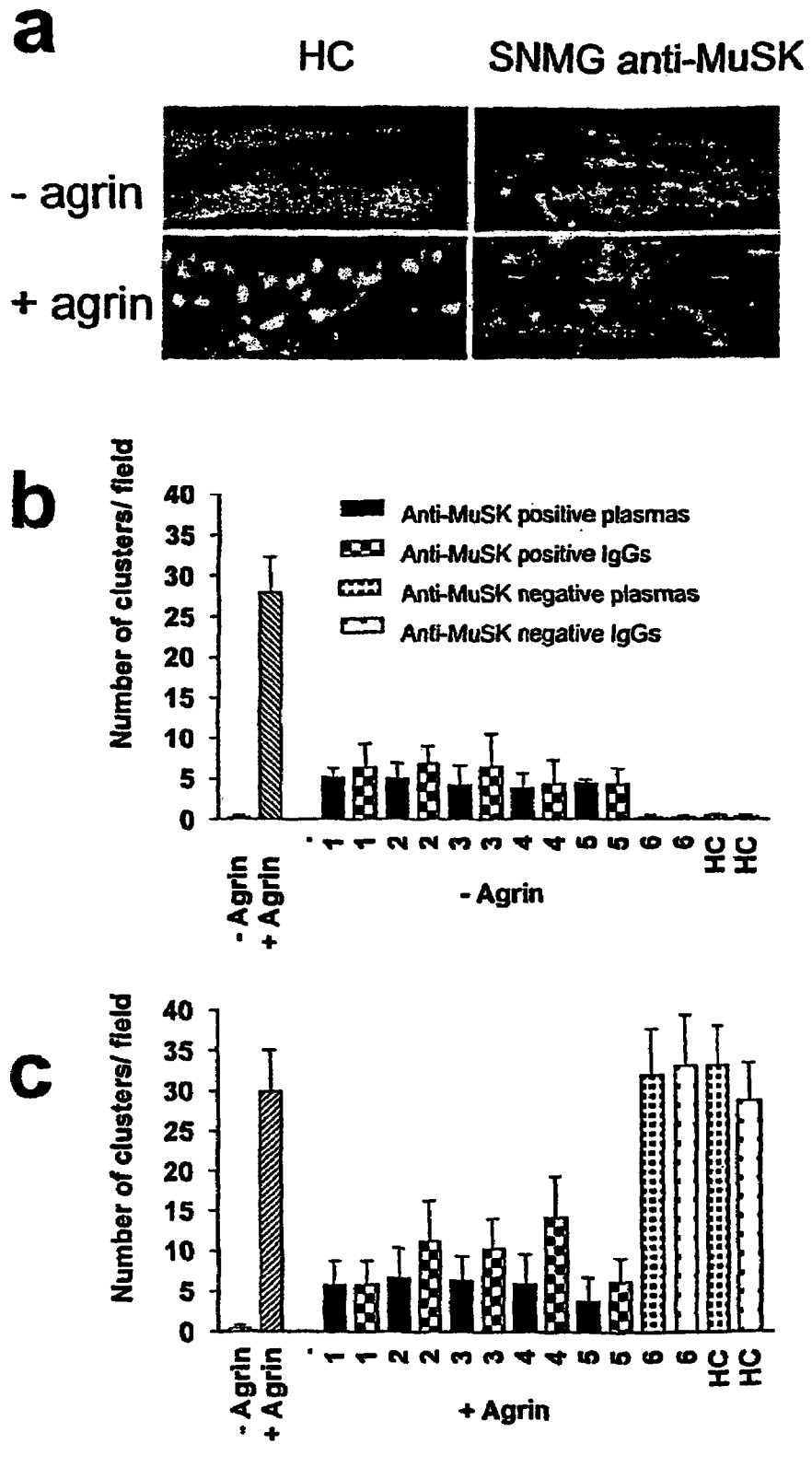

a
HC
SNMG anti-MuSK
- agrin
+ agrin
b
Number of clusters/ field
Anti-MuSK positive plasmas
Anti-MuSK positive IgGs
Anti-MuSK negative plasmas
Anti-MuSK negative IgGs
- Agrin
+ Agrin
1 1 2 2 3 3 4 4 5 5 6 6 HC HC
- Agrin
c
Number of clusters/ field
- Agrin
+ Agrin
1 1 2 2 3 3 4 4 5 5 6 6 HC HC
+ Agrin

FIG. 4.

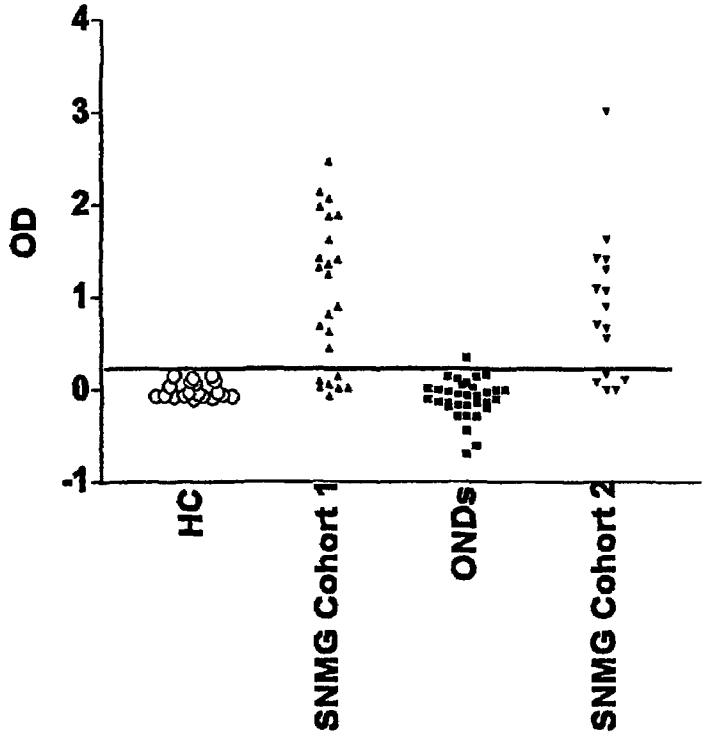

OD
4
3
2
1
0
-1
HC
SNMG Cohort 1
ONDs
SNMG Cohort 2

FIG. 5.

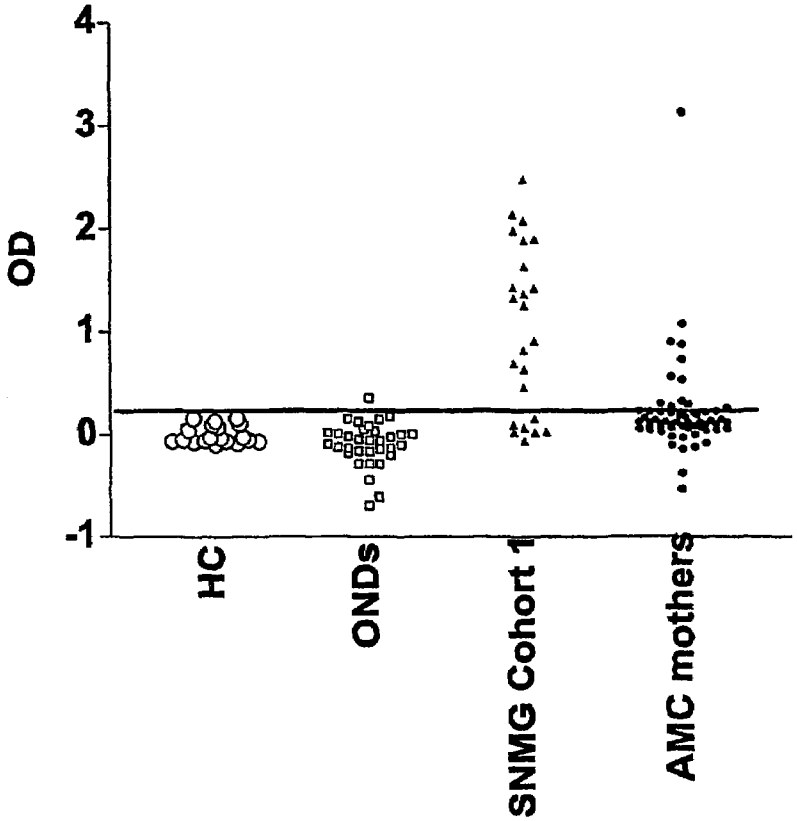

OD
4
3
2
1
0
-1
HC
ONDs
SNMG Cohort 1
AMC mothers

FIG. 6.

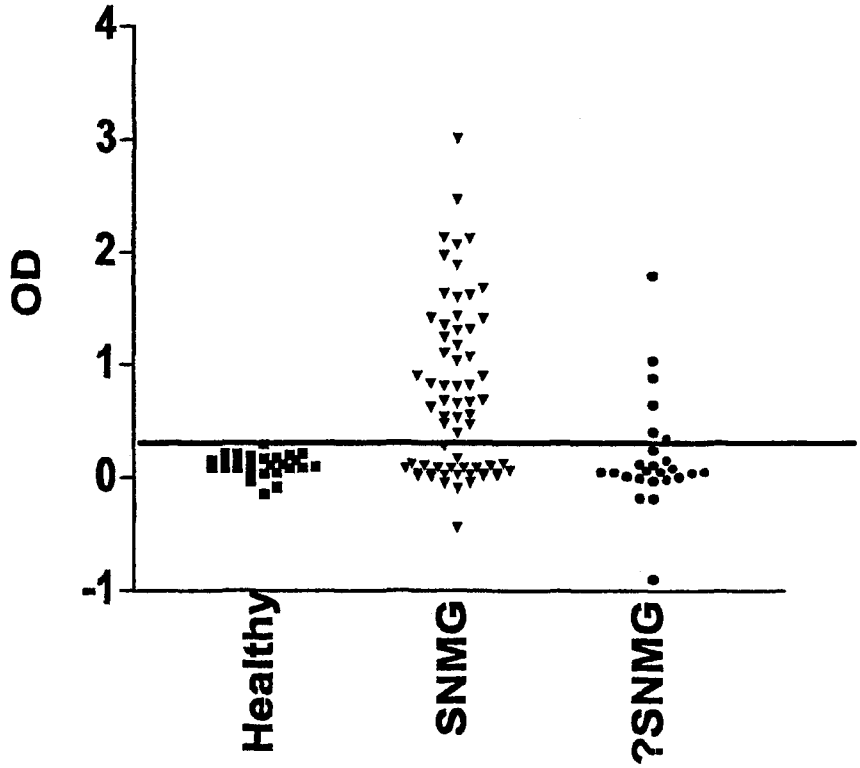

OD
4
3
2
1
0
-1
Healthy
SNMG
?SNMG

FIG. 7.

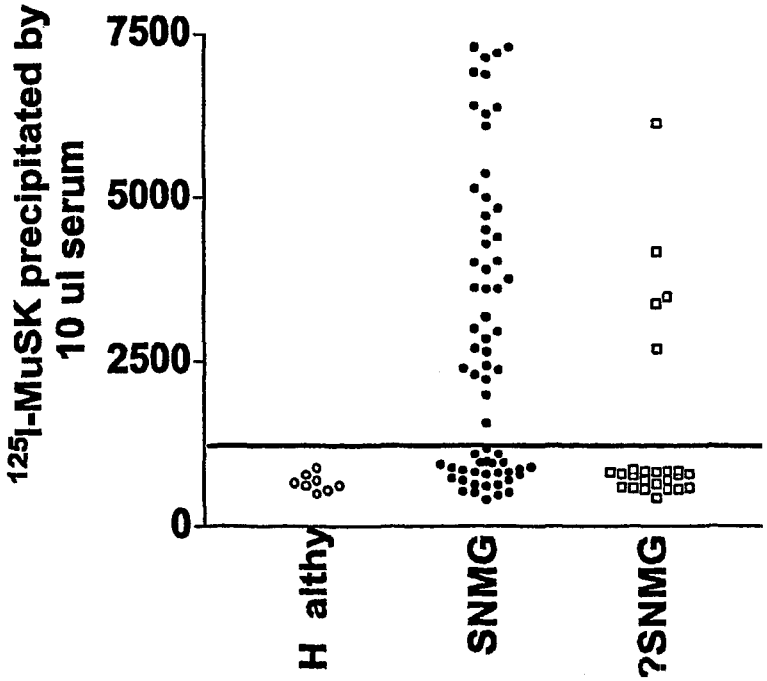
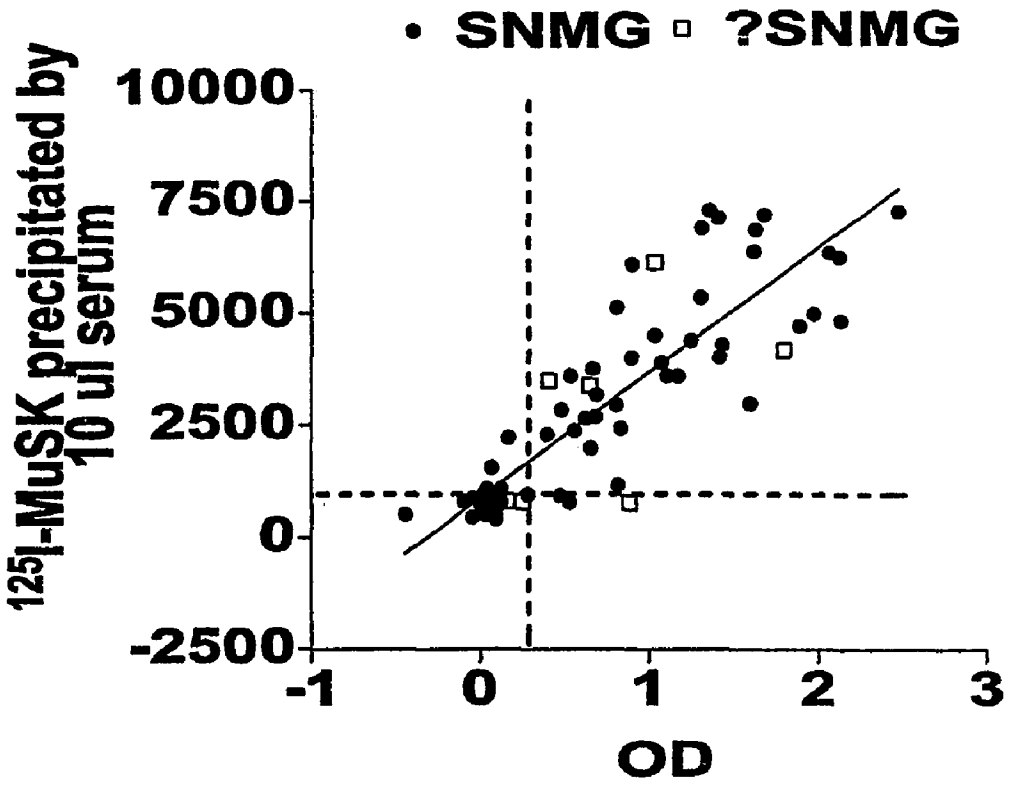

125I-MuSK precipitated by 10 ul serum
7500
5000
2500
0
H althy
SNMG
?SNMG

FIG. 8.


• SNMG ▫ ?SNMG
^{125}I-MuSK precipitated by 10 ul serum
10000
7500
5000
2500
0
-2500
-1
0
1
2
3
OD

NEUROTRANSMISSION DISORDERS

RELATED APPLICATIONS

This application is a national stage filing under 35 U.S.C. § 371 of PCT International application PCT/GB01/02661, filed Jun. 15, 2001, which was published under PCT Article 21(2) in English.

The present invention is concerned with neurotransmission disorders and, in particular, with a method of diagnosing such disorders in mammals. Also provided by the present invention are kits for use in said diagnosis.

Myasthenia gravis (MG) is a chronic autoimmune disorder of neuromuscular transmission resulting in muscle weakness. The key feature of weakness due to MG is its variability. Patients generally experience a waning of strength throughout the day with a tendency to fatigue later in the day or even towards the end of a particular task. A symptom of MG is often ocular weakness, causing ptosis (drooping eyelids) and/or diplopia (double vision). Other symptoms include leg weakness, dysphagia and slurred or nasal speech. Symptoms of weakness tend to worsen with various stressors, such as, exertion, heat and infection.

In 1960 it was discovered that MG was caused by antibodies against the acetyl choline receptor (AChR) and that it is therefore autoimmune in origin. Today MG is one of the most characterised of neurological disorders which has consequently lead to treatments which vastly improve the length and quality of life of myasthenics. Approximately 10 people in every million of a population contract this disease in one year. There is no racial predominance and 75% of MG patients less than 40 years of age are female and 60% of those older than 40 years are male.

Approximately 80% of patients with MG possess within their plasma autoantibodies that are immunoprecitipatable with radiolabelled AChR. The remaining 20% of MG patients do not, however, exhibit such antibodies in their plasma but do have similar symptoms and respond to the same therapies such as plasma exchange and immunosuppression. Accordingly, it has not been established whether these patients have the same or a distinct and separate MG condition(3,4). Autoantibodies are naturally occurring antibodies directed to an antigen which an individual's immune response recognises as foreign even though that antigen actually originated in the individual. They may be present in the circulatory system as circulating free antibodies or in the form of circulating immune complexes bound to their target depending on the nature of the antigen concerned.

Human plasma from patients who were anti-AChR autoantibodies negative (AAAN or previously known as sero-negative MG), were investigated for alternative autoantibodies and one candidate autoantibody was that one for the MuSK protein.

The present inventors surprisingly found that many of the 20% of MG patients which do not exhibit any autoantibodies to AChR, instead have IgG antibodies directed against the extracellular N-terminal domains of MuSK, a receptor tyrosine kinase located on the cell surface of neuromuscular junctions, indicating that they are afflicted with a form of MG which has a different etiology from MG characterised by circulating autoantibodies to AChR.

The MuSK protein has been sequenced and the protein characterised recently by Valenzuela et al (International patent application number PCT/US96/20696, published as WO97/21811). It is a receptor tyrosine kinase (RTK) located on the cell surface of muscle cells at the neuromuscular junction. Ligands bind to RTKs at the binding site on the extracellular side of the receptor, which induces transmission of a signal cascade to intracellular target proteins. RTKs are classified according to their function and members of these families share high homology in their amino acid sequence as well as functionality.

At the neuromuscular junction (NMJ) where the motor nerve axon dendrites meet the muscle cell basal membrane, important physiological signals are exchanged between these adjacent cells. An example of this is the chemical transmitter acetyl choline which passes through the synaptic cleft from the nerve cell, and is then rapidly and specifically bound by the AChR at the muscle cell wall. This in turn begins a cascade of events which ultimately leads to contraction of the muscle cells.

The post synaptic structure at the muscle cell wall is termed the motor endplate which is densely packed with protein and lipid, thereby giving an electron dense appearance when observed by electron microscopy. The muscle AChRs are present here, and it is believed that signalling gives rise to concentrations of proteins there by two mechanisms; one is altered distribution of pre-existing membrane proteins and the other is by induction of localised transcription of specific genes only by subsynaptic nuclei underlying the NMJ.

Development of the neuromuscular junction is initiated through activation of MuSK. Agrin isoforms, released from the motorneuron, trigger MuSK and muscle acetylcholine receptor (AChR) phosphorylation resulting in clustering of AChRs and other proteins of the postsynaptic apparatus(1). Agrin's ability to cause AChR clustering in cultured myotubes has been shown to be inhibited by anti agrin antibodies. It is currently accepted that agrin does not bind directly to MUSK, but via a hypothetical agrin-binding component termed Myotubule Associated Specificity Component (MASC) (1,11). No disease associated with either MuSK, MASC, or agrins has been reported and their roles in adult muscle have not yet been elucidated.

It has already been shown that anti AChR autoantibody negative MG is caused by humoral IgG antibodies: it can be successfully treated by plasma exchange and other immune therapies(5); transient neonatal MG was reported in the newborn infant of one of the patients with anti-MuSK antibodies(17); and injection of immunoglobulin or IgG preparations into mice caused defects in neuromuscular transmission (5).

The present inventors have therefore now shown that anti-MuSK antibodies have functional effects on agrin-induced AChR clustering in vitro, and direct interference with this agrin/MuSK/AChR pathway may be an important disease mechanism in vivo. MuSK is a relatively new member of the receptor tyrosine kinase (RTK) family. With very few exceptions (for example, see 18), autoantibodies to RTKs have not been implicated in human disorders but the combination of large extracellular domains and functional activities make them attractive potential antigens in other autoimmune conditions. Other members of the RTK family are mutated in inherited diseases, and somatic mutations have been found in various tumors (19). MuSK may prove to be involved in congenital as well as acquired muscle disorders.

Therefore, there is provided by a first aspect of the present invention a method of diagnosing neurotransmission disorders in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of the muscle specific tyrosine kinase, MuSK.

More specifically the neurotransmission disorder will preferably be *Myasthenia gravis* and more particularly a

subclass or subtype of MG which is generally found in patients who do not exhibit the ability to immunprecipitate radiolabelled AChR with their bodily fluids.

This aspect of the invention is particularly advantageous because the identification of this new subclass or subtype of MG patients will allow for more accurate and speedy diagnosis of individuals by medical practitioners. The method according to this aspect of the invention will allow for detection of neurotransmission abnormalities that are either congenital or acquired, for example, postnatally or prenatally from transmission from the mother to the foetus. As set out in more detail in the example provided, some mothers of babies with developmental disorders, such as paralysis and fixed joints were identified as having antibodies to MuSK, which were transferred placentally.

Until now, MuSK has been studied primarily in NMJ development. The presence of antibodies to the extracellular domain of MuSK in an acquired disorder implies that MuSK is functional at the adult NMJ, and implicates MuSK as a novel target for pathogenic autoantibodies causing *Myasthenia gravis*. The isolation and purification of this anti-MUSK autoantibody will give rise to a useful product which may be exploitable as an indicator of neurotransmission diseases.

Preferably, the method according to the first aspect of the invention, comprises the steps of a) contacting said bodily fluid with said MUSK or an antigenic determinant thereof; and b) detecting any antibody-antigen complexes formed between said MuSK or an antigenic fragment thereof and antibodies present in said bodily fluid, wherein the presence of said complexes is indicative of said mammal suffering from said neurotransmission disorders.

The actual steps of detecting autoantibodies in a sample of bodily fluids may be performed in accordance with immunological assay techniques known per se in the art. Examples of suitable techniques include ELISA, radioimmunoassays and the like. In general terms, such assays use an antigen which may be immobilised on a solid support. A sample to be tested is brought into contact with the antigen and if autoantibodies specific to the protein are present in a sample they will immunologically react with the antigen to form autoantibody-antigen complexes which may then be detected or quantitatively measured. Detection of autoantibody-antigen complexes is preferably carried out using a secondary anti-human immunoglobulin antibody, typically anti-IgG or anti-human IgM, which recognizes general features common to all human IgGs or IgMs, respectively. The secondary antibody is usually conjugated to an enzyme such as, for example, horseradish peroxidase (HRP) so that detecting of autoantibody/antigen/secondary antibody complexes is achieved by addition of an enzyme substrate and subsequent calorimetric, chemiluminescent or fluorescent detection of the enzymatic reaction products.

Thus, in one embodiment the antibody/antigen complex may be detected by a further antibody, such as an anti-IgG antibody. Complexes may alternatively be viewed by microscopy. Other labels or reporter molecules which may be used in a method according to the invention. Preferably, said reporter molecule or label includes any of a heavy metal, a fluorescent or luminescent molecule, radioactive or enzymatic tag. Preferably, the label or reporter molecule is such that the intensity of the signal from the anti-human IgG antibody is indicative of the relative amount of the anti-MuSK autoantibody in the bodily fluid when compared to a positive and negative control reading.

An alternative method of detecting autoantibodies for MuSK or an epitope thereof relies upon the binding of a MuSK or its epitope, together with a revealing label, to the autoantibodies in the serum or bodily fluid. This method comprises contacting MuSK or an epitope or antigenic determinant thereof having a suitable label thereon, with said bodily fluid, immunoprecipitating any antibodies from said bodily fluid and monitoring for said label on any of said antibodies, wherein the presence of said label is indicative of said mammal suffering from said neurotransmission or developmental disorder. Preferably, the label is a radioactive label which may be ^{125}I, or the like. Iodination and immunoprecipitation are standard techniques in the art, the details of which may be found in references (4 and 6).

In a further aspect of the invention, there is provided an assay kit for diagnosing neurotransmission disorders in mammals comprising an epitope of muscle specific tyrosine kinase (MuSK) and means for contacting said MuSK with a bodily fluid from a mammal. Thus advantageously, an assay system for detecting neurotransmission disorders, and particularly *Myasthenia gravis* in patients who are anti-AChR autoantibody negative (AAAN) is provided. Prior to the present invention there was no basis for providing an immediate clinical diagnosis for such patients.

Also provided by the invention is an isolated or purified autoantibody specific for MuSK. Such an antibody can be detected in bodily fluids of mammals and isolated or purified therefrom using techniques which would be known to the skilled practitioner, such as, immunoabsorption, or immunoaffinity chromatography or high pressure chromatography.

In a further aspect the invention also comprises an isolated or purified antibody specific for an anti-MuSK autoantibody from bodily fluid of a mammal. Such a purified or isolated antibody which is specific for anti-MuSK autoantibody may advantageously be used as a medicament, or in the preparation of a medicament for treating neurotransmission disorders in a mammal, and preferably a human suffering from *Myasthenia gravis*. Such an antibody may also be included in a pharmaceutical composition together with a pharmaceutically acceptable carrier, excipient or diluent therefor. Antibodies, polyclonal or monoclonal may be prepared using techniques which are known in the art. For example, the technique described by Kohler & Milstein (1975, Nature 256:495-497) for developing hybridomas capable of producing monoclonal antibodies may be used. Monoclonal antibodies for therapeutic use may be human monoclonal antibodies or chimeric human-mouse monoclonal antibodies. Chimeric antibody molecules may be prepared containing a mouse antigen binding domain with human constant regions (Morrison et al., 1984, Proc. Natl. Acad. Sci. USA 81:6581, Takeda et al., 1985, Nature 314: 452). For production of antibody various host animals can be immunized by injection with anti-MuSK autoantibody, or a fragment or derivative thereof, including but not limited to rabbits, mice, rats, etc. Various adjuvants may be used to increase the immunological response, depending on the host species, and including but not limited to Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronicpolyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (Bacille Calmette-Guerin) and *Corynebacterium parvum*.

The present invention includes not only complete antibody molecules but fragments thereof. Antibody fragments which contain the idiotype of the molecule can be generated by known techniques, for example, such fragments include but are not limited to the $F(ab')_2$ fragment which can be

produced by pepsin digestion of the antibody molecule; the Fab' fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments and the Fab fragments which can be generated by treating the antibody molecule with papain and a reducing agent.

The antibody which is specific for anti-MuSK autoantibodies may also, advantageously, be used in a diagnostic kit for detecting neurotransmission disorders, such as *Myasthenia gravis*. As aforementioned any protein which binds to the autoantibody may also be used such as an epitope or fragment of the MuSK protein itself. Such a kit comprises an isolated or purified antibody specific for anti-MuSK autoantibody according to the invention and means for contacting said antibody with a bodily fluid of a said mammal.

In accordance with the present invention a bodily fluid should be taken to mean plasma, serum, whole blood, urine, sweat, lymph, faeces, cerebrospinal fluid or nipple aspirate. In general, however, the methods of the invention will be performed on samples of serum or plasma.

In the pharmaceutical composition of the invention, preferred compositions include pharmaceutically acceptable carriers including, for example, non-toxic salts, sterile water or the like. A suitable buffer may also be present allowing the compositions to be lyophilized and stored in sterile conditions prior to reconstitution by the addition of sterile water for subsequent administration. The carrier can also contain other pharmaceutically acceptable excipients for modifying other conditions such as pH, osmolarity, viscosity, sterility, lipophilicity, solubility or the like. Pharmaceutical compositions which permit sustained or delayed release following administration may also be used.

The antibody or the MuSK protein or fragment thereof or the pharmaceutical composition of the invention may be administered orally. In this embodiment the antibody, MuSK or its eptopic fragment, or pharmaceutical composition of the invention may be encapsulated and/or combined with suitable carriers in solid dosage forms which would be well known to those of skill in the art.

Furthermore, as would be appreciated by the skilled practitioner, the specific dosage regime may be calculated according to the body surface area of the patient or the volume of body space to be occupied, dependent on the particular route of administration to be used. The amount of the composition actually administered will, however, be determined by a medical practitioner based on the circumstances pertaining to the disorder to be treated, such as the severity of the symptoms, the age, weight and response of the individual.

In a further aspect, the present invention comprises a method of treating a patient suffering from a neurotransmission disorder such as *Myasthenia gravis* comprising administering to said patient an effective amount of an antibody according to the invention or a MuSK protein or an epitope thereof.

In an even further aspect, the invention comprises a method for making a pharmaceutical formulation for the treatment of neurotransmission disorders, comprising the steps of isolating or purifying an antibody or MuSK protein or fragment thereof according to the invention, manufacturing bulk quantities of said antibody and formulating the antibody in a compound including a pharmaceutically acceptable carrier, diluent or excipient therefor.

In an even further aspect, the invention comprises a method of identifying compounds capable of alleviating or treating neurotransmission disorders, comprising the steps of contacting a candidate compound in the presence of MuSK or an epitope thereof and an antibody capable of binding MuSK, wherein a compound that prevents binding of said antibody to MuSK or an epitope thereof is a candidate for treating neurotransmission disorders. Such compounds may also be used in treating neurotransmission or developmental disorders or in the manufacture of a medicament for treating such disorders. The compounds identified may also, as would be appreciated by those of skill in the art, serve as lead compounds for the development of analogue compounds. The analogues should have a stabilized electronic configuration and molecular conformation that allows key functional groups to be presented to the polypeptides of the invention in substantially the same way as the lead compound. In particular, the analogue compounds have spatial electronic properties which are comparable to the binding region, but can be smaller molecules than the lead compound, frequently having a molecular weight below about 2 kD and preferably below about 1 kD. Identification of analogue compounds can be performed through use of techniques such as self-consistent field (SCF) analysis, configuration interaction (CI) analysis, and normal mode dynamics analysis. Computer programs for implementing these techniques are available; e.g., Rein, Computer-Assisted Modelling of Receptor-Ligand Interactions (Alan Liss, New York, 1989). Methods for the preparation of chemical derivatives and analogues are well known to those skilled in the art and are described in, for example, Beilstein, Handbook of Organic Chemistry, Springer edition New York Inc., 175 Fifth Avenue, New York, N.Y. 10010 U.S.A. and Organic Synthesis, Wiley, N.Y., USA. Furthermore, said derivatives and analogues can be tested for their effects according to methods known in the art; see also supra. Furthermore, peptidomimetics and/or computer aided design of appropriate derivatives and analogues can be used.

The present invention may be more clearly understood with reference to the following examples and accompanying Figures wherein:

FIG. **1**: is an illustration of the results obtained using antibodies from AAAN patients reacting with the extracellular domain of MuSK. Samples from AAAN patients are indicated as SNMG (sero-negative MG) as it was previously known. a, The MuSK constructs used are shown in FIG. **1***a*. b, AAAN plasmas bound to COS-cells expressing full length MuSK (AAAN/MuSK). MuSK immunoreactivity appeared as a speckled pattern, similar to that seen previously with rabbit anti-MuSK antibodies(13). Non-transfected cells in the same field, demonstrated below by phase contrast microscopy. (arrows), showed non-specific binding only. There was no specific binding of AAAN plasmas to cells expressing MuSK lacking the extracellular domains (MuSK D) or binding of healthy control plasma (HC/MuSK). c, Two AAAN plasmas, but not a healthy control plasma, immunoprecipitated MuSK from detergent extracts of COS-cells expressing MuSK, and C2C12 myotubes. MuSK was identified by binding of an affinity-purified rabbit anti-MuSK. It appears as a 110 kD band from COS-cells and as several bands representing different MuSK splice variants in the C2C12 cells.

FIG. **2**: is an illustration of results obtained by using IgG antibodies to the extracellular domains of MuSK in seronegative MG measured by ELISA. a, Anti-MuSK antibodies were found in 17/24 AAAN patients compared with 13 controls. Negative or borderline values only were found in 39 anti-AChR positive MG patients. Non-specific binding of IgG to the plates has been subtracted. b, Titration of one AAAN plasma against different domains of MuSK. The antibodies bound strongly to MuSK constructs expressing

the distal immunoglobulin like domains, Ig1-4 and Ig1-2 (see FIG **1***a*), but not to the Ig3-4 membrane-proximal domains.

FIG. **3**: is an illustration of the results that show that AAAN antibodies induce AChR clusters but inhibit agrin-induced AChR clustering. a, In the absence of agrin, a moderate number of AChR clusters (as demonstrated by rhodamine-a-bungarotoxin fluorescence) were induced in the presence of AAAN plasma compared to that in control plasma (HC). Agrin-induced clusters were found in the presence of healthy control plasma but were inhibited in the presence of AAAN plasma. b,c, The AChR clusters without (b) or with (c) added agrin in plasma and IgG treated cultures. AAAN samples are labelled 1-6. Only the anti-MuSK positive plasmas and IgG preparations affected AChR clusters.

FIG. **4** is an illustration of the results obtained from further tests to confirm the specificity of the test for *Myasthenia gravis* set out in the examples provided.

FIG. **5** is an illustration of the results obtained from a test to detect MuSK antibodies in mothers of babies with development defects.

FIG. **6** is an illustration of the results obtained using an ELISA assay to detect MuSK antibodies in sera sent for analysis.

FIG. **7** is an illustration of the results obtained using an immunoprecipitation assay to detect MuSK antibodies in the sera of FIG. **6**.

FIG. **8** is correlation of the results of ELISA and immunoprecipitation assays of FIGS. **6** and **7** for detection of MuSK antibodies.

EXAMPLE

Patient Identification

Samples were obtained from 24 patients (18F, 6 M) with moderate or severe generalised MG, diagnosed by clinical electrophysiology, but in whom the standard radioimmunoprecipitation assay for anti-AChR antibodies(4) was negative on several occasions. The age at onset ranged between 2 and 68 years (median 24) and the duration of symptoms at sampling was between one month and 13 years (median 1.0 year). In 18 cases, plasma was obtained during therapeutic plasmapheresis which improved muscle strength. The remaining 6 samples were sera taken on first examination. Six of the patients had received corticosteroids for up to two months before sampling. Sera or plasmas were also obtained from healthy volunteers and from patients with anti-AChR antibody positive MG. IgG preparations were made using a Pierce ImmunoPureÒ (G) IgG purification kit.

MuSK and Agrin Expression Constructs

Constructs encoding full length MuSK(13) and the soluble fragment s-agrin (4/19)(20) have been described previously. MuSK deletion fragments comprising the entire extracellular domain (Ig1-4; aa 1-490, numbers according to ref (10)) or the first half encomprising two Ig-domains (Ig1-2; aa 1-230) were generated by insertion of artificial stop signals at these positions. N-terminal fragments of MuSK comprising the membrane-proximal extracellular domains, including Ig-domains 3 and 4 (Ig3-4; aa 198-430), or the transmembrane region and intracellular domain (MuSK D, aa 491-869) were generated. The corresponding c-DNA-fragments, including a newly introduced SphI-site, were linked to a vector containing an artificial signal sequence followed by six histidines and a 10aa epitope-tag (20). All constructs were transiently transfected into COS7 cells(12). For the production of soluble agrin and MuSK constructs, cells were switched to serum-free medium the second day after transfection. Conditioned media, containing MuSK or agrin fragments were removed 24 hours later and analyzed by Western blotting to confirm expression.

Immunostaining of MuSK-transfected COS7 Cells

COS7 cells were plated onto chamber slides the day after transfection. Two days later, cells were fixed with 2% paraformaldehyde and stained as described(13). Plasmas of myasthenia gravis patients and controls were analyzed in various dilutions (between 1:20 and 1:5000). Bound antibodies were visualized with secondary antibodies conjugated to Cy3 (anti-human IgG, Dianova). In all experiments, expression of transfected MuSK constructs was confirmed by staining parallel slides with rabbit-anti MuSK antibodies (13).

Immunoprecipitation Experiments

Detergent extracts were prepared from MuSK-transfected COS7 cells or from C2C12 myotubes that had been fused for five days. The immunoprecipitation was performed as described previously(12,13). AAAN and control plasmas incubated with the extracts at 1:20. Rabbit anti-MuSK serum was used at 1:100. MuSK in the immunoprecipitates was analysed by Western blotting using affinity-purified serum antibodies directed against the a MuSK cytoplasmic sequence(13).

ELISA Detection of Anti-MuSK Antibodies

Conditioned medium from MuSK-transfected COS-cells or from control cells mock-transfected with fish sperm DNA, was diluted 1:1 with 100 mM NaHCO3-buffer, pH 9.5 and applied overnight to ELISA plates. Plasmas were first tested at 1:5 in triplicates and subsequently at 1:10 in duplicates. Bound antibodies were detected by horse radish peroxidase-protein A (Amersham) followed by o-phenylenediamine and measuring A_{492}. For each sample, nonspecific immunoreactivity, determined by incubation of plates coated with conditioned medium from mock-transfected COS7 cells, was subtracted.

AChR Aggregation Assay

The mouse muscle cell line, C2C12, was used to determine functional effects of antibodies. Cells were plated onto chamber slides, fused and treated with or without agrin and/or plasmas or IgGs for five hours[13]. After fixation, AChRs were visualised with rhodaminea-bungarotoxin and the number of aggregates from more than 20 microscopic fields and at least two independent cultures were measured as described(20).

Results

We initially looked for IgG antibodies in five AAAN plasmas and three plasmas from healthy individuals using COS7 cells transfected with rat MuSK constructs (FIG. **1***a*). The experiments were performed blind. All five AAAN plasmas (eg FIG. **1***b*, AAAN), but none of the healthy control plasmas (eg HC), labelled MuSK aggregates on the cell surface at dilutions up to 1:1000. The pattern of immu-

noreactivity was indistinguishable from labelling observed with antibodies raised against recombinant MuSK in rabbits. (13) Each of the AAAN plasmas recognized the extracellular domains of MuSK, since no immunoreactivity was observed with COS7 cells expressing the transmembrane and cytoplasmic domains only (FIG. **1***b*, MuSK D). Not all cells expressed MuSK (compare FIG. **1***b*, AAAN/MuSK and Phase contrast, below), and these non-transfected cells and mock-transfected cells (not shown) did not bind the AAAN IgG antibodies.

Immunoprecipitation experiments confirmed that IgG antibodies in the AAAN plasmas recognized the native MuSK protein. Detergent extracts from MuSK-expressing COS7 cells and from mouse C2C12 myotubes, that express functional MuSK, were incubated with plasmas from two AAAN patients and a healthy control. Antibodies from both AAAN patients, but not from the control, immunoprecipitated bands of 110 kDa that were identified as MuSK by binding of a specific anti-MuSK antibody (FIG. **1***c*). With each extract, similar-sized bands were immunoprecipitated by a rabbit anti-MuSK serum from parallel extracts (FIG. **1***c*).

Sera and plasmas from AAAN, anti-AChR positive MG and healthy individuals were then tested in an ELISA. Fragments comprising only extracellular domains of MuSK were expressed in COS7 cells from which these soluble constructs are secreted, and the media were used as a source of the polypeptide antigen. IgG anti-MuSK antibodies, substantially greater than the mean+3SDs of the healthy control values (0.08 OD units) were found in 17/24 AAAN samples, whereas only borderline or negative values were found in the anti-AChR positive patients (FIG. **2***a*). Four of the seven negative, compared with only two of the 17 positive samples, were from patients who had received corticosteroid therapy before sampling.

Interestingly, in the 11 patients tested in both assays, the OD values for binding of antibodies to MuSK correlated ($p<0.02$) with IgG binding to the human TE671 cell line (which has features of human muscle) as measured previously(8). This suggests that MuSK is the target for AAAN IgG antibodies on the TE671 surface and that the negative values in seven samples are unlikely to be due to a lack of reactivity with rat MuSK Further results with four AAAN plasmas (eg FIG. **2***b*) indicated that the majority of antibodies are directed against the N-terminal sequences (construct Ig1-2 in FIG. **1***a*) and there was little reactivity with the membrane proximal half (construct Ig3-4 in FIG. **1***a*). We found no evidence of IgM antibodies to MuSK (data not shown), suggesting that the target for the putative non-IgG antibodies reported previously in some of the AAAN patients(15) will still need to be defined.

To investigate functional effects of the MuSK autoantibodies, we examined AChR clustering in myotubes derived from the mouse cell line, C2C12. In the absence of agrin (FIG. **3***a* upper panels), the control plasma produced very few clusters of AChRs (HC), whereas anti-MuSK positive plasma induced AChR, aggregates along the surface of the myotubes (AAAN). A similar antibody-induced induction of AChR-clustering by artificial dimerization of the kinase has previously been reported for rabbit antibodies induced against purified MuSK(13). Strikingly, when agrin was added with the plasmas (FIG. **3***a*, lower panels), the marked agrin-induced clustering which occurred in the presence of control plasma (HC) was not seen in the presence of AAAN plasma indicating that the anti-MuSK antibodies had inhibited the agrin-induced AChR clustering. Both the clustering (FIG. **3***b*) and the inhibitory activity (FIG. **3***c*) were found with each anti-MuSK positive plasmas or IgGs but not with anti-MuSK negative preparations. Since it is currently accepted that agrin does not bind directly to MUSK, but via a hypothetical agrin-binding component called MASC(1, 11), we speculate that the antibodies in AAAN patients bind to MuSK in such a manner as to prevent its interaction with MASC. This interaction is known to depend on the N-terminal half of the extracelluar domain of MuSK(16) which we find to be the main target for the IgG antibodies in anti AChR autoantibody negative patients (FIG. **2***b*).

To confirm the specificity of the test for myasthenia gravis, we tested a new group of controls (OND's) from patients with other neurological disorders. (FIG. **4**). Only one serum was borderline positive. The relative incidence of MuSK antibodies in AAAN samples, was tested using a second cohort (Cohort 2) of *Myasthenia gravis* patients who were negative for acetylcholine receptor antibodies. All of these patients had generalised disease and 11/16 of them were positive for MuSK antibodies.

Antibodies to the fetal isoform of the acetylcholine receptor are found in a few mothers who have had babies born with complete paralysis and fixed joints (22,23). This severe condition is relatively common, but maternal antibodies to fetal acetylcholine receptor are found in only about 1% (Vincent, Dalton, unpublished findings). We asked whether MuSK antibodies might be present in some of these mothers. FIG. **5** shows, in comparison with the previously described results, that six mothers of affected babies out of a total of 200 tested (only 60 shown here) have these antibodies in their serum. This indicates that each of these six mothers has made an autoimmune response to MuSK and suggests that, after transfer of these antibodies across the placenta, they might be involved in causing the babies' condition. Testing for antibodies to MuSK in mothers of babies with muscle paralysis and/or fixed joints might indicate a fetal condition due to maternal antibodies.

To assess how the assay works out in practice, we have begun to compare results from patients with definite SNMG or a strong suspicion of SNMG with those in whom the diagnosis is questionable (?SNMG). FIG. **6** shows that among the first group, which includes cohort 1 and cohort 2, the assay is positive in 39/66 and among those with a questionable diagnosis the proportion is 6/25. The assay continues to be negative in healthy individuals.

The ELISA assay used as identified in the above example is difficult to standardise and we have tested an alternative assay, using immunoprecipitation of ^{125}I-MuSK. For this test, the purified extracellular domain of MuSK is iodinated using ^{125}I (carrier free from Amersham as for bungarotoxin in Ref (4, 6) or with chloramine T (standard conditions)). The iodinated MuSK is then separated from free ^{125}I by gel filtration. The ^{125}I-MuSK (approximately 50,000 cpm) is then added to 10 microlitres of the patient's serum over night. To immunoprecipitate the patients' antibodies and any ^{125}I-MuSK that is bound by them, excess of a sheep antibody to human IgG is added. The precipitate is centrifuged to form a pellet, washed and counted for radioactivity. The results (FIG. **7**) show that healthy controls precipitated less than 1200 cpm, whereas 38/66 of the SNMG patients precipitated over 1200 cpm, the value rising to 7500 cpm which corresponds to approximately 1 nmole of MuSK precipitated per liter of serum. The assay was also positive in 5/25 patients with ?SNMG.

The results of the ELISA and immunoprecipitation assays were highly correlated (FIG. **8**). Most of the sera were positive with both assays or negative with both assays; there were three sera that gave negative results with the immunopreciptation and positive with ELISA, and two sera that were negative with the ELISA and positive with the immunoprecipitation.

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The invention claimed is:

1. A method for diagnosing neurotransmission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK).

2. A method according to claim **1** wherein said method comprises the steps of:

a) contacting said bodily fluid with muscle specific tyrosine kinase (MuSK) or an antigenic determinant thereof; and

b) detecting any antibody-antigen complexes formed between said receptor tyrosine kinase or an antigenic fragment thereof and antibodies present in said bodily fluid, wherein the presence of said complexes is indicative of said mammal suffering from said neurotransmission or developmental disorders.

3. A method according to claim **2** wherein said antibody-antigen complex is detected using an anti-IgG antibody tagged or labeled with a reporter molecule.

4. A method according to claim **3** wherein said reporter molecule or label includes any of a heavy metal, a fluorescent or luminescent molecule, radioactive or enzymatic tag.

5. A method according to claim **4** wherein said enzymatic tag comprises horseradish peroxidase-protein A followed by reaction with o-phenylenediamine for subsequent measurement at A492.

6. A method according to claim **3** whereby the intensity of the signal from the anti-human IgG antibody is indicative of the relative amount of the anti-MuSK autoantibody in the bodily fluid when compared to a positive and negative control reading.

7. A method according to claim **1**, comprising contacting MuSK or an epitope or antigenic determinant thereof having a suitable label thereon, with said bodily fluid, immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid and monitoring for said label on any of said antibody/

MuSK complex or antibody/MuSK epitope or antigen determinant complex, wherein the presence of said label is indicative of said mammal is suffering from said neurotransmission or developmental disorder related to muscle specific tyrosine kinase (MuSK).

8. A method according to claim **7** wherein said label is a radioactive label.

9. A method according to claim **8** wherein said label is 125I.

10. A method according to claim **1** wherein said neurotransmission disorder is *Myasthenia gravis*.

11. A method according to claim **1**, wherein said developmental disorder is muscle paralysis and/or fixed joints in newborn offspring due to maternal antibodies to MuSK.

12. A method for diagnosing neurotransmission or developmental disorders related to interference of the agrin/MuSK/AChR pathway within a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK).

* * * * *

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ATHENA DIAGNOSTICS, INC., Plaintiff, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	CIVIL ACTION NO. _____ **DEMAND FOR JURY TRIAL**

COMPLAINT

Plaintiff Athena Diagnostics, Inc. ("Athena"), by and through its undersigned counsel, bring this complaint for patent infringement against Defendants Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories ("MML") and Mayo Clinic (together, "Mayo").

NATURE OF THE ACTION

1. This is an action for patent infringement under 35 U.S.C. § 271 *et seq.* by Athena against Defendants for infringement of U.S. Patent No. 7,267,820 (the "'820 patent").

THE PARTIES

2. Plaintiff Athena Diagnostics, Inc. is a Delaware corporation with a principal place of business at Four Biotech Park, 377 Plantation Road, Worcester, Massachusetts 01605.

3. Defendant Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories is a Minnesota limited liability company, with a principal place of business at 3050 Superior Drive NW, Rochester, Minnesota 55901.

4. Defendant Mayo Clinic is a Minnesota corporation, with a principal place of business at 200 First St. NW, Rochester, Minnesota 55905.

JURISDICTION AND VENUE

5. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338.

6. Defendants have significant specific contacts in this jurisdiction sufficient to confer this Court with personal jurisdiction over both Defendants.

7. Defendant MML is a reference laboratory that operates within Mayo Clinic's Department of Laboratory Medicine and Pathology, and offers more than 3,000 tests across the full spectrum of health care subspecialties. According to the "Contact Us" page on Defendant's website, http://www.mayomedicallaboratories.com/customer-service/contacts.html, MML has a physical location at 160 Dascomb Road, Andover, Massachusetts 01810. In addition, Defendant MML performs commercial activities at its Andover, Massachusetts facility, including, upon information and belief, coordinating testing services provided in response to requests from physicians and medical providers in this judicial district.

8. Defendant Mayo Clinic is a medical facility based in Minnesota that, in 2013, was a founding partner of Optum Labs, a collaborative research and innovation center based in Cambridge, Massachusetts. *See* https://www.optum.com/news-events/news/optum-labs.html. In addition, Defendant Mayo Clinic posts job listings on its website for positions located in Massachusetts, including an Assistant Lab Supervisor position at its Andover facility in this judicial district. *See* http://www.mayoclinic.org/jobs.

9. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b), (c) and/or 1400(b), because, *inter alia,* both Defendants are subject to personal jurisdiction in this district.

FACTUAL BACKGROUND

10. On September 11, 2007, the U.S. Patent & Trademark Office ("USPTO") duly and legally issued the '820 patent, entitled "Neurotransmission Disorders," to Angela Vincent and Werner Hoch. The '820 patent is presumed valid, and is enforceable until its expiration.

11. Athena is an exclusive licensee and has standing to file this patent infringement lawsuit.

12. The face of the '820 patent names two assignees: Isis Innovation Limited, a company located in and organized under the laws of England, and Max-Planck Gesellschaft zur Foerderung der Wissenschaften e.V., an organization located in and organized under the laws of Germany. Those two parties cannot be joined at this time because they are foreign entities that do not appear to be subject to this Court's jurisdiction.

13. The claims of the '820 patent cover, *inter alia*, useful methods that involve using man-made chemical reagents capable of detecting antibodies to an epitope of a protein called muscle-specific tyrosine kinase ("MuSK").

14. Prior to May 19, 2015, and to the present, Athena has marketed, and plans to continue marketing in the future, a test useful to evaluate the presence of quantitative antibodies to MuSK involving detection of MuSK associated antibodies. Athena offered this test – "FMUSK" – under Code No. 91445.

15. Prior to May 19, 2015, medical practitioners associated with Defendants have ordered FMUSK tests from Athena, indicating to those medical professionals that FMUSK tests would be performed by Athena.

16. Prior to May 2015, Defendants availed themselves of the technology disclosed and claimed in the '820 patent, and developed two infringing tests: (1) Muscle-Specific Kinase (MuSK) Autoantibody, Serum (hereinafter, "MUSK"), and (2) Myasthenia Gravis Evaluation

with MuSK Reflex, Serum (hereinafter, "MGRM"). Both tests employ methods that practice each and every step of one or more claims of the '820 patent.

17. On or about April 16, 2015, Defendants circulated a notice to their practitioners that, as of May 19, 2015, Athena's FMUSK test would no longer be available for requisition through the Mayo network.

18. Defendants, with specific knowledge of the '820 patent and the methods it covers, surreptitiously and purposefully designed an alternate test to avoid paying Athena for Athena's licensed FMUSK test.

19. Defendants are not licensed to offer either MUSK or MGRM, and therefore, Defendants have and will continue to infringe one or more claims of the '820 patent by continuing to offer those tests to the public.

20. Defendants' conduct has damaged and will continue to damage Athena, which loses profits from, at a minimum, every MUSK and MGRM test Defendants run.

COUNT I: PATENT INFRINGEMENT OF U.S. PATENT NO. 7,267,820

21. Athena incorporates by reference paragraphs 1-20 as if fully set forth herein.

22. By offering the MUSK and MGRM tests to the public without license, Defendants infringe, either directly or indirectly, and either literally or under the doctrine of equivalents, at least claims 8 and 9 of the '820 patent.

23. Defendants were aware of the '820 patent, and their infringement is deliberate, willful and in reckless disregard of Athena's rights.

24. Athena has been and continues to be injured by the infringing activities of Defendants.

PRAYER FOR RELIEF

WHEREFORE, Athena respectfully requests the following relief:

(a) a final judgment that the Defendants' activities infringe the '820 patent;

(b) entry of preliminary and/or permanent equitable relief, including but not limited to a preliminary and/or permanent injunction that enjoin Defendants and any of their officers, agents, employees, assigns, representatives, privies, successors, and those acting in concert or participation with them from infringing and/or inducing infringement of the '820 patent;

(c) an award of damages sufficient to compensate Athena for infringement of the '820 patent by Defendants, together with prejudgment and post-judgment interest;

(d) a declaration or order finding that Defendants' infringement is willful and/or an order increasing damages under 35 U.S.C. § 284;

(e) a judgment holding that this is an exceptional case under 35 U.S.C. § 285 and awarding Athena its reasonable attorneys' fees, costs, and expenses; and

(f) such other relief deemed just and proper.

JURY DEMAND

Under Rule 38 of the Federal Rules of Civil Procedure, Athena hereby demands trial by jury of all issues so triable by a jury in this action.

Dated: June 2, 2015

Respectfully submitted,

/s/ *Manleen Singh*

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IN THE UNITED STATES DISTRICT COURT
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ATHENA DIAGNOSTICS, INC. AND ISIS INNOVATION LIMITED, Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	CIVIL ACTION NO. 4:15-cv-40075 **DEMAND FOR JURY TRIAL**

AMENDED COMPLAINT

Plaintiffs Athena Diagnostics, Inc. ("Athena") and Isis Innovation Limited ("Isis") (together, "Plaintiffs"), by and through their undersigned counsel, bring this amended complaint for patent infringement against Defendants Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories ("MML") and Mayo Clinic (together, "Mayo").

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3. Plaintiff Isis Innovation Limited is a corporation organized and existing under the laws of England, with a principal place of business at University Offices, Wellington Square, Oxford OX1 2JD, England.

4. Defendant Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories is a Minnesota limited liability company, with a principal place of business at 3050 Superior Drive SW, Rochester, Minnesota 55901.

5. Defendant Mayo Clinic is a Minnesota corporation, with a principal place of business at 200 First St. NW, Rochester, Minnesota 55905.

JURISDICTION AND VENUE

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10. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b), (c) and/or 1400(b), because, *inter alia*, both Defendants are subject to personal jurisdiction in this district.

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11. On September 11, 2007, the U.S. Patent & Trademark Office ("USPTO") duly and legally issued the '820 patent, entitled "Neurotransmission Disorders," to Angela Vincent and Werner Hoch. The '820 patent is presumed valid, and is enforceable until its expiration.

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13. The face of the '820 patent names two assignees: Isis and Max-Planck Gesellschaft zur Foerderung der Wissenschaften e.V., an organization located in and organized under the laws of Germany. Isis is a party to this action. Max-Planck Gesellschaft zur Foerderung der Wissenschaften e.V. cannot be joined under Rule 19 of the Federal Rules of Civil Procedure at this time because it is a foreign entity that does not appear to be subject to this Court's jurisdiction.

14. The claims of the '820 patent cover, *inter alia*, useful methods that involve using man-made chemical reagents capable of detecting antibodies to an epitope of a protein called muscle-specific tyrosine kinase ("MuSK").

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18. On or about April 16, 2015, Defendants circulated a notice to their practitioners that, as of May 19, 2015, Athena’s FMUSK test would no longer be available for requisition through the Mayo network.

19. Defendants, with specific knowledge of the ’820 patent and the methods it covers, surreptitiously and purposefully designed an alternate test to avoid paying Athena for Athena’s licensed FMUSK test.

20. Defendants are not licensed to offer either MUSK or MGRM, and therefore, Defendants have and will continue to infringe one or more claims of the ’820 patent by continuing to offer those tests to the public.

21. Defendants’ conduct has damaged and will continue to damage Athena, which loses profits from, at a minimum, every MUSK and MGRM test Defendants run.

COUNT I: PATENT INFRINGEMENT OF U.S. PATENT NO. 7,267,820

22. Plaintiffs incorporate by reference paragraphs 1-21 as if fully set forth herein.

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24. Defendants were aware of the ’820 patent, and their infringement is deliberate, willful and in reckless disregard of Plaintiffs’ rights.

25. Plaintiffs have been and continue to be injured by the infringing activities of Defendants.

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WHEREFORE, Plaintiffs respectfully request the following relief:

(a) a final judgment that the Defendants' activities infringe the '820 patent;

(b) entry of preliminary and/or permanent equitable relief, including but not limited to a preliminary and/or permanent injunction that enjoin Defendants and any of their officers, agents, employees, assigns, representatives, privies, successors, and those acting in concert or participation with them from infringing and/or inducing infringement of the '820 patent;

(c) an award of damages sufficient to compensate Plaintiffs for infringement of the '820 patent by Defendants, together with prejudgment and post-judgment interest;

(d) a declaration or order finding that Defendants' infringement is willful and/or an order increasing damages under 35 U.S.C. § 284;

(e) a judgment holding that this is an exceptional case under 35 U.S.C. § 285 and awarding reasonable attorneys' fees, costs, and expenses to Plaintiffs; and

(f) such other relief deemed just and proper.

JURY DEMAND

Under Rule 38 of the Federal Rules of Civil Procedure, plaintiffs hereby demand trial by jury of all issues so triable by a jury in this action.

Dated: July 24, 2015

Respectfully submitted,

/s/ *Manleen Singh*

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Attorneys for Plaintiffs Athena Diagnostics, Inc. and Isis Innovation Limited

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ATHENA DIAGNOSTICS, INC. AND ISIS INNOVATION LIMITED, Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	CIVIL ACTION NO. 4:15-cv-40075 **SECOND AMENDED COMPLAINT** (Leave to file granted 8/17/15) **DEMAND FOR JURY TRIAL**

Plaintiffs Athena Diagnostics, Inc. ("Athena") and Isis Innovation Limited ("Isis") (together, "Plaintiffs"), by and through their undersigned counsel, bring this second amended complaint for patent infringement against Defendants Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories ("MML") and Mayo Clinic (together, "Mayo").

NATURE OF THE ACTION

1. This is an action for patent infringement under 35 U.S.C. § 271 *et seq.* by Athena against Defendants for infringement of U.S. Patent No. 7,267,820 (the "'820 patent").

THE PARTIES

2. Plaintiff Athena Diagnostics, Inc. is a Delaware corporation with a principal place of business at 200 Forest Street, Marlborough, Massachusetts 01752.

3. Plaintiff Isis Innovation Limited is a corporation organized and existing under the laws of England, with a principal place of business at University Offices, Wellington Square, Oxford OX1 2JD, England.

4. Defendant Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories is a Minnesota limited liability company, with a principal place of business at 3050 Superior Drive SW, Rochester, Minnesota 55901.

5. Defendant Mayo Clinic is a Minnesota corporation, with a principal place of business at 200 First St. NW, Rochester, Minnesota 55905.

JURISDICTION AND VENUE

6. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338.

7. Defendants have significant specific contacts in this jurisdiction sufficient to confer this Court with personal jurisdiction over both Defendants.

8. Defendant MML is a reference laboratory that operates within Mayo Clinic's Department of Laboratory Medicine and Pathology, and offers more than 3,000 tests across the full spectrum of health care subspecialties. According to the "Contact Us" page on Defendant's website, http://www.mayomedicallaboratories.com/customer-service/contacts.html, MML has a physical location at 160 Dascomb Road, Andover, Massachusetts 01810. In addition, Defendant MML performs commercial activities at its Andover, Massachusetts facility, including, upon information and belief, coordinating testing services provided in response to requests from physicians and medical providers in this judicial district.

9. Defendant Mayo Clinic is a medical facility based in Minnesota that, in 2013, was a founding partner of Optum Labs, a collaborative research and innovation center based in Cambridge, Massachusetts. *See* https://www.optum.com/news-events/news/optum-labs.html. In addition, Defendant Mayo Clinic posts job listings on its website for positions located in Massachusetts, including an Assistant Lab Supervisor position at its Andover facility in this judicial district. *See* http://www.mayoclinic.org/jobs.

10. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b), (c) and/or 1400(b), because, *inter alia*, both Defendants are subject to personal jurisdiction in this district.

FACTUAL BACKGROUND

11. On September 11, 2007, the U.S. Patent & Trademark Office ("USPTO") duly and legally issued the '820 patent, entitled "Neurotransmission Disorders," to Angela Vincent and Werner Hoch. The '820 patent is presumed valid, and is enforceable until its expiration.

12. Athena is an exclusive licensee and has standing to file this patent infringement lawsuit.

13. The face of the '820 patent names two assignees: Isis and Max-Planck Gesellschaft zur Foerderung der Wissenschaften e.V., an organization located in and organized under the laws of Germany. Isis is a party to this action. Max-Planck Gesellschaft zur Foerderung der Wissenschaften e.V. cannot be joined under Rule 19 of the Federal Rules of Civil Procedure at this time because it is a foreign entity that does not appear to be subject to this Court's jurisdiction.

14. The claims of the '820 patent cover, *inter alia*, useful methods that involve using man-made chemical reagents capable of detecting antibodies to an epitope of a protein called muscle-specific tyrosine kinase ("MuSK").

15. Prior to May 19, 2015, and to the present, Athena has marketed, and plans to continue marketing in the future, a test useful to evaluate the presence of quantitative antibodies to MuSK involving detection of MuSK associated antibodies. Athena offered this test – "FMUSK" – under Code No. 91445.

16. Prior to May 19, 2015, medical practitioners associated with Defendants have ordered FMUSK tests from Athena, indicating to those medical professionals that FMUSK tests would be performed by Athena.

17. Prior to May 2015, Defendants availed themselves of the technology disclosed and claimed in the ’820 patent, and developed two infringing tests: (1) Muscle-Specific Kinase (MuSK) Autoantibody, Serum (hereinafter, “MUSK”), and (2) Myasthenia Gravis Evaluation with MuSK Reflex, Serum (hereinafter, “MGRM”). Both tests employ methods that practice each and every step of one or more claims of the ’820 patent.

18. On or about April 16, 2015, Defendants circulated a notice to their practitioners that, as of May 19, 2015, Athena’s FMUSK test would no longer be available for requisition through the Mayo network.

19. Defendants, with specific knowledge of the ’820 patent and the methods it covers, surreptitiously and purposefully designed an alternate test to avoid paying Athena for Athena’s licensed FMUSK test.

20. Defendants are not licensed to offer either MUSK or MGRM, and therefore, Defendants have and will continue to infringe one or more claims of the ’820 patent by continuing to offer those tests to the public.

21. Defendants’ conduct has damaged and will continue to damage Athena, which loses profits from, at a minimum, every MUSK and MGRM test Defendants run.

COUNT I: PATENT INFRINGEMENT OF U.S. PATENT NO. 7,267,820

22. Plaintiffs incorporate by reference paragraphs 1-21 as if fully set forth herein.

23. By offering the MUSK and MGRM tests to the public without license, Defendants infringe, either directly or indirectly, and either literally or under the doctrine of equivalents, at least claims 8 and 9 of the ’820 patent.

24. Defendants were aware of the ’820 patent, and their infringement is deliberate, willful and in reckless disregard of Plaintiffs’ rights.

25. Plaintiffs have been and continue to be injured by the infringing activities of Defendants.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

(a) a final judgment that the Defendants' activities infringe the '820 patent;

(b) entry of preliminary and/or permanent equitable relief, including but not limited to a preliminary and/or permanent injunction that enjoin Defendants and any of their officers, agents, employees, assigns, representatives, privies, successors, and those acting in concert or participation with them from infringing and/or inducing infringement of the '820 patent;

(c) an award of damages sufficient to compensate Plaintiffs for infringement of the '820 patent by Defendants, together with prejudgment and post-judgment interest;

(d) a declaration or order finding that Defendants' infringement is willful and/or an order increasing damages under 35 U.S.C. § 284;

(e) a judgment holding that this is an exceptional case under 35 U.S.C. § 285 and awarding reasonable attorneys' fees, costs, and expenses to Plaintiffs; and

(f) such other relief deemed just and proper.

JURY DEMAND

Under Rule 38 of the Federal Rules of Civil Procedure, plaintiffs hereby demand trial by jury of all issues so triable by a jury in this action.

Dated: August 17, 2015

Respectfully submitted,

/s/ *Manleen Singh*

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IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS
EASTERN DIVISION

ATHENA DIAGNOSTICS, INC., ISIS INNOVATION LIMITED, AND MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V., Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	CIVIL ACTION NO. 4:15-cv-40075 **THIRD AMENDED COMPLAINT [LEAVE TO FILE GRANTED ON 7/6/2016]** **DEMAND FOR JURY TRIAL**

Plaintiffs Athena Diagnostics, Inc. ("Athena"), Isis Innovation Limited ("Isis") and Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V. ("Max Planck") (together, "Plaintiffs"), by and through their undersigned counsel, bring this third amended complaint for patent infringement against Defendants Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories ("MML") and Mayo Clinic (together, "Mayo").

NATURE OF THE ACTION

1. This is an action for patent infringement under 35 U.S.C. § 271 *et seq.* by Plaintiffs against Defendants for infringement of U.S. Patent No. 7,267,820 (the "'820 patent").

THE PARTIES

2. Plaintiff Athena Diagnostics, Inc. is a Delaware corporation with a principal place of business at 200 Forest Street, Marlborough, Massachusetts 01752.

3. Plaintiff Isis Innovation Limited is a corporation organized and existing under the laws of England, with a principal place of business at University Offices, Wellington Square, Oxford OX1 2JD, England.

4. Plaintiff Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V. is a non-profit research institution organized and existing under the laws of Germany, with its principal offices located at Hofgartenstr. 8, 80539 München, Germany.

5. Defendant Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories is a Minnesota limited liability company, with a principal place of business at 3050 Superior Drive SW, Rochester, Minnesota 55901.

6. Defendant Mayo Clinic is a Minnesota corporation, with a principal place of business at 200 First St. NW, Rochester, Minnesota 55905.

JURISDICTION AND VENUE

7. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338.

8. Defendants have significant specific contacts in this jurisdiction sufficient to confer this Court with personal jurisdiction over both Defendants.

9. Defendant MML is a reference laboratory that operates within Mayo Clinic's Department of Laboratory Medicine and Pathology, and offers more than 3,000 tests across the full spectrum of health care subspecialties. According to the "Contact Us" page on Defendant's website, http://www.mayomedicallaboratories.com/customer-service/contacts.html, MML has a physical location at 160 Dascomb Road, Andover, Massachusetts 01810. In addition, Defendant MML performs commercial activities at its Andover, Massachusetts facility, including, upon information and belief, coordinating testing services provided in response to requests from physicians and medical providers in this judicial district.

10. Defendant Mayo Clinic is a medical facility based in Minnesota that, in 2013, was a founding partner of Optum Labs, a collaborative research and innovation center based in Cambridge, Massachusetts. See https://www.optum.com/news-events/news/optum-labs.html. In addition, Defendant Mayo Clinic posts job listings on its website for positions located in Massachusetts, including, at one time, an Assistant Lab Supervisor position at its Andover facility in this judicial district. See http://www.mayoclinic.org/jobs.

11. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b), (c) and/or 1400(b), because, *inter alia*, both Defendants are subject to personal jurisdiction in this district.

FACTUAL BACKGROUND

12. On September 11, 2007, the U.S. Patent & Trademark Office ("USPTO") duly and legally issued the '820 patent, entitled "Neurotransmission Disorders," to Angela Vincent and Werner Hoch. The '820 patent is presumed valid, and is enforceable until its expiration.

13. Athena is an exclusive licensee of the '820 patent in the relevant field and has standing to bring this patent infringement lawsuit.

14. The face of the '820 patent names two assignees: Isis and Max Planck. Both are named as Plaintiffs in this action.

15. The claims of the '820 patent cover, *inter alia*, useful methods that involve using man-made chemical reagents capable of detecting antibodies to an epitope of a protein called muscle-specific tyrosine kinase ("MuSK").

16. Prior to May 19, 2015, and to the present, Athena has marketed, and plans to continue marketing in the future, a test useful to evaluate the presence of quantitative antibodies to MuSK involving detection of MuSK associated antibodies. Athena offered this test—"FMUSK"—under Code No. 91445.

17. Prior to May 19, 2015, medical practitioners associated with Defendants have ordered FMUSK tests from Athena, indicating to those medical professionals that FMUSK tests would be performed by Athena.

18. Prior to May 2015, Defendants availed themselves of the technology disclosed and claimed in the ’820 patent, and developed two infringing tests: (1) Muscle-Specific Kinase (MuSK) Autoantibody, Serum (hereinafter, “MUSK”), and (2) Myasthenia Gravis Evaluation with MuSK Reflex, Serum (hereinafter, “MGRM”). Both tests employ methods that practice each and every step of one or more claims of the ’820 patent.

19. On or about April 16, 2015, Defendants circulated a notice to their practitioners that, as of May 19, 2015, Athena’s FMUSK test would no longer be available for requisition through the Mayo network.

20. Defendants, with specific knowledge of the ’820 patent and the methods it covers, surreptitiously and purposefully designed an alternate test to avoid paying Athena for Athena’s licensed FMUSK test.

21. Defendants are not licensed to offer either MUSK or MGRM, and therefore, Defendants have and will continue to infringe one or more claims of the ’820 patent by continuing to offer those tests to the public.

22. Defendants’ conduct has damaged and will continue to damage Athena, which loses profits from, at a minimum, every MUSK and MGRM test Defendants run.

COUNT I: PATENT INFRINGEMENT OF U.S. PATENT NO. 7,267,820

23. Plaintiffs incorporate by reference paragraphs 1-22 as if fully set forth herein.

24. By offering the MUSK and MGRM tests to the public without license, Defendants infringe, either directly or indirectly, and either literally or under the doctrine of equivalents, at least claims 8 and 9 of the ’820 patent.

25. Defendants were aware of the ’820 patent, and their infringement is deliberate, willful and in reckless disregard of Plaintiffs’ rights.

26. Plaintiffs have been and continue to be injured by the infringing activities of Defendants.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

(a) a final judgment that the Defendants’ activities infringe the ’820 patent;

(b) entry of preliminary and/or permanent equitable relief, including but not limited to a preliminary and/or permanent injunction that enjoin Defendants and any of their officers, agents, employees, assigns, representatives, privies, successors, and those acting in concert or participation with them from infringing and/or inducing infringement of the ’820 patent;

(c) an award of damages sufficient to compensate Plaintiffs for infringement of the ’820 patent by Defendants, together with prejudgment and post-judgment interest;

(d) a declaration or order finding that Defendants’ infringement is willful and/or an order increasing damages under 35 U.S.C. § 284;

(e) a judgment holding that this is an exceptional case under 35 U.S.C. § 285 and awarding reasonable attorneys’ fees, costs, and expenses to Plaintiffs; and

(f) such other relief deemed just and proper.

JURY DEMAND

Under Rule 38 of the Federal Rules of Civil Procedure, plaintiffs hereby demand trial by jury of all issues so triable by a jury in this action.

Dated: July 8, 2016

Respectfully submitted,

/s/ Manleen Singh

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Attorneys for Plaintiffs Athena Diagnostics, Inc., Isis Innovation Limited, Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.

CERTIFICATE OF SERVICE

I, Manleen Singh, hereby certify that on this 8th day of July, 2016, the foregoing document was filed electronically with the Clerk of the Court using the CM/ECF system and will be sent electronically to the registered participants as identified on the Notice of Electronic Filing.

/s/ Manleen Singh

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS
BOSTON DIVISION

ATHENA DIAGNOSTICS, INC. AND ISIS INNOVATION LIMITED, Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	Civil Action No. 1:15-cv-40075-IT **ORAL ARGUMENT REQUESTED**

DEFENDANTS' RULE 12(B)(6) MOTION TO DISMISS THE SECOND AMENDED COMPLAINT

Pursuant to Fed. R. Civ. P. 12(b)(6), Defendants, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories and Mayo Clinic (hereinafter, "Mayo"), hereby move to dismiss Plaintiffs Athena Diagnostics, Inc.'s and Isis Innovation's Second Amended Complaint because all claims of asserted U.S. Patent No. 7,267,820 are invalid as directed to patent-ineligible subject matter under 35 U.S.C. § 101. The claims of this patent are directed to routine and conventional methods of applying a law of nature (specifically, the natural cause of a disease), and are thus unpatentable under the Supreme Court's 2012 decision in *Mayo v. Prometheus*.

In further support of this Motion, Mayo relies on its Memorandum of Law filed herewith, together with the Declaration of Adam J. Kessel and associated exhibits.

WHEREFORE, Mayo respectfully requests that this Court grant this Motion and dismiss the Second Amended Complaint, with prejudice.

CERTIFICATE OF COMPLIANCE WITH L.R. 7.1(a)(2)

I hereby state that counsel for Defendants complied with the requirements of Local Rule 7.1(a)(2) by attempting in good faith to resolve the issues presented in this motion. Specifically, Counsel for Mayo conferred with counsel for Plaintiffs by phone, and counsel for Plaintiffs indicated that they will oppose this motion.

/s/ Adam J. Kessel
Adam J. Kessel

REQUEST FOR ORAL ARGUMENT

Pursuant to Local Rule 7.1(d), Mayo respectfully requests oral argument to address this motion as such argument will assist the Court in addressing the issues raised herein.

Dated: September 15, 2015

/s/ Adam J. Kessel

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Attorneys for Defendants
Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories and Mayo Clinic

CERTIFICATE OF SERVICE

I hereby certify that DEFENDANTS' RULE 12(B)(6) MOTION TO DISMISS THE SECOND AMENDED COMPLAINT is being filed through the Court's electronic filing system on September 15, 2015, which serves counsel for other parties who are registered participants as identified on the Notice of Electronic Filing (NEF). Any counsel for other parties who are not registered participants are being served by first class mail on the date of electronic filing.

/s/ Adam J. Kessel
Adam J. Kessel

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS
BOSTON DIVISION

ATHENA DIAGNOSTICS, INC. AND ISIS INNOVATION LIMITED, Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	Civil Action No. 4:15-cv-40075-IT

DEFENDANTS' MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS' RULE 12(B)(6) MOTION TO DISMISS THE SECOND AMENDED COMPLAINT

’820 patent both teach that an antigen can be iodinated using standard techniques, and commercial reagents, before being used in a diagnostic immunoprecipitation method.

D. The ’820 Patent Claims Diagnostic Methods Based on the Detection of Naturally-Occurring Autoantibodies Using Established Prior Art Techniques

The patent’s twelve claims recite methods of diagnosing neurotransmission or development disorders related to MuSK based on the presence of autoantibodies to MuSK[5] in a bodily fluid sample. These claims can be divided into three general categories.

First, claims 1 and 10-12[6] recite methods for diagnosing a disease by detecting naturally-occurring autoantibodies in a bodily fluid sample. Claim 1 is representative:

> 1. A method for diagnosing neurotransmission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK).

(Ex. A, ’820 patent at 12:31-35.) Claim 1 describes nothing more than the identification of the natural, pre-existing relationship between the presence of autoantibodies to MuSK and disorders related to the MuSK protein. Claims 10 and 11 depend from and further refine claim 1 by specifying the particular disease or disorder that is being diagnosed: MG (claim 10) or muscle paralysis or fixed joints in newborns (claim 11). (*Id.* at 13:10-14:3.) Claim 12 is parallel to claim 1, but specifies that the disorder being diagnosed is related “to interference of the agrin/MuSK/AChR pathway within a mammal.” (*Id.* at 14:4-9.)

---

[5] The claims refer to MuSK, “epitopes” of MuSK, and/or “antigenic determinants” of MuSK. These latter two terms of art simply refer to the specific portions of the MuSK protein that the antibody interacts with. (ECF No. 11, ¶ 14; Ex. A, ’820 patent at 5:9-11 (“As aforementioned any protein which binds to the autoantibody may also be used such as an epitope or fragment of the MuSK protein itself.”); *see also id.* at 5:32-38.)

[6] The ’820 patent includes two independent claims—claims 1 and 12—and ten dependent claims—claims 2-11. Dependent claims 2-11 each modify and refer back to another claim and, as structured, ultimately all refer back to independent claim 1.

Claim 2 depends from claim 1 and adds that the method proceeds in two steps: first, contacting a fluid sample with MuSK; and second, detecting any resulting autoantibody-MuSK antigen complexes. (*Id.* at 12:36-46.) Claim 2 does not provide details about how to detect the complex. Claim 2 therefore describes no more than a prerequisite step for detecting autoantibodies from a fluid sample—putting the sample that contains the autoantibodies in contact with the antigen.

Claims 3-6, each of which ultimately depend from claim 2, all involve the known immunoprecipitation method that uses a labeled secondary antibody. Claim 3 limits the labeled secondary antibody to an anti-IgG antibody. (*Id.* at 12:47-49.) Claim 4 limits the universe of labels on the secondary antibody to a specific group. (*Id.* at 12:50-52.) Claim 5 further restricts the label to an enzymatic HRP label, and requires that the detection method include reaction with the substrate o-phenylenediamine for subsequent measurement of the label at a wavelength of A492. (*See id.* at 12:53-56.) Claim 6 merely adds the common sense idea that the intensity of the sample's signal could be compared to the signal of both positive and negative controls to indicate the relative amount of the autoantibody in the sample. (*Id.* at 12:57-61.)

Claims 7-9, each of which ultimately depend from claim 1, all involve the known immunoprecipitation method that uses a labeled antigen. Claim 7 describes the known steps required to precipitate an antibody from a fluid sample using a labeled antigen, in this case MuSK, and to then monitor for the label associated with the resulting autoantibody/MuSK complex. (*Id.* at 12:62-13:5.) The label would indicate the presence of the autoantibody, and thus identify disease. (*Id.*) Claims 8 and 9 further refine the type of label on the MuSK antigen introduced to the sample—namely, a standard radioactive label like ^{125}I. (*Id.* at 13:6-9.)

organism." *Genetic Veterinary Sci., Inc. v. Canine EIC Genetics, LLC*, --- F.Supp.3d ----, 2015 WL 1505669, at *10 (D. Minn. Mar. 31, 2015). The '820 patent's claims are no different because they are also directed to identifying the naturally-occurring source of certain diseases—autoantibodies that complex with MuSK, and testing bodily fluid samples for that autoantibody.

So "[w]hat else is there in the claims before us" besides this natural law? *Mayo*, 132 S. Ct. at 1297. As demonstrated below, in the '820 patent, there is "not[hing] sufficient to transform unpatentable natural correlations into patentable applications[]." *Id.* at 1298.

2. Claims 1, 2 and 10-12 Cover Only a Law of Nature and the General Concept of Detecting That Law of Nature

Claims 1 and 10-12 cover nothing more than the natural correlation between the presence of autoantibodies directed to MuSK and the existence of certain neurotransmission and developmental disorders. They differ only with respect to which disorder is diagnosed. Claim 1 generically states that the disorder to be diagnosed is related to MuSK. (Ex. A, '820 patent at 12:31-35.) Claims 10 and 11 each depend from claim 1 and narrow it by specifying that the disorder is either MG or "muscle paralysis and/or fixed joints in newborn offspring" based on the detection of maternal autoantibodies to MuSK. (*Id.* at 13:10-14:3; *see also id.* 1:54-61, 3:12-15, 10:21-38.) Like claim 1, claim 12 generically states only that the disorder to be diagnosed by detecting autoantibodies to MuSK is "related to the interference of the agrin/MuSK/AChR pathway." (*Id.* at 14:4-9; *see also id.* at 2:25-37, 2:46-50.)

That each of these claims requires "detecting" autoantibodies is not enough to make them patent eligible. As one court recently put it, "[s]imply detecting a patent-ineligible concept—in this case a natural law—and then identifying the law once it is detected, is not enough to render the subject matter patentable." *Genetic Veterinary*, 2015 WL 1505669, at *11. Claims 1 and 10-12 fail the second step of the *Mayo* test for this reason.

Claim 2 fares no better. Claim 2 requires first "contacting" a fluid sample with the MuSK antigen before "detecting" for antibody-antigen complexes that would indicate that the presence of disease. (Ex. A, '820 patent at 12:36-46.) There is nothing new or unconventional about putting together the two things required to make use of this natural law—the fluid sample that may contain autoantibodies to MuSK and MuSK. Nor is there anything new or unconventional about thereafter detecting any antibody-antigen complexes that form as a result. Indeed, the patent describes these exact "contacting" and "detecting" steps as part of the "techniques known per se in the art" for detecting autoantibodies in fluid samples as a general matter:

> A sample to be tested is brought into contact with the antigen and if autoantibodies specific to the protein are present in a sample they will immunologically react with the antigen to form autoantibody-antigen complexes which may then be detected or quantitatively measured.

('820 patent at 3:38-43.) Whether viewed alone or as an ordered combination, the process steps in claim 2 do not amount to an "inventive concept" worthy of patent protection. *Genetic Techs.*, 2014 WL 4379587, at *12 (concluding that a generic, non-specific "detecting step" does not recite "anything more than the employment of a routine, conventional process"); *see Alice*, 134 S. Ct. at 2357 ("'Simply appending conventional steps, specified at a high level of generality,' [is] not '*enough*' to supply an 'inventive concept'.") (citing *Mayo*, 132 S. Ct. at 1300).

3. The Process Steps in the Claims 3-9 Are Well-Known and Conventional, as the Patent Admits

Although remaining claims 3-9 include more than generic steps to detect a natural law, they do not contain enough to clear the patent-eligibility hurdle.

None of the additional process steps described in claims 3 through 6—which concern the use of labeled anti-human antibodies to detect autoantibodies to MuSK—contain a patent-worthy inventive concept because they describe standard techniques that even the patent teaches were

"known per se in the art." ('820 patent at 3:33-65.) To illustrate, claim 3 builds off of claim 2's step of "detecting" autoantibody-antigen complexes by specifying that "an anti-IgG antibody tagged or labeled with a reporter molecule" is used to detect the complexes. (*Id.* at 12:47-49.) But the patent itself explains that the use of anti-IgG antibodies for that purpose is common in describing the techniques "known per se in the art" for detecting autoantibodies from a sample:

> Detection of autoantibody-antigen complexes is preferably carried out using a secondary anti-human immunoglobulin antibody, typically anti-IgG or anti-human IgM, which recognizes general features common to all human IgGs or IgMs, respectively.

(*Id.* at 3:43-47.) The patent goes on to list each of the tags and labels recited in claim 4 that can be associated with the anti-IgG antibody. (*Id.* at 3:57-61.) Claim 5, while reciting a specific HRP enzymatic tag and the additional step of reacting it with a reagent called o-phenylenediamine for measurement at the A492 wavelength, fails to describe anything new. As the patent describes, the HRP enzymatic tag and the step of reacting it with o-phenylenediamine was also "known per se in the art"—known so well that reagents with that tag were available for purchase. (*Id.* at 3:33-53, 8:41-43.)

In essence, claims 3, 4 and 5 tell one of ordinary skill in the art to re-apply well-understood techniques to a newly uncovered natural law. The steps in these claims, both alone and as viewed as ordered combinations, do not amount to an inventive concept. *In re BRCA1*, 774 F.3d at 764 (finding patent ineligible methods of comparing DNA sequence using standard techniques); *see also Celsis*, 2015 WL 1523818, at *7-8 (finding invalid methods drawn to the law of nature that cells are capable of surviving multiple freeze-thaw cycles and using conventional freezing methods); *Exergen Corp. v. Brooklands Inc.*, No. 12-12243, 2015 WL 5096464, at *6 (D. Mass. Aug. 28, 2015) (finding invalid as patent ineligible methods based upon conventional step known in the field).

Claim 6 builds off of claim 3 but, rather than adding another step to the method, offers another patent ineligible concept—a mental process of comparing data to determine relative amounts of autoantibodies. *See In re BRCA1*, 774 F.3d at 763 (explaining that "an abstract mental process of 'comparing' and 'analyzing' two gene sequences" is a patent ineligible abstract idea); *Perkin Elmer*, 496 F. App'x at 68 ("These exceptions make ineligible, for example, mental processes.") The additional element of claim 6 tells one that the strength of the sample's signal can indicate the relative amount of autoantibodies in the sample by comparison the signals of both positive and negative controls. The claims do not require one to even make this comparison, let alone do anything with it. Thus, claim 6 adds only a patent-ineligible mental process to claim 3, which does not supply the "inventive concept" necessary to confer patent eligibility. *Id.* at 70 ("The claims thus recite the mental process of comparing data to determine a risk level . . . No action beyond the comparison is required.").

Claims 7 through 9 also lack an inventive concept because the additional process steps they outline are, as cited in the patent, nothing more than "standard techniques in the art." ('820 patent at 3:66-4:12.) As described above, the additional process steps in these claims specify that the autoantibodies are detected through the use of a labeled antigen. The steps in claim 7 include (1) contacting a labeled MuSK antigen with a patient's bodily fluid sample to generate complexes of the autoantibody and labeled MuSK, (2) immunoprecipitating those complexes, and (3) monitoring for the label. Claim 8 refines claim 7 by requiring the use of a radioactive label, and claim 9 further refines that label to a particular one—^{125}I; they do not add additional steps to claim 7.[7]

[7] Claim 7 also includes a "wherein" clause that amounts to a restatement of the underlying natural law and therefore does not qualify as an inventive concept. *Mayo*, 132 S. Ct. at 1297.

The ’820 patent in fact directs the reader to two scientific publications that describe previous use of each step of this technique, only with a different ^{125}I-labeled antigen. (’820 patent at 4:9-12 (citing references 4 and 6), 11:19-22, 26-29 (citations for references 4 and 6); *see also id.* at 10:50-53.) One of those publications—the Vincent et al. reference—describes this technique in section (b) of the *Acetylcholine receptor assay* description, which involves (1) contacting a serum sample with AChR containing a ^{125}I-label, (2) precipitation, and (3) “count[ing]” the label. (Ex. C at 1247.) The other of those publications—the Lindstrom et al. reference—describes the same thing: immunoprecipitating autoantibodies using a ^{125}I-labeled antigen and monitoring for the radioactive label. (Ex. B at 1055.)

Based on ’820 patent itself and the publications cited in it, anyone wishing to detect the presence of autoantibodies that target a specific antigen would have known that it could be done by (1) contacting a bodily fluid sample with the labeled antigen, (2) precipitating the antibodies in the sample, and (3) monitoring for the label. Thus, claims 7-9 “do nothing more than spell out what practitioners already knew”—how to detect autoantibodies in a bodily fluid sample by using a radiolabeled antigen that would complex with the autoantibody, precipitate along with it, and signal its presence. *See In re BRCA1*, 774 F.3d at 764; *see also BMS*, 72 F. Supp. 3d at 532 (finding claims invalid where “[a]ccording to the patent itself, all of the techniques . . . were previously well known methods”). Thus, when viewing the process steps in claims 7-9 separate from the natural law, either alone or in an ordered combination, it is plain that they recite nothing more than conventional and ordinary techniques for detecting autoantibodies in a bodily fluid sample, which does not make the claims patent eligible. *See Mayo*, 132 S. Ct. at 1298 (“Purely ‘conventional or obvious’ ‘[pre]-solution activity’ is normally not sufficient to transform an

unpatentable law of nature into a patent-eligible application of such a law."); *BMS*, 72 F. Supp. 3d at 533 ("*Mayo* requires that the additional steps be viewed apart from the natural law.").

The simple fact that scientists modify MuSK by adding a label to it before using it in the methods of claims 7-9 does not amount to an inventive concept or otherwise confer patent eligibility. As another court put it, "[t]he question is not whether any aspect of the patent involves non-natural processes; it is what the patent is directed to and—if the patent is directed to a patent-ineligible concept—whether the non-natural processes provide an additional inventive concept of enough heft to make the patent valid." *Genetic Veterinary*, 2015 WL 1505669, at *14. Here, the use of a radiolabeled antigen does not provide any "heft" because, as set out above, the use of radiolabeled antigens in immunoprecipitation techniques was routine and well-known before the inventors' discovery.

The patent's written description thus shows—both by calling out the claimed immunoprecipitation methods as "known" and "standard" and by citing articles employing the use of an ^{125}I radiolabeled antigen to detect autoantibodies—that the claimed methods for detecting autoantibodies and diagnosing disease add nothing that was not already well known and routine in the art. Because the method steps in claims 2-9 precisely track those well-understood, routine and conventional immunoprecipitation techniques, they do not amount to an "inventive concept" under the *Mayo* framework and the claims should be found patent ineligible. *See BMS*, 72 F. Supp. 3d at 531-32 (concluding method claims ineligible on a motion to dismiss where patents state "outright" that the steps were routine and conventional).

IV. CONCLUSION

For the reasons stated herein, Mayo respectfully requests that the Court grant this Motion to Dismiss and declare each claim of the '820 patent invalid.

EXHIBIT B

Article abstract

Elevated amounts of antibodies specific for acetylcholine receptors were detected in 87 percent of sera from 71 patients with myasthenia gravis but not in 175 sera from individuals without myasthenia gravis, including those with other neurologic or autoimmune diseases. Antireceptor antibodies were not directed at the acetylcholine binding site of the receptor. Presence or titer of antibody did not appear to correlate with age, sex, steroid therapy, or duration of symptoms. Myasthenia gravis patients with only ocular symptoms had lower antibody titers, while the majority of titers in myasthenia gravis patients with thymoma exceeded the median titer of the myasthenia gravis group as a whole. Assay of antireceptor antibody should prove a useful test in the diagnosis of myasthenia gravis.

Antibody to acetylcholine receptor in myasthenia gravis

Prevalence, clinical correlates, and diagnostic value

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Animals immunized with acetylcholine receptor purified from electric organs of *Electrophorus electricus* or *Torpedo Californica* demonstrate striking similarities to patients with myasthenia gravis.[1] These similarities include easy fatigability,[2,3] decrementing muscle action potential responses to repetitive nerve stimulation,[2,3] improvement with anticholinesterase drugs,[2,3] increased sensitivity to curare,[2,3] small miniature end-plate potentials,[4] and simplification of the postsynaptic membrane of the neuromuscular junction.[5,6] Animals with experimental autoimmune myasthenia gravis develop antibodies to electric organ acetylcholine receptor, a small fraction of which also recognizes muscle acetylcholine receptor.[2,10] The paucity of acetylcholine binding sites demonstrable in nerve-muscle junctions of patients with myasthenia gravis suggested that antibody to acetylcholine receptor might be present.[7] Almon, Andrew, and Appel[8] reported that 30 percent of myasthenia gravis sera tested contained a globulin that blocked the binding of iodine ^{125}I α-bungarotoxin to acetylcholine receptor prepared from denervated rat muscle. Employing acetylcholine receptor prepared from human muscle as antigen, we found that in myasthenia gravis,[9,10] as in experimental autoimmune myasthenia gravis,[2,9,10,11] antibodies to homologous muscle acetylcholine receptor (antireceptor antibodies) are directed predominantly at sites on the acetylcholine receptor other than the acetylcholine binding site. Appel, Almon, and Levy[12] recently published similar findings in human myasthenia gravis. In this report, we examine the correlation of antibody titers with the clinical parameters of myasthenia gravis and discuss the usefulness of antibody determinations as a diagnostic test for myasthenia gravis.

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Methods. *Subjects.* In 69 of the 71 patients with myasthenia gravis included in this study, the diagnosis

was confirmed by a positive response to edrophonium or neostigmine, increased sensitivity to curare, and/or a decrementing motor action potential response to repetitive nerve stimulation. Patients who did not have such testing were included only if the case history was entirely compatible with myasthenia gravis. (All histories were reviewed by MES.)

For patients with disorders other than myasthenia gravis, the diagnoses of the referring physicians were accepted. These included 100 patients with other neurologic diseases: diabetic neuropathy (five), chronic inflammatory polyradiculoneuropathy (three), Friedreich's ataxia (five), Charcot-Marie-Tooth disease type II (six), Duchenne's muscular dystrophy (five), Duchenne's dystrophy carrier (four), facioscapulohumoral dystrophy (two), myotonic dystrophy (six), Becker's dystrophy (four), limb-girdle muscular dystrophy (six), amyotrophic lateral sclerosis (20), Werdnig-Hoffman disease (one), Kugelberg-Welander disease (one), McArdle's disease (one), multiple sclerosis (six), epilepsy (one), cerebrovascular accident (three), cerebral tumor (one), spinocerebellar degeneration (one), Eaton-Lambert syndrome (13), and Guillain-Barré syndrome (six). Also included were two patients with thymoma without myasthenia gravis, five patients with diabetes mellitus without neuropathy, and 50 patients with presumed autoimmune diseases: dermatomyositis or polymyositis (10), polymyositis with scleroderma (one), scleroderma (six), Sjögren's syndrome (13), Sjögren's syndrome and rheumatoid arthritis (eight), and systemic lupus erythematosus (12). Normal subjects included 11 males and eight females 20 to 62 years old.

Comparison of antibody titers between groups was made using median titers evaluated by chi-square and Fisher's exact tests.

Antibody assay. All sera were assayed for antibodies to human muscle acetylcholine receptor (antireceptor antibody) by immunoprecipitation using a modification of the previously described method.[10] (Here, α-bungarotoxin is substituted for *Naja naja siamensis* toxin, and benzoquinonium is used in control assays.) Full details will be published elsewhere.[13] Human muscle acetylcholine receptor labeled with ^{125}I α-bungarotoxin was used as antigen. In triplicate assays, 5 μl volumes of serum were added to 1 ml volumes of triton X-100 extracts of human muscle containing acetylcholine receptor (2×10^{-10}M). After incubation overnight at 4° C, immunoglobulins in the sera, along with any complexes of antibody-acetylcholine receptor-^{125}I-toxin, were precipitated by addition for 4 hours of goat antihuman immunoglobulin G, and the radioactivity of the washed pellet was determined. For each serum tested, triplicate control assays were done with benzoquinonium (10^{-4}M), added to inhibit toxin binding to receptor. This value approximated ^{125}I-toxin trapped nonspecifically in the pellet and was subtracted from the value in the absence of benzoquinonium. Sera with high titers ($\geq 10^{-8}$M) of antireceptor antibody were further tested after 10-fold dilution in normal human serum. Titers of antireceptor antibody were expressed as moles of ^{125}I-toxin binding sites precipitated per liter of serum.

Inhibition of toxin binding was used to assay antibody to the acetylcholine binding site (antiacetylcholine site antibody) in sera from 16 myasthenia gravis patients and 12 normal subjects. Immunoglobulin fractions of sera were used in these experiments to minimize nonspecific blockage of toxin binding. Aliquots (20 to 100 μl) of acetylcholine receptor extract were incubated overnight at 4° C with 200 μl of test serum globulin or with buffer as control. Next, ^{125}I-*Naja naja siamensis* toxin (1×10^{-9}M) was added to the samples. Then, ^{125}I-toxin-labeled acetylcholine receptor was separated from free ^{125}I-toxin by column chromatography on Sephadex G200 and the radioactivity was measured. Results were expressed as percent of toxin binding with respect to control samples lacking immunoglobulin.

Results. Titers of antireceptor antibody for patients with myasthenia gravis and subjects without myasthenia gravis are summarized in table 1 and the figure. Only sera from myasthenia gravis patients caused precipitation of large

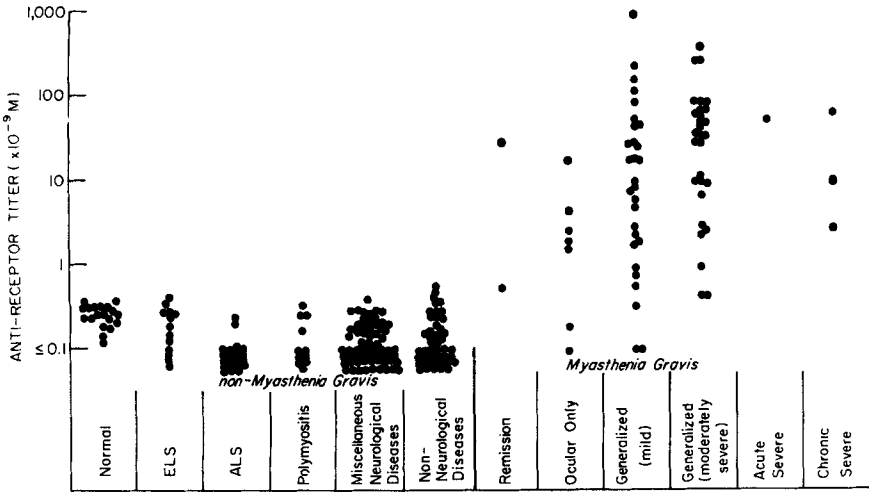

Figure. Distribution of antireceptor antibody titers in subjects with and without myasthenia gravis. ELS = Eaton-Lambert syndrome, ALS = amyotrophic lateral sclerosis.

Table 1. Acetylcholine receptor anitbody in patients with myasthenia gravis and controls

Diagnosis	No. tested	Mean titer x 10^{-9}M	Median titer x 10^{-9}M	Range x 10^{-9}M	Percent positive*
Myasthenia gravis	71	54.3	16.3	0.844	87
Controls					
Neurologic diseases	100	0.093	0.039	0-0.415	0
Autoimmune and endrocrine diseases	54	0.133	0.095	0-0.563	0
Thymoma without myasthenia gravis	2	0.0830	0.083	0-0.165	0
Healthy subjects	19	0.258	0.253	0.111-0.391	0
Total	175	0.123	0.098	0-0.563	0

*Positive $\geq$ 0.62, that is, 0.123 + 4 SD

Table 2. Distribution of antireceptor antibody titers in patients with myasthenia gravis

	Number	Mean (x 10^{-9}M)	Median (x 10^{-9}M)	Range (x 10^{-9}M)
Sex				
Female	40	77.6	22.5	0 - 844
Male	31	24.1	16.0	0 - 82.3
Age				
20 years	15	135.0	44.8	0.389 - 844
21 - 40 years	15	46.0	31.5	0.656 - 254
41 - 60 years	18	26.4	13.0	0 - 209
61 years	23	28.8	9.60	0.182 - 137
Duration myasthenia gravis				
1 year	26	29.1	9.30	0 - 235
1 - 5 years	24	61.2	31.6	0.319 - 395
5 years	20	81.4	13.1	0.0560 - 844
Thymic status				
Thymoma	14	50.6	47.4	6.52 - 137
Thymectomy without thymoma	12	92.2	9.7	0 - 844
Nonoperated	41	48.9	9.0	0 - 395
Medication				
Steroids	9	19.8	16.3	0.520 - 59.1
No steroids	57	63.1	26.8	0 - 844
Severity*				
A	2	14.7	14.7	0.520 - 28.8
1	7	3.76	1.92	0.0560 - 16.0
2A	29	66.3	16.3	0 - 844
2B	29	60.3	34.4	0.389 - 395
3	1	53.3	----	----
4	3	24.8	24.8	2.56 - 62

*Modified Osserman classification: A = remission, 1 = ocular only, 2A = mild generalized, 2B = moderately severe generalized, 3 = acute severe, 4 = chronic severe.

amounts of ^{125}I-toxin-labeled acetylcholine receptor. Sera from nonmyasthenic subjects caused precipitation that differed only slightly from the amount of ^{125}I-toxin-labeled acetylcholine receptor nonspecifically trapped in the control (benzoquinonium) treated pellet. The upper limit of normal was defined as 0.62 $\times^{-9}$M. This value is equal to the mean value plus 4 standard deviations for subjects without myasthenia gravis (table 1). Because of the non-Gaussian distribution of titers, this definition of normal range is arbitrary. Similar values were found among all the subgroups without myasthenia gravis: normal, other neurologic diseases, presumed autoimmune

Table 3. Effect of immunoglobulin on ^{125}I-toxin binding to acetylcholine receptor (AChR)

Sera	Number	Mean percent ^{125}I-toxin bound* (± SD) after adding 200 μl immunoglobulin to: 1 x 10^{-14} mole AChR	5 x 10^{-14} mole AChR	25 x 10^{-14} mole AChR
Normal	12	86 ± 32	99 ± 17	99 ± 24
All myasthenia gravis	16	59 ± 43	78 ± 39	72 ± 31
Myasthenia gravis inhibiting binding	6	8.2 ± 5.1	31 ± 9.8	40 ± 11

*In the absence of immunoglobulin, binding of toxin to AChR was 100 percent.

or endocrine diseases, or thymoma without myasthenia gravis (table 1). The mean value for the total group without myasthenia gravis (No. = 175) was 0.123, $\times 10^{-9}$M, the median 0.098 $\times 10^{-9}$M, and range 0 - 0.563 $\times 10^{-9}$M.

Significant titers were found in 62 of 71 (87 percent) patients with myasthenia gravis (table 1). The range of antireceptor antibody titers in patients with myasthenia gravis was very wide (0 - 844 $\times 10^{-9}$M), with a mean of 54.3 $\times$ 10^{-9}M and median of 16.3 $\times$ 10^{-9}M. The difference between the groups with and without myasthenia gravis is highly significant ($p < 0.001$).

Comparisons of titers were made on the basis of sex, age, duration of symptoms, thymoma or thymectomy, modified Osserman classification of severity,[14] and treatment with steroid medication (table 2). Using median values, myasthenia gravis patients with thymoma had higher titers than thymectomized patients without thymoma ($p = 0.013$), and individuals with ocular myasthenia gravis had lower titers than those with mild or moderately severe generalized disease ($p = 0.01$). All other comparisons were not statistically significant.

Sera from a woman with myasthenia gravis and from her twin newborn sons with neonatal myasthenia gravis were assayed but not included in the statistical analyses because of the lack of detailed clinical information. The mother and both infants had significant levels of antibody (31.1 $\times$ 10^{-9}M, 7.88 $\times$ 10^{-9}M, and 6.89 $\times$ 10^{-9}M, respectively).

Antibody to the acetylcholine binding site of the receptor molecule was assayed by examining binding of ^{125}I-toxin to acetylcholine receptor preincubated with serum (table 3). Fixed amounts of serum were incubated with three different concentrations of receptor. At all concentrations of receptor, normal sera caused little blockage of ^{125}I-toxin binding, but standard deviations were large. The average for myasthenia gravis patients indicated that some sera may have inhibited toxin binding. However, only six (38 percent) of the 16 sera from myasthenia gravis patients inhibited toxin binding to a greater extent than any normal serum under all three conditions tested. Thus, the detection of myasthenia gravis patients by immunoprecipitation assay is significantly greater than by the toxin binding method (chi-square $p = < 0.001$).

Discussion. No significant titer of antireceptor antibody was found in subjects without myasthenia gravis. This group included patients with disorders that may show decrementing motor action potential responses to repetitive nerve stimulation, such as amyotrophic lateral sclerosis,[15] and patients with Eaton-Lambert syndrome,[16] a disorder associated with a defect of neuromuscular transmission, Patients with systemic lupus erythematosus, a disease characterized by autoantibodies, did not have significant levels of antireceptor antibody, suggesting that this antibody is not merely indicative of an autoimmune diathesis.

Eight-seven percent of patients with myasthenia gravis had antireceptor antibody in excess of that seen in any person without this disease. No correlation was found, however, with duration of the disease, age, sex, or steroid therapy. Although patients with thymoma generally had high antibody titers, this does not appear valuable diagnostically since many patients without thymoma also had high titers. As a group, patients with only ocular signs have lower antibody titers than those with generalized disease. However, within the generalized group, it is not possible to predict severity on the basis of antibody titer.

A review of the nine myasthenia gravis patients without detectable antireceptor antibody failed to reveal a consistent similarity; neither sex, age, nor duration of symptoms seemed a common factor. Two had a thymectomy prior to collection of the sera but neither had a thymoma. Only one of the nine was known to be receiving steroid medication at the time of the study, and that patient was in remission. The others were classified in severity as groups 1 (two), 2A (four), or 2B (two).

The absence of significant antibody titers in some myasthenia gravis patients is unexplained. It is possible that myasthenia gravis represents not one but two or several disorders with similar clinical and neurophysiologic appearances. One "variety" of myasthenia gravis, apparently the most common one, could be characterized by antireceptor antibody. Alternatively, our present sensitivity may not be sufficient to reliably detect very low titers of antireceptor antibody. There is some evidence that this may be the case, since 25 percent of myasthenia gravis patients had titers between 0.6 and 5.0 $\times 10^{-9}$M. Another possibility is that serum antibody titers do not necessarily reflect antibody activity

in the microenvironment of the end-plate. Finally, titers may fluctuate in response to factors as yet unrecognized.

It is clear that the disease process involves more than the binding of antibody to acetylcholine receptor. There is not a close correlation between antibody titer and disease intensity, as would be expected if antibodies acted only as curarelike antagonists of acetylcholine receptor. In addition, postsynaptic membrane structure is simplified in myasthenia gravis,[5,6] suggesting that a reduction in the number of acetylcholine receptor molecules and alteration of their arrangement account for some of the defect in transmission. Simplification of postsynaptic membrane structure probably results from the antibody response to acetylcholine receptor, since it is also observed in the immunologically induced experimental model experimental autoimmune myasthenia gravis.[5,6] Thus, the defect in transmission in myasthenia gravis probably involves synthesis and destruction as well as antagonism of acetylcholine receptor.

Most of the antibody to receptor found in patients with myasthenia gravis was directed at determinants other than the acetylcholine binding site. Antiacetylcholine site antibody would be expected to prevent binding of toxin to acetylcholine receptor. Although 38 percent of the sera tested did reduce toxin binding to acetycholine receptor, the effect was small and seen only when the concentration of antireceptor antibody exceeded that of acetylcholine receptor by a factor of 200 to 1,000-fold. Inhibition observed under these conditions might result from steric hindrance by extensive binding of antibodies to sites on acetylcholine receptor other than the acetylcholine site. By the criterion for significance that we applied to antireceptor titers, none of the myasthenia gravis sera differ from normal in inhibition of toxin binding.

Other investigators also have reported detection of antibodies to acetylcholine receptor in sera from patients with myasthenia gravis. Using acetylcholine receptor isolated from denervated rat muscle as antigen, antibodies were detected in 30 percent of the sera tested by inhibition of toxin binding[8] and in 68 percent of the sera by binding to toxin-acetylcholine receptor complexes.[12] Using acetylcholine receptor isolated from *Torpedo* electric organ as antigen, antibodies were detected in 66 percent of sera by complement fixation.[17] Using acetylcholine receptor isolated from human muscle as antigen, we have found antibodies in the sera of 87 percent of patients with myasthenia gravis, the average value being 440-fold that of nonmyasthenics. With the other methods for quantitating antibody, sera from patients with myasthenia gravis differed from normals by only 0.2 to 3-fold. Using sections of nonmyasthenic human muscle as substrate, inhibition of toxin binding was detected histologically in 75 percent of sera from myasthenia gravis patients tested.[18] This method, while more sensitive than methods using nonhuman acetylcholine receptor, is not quantitative and is more tedious and less sensitive than the method we have described.

Defective neuromuscular transmission in myasthenia gravis probably results in part from the action of antireceptor antibodies. The number of toxin binding sites at end-plates is reduced in both myasthenia gravis[7] and experimental autoimmune myasthenia gravis.[19,20] This presumably results from antibody binding to receptors in the membrane and/or from the simplification of the postsynaptic membrane. Antibodies in animals with experimental autoimmune myasthenia gravis, like those in patients with myasthenia gravis, are directed mostly at sites on the receptor other than the acetylcholine site. Experimental autoimmune myasthenia gravis sera block the electrophysiologic activity of receptors on electroplaques[10,11] and muscle.[19,21] These observations may also apply to myasthenia gravis. Rats immunized with eel acetylcholine receptor demonstrate rising titers of antirat muscle acetylcholine receptor antibody during the development of the late stage of experimental autoimmune myasthenia gravis, the stage that closely resembles myasthenia gravis.[10] However, since serial titers in individual patients were not included in this study, comparison of fluctuations in disease with antibody titer cannot be made.

Detection of antireceptor antibodies in a mother with myasthenia gravis and her neonatally myasthenic babies suggests transplacental transfer of these antibodies. Simpson[22] first suggested that such antibodies could be responsible for neonatal myasthenia and that this form of myasthenia was transient because maternal antibodies were eliminated from the newborn.

The results thus far obtained indicate that antireceptor antibody is present in the serum of most myasthenia gravis patients and is specific to myasthenia gravis. Assay of antireceptor antibody offers an additional diagnostic test for myasthenia gravis. The two most frequently used diagnostic tools for myasthenia gravis, edrophonium testing and repetitive nerve stimulation, while highly characteristic in myasthenia gravis, may yield positive results in disorders other than myasthenia gravis. The supplementation of edrophonium and electromyography by antireceptor antibody studies should increase the reliability of the usual diagnostic approach.

In summary, antireceptor antibody, similar to that found in animals with experimental autoimmune myasthenia gravis, is detectable in patients with myasthenia gravis. Antireceptor, but not antiacetylcholine site, antibody is detected in most patients with myasthenia gravis but not in persons without myasthenia gravis. Presence or level of antibody does not appear to correlate with age, sex, duration of symptoms, or steroid therapy. Correlation was observed between antibody titer and both the presence of thymoma and the restriction of the disease to the ocular muscles. Assay of antireceptor antibody may prove a useful test in the diagnosis of myasthenia gravis.

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Antibody to acetylcholine receptor in myasthenia gravis: Prevalence, clinical correlates, and diagnostic value

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EXHIBIT C

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Acetylcholine receptor antibody as a diagnostic test for myasthenia gravis: results in 153 validated cases and 2967 diagnostic assays

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SUMMARY Anti-acetylcholine receptor (AChR) antibody was undetectable in 26/153 (17%) sera from myasthenia gravis patients assayed by standard RIA using human acetylcholine receptor. Eight of these were found to be positive with a modified protocol using a mixture of normal and denervated AChR, reducing the proportion of "negative" sera to 12%. Many of these were from patients with a short history; two such patients later developed low positive values. Anti-AChR without clinical evidence of myasthenia was found in one of three monozygotic twins of myasthenia gravis patients, and in one of thirty other first degree relatives of a further 17 patients. Anti-AChR is a valuable and highly specific diagnostic test which, with the assay used here, is positive in about 88% of patients with clinical features of myasthenia gravis

In the last eight years it has been established that anti-acetylcholine receptor (anti-AChR) antibody is implicated in the loss of functional receptors in the post-synaptic membrane that underlies the defect in neuromuscular transmission in myasthenia gravis (for reviews see refs 1, 2). This antibody is usually detected by an immunoprecipitation assay in which AChR is labelled with ^{125}I-alpha-Bungaratoxin (a-BuTx), a snake toxin that binds to AChR with high affinity. Anti-AChR antibody appears to be specific for myasthenia gravis[3]. Its clinical acceptance as a diagnostic test is suggested by the steadily increasing number of serum samples sent to us for this assay (over 4,000 since 1980). In this paper we describe our assay methods and results in 153 myasthenia gravis cases studied before treatment by thymectomy or immunosupressive drugs, and we assess the value of this assay in diagnosis.

Methods

Iodination of alpha-bungarotoxin (a-BuTx)

Alpha-bungarotoxin was obtained from the Miami Serpentarium (Florida, USA) or from Biotoxins Incorporated (California, USA), iodinated by a modification of the method of Vogel *et al*[4] using 12·5 nmoles (100μg) of a-BuTx, 5mCi Na^{125}I and 28 nmoles (55μl) iodine monochloride in 205μl 0·3M NH_4Cl/NH_4OH, pH 8·9. The reaction was terminated after two minutes at room temperature by addition of 20μl sodium thiocyanate (0·1M) followed by 20μl 0·1M potassium iodide as carrier. The reaction products were diluted into 20 ml of 3mM phosphate buffer, pH 7·4 and applied directly to 1ml of DEAE-Sephadex (Pharmacia Fine Chemicals Ltd) equilibrated in the same buffer. After loading at 5ml/h and washing briefly the iodinated toxin was eluted using a gradient of 0–0·08M NaCl/3mM phosphate. 0·7–1ml fractions were collected and stored at 4°C after addition of phenylmethyl sulphonylfluoride (PMSF, 0·1M in propan-2-ol diluted 1 in 1,000 to give to give 0·1mM final concentration) as preservative. The bimodal peak obtained consisted of varying proportions of di-iodo and mono-iodo a-BuTx. The specific activity of the di-iodo a-BuTx which was used in all the assays described was 200-500 cpm/fmole counted on a Packard Autogamma.

Preparation of muscle extracts

Human muscle from amputated limbs, used in the standard assay, was obtained as fresh as possible and stored at −70°C until required. For the modified assay, gastrocnemius/soleus muscle was obtained 3–8 hours after death from patients with no neuromuscular disease and from two patients with amyotrophic lateral sclerosis. Muscle was cleaned of fibrous connective tissue and chopped roughly before homogenisation in an MSE atomix liquidizer in two volumes of 0·1M phosphate buffer, pH 7·4 with

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0·02% sodium azide and PMSF to inhibit proteolysis. Homogenisation at top speed was performed for periods of up to half a minute until a thick slurry was obtained. A further two volumes of buffer were added and the mixture centrifuged in an MSE angle 18, 6 × 250 ml rotor for 30 minutes at 13,000 rpm. On some occasions the pellet was resuspended in buffer and recentrifuged to eliminate most of the soluble proteins. The membrane pellets were then resuspended with agitation in an equal volume of 0·02M phosphate, pH 7·4, containing 2% Triton × 100 and PMSF (0·1mM), and rotated at room temperature for two hours or overnight at 4°C. The supernatants were separated by centrifugation at 13,000 rpm and filtered through Whatman standard filter paper. Further PMSF (0·1mM) was added before storage at 4°C.

The use of PMSF (0·1mM) as a protease inhibitor during preparation and storage of the extracts was crucial to prevent proteolysis and loss of AChR activity.

Acetycholine receptor assay

5–100 μl aliquots of muscle extracts were incubated at room temperature for at least two hours with dilutions of ^{125}I-a-BuTx (di-iodo) ranging from 0·5 to 5nM, and binding of toxin assessed by one of two methods: (a) binding of AChR-^{125}I-a-BuTx to DE 81 filter discs (Whatman Ltd) as described by Schmidt and Raftery[5]; (b) precipitation with anti-AChR. In (a), 25μl of the labelled extract was diluted into 250μl PTX buffer (20mM phosphate pH 7·4, 0·1% triton X 100), applied to presoaked double filter discs and washed with 10ml of PTX buffer. The discs were counted on a Packard Autogamma. In (b) the labelled extract was incubated with excess of a positive myasthenia gravis serum for two hours followed by incubation with excess antihuman IgG overnight (see below). The precipitate was pelleted, washed and counted as described below. As controls for both methods, a duplicate aliquot of extract was preincubated in cold a-BuTx, before addition of ^{125}I-a-BuTx, and the counts subtracted. Results were expressed as pmoles of toxin binding sites/ml of extract.

Standard anti-acetycholine receptor antibody assay

One hundred and fifty-three patients (103 F, 50 M) were examined by one of us (JND) and diagnosed as clinically definite myasthenia gravis on the basis of typical clinical features and responses to anti-choline esterase medication. These patients included 26 who clinically had only ocular muscle involvement, and 15 who had a thymoma. None of these patients had been treated by thymectomy, immunosuppressive drugs or plasma exchange before the serum sample was obtained. Sera were stored at −20° until required.

Myasthenia gravis sera were incubated at 1, 2·5 and 10 μl with 10–20 fmoles of ^{125}I-a-BuTx binding sites (labelled with ^{125}I-a-BuTx to about 80% saturation) in a volume of 75 μl. For the two smaller volumes, sera were diluted 1 in 20 in PTX buffer and 20 and 50 μl added to the 25 μl labelled muscle extract. The 10 μl assay was set up by adding 10 μl directly to the labelled extract. The volumes were made up with PTX buffer. After two to four hours at room temperature anti-human IgG (Seward Laboratories Ltd; 15–30 μl diluted 1:3 in PTX) was added to the 1 and 2·5 μl assays and the tubes left overnight at 4°C. The precipitates were pelleted, washed and counted as above. To the 10 μl asay an equal volume of 16% polyethylene glycol (PEG) was added and after overnight incubation and centrifugation the pellets were washed twice very briefly with 1 ml of PTX buffer (see ref 6) and counted.

Control incubations were performed with sera from normal healthy persons or neurological controls. The mean results from three control incubations were subtracted from each of the test assays. One high titre serum and one low titre (0·5–1·0 nmoles/l) serum were included as positive controls. Results were expressed as nmoles of ^{125}I-a-BuTx, binding sites precipitated/litre of serum.

The results were given as positive only if all three tests (1, 2·5 and 10 μl serum) were positive and consistent with each other. If there were inconsistencies, or the values obtained were less than 1·0 nmoles/l, the serum was retested. Titres greater than 0·5 nmoles/l were given as positive and based on the value obtained with 1 μl of serum, or with 2·5 μl in the case of relatively low titres (for example <2·0 nmoles/l). 1 μl of serum often precipitated most or all of the available AChR in which case the titre was given as a minimum value.

The mean cpm of three control sera was subtracted from these values, which in some test sera gave negative results. Sera from other normal controls or non-myasthenic neurological patients gave values between −0·3 and 0·3 nmoles/l (based on 2·5 μl serum). However, on repeat testing no control serum consistently gave values over 0·2 nmoles/l (see also ref 7). Thus sera whose values repeatedly fell in the range 0·2 to 0·5 nmoles/l were designated as equivocal.

Modified Assay

Some sera, particularly those with low anti-AChR titres, have recently been shown to react preferentially with AChR extracted from normal leg muscle or extraocular muscle[8,9] rather than with denervated leg AChR. In order to improve detection of such antibodies in those sera which were negative with the standard assay as described above, we used 50 μl of normal postmortem AChR and 5–10 μl of highly denervated AChR for each assay. In addition both membrane preparations were given an extra wash in

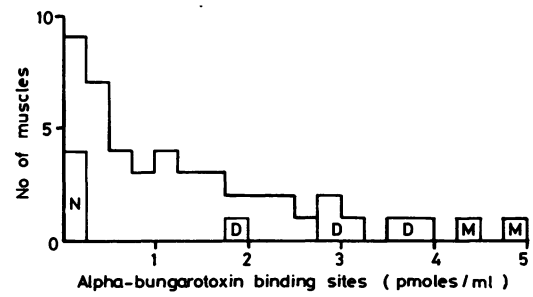

Fig 1 *Distribution of AChR concentrations in extracts from amputated muscles, including those with clinical diabetic neuropathy (D), compared with that for normal postmortem muscle (N) and postmortem muscle from patients with motor neurone disease (M).*

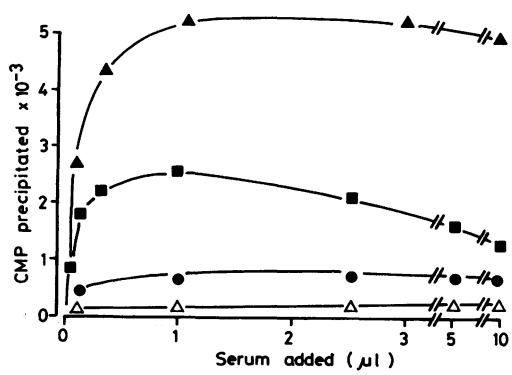

Fig 2 *Examples of titrations of three myasthenia gravis sera (filled symbols) and one control serum (open symbols) against a constant amount of ^{125}I-a-BuTx-AChR (5400 cpm). Some sera (for example ■ and to a lesser extent ▲) do not appear to precipitate all the available AChR and at antibody excess displace ^{125}I-a-BuTx from the AChR so that the cpm precipitated decrease. Another (●) appears to react with a subpopulation of the AChR preparation, in this case the normal AChR which represented less than 20% of the total in this partially denervated muscle extract.*

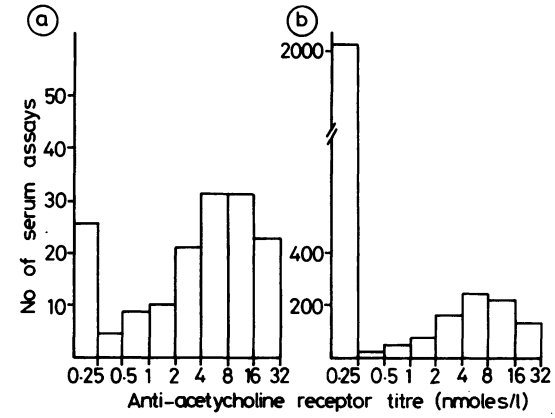

Fig 3 *Distribution of results of assays from 153 validated myasthenia gravis cases (3a) and of 2967 diagnostic assays (3b). Note the $\log_2$ scale of the abscissa.*

buffer before extraction to reduce the protein and IgG content; a longer incubation (2 hours at room temperature and overnight at 4°C) was used; and after addition of anti-IgG and formation of a visible immune precipitate 200 μl—1 ml of PTX buffer was added to each tube to reduce non-specific precipitation.

Results

The anti-AChR assay

The majority of muscles used in the assays (n = 47) were from ischaemic limbs and the range of acetycholine receptor concentrations was wide (fig 1). The denervation present in muscle from patients with diabetic neuropathy and/or with ischaemia increased the yield of AChR, but amputated muscles from patients without clinical evidence of peripheral neuropathy also frequently contained a higher concentration of AChR than was found in the normal post-mortem muscles. Typically, the atrophied, discoloured muscles produced the highest concentration of AChR, whereas healthy looking, bulky muscles gave poor yields. The time elapsed (up to 8 hours) between amputation or death and removal of the muscle did not appear to influence the yield of AChR.

In the standard assay, three different serum concentrations were used. Anti-IgG was used to precipitate antibody AChR complexes because it gave lower non-specific precipitation than anti-Ig. We found no evidence of non-IgG antibodies which would have been detected by the 10 μl, 8% PEG precipitation.

The precipitation of CPM at 10 and 2·5 μl was in some sera substantially less than that at lower serum concentrations (fig 2) suggesting the presence of "toxin displacing antibodies".[10] These would have led to a false negative result if only high serum/AChR ratios had been used. Figure 2 also shows an example of a serum which reacted only with the normal AChR in the partially denervated muscle extract.

A potential deficiency of the assay is that antibodies directed against the a-BuTx binding site on the acetylcholine receptor are not detected because their binding site is occupied by the toxin. However, as we have shown,[11 12] if the acetylcholine receptor is only partially saturated (ideally 75–80%) with a-BuTx, the presence of a-BuTx site antibodies can be detected, and the lower concentration of ^{125}I-a-BuTx required reduced non-specific precipitation of radioactivity.

Anti-AChR in validated myasthenia gravis cases.

Figure 3a shows the distribution of serum titres using the standard anti-AChR assay in the 153 validated cases of myasthenia gravis. The results were bimodal with 26 sera (17%) clearly within the control range (see *Methods*). The highest values obtained (32 nmoles/l) were limited by the amount of serum used (1 μl) and the amount of AChR (20–50 fmoles); titres in these cases are expressed as a minimum value (for example >32 nmoles/l; much higher dilutions are required to achieve an accurate value in sera with high titres). Titres greater than

Table 1 *Distribution of results in 153 validated myasthenia gravis cases and 2967 diagnostic assays*

	Total	*Negative (< 0·2 nmoles/l)*	*Equivocal (0·2–0·5 nmoles/l)*	*Positive (> 0·5 nmoles/l)*
Myasthenia gravis cases (%)	153	26 (17%)	4 (3%)	123 (80%)
Diagnostic	2967	2037	22	872
Predicted*	1084	184	28	872

*Calculated by multiplying the observed number of validated myasthenia gravis cases in each group by the ratio of the number of diagnostic assays (872) to the number of +ve assays in the validated myasthenia gravis cases (123) (= 7·09).

0·5 nmoles/l were given as positive. The 4 (3%) sera whose titre lay between 0·20 nmoles/l and 0·5 nmoles/l on repeated testing were given as equivocal (see *Methods*), and those <0·20 nmoles/l as "negative".

Anti-AChR as a diagnostic test

During the years 1980–1983, 2967 sera were sent to us for anti-AChR assay. The results are presented in fig 3b. These include the 153 sera from validated myasthenia gravis cases described above. Eight hundred and seventy-two sera were positive, 22 were given as equivocal and 2073 were negative. Using the distribution of anti-AChR values in the validated cases, we calculated the expected incidence of myasthenia gravis in the sera sent for diagnostic assays (see table 1). This indicated that about 1084 samples (36%) came from "true" myasthenia gravis cases. The number of equivocal titres (22) accords well with the calculated value of 28 and suggests that most sera with equivocal titres came from patients with myasthenia gravis. In addition, about 184 of the sera which were negative would also have come from myasthenia gravis patients.

Further study of negative sera

The sera from 26 validated cases that had been negative using the standard assay were subsequently reassayed using a modified protocol (see methods) designed to detect anti-AChR of restricted specificity (that is reacting only with normal AChR) and of low affinity. Low positive titres (0·26–0·67 nmoles/l) were found in eight of the 26 MG sera which were previously negative, reducing the overall proportion of sera with undetectable anti-AChR to 12%.

Two further cases with ocular myasthenia gravis, in whom the first serum sample was negative on standard testing, developed low positive anti-AChR values by the modified assay when followed serially over a period of months (fig 4a). These cases were interesting because both had had an episode of ocular symptoms 11–15 years previously which had remitted spontaneously.

Five other anti-AChR negative cases were followed serially for 2–11 months. Anti-AChR was detected in only one who transiently showed an equivocal serum titre.

In general, patients whose sera were negative even with the modified protocol (n = 18) tended to have disease of short duration or symptoms restricted to ocular muscles. Only four anti-AChR negative patients had generalised disease of duration greater than one year.

Three patients with generalised myasthenia gravis (not included in the 153 validated cases), whose sera had been sent for diagnostic assay, were found to have negative titres on initial testing but moderately high levels subsequently. Their results are plotted in fig 4b. One of them, who had a steep rise in anti-AChR antibody over a period of one month, showed a similarly steep fall following thymectomy.

Raised anti-AChR without clinical evidence of myasthenia gravis

(a) Family studies Three of our female myasthenia gravis patients had a monozygotic twin; in each case,

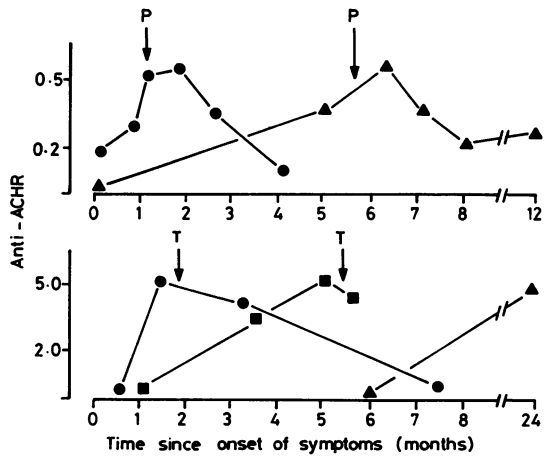

Fig 4 *Appearance of anti-AChR in sera from five patients all of which were negative on initial standard testing. (a) Two patients with previous histories of a single period of ocular weakness many years previously. Their results are plotted against the duration of the present symptoms. They were both started on prednisolone (P). (b) Three patients with generalised disease whose anti-AChR values rose substantially over a period of 1–6 months. Two patients underwent thymectomy (T); the other was a 2-year-old boy.*

Table 2 *Family studies*

	Proband		*Relatives*		
	Sex	*Anti-AChR (nmoles/l)*	*Examined*	*Clinical myasthenia gravis*	*Anti-AChR > 0·2 nmoles/l*
1	F	262	Mzt	–	24·5
2	F	470	Mzt	–	
3	F	22·8	Mzt	–	
4	F	93·7	S	+	18·0
5	F	46·9	F	+	8·3
6	M	16·0	B, M, F, S	+	3·0
7	F	1030	B	–	
8	F	229	M, F, B	–	
9	F	216	S, B	–	
10	F	143	S	–	
11	F	103	M, F	–	
12	F	93·6	M, F, B	–	
13	F	71·7	M, F	–	
14	F	62·0	S, B	–	
15	F	19·0	D	–	
16	M	19·0	F	–	
17	F	13·3	D	–	
18	F	7·4	S	–	
19	M	6·2	B, B	–	
20	F	4·4	F, M	–	0·45
21	F	1·8	M	–	
22	F	1·5	M, F	–	
23	F	< 2·0	M, F, B	–	

Mzt = Monozygotic twin; B = Brother; S = Sister; M = Mother; F = Father; D = Daughter. Underlining indicates raised anti-AChR titre. Three individuals (4, 5 and 6B) also had clinical myasthenia gravis.

the twin was unaffected, but in one of them anti-AChR was detected at a titre that was about 10% of that in the symptomatic twin (table 2). Three other myasthenia gravis patients had one other family member affected in whom serum anti-AChR was also detected; in one of these families, sera from other family members (mother, father, sister) were negative. Sera from 30 first degree relatives of a further 17 randomly selected myasthenia gravis cases were also analysed. An equivocal titre was found in one, the asymptomatic mother of a 16-year old girl who had a 10 year history of ocular myasthenia gravis. All other family sera were negative.

(b) Thymoma We have found titres of 0·4 and 0·6 nmoles/l in two patients with thymoma who had no clinical evidence of myasthenia gravis.

Discussion

The anti-AChR assay we have used is a modification of the method first reported in detail by Almon and Appel 1975,[13] Lindstrom 1976[3] and Lindstrom *et al.*[14] It differs in the relatively high concentration of serum used (up to 10 μl in 75–100 μl compared with 5 μl in 1ml), although not in the overall concentration of AChR ($1–2 \times 10^{-10}$M). Like Lindstrom[3] we use crude human AChR extract rather than partially purified AChR (see for example ref 15). We use a range of serum concentrations to avoid false negative results caused by displacement of toxin by antibodies,[10 16] and only partially label the AChR with a-BuTx in order to detect anti-a-BuTx site antibodies.[11 12] Our results in 153 validated myasthenia gravis cases (12% negative), which included 26 with purely ocular symptoms, are similar to those reported by others[3 7 14 15 17–19] using human antigen. The percentage of positive values in clinically definite cases of myasthenia gravis varies between 80 and 90% when human AChR is used as antigen but drops substantially if rat AChR is used.[20 21] On the other hand baboon AChR appears antigenically similar to human[22] and fetal calf AChR has also been used successfully.[23]

A proportion of patients (about 3%) with clinically definite myasthenia gravis have equivocal titres in the standard anti-AChR assay. The titres, although very low (0·20–0·5 nmoles/l), are not found in normal healthy controls and we conclude that an anti-AChR titre in this range indicates that the diagnosis of myasthenia gravis is likely.

We were concerned at the proportion of negative anti-AChR titres (< 0·2 nmoles/l) in patients with clinically definite myasthenia gravis, several of whom had responded to plasma exchange (unpublished observation) suggesting the presence of a humoral immune factor, and also to immunosuppressive drug treatment. Since about half of these patients had purely ocular symptoms, and there was evidence that this subgroup have antibodies which react better with normal AChR,[9] we re-assayed the

sera against a mixture of normal and denervated receptor using conditions designed to optimise the reaction and reduce background precipitation. A further eight patients were shown to have low anti-AChR and these modifications have now been included in our standard assay. Interestingly Oda and Ito[24] also improved the sensitivity of their assay by concentrating normal muscle AChR.

Some patients with myasthenia gravis of recent onset may not show a raised serum anti-AChR titre because the available anti-AChR is bound to the endplate receptors. The high affinity of anti-AChR[8] makes this likely, and indeed in the passive transfer model, human anti-AChR antibody can be bound to mouse endplate receptors in the absence of detectable serum levels in the patient (or in the mouse) (Mossman, Vincent and Newsom-Davis, unpublished observations). Such a mechanism might account for the negative anti-AChR titres in eight of our cases, whose symptoms were of recent onset (< 1 year).

The possibilities therefore exist that in some cases either serum anti-AChR never becomes high enough to detect *in vitro*, or that the antibodies present react with determinants which are not present on detergent-solubilised AChR. A further interesting possibility is that some patients have antibodies directed against a different component of the neuromuscular junction. Preliminary results of passive transfer of Ig from anti-AChR negative myasthenia gravis patients suggest that all three mechanisms may operate in different patients (Mossman *et al*, unpublished observations).

A serum titre of anti-AChR > 0·20 nmoles/l does not necessarily imply current clinical evidence of myasthenia gravis, and indeed raised titres are commonly found in known myasthenia gravis patients in remission.[7] Low positive results have also been reported in a proportion of subjects without clinical evidence of myasthenia gravis: in relatives of myasthenia gravis patients,[25] thymoma cases,[26] tardive dyskinesia[27] or elderly and Down's syndrome Japanese individuals.[28] In addition, we found two low positive titres in 56 patients undergoing penicillamine treatment for rheumatoid arthritis,[29] and we have also detected anti-AChR in three of 40 elderly Caucasian patients selected for high anti-thyroid autoantibodies, and who were thus predisposed to autoimmune disease.[30] However, no anti-AChR was detected in 53 elderly Caucasian subjects with miscellaneous disorders or in 30 individuals with Down's syndrome.[30] Moreover, in the small family study described here, anti-AChR (at equivocal titres) was found in only one of 30 unselected first degree relatives of myasthenia gravis patients. This is far lower than the incidence reported by Pirskanen *et al* in a similar number of Scandinavian subjects[25] and we cannot account for this difference. The only high value we found was in the monozygote twin sister of a patient whose own value was ten times higher. Two other identical twins of myasthenia gravis patients were negative. Our results confirm the presence of very low titres in two cases of thymoma without evidence of myasthenia gravis, but in none of eight polymyositis cases (unpublished results).

Our experience suggests that determination of anti-AChR is now the single most useful clinical test for myasthenia gravis. Using our current modified assay it is positive in 88% of patients with validated myasthenia gravis, but only in about 60% of patients with purely ocular symptoms. It is negative in all cases of congenital myasthenia in which immunological factors are not implicated.[31] The assay should be repeated after about six months in patients with suspected myasthenia gravis in whom it is negative. Some of these cases, however, may have antibodies which cannot be detected using the assay described here.

Technical false positives in this assay appear to be very infrequent. Biological false positives (that is patients without clinical evidence of myasthenia gravis) are very rare but may occur in first degree relatives of myasthenia gravis patients, in elderly patients with a pre-disposition to autoimmunity, in non-myasthenic thymoma patients and in those undergoing pencillamine treatment. In each of these groups, there is, of course, the possibility of later development of myasthenic symptoms.

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IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS
EASTERN DIVISION

ATHENA DIAGNOSTICS, INC. AND ISIS INNOVATION LIMITED, Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	CIVIL ACTION NO. 1:15-cv-40075-IT

PLAINTIFFS' MEMORANDUM OF LAW
IN OPPOSITION TO DEFENDANTS' RULE 12(B)(6) MOTION
TO DISMISS THE SECOND AMENDED COMPLAINT

I. INTRODUCTION

The inventors of U.S. Patent No. 7,267,820 ("the '820 patent") were the first to make ^{125}I labeled MuSK (^{125}I-MuSK), a laboratory-created molecule comprising some or all of the human MuSK protein chemically bonded with ^{125}I, a radioactive isotope of iodine. The radioactive ^{125}I-MuSK appears nowhere in nature. Claims 7-9 of the '820 patent cover the steps of using man-made molecules like ^{125}I-MuSK and other labeled MuSK molecules, and detecting man-made complexes of those labeled MuSK molecules and anti-MuSK antibodies.

Despite the strength of these patent claims and the applicable law, Defendants Mayo Collaborative Services, LLC and Mayo Clinic (collectively "Defendants") abruptly stopped sending their MuSK tests to Athena and announced they were going to offer and use tests which clearly are covered by these claims. Now, after forcing this litigation, Defendants ask the Court to dismiss the case without any discovery. Defendants create confusion by characterizing the underlying issue as involving correlations between a naturally occurring bodily substance and the cause of a disease. Yet, the claims at issue are completely different than Defendants' self-serving and incorrect characterization. The claims here are directed to using man-made radioactive MuSK and detecting a man-made complex containing radioactive MuSK and anti-MuSK antibodies. The use and detection of man-made matter is not a law of nature. And, just two years ago, the Supreme Court expressly held that matter made in a laboratory, that does not appear in nature, is patentable, even if – as alleged by Defendants - it was made using well-known techniques. Numerous other reasons mandate that the pending motion be denied, including Defendants' reliance upon extrinsic hearsay and disputed facts from outside the pleadings that cannot be considered in the context of a Rule 12(b)(6) motion.

Defendants devote most of their argument to attacking claims 1–5 and 10–12 of the '820 patent. However, those claims will not be asserted in this case.[1] Had Defendants conducted a meaningful meet and confer prior to filing this motion, they would have known this and could have narrowed the issues before the Court to claims 7-9. Plaintiffs Athena Diagnostics, Inc. ("Athena") and Isis Innovation Limited (together, "Plaintiffs") will focus on claims 7–9, and to a lesser extent claim 6. Thus, Defendants have unnecessarily raised issues that are not before the Court.

II. STATEMENT OF FACTS IN OPPOSITION

Headquartered in Marlborough, Massachusetts, Athena is the exclusive licensee of the '820 patent, and offers commercial clinical assays or tests to assist with medical diagnoses of neurological disorders like myasthenia gravis ("MG"). (Dkt. 1 at ¶¶ 2, 12, 14, 15). For years, medical practitioners associated with Defendants requisitioned such tests from Athena. (Dkt. 1 at ¶ 16). In May of this year, however, Defendants purposefully availed themselves of Plaintiffs' intellectual property by offering an infringing product without a license (Dkt. 1 at ¶¶ 17-20).

A. The '820 patent discloses and claims novel approaches for detecting a man-made, radioactive chemical complex to solve a difficult known problem that had eluded the field for many years.

Muscles contract because of activity of nerve cells in the brain and spinal cord. Those nerve cells project to muscles and carry electrical signals that, at the nerve terminal, cause neurotransmitter molecules called acetylcholine to be released into the neuromuscular junction. Acetylcholine molecules bind to the numerous acetylcholine receptors ("AChR") on muscle cells; that binding event stimulates muscle cells to contract.

[1] *See infra* at Section III(C).

As Defendants and the '820 patent specification both acknowledge, AChR autoantibodies[2] ("anti-AChR antibodies") in patients had long been identified as a cause of MG because those antibodies interfered with acetylcholine receptor function. (Dkt. 26 at 6). Based on that initial discovery, a widely used (and patented) diagnostic test was later developed for detecting anti-AChR antibodies. ('820 patent at 1:34-36; Dkt. 26 at 6 (citing references (Dkt. 27-2 and 27-3)[3])). A study in 1985 identified a significant proportion of patients who exhibited MG symptoms but did not possess anti-AChR antibodies, called seronegative MG ("SNMG") patients. ('820 patent at 1:36-42; Dkt. 27-3 at 1250-51). Although researchers in the field had appreciated the failure of the widely-used MG diagnostic assay to detect anti-AChR antibodies in SNMG patients, no cause had been identified for more than a decade after the phenomenon was first characterized. ('820 patent at 1:40-42 (citing Ref. 3), 11:16-18 (Ref. 3); *see, e.g.*, McMahon Decl. Ex. A at S40 (suggesting several possible limitations of the MG diagnostic assay as explaining SNMG observations, but not suggesting anti-MuSK antibodies as the cause)).

Although muscle-specific tyrosine kinase ("MuSK") had been identified as a protein in muscle with certain identified properties ('820 patent at 1:62-67), a physiological connection to MG was not established until the '820 patent's inventors' hypothesis that SNMG patients had autoantibodies targeting MuSK ("anti-MuSK antibodies"). ('820 patent at 1:54-61, 2:25-3:3). Indeed, the patent is clear that until the inventors' contribution, MuSK had been studied only during development, and had no known function in the adult neuromuscular junction. ('820

[2] An autoantibody is an antibody that a person generates against one of her own proteins.

[3] As discussed below in more detail, such extra-pleading references are not properly considered in connection with this Rule 12 motion. To preserve their rights, however, Plaintiffs cite to those and other extra-pleading references only to rebut Defendants' improper factual allegations. In further preservation of their rights, Plaintiffs object to the admissibility of the references found at Dkt. 27-2 and 27-3 as hearsay to which no exception applies. Fed. R. Evid. 802.

patent at 3:16-21). Armed with that knowledge, the inventors created a novel, specific assay to detect anti-MuSK antibodies in SNMG patients which is covered by claims 7–9.

Defendants do not (and cannot) question the novelty of this invention, as nobody in the field had previously identified MuSK as playing any role in MG pathophysiology. ('820 patent at 1:54-61). This means that regardless of how "standard" or "known" techniques used in claimed methods might have been in the field, a conclusion that cannot be reached on the pleadings alone,[4] prior to the inventors' efforts, those techniques had never been applied to determine the possible role of anti-MuSK antibodies in MG.

B. The anti-MuSK antibody detection assay of representative Claim 9 involves the use of a man-made composition of matter—radioactive MuSK—to detect a man-made complex containing radioactive MuSK and anti-MuSK antibodies.

Claim 9 is representative of claims 7-9 at issue in this case. That claim incorporates the elements and limitations in claims 1, 7 and 8, and reads as follows when all elements and limitations are considered as a whole:

> A method for diagnosing neurotransmission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase, said method comprising contacting MuSK or an epitope or antigenic determinant thereof [labeled with] ^{125}I, with said bodily fluid, immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid and monitoring for ^{125}I on any of said antibody/MuSK complex or antibody/MuSK epitope or antigen determinant complex, wherein the presence of ^{125}I is indicative of said mammal is suffering from said neurotransmission or developmental disorder related to muscle specific tyrosine kinase (MuSK).

[4] Expert testimony is necessary to determine whether aspects of the claimed methods were in fact routine ***in their application***, given the uncertainty at the time of the invention associated with applying those known techniques in an uncharacterized system.

('820 patent at 12:31-35, 12:62-13:9). In the method of claim 9, MuSK is covalently attached (chemically bonded through shared electrons) to ^{125}I, which permits an anti-MuSK antibody/^{125}I-MuSK complex to be detected by monitoring radiation. ***Those antibody/MuSK complexes are created in the laboratory and result from the use of a non-naturally-occurring laboratory-created molecule, ^{125}I-MuSK, and therefore, the antibody/MuSK complexes formed and detected by claim 9 are not found in nature.***

Indeed, the '820 patent discloses the specific laboratory interventions the inventors undertook to make ^{125}I-MuSK useful for antibody/MuSK complex formation and detection. The inventors created different deletion fragments of the DNA sequence encoding the MuSK protein and cloned those DNA constructs into expression vectors containing "an artificial signal sequence followed by six histidines and a 10aa epitope tag." ('820 patent at 7:55-8:2).[5] A monkey kidney host cell line therefore produced an artificial, non-naturally-occurring MuSK protein that could be isolated from the cell culture medium and then covalently labeled with ^{125}I in a subsequent step. ('820 patent at 8:34-46, 10:48-67).

The purposeful steps taken to create ^{125}I-MuSK in the laboratory differ considerably from methods used in the earlier assay for detecting anti-AChR antibodies. The anti-AChR antibody assay did not require making a ^{125}I-labeled AChR. Instead, AChR was labeled using α-bungarotoxin ("α-BuTx"), a protein from snake venom that binds specifically to AChR. (Dkt. 27-3 at 1246). That earlier test used α-BuTx labeled with ^{125}I to detect anti-AChR antibody complexes with ^{125}I-α-BuTx/AChR complexes, a step that improved sensitivity in the assay and aided MG diagnosis. *See* Dkt. 27-2 at 1058. Here, the inventors did something different and, in

[5] An expression vector is a piece of DNA that, when inserted into a host cell, will express mRNA that the host cell converts into protein. The artificial signal sequence, six histidines, and 10aa epitope tag are methods for assisting with the production and recovery of proteins from host cells.

so doing, created a new molecule, made in the laboratory for the detection of an antibody/MuSK complex. Contrary to any suggestion by Defendants, the methods of detecting anti-AChR antibodies does not help Mayo demonstrate that creating the man-made molecule was routine.

III. ARGUMENT

A. Legal Standard

When considering a motion to dismiss pursuant to Rule 12(b)(6), a court must "take all factual allegations as true and draw all reasonable inferences in favor of the plaintiff." *Rodriguez-Ortiz v. Margo Caribe, Inc.*, 490 F.3d 92, 96 (1st Cir. 2007) (emphasis omitted). The court must "neither weigh the evidence nor rule[ ] on the merits because the issue is not whether the plaintiffs will ultimately prevail, but whether they are entitled to offer evidence to support their claims." *Day v. Fallon Cmty. Health Plan, Inc.*, 917 F. Supp. 72, 75 (D. Mass. 1996). Thus, a motion to dismiss should be denied if plaintiffs have shown "a plausible entitlement to relief." *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 559 (2007).

Here, drawing all reasonable inferences in Plaintiffs' favor, and taking the factual allegations as true, Plaintiffs have unquestionably demonstrated a prima facie case that they are entitled to relief. The Second Amended Complaint amply demonstrates that Defendants were well-aware of the '820 patent, ordered tests from Athena for years that implemented the technology of the '820 patent, and then developed their own test that employs precisely the same methods as those covered by the asserted claims to avoid paying Athena. These facts state a plausible claim for relief and entitle Plaintiffs to offer evidence in support of their claims.

B. Claims 7-9 of the '820 patent are not invalid under Section 101.

1. A method claim containing either known techniques or non-conventional steps that create matter not found in nature is patent-eligible under Section 101.

The Patent Act provides that "[w]hoever invents or discovers any new and useful process

. . . or any new and useful improvement thereof, may obtain a patent therefor." 35 U.S.C. § 101. "'In choosing such expansive terms modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope.'" *Bilski v. Kappos*, 561 U.S. 593, 601 (2010) (*quoting Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). The Supreme Court has interpreted Section 101 to exclude only "[l]aws of nature, natural phenomena, and abstract ideas" from patent eligibility. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l.*, 134 S. Ct. 2347, 2354 (2014). The concern underlying these exceptions is one of preemption, and in particular that a monopoly on one of the "building blocks of ingenuity" may "impede innovation more than it would tend to promote it." *Id.* (quoting *Mayo Collaborative Servs., Inc. v. Prometheus Labs, Inc.*, 132 S. Ct. 1289, 1301 (2012)).

However, "too broad an interpretation of this exclusionary principle could eviscerate patent law." *Prometheus*, 132 S. Ct. at 1293. This is because all inventions "at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." *Id.* Therefore, courts must distinguish between patents that claim the "building blocks" of human ingenuity—and "'would risk disproportionately tying up the use of the underlying'" natural laws, *Alice*, 134 S. Ct. at 2354-55 (quoting *Prometheus*, 132 S. Ct. at 1294, 1303)—and patents that "integrate the building blocks into something more, thereby 'transform[ing]' them into a patent-eligible invention," such that they pose no comparable risk of preemption. *Alice.* at 2354-55.

The United States Supreme Court addressed whether man-made compositions of matter are patentable under Section 101 in *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) ("*AMP*"). That case involved patentability of isolated DNA and cDNA. DNA occurs naturally and contains "exons," a section of DNA that codes for proteins, as well as "introns" that do not. cDNA, also known as "complimentary DNA" or "synthetic DNA," is

made by humans in a laboratory and contains only the exons, omitting the intervening introns. *Id.* at 2119. The Court held that DNA appears in nature and is not patentable subject matter. However, it also held that cDNA *is* patentable subject matter under Section 101 because "the lab technician unquestionably creates something new when cDNA is made." *Id.* And, the Court expressly recognized that cDNA was created "through processes similarly ***well known*** in the field of genetics." *Id.* at 1221 (emphasis added). Clearly, man-made molecules are patentable subject matter, *even if created through well-known techniques. Id.*

The Federal Circuit opinion, from which the *AMP* Supreme Court appeal of composition claims was taken, addressed Section 101's patentability of a method claim that required growing a transformed eukaryotic host cell containing an altered BRCA1 gene. *Ass'n for Molecular Pathology v. United States PTO,* 689 F.3d 1303, 1310 (Fed. Cir. 2012*), aff'd in part, rev'd in part on other grounds,*[6]133 S. Ct. 2107 (2013). The Federal Circuit found the claim patentable because the host cells were not naturally occurring. *Id.* at 1336. The Federal Circuit further determined that applying known types of procedures to patent-eligible compositions constitutes more than just "conventional steps." *Id.* Specifically, it held that, "[o]nce one has determined that a claimed composition of matter is a patent-eligible subject matter, *applying various known types of procedures to it is not merely applying conventional steps to a law of nature.*" *Id.* (emphasis added). It further held that "*the transformed, man-made nature of the underlying subject matter in [the asserted method claim] makes the claim patent eligible.*" *Id.* Thus, the recited *use* of a man-made, patent eligible composition is sufficient to "differentiate the claimed method from the natural laws encompassed by the claims." *Id.*

[6] The ruling on the method claim was not appealed to the Supreme Court and remains undisturbed by the subsequent *AMP* decision.

Much of the jurisprudence on Section 101 patentability draws upon *Diamond v. Diehr*, 450 U.S. 175, 188–89 (1981). *Diehr* involved method claims for operating a rubber press, including constantly determining the temperature, making repetitive calculations using a mathematical equation that was merely an abstract idea, and using a man-made "thermocouple" to record constant temperature measurement. *See Alice,* 134 S. Ct. at 2358 (explaining *Diehr).* Thus, a method claim reciting a non-patentable abstract idea was patent eligible when employing a new, man-made product, even though some steps recited known techniques. All of the foregoing authority makes clear that methods that use new, man-made products or composition of matter are patentable under Section 101.

AMP, Diehr and their progeny establish that Defendants' motion lacks merit. ^{125}I-MuSK is man-made, does not appear in nature and, like the cDNA in *AMP,* is patent eligible. And, "[o]nce one has determined that a claimed composition of matter is a patent-eligible subject matter, *applying various known types of procedures to it is not merely applying conventional steps to a law of nature.*" *AMP,* 689 F.3d at 1336 (emphasis added). Claims 7–9 clearly are patent eligible.

None of the cases cited by Defendants involve claims that recite the use of a man-made, patent eligible molecule, or monitoring a man-made complex. Defendants rely upon *In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litig.,* 774 F.3d 755, 764 (Fed. Cir. 2014), but that case addressed method claims that merely required comparing *naturally-*occurring genetic sequences through common techniques. They did not require the creation and detection of man-made molecules and complexes. Defendants also cite *Ariosa Diagnostics, Inc. v. Sequenom, Inc.,* 788 F.3d 1371, 1378 (Fed. Cir. 2015), but in that case, the Federal Circuit specifically noted that the claimed method at issue "begins and ends with naturally occurring

phenomena," and further noted that there was no allegation that the inventors "created or altered any of the genetic information." *Id.* at 1376. Nor do the other cases cited by Defendants involve claims that recite the creation and detection of man-made DNA or molecules. *See Genetic Techs. Ltd. v. Bristol-Myers Squibb Co.*, 72 F. Supp. 3d 521 (D. Del. 2014) (claims directed to detecting genetic variations of naturally-occurring genes); *Genetic Techs. Ltd. v. Lab. Corp. of America Holdings*, No. 12-1736, 2014 U.S. Dist. LEXIS 122780 (D. Del. Sept. 3, 2014) (claims directed to predicting a human's physical performance based on detecting genetic variations of naturally-occurring genes); *Genetic Veterinary Sci., Inc. v. Canine EIC Genetics, LLC,* 14-cv-1598 (JRT/JJK), 2015 U.S. Dist. LEXIS 41156 at *24 (D. Minn. Mar. 31, 2015)("GVS") (claims directed to "identifying the naturally occurring source" of exercise induced collapse in dogs by detecting naturally occurring genetic mutations). Indeed, *GVS* expressly recognized that, "unlike the cDNA patent in [*AMP*], the patent claims at issue here are not directed at entirely new, non-technical material." *Id.* at 26.

Defendants' reliance on *Prometheus* is also misplaced. As noted by that Court, "[b]eyond picking out the relevant audience, namely those who administer doses of thiopurine drugs, the claim at issue simply tells doctors to (1) measure (somehow) the level of the relevant metabolite, (2) use particular (unpatentable) laws of nature (which the claims set forth) to calculate the current level of toxicity/inefficacy limits, and (3) reconsider the drug dosage in light of the law of nature." *Prometheus*, 132 S. Ct. at 1299 (parenthetical in original). Unlike this case, the claims were not directed to creation and detection of man-made matter in a laboratory. None of Defendants' authority is applicable to this case.

2. Radioactive MuSK and radioactive MuSK complexes are not found in nature and are unlike anything found in nature.

The method of representative claim 9 requires the purposeful creation of a non-naturally-occurring radioactive molecule, ^{125}I-MuSK. That man-made, radioactive molecule is then used to create and detect a complex of ^{125}I-MuSK and anti-MuSK antibodies. Those facts are not in dispute, as Defendants concede that those claims require "scientists ***modify the MuSK***" and acknowledge they involve "***creating a complex***." (Dkt. 26 at 5, 20 (emphasis added)). Indeed, Defendants have not, and cannot, argue that either the radioactive ^{125}I- MuSK molecule or the anti-MuSK antibody/^{125}I-MuSK complex, or methods of using them, are laws of nature, natural phenomena or abstract ideas.

Claim 8 is broader than claim 9, covering any radioactive label for MuSK and the anti-MuSK antibody complex, versus the ^{125}I label required by claim 9. Claim 7 is similar, except the MuSK molecule and anti-MuSK antibody complex need not be radioactive, they can be non-radioactive as well, but still must be labeled in a way that enables their detection. Those non-radioactive labels, like the radioactive ones, are present because of a purposeful laboratory method. They are man-made in a laboratory, and are unlike anything found in nature. Therefore, like claim 9, the other claimed molecules or complexes are not laws of nature, natural phenomena or abstract ideas.

3. Because patent-eligible subject matter includes methods that create and detect man-made molecules and complexes that do not appear in nature, and because claims 7-9 perform steps that create and detect man-made molecules and complexes that do not appear in nature, those claims comprise patentable subject matter.

As established previously, steps that create a man-made molecule, including ^{125}I-MuSK, constitute patent eligible subject matter. *See* Section III(B)(1). Claims 7–9 require creation of those man-made molecules. Defendants admit as much. (Dkt. at 5, 20). In fact, the claims at

issue go well beyond creating the man-made labels such as radioactive ^{125}I-MuSK—they also require detecting a man-made complex containing radioactive MuSK and anti-MuSK antibodies. Just like the cDNA that is patent eligible because it was made by a lab technician and is not identical to any natural DNA, the labeled MuSK, including ^{125}I-MuSK, and the subsequently detected complexes, are made by a laboratory technician and are patentable subject matter. And, just like the patentable methods employing known types of procedures to patent eligible compositions, the methods that use radioactive MuSK and detect radioactive MuSK/anti-MuSK antibody complexes are patentable subject matter.

4. Defendants make numerous misstatements regarding the patent and rely upon flawed legal analysis and extrinsic hearsay that cannot be considered in this Rule 12(b)(6) motion.

a. Defendants fail to consider the claims as a whole.

Defendants invite error because they improperly dissect claims 7-9 based upon the component independent and dependent claims. "A claimed invention must be considered as a whole." *Kenexa Brassring, Inc. v. Hireability.com, LLC*, 12-cv-10943, 2015 U.S. Dist LEXIS 56156, at *9 (D. Mass. Apr. 28, 2015) (citing *Diehr*, 450 U.S. at 188). Moreover, "a new combination of steps may be patentable even though all of the constituents of the combination were well known and in common use before the combination was made." *Id.* at *9-10. After *Diehr,* in *Prometheus,* the Supreme Court again held that process claims may be eligible under Section 101 even if all the constituent steps were "well known and in common use." 132 S. Ct. at 1298. The Court required the claims to be considered "in context," as an ordered combination. *Id.* And on a third occasion, the Supreme Court held that the Section 101 analysis must consider the claim as a whole, evaluating the significance of additional steps not in isolation, but in the ordered combination recited by the claim. *Alice,* 132 S. Ct. at 2355 n.3. Despite this clear precedent, Defendants separately argue that Claim 1 is directed to a law of nature and is patent-

ineligible, and separately argue that the subject matter contained in dependent claims was well known and routine. Their methodology is flawed because they do not consider the claims as a whole.

In examining each step of the asserted claims individually, rather than as a whole, Defendants ignore the transformative nature of the specific tests called for in claims 7-9. Claim 9, for example, calls for the transformation of MuSK by the purposeful laboratory creation of a specific radiolabeled molecule. Claim 9 further targets "any antibody/MuSK complex," thereby calling for the use of a specific, man-made molecular complex that is neither a product of nature nor a natural law. Notably, the *final* step of this method requires monitoring the man-made complex for the man-made radioactive MuSK. The fact that the asserted claims affect a physical transformation as part of the process further supports the claims' patent eligibility. *See, e.g., Exergen Corp. v. Brooklands Inc.*, 2015 U.S. Dist. LEXIS 114699, at *16 (D. Mass. Aug. 28, 2015) (citing *Diehr* in explaining that processes that affect a physical transformation are more likely to be patent eligible).

b. Defendants' *Alice* step-one analysis is flawed because it incorrectly interprets claims 7-9 as being directed to a correlation of naturally occurring matter to a disease, when the claims are actually directed to detecting the presence of a man-made radioactive complex.

In order to establish that Plaintiffs' method claims for monitoring a man-made complex for the presence of a man-made, radioactive ^{125}I-MuSK fails under Section 101, Defendants must satisfy both prongs of a two-step analysis set forth by the Supreme Court in *Alice*. The first step requires a Court to determine whether the claims at issue are directed to one of those patent-ineligible concepts identified in 35 U.S.C. § 101 and, if so, to decide, in a second step whether the claims include "an element or combination of elements that is sufficient to ensure that the

patent in practice amounts to significantly more than a patent upon the ineligible concept itself." *Alice*, 134 S. Ct. at 2355 (quoting *Prometheus*, 132 S. Ct. at 1294).

In an attempt to satisfy step-one, Defendants erroneously argue that the claims cover the "general concept of detecting the law of nature." (*See* Dkt. 26 at 15). Defendants misread the claims. In particular, representative claim 9, when read as a whole to include all claims incorporated therein, requires at least creating a man-made radioactive molecule, ^{125}I-MuSK, and using that molecule in the purposeful step of "monitoring for ^{125}I on any of said antibody/MuSK complex." The claims are simply not drawn to detecting a correlation of naturally occurring matter to a disease.

c. Defendants' *Alice* step two analysis is fatally flawed because it improperly relies upon extrinsic hearsay and disputed allegations that the use of a man-made radioactive MuSK and detection of a man-made radioactive MuSK/anti-MuSK antibody complex were well known and routine.

The failure to satisfy *Alice* step-one confirms the patent eligibility of claims 7-9. But even if Defendants were able to satisfy step-one, their *Alice* step-two analysis is also fatally flawed.

Relying on two publications cited in the patent, Defendants argue that creation of a man-made, radioactive MuSK, which does not appear in nature, and the subsequent monitoring of the man-made MuSK/antigen complex, were well known and routine. (Dkt. 26 at 6, 19; *see id.* at 16, 17) (citing Dkt. 27-2 and 27-3)). Their argument should be rejected for several reasons.

First, as a matter of procedural law, Defendants' argument is improper at this time and should be disregarded. The law of this circuit precludes consideration of extrinsic evidence at this stage. "Ordinarily . . . any consideration of documents not attached to the complaint, or not expressly incorporated therein, is forbidden" when deciding a motion to dismiss pursuant to Rule

12(b)(6).[7] *Orbusneich Med. Co., Ltd. v. Boston Scientific Corp.*, 694 F. Supp. 2d 106, 110 (D. Mass. 2010) (quoting *Watterson v. Page*, 987 F.2d 1, 3 (1st Cir. 1993)). In *Orbusneich*, the court excluded from consideration at the Rule 12(b)(6) stage, for example, patent applications and other documents submitted by the moving party that were not incorporated by reference in the complaint by the non-moving party. 694 F. Supp. 2d at 112. While there are certain "narrow exceptions" to that rule, none apply here. *Id.* at 111 (noting narrow exceptions such as official public records, etc.); *Foley v. Wells Fargo Bank, N.A.*, 772 F.3d 63, 72 (1st Cir. 2014) (explaining that courts "usually consider only the complaint, documents attached to it, and documents expressly incorporated into it"). Defendants cannot rely on extraneous publications to support their factual contentions regarding the routineness of claimed techniques.

Second, Defendants' reliance on extrinsic publications and related arguments is also improper because they require consideration of "novelty," – a factual inquiry under Section 102 that is not properly part of a Section 101 analysis. The publications relied on by Defendants describe prior art processes to detect anti-AChR antibodies using a man-made radioactive α-BuTX/AChR complex, which is completely different than the man-made radioactive ^{125}I-MuSK of representative claim 9. Nevertheless, despite these differences, Defendants dig deep into those extrinsic publications and ask the Court to draw unsupported conclusions about the "only difference" between the methods described in those publications and the asserted claims. (Dkt. 26 at 6). By asking the Court to compare the publications cited in the patent with the asserted

[7] "It is well established that at the motion to dismiss stage, any consideration of documents not attached to the complaint, or not expressly incorporated therein, is forbidden, unless the proceeding is properly converted into one for summary judgment under Rule 56." *Rocket Learning, Inc. v. Riviera-Sanchez*, 715 F.3d 1, 9 n5 (1st Cir. 2013). While a court is permitted to convert a Rule 12(b) motion into a Rule 56 motion, it must give the non-moving party a reasonable opportunity to present materials to counter the movant's evidence. Fed. R. Civ. P. 12(d); *Foley*, 772 F.3d at 73.

claims, Defendants improperly inject novelty arguments into the Section 101 analysis. However, there is "no relevance" to consideration of the "'novelty' of any element or steps in a process or even of the process itself ... when determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter." *Diamond v. Diehr*, 450 U.S. 175, 188–89 (1981) (emphasis added).

Third, Defendants' arguments also implicate Section 103, which addresses whether an invention is obvious. Like the novelty arguments, obviousness issues cannot be resolved on the pleadings because they often turn on a number of factual considerations, including secondary indicia of nonobviousness. *See*, *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012).

Fourth, the only evidence from the pleadings Defendants rely upon is a nine word passage from the specification saying "iodination and immunoprecipitation are standard techniques in the art." ('820 patent at 4:10-11). This statement says nothing about whether such techniques were ***routine*** or, more importantly, whether the ***application of those techniques*** to a then-uncharacterized system would have been considered "well known and routine" to one of ordinary skill practicing in the relevant field. And, even if application of those techniques would have been routine, which is denied, such limited evidence does not make the claims involving man-made radioactive MuSK non-patentable. The Court must allow further development of the factual record before it can reach any such conclusion. *See Genetic Techs. Ltd. v. Agilent Techs., Inc.*, 24 F. Supp. 3d 922, 929 n.9 (N.D. Cal. 2014). As explained previously, Plaintiffs dispute the statements in those hearsay publications. (*See* supra, n. 2).

In addition to their reliance on external documents and factual issues, Defendants invite even more error when they suggest that the addition of a "well-known" step is fatal to Section

101 patentability. (*E.g.*, Dkt. 26 at 16-17). To the contrary, as previously discussed, a well-known step can convert a claim directed to a law of nature into a patent-eligible ***application*** of that law. *See Diehr*, 450 U.S. 175 (claim drawn to a method of curing rubber was patent eligible when considered as a whole, even though each step was previously known and the core of the claim was an ineligible algorithm).

Finally, in their attack on claims 7-9, Defendants draw improper analogies to three Section 101 cases in which courts referred to certain types of procedures as "well known" or "routine." However, each of those cases involved procedures for amplifying DNA, and some included "primer pair defining" and "analyzing" steps relating to the amplification process. *See,* Dkt 26 at 19–20, *citing In re BRCA1*, 774 F.3d 755, *Genetic Techs,* 72 F. Supp 3d at 533 and *Genetic Veterinary Sciences,* 2015 U.S. Dist. LEXIS 41156. But those cases did not involve methods employing the use of man-made matter, and they certainly did not address the use of ^{125}I-MuSK. The alleged routine use of DNA amplification is not relevant to anything in claims 7–9, and is irrelevant to the second step of the *Alice* test in this case.

5. Patentability of the claims involving man-made radioactive MuSK does not run afoul of the Supreme Court's concern about pre-empting laws of nature.

The Supreme Court has stated that the Section 101 inquiry is motivated by concerns over preempting the basic tools of human ingenuity. *Alice,* 134 S. Ct. at 2354. Indeed, claims may cover "an application of a law of nature," but that does not mean they are excluded from patent protection. *E.g., Diehr*, 450 U.S. at 187. ("[A]n application of a law or nature . . . to a known . . . process may well be deserving of patent protection."). Defendants do not address preemption —despite the clear language from the Supreme Court that preemption guides the entire Section 101 inquiry. *Alice,* 134 S. Ct. at 2354. Defendants' failure likely reflects the fact that the asserted claims are narrowly drawn to specific, concrete, and limited methods for detecting anti-

MuSK antibodies, and that numerous alternative methods for arriving at the same end result exist and are not preempted (*See* '820 patent at 3:33-45 (identifying various ways of measuring anti-MuSK antibodies)). Accordingly, the asserted claims of the '820 patent do not "risk disproportionately tying up the patent-eligible invention." They demonstrate the lack of preemption. *Id.*

C. Claims 1-5 and 10-12 are not at issue and are beyond the Court's jurisdiction.

Based upon publicly-available information about Defendants' infringement, Plaintiffs reasonably believe facts exist to support infringement of claims 7 through 9 of the '820 patent. Had Defendants conducted a meaningful meet and confer before filing this motion, they would have known the extent of the case so that the issues could have been narrowed.[8]

There is no case or controversy with respect to claims 1-5 and 10-12. Plaintiffs hereby state that, based on information presently available, they have no intention to, and will not, sue Defendants for infringement of those other claims of the '820 patent based on its current knowledge about Defendants' infringing MuSK tests. Because those other claims are not alleged to infringe, the Court lacks jurisdiction to address them. *See, e.g., Fox Group, Inc. v. Cree, Inc.*, 700 F.3d 1300, 1308-09 (Fed. Cir. 2012) (reversing summary judgment on claims that were withdrawn after the claim construction process because the Court did not have jurisdiction to rule on those claims); *Kingspan Insulated Panels v. Centria, Inc.*, No. 6:11-cv-1904, 2012 U.S. Dist. LEXIS 76892 at *4 (M.D. Fla. Jun. 4, 2012) (patent holders "clarification" in a motion to

[8] Rather than engage in a meaningful meet and confer with Plaintiffs prior to filing this motion, counsel for Defendants contacted Plaintiffs' counsel on September 15, 2015, just hours before the motion was filed. In that one brief phone call, counsel advised that Defendants intended to file the Rule 12(b)(6) motion, and when asked about the basis, counsel explained that Defendants would seek dismissal based on Section 101. (McMahon Decl. at ¶ 3). Defendants did not indicate any interest in discussing the motion other than to ask if Plaintiffs would agree at that moment to dismiss the case. *Id.* at ¶ 4.

dismiss, that it was only asserting certain claims, was sufficient to put the parties on notice of what was at issue); *Genetic Techs.*, 2014 U.S. Dist. LEXIS 122780 at *9-10 n.4 (addressing the subject matter eligibility of only the asserted claims on motion made pursuant to Rule 12(b)(6)). Because there is no case or controversy concerning claims 1-5 and 10-12, the Court does not possess subject matter jurisdiction over those claims and their validity is not at issue in this action.

D. Claim 6 is not at issue at this time and Plaintiffs need discovery before unequivocally removing it from the case.

Plaintiffs require discovery before they can permanently eliminate claim 6 from the case. While the claim does not require radioactive MuSK or complexes, many other arguments relating to claims 7-9 apply to claim 6. Defendants have not considered claim 6 as a whole in order to determine patentability. They also mischaracterize the claim as being directed to the mental process of comparing data to determine relative amounts of antibodies. (Dkt. 26 at 18). Indeed, the anti-IgG antibody of claim 6 requires immunizing another animal with human IgG and obtaining antibodies from the animal. It is hardly a "natural law" for an animal to possess anti-human IgG antibodies. And the antibodies are definitely non-naturally occurring when tagged or labeled with a reporter molecule as required by the claim. In any event, Plaintiffs need additional discovery to determine whether Defendants are infringing claim 6.

E. Defendants' motion to dismiss is premature at this stage and based on documents improperly before the Court.

A review of Defendants' limited arguments relating to asserted claims 7-9 proves that Defendants' motion is premature and cannot be resolved in their favor at this stage of the litigation. Numerous factual disputes remain.

While some Courts have considered Section 101 patentability at the pleadings stage, dismissal for lack of patentable subject matter at this stage "should be the 'exception, not the

rule.'" *Kenexa*, 2015 U.S. Dist. LEXIS 56156, at *6 (quoting *Ultramercial, Inc. v. Hulu, LLC*, 772 F.3d 1335, 1338-39 (Fed. Cir. 2013)). Indeed, "it will be rare that a patent infringement suit can be dismissed at the pleading stage for lack of patentable subject matter. This is so because every issued patent is presumed to have been issued properly, absent clear and convincing evidence to the contrary." *Id.* The presence of factual issues about the patent's asserted claims often preclude a court from resolving Section 101 issues at such an early stage. *See, e.g., Certified Measurement, LLC v. Centerpoint Energy Houston Elec., LLC*, No. 2:14-cv-627-RSP, 2015 U.S. Dist. LEXIS 39821, at *4 (E.D. Tex. Mar. 30, 2015) ("[T]he issue of patentable subject matter requires a legal analysis that can—and often does—contain underlying factual issues."); *Kenexa*, 2015 U.S. Dist. LEXIS 56156 at *19 (noting that whether business practices were "routine" was a factual matter that could not be resolved at the pleading stage).

Many of the cases Defendants rely upon were actually decided upon a factual record. Two of the three cases cited in support of Defendants' allegation that claims 7–9 involve well-known and conventional steps actually arose from a developed factual record. *See BRCA1,* 774 F.3d 755, which involved an appeal from a denial of a preliminary injunction order entered after an evidentiary hearing, and *Genetic Veterinary Sciences,* 2015 U.S. Dist. LEXIS 41156, which involved a summary judgment motion. While *BMS*, 72 F. Supp. 3d 521, did arise from a 12(b)(6) motion, that case still involved the unremarkable ruling that DNA amplification and related techniques were routine. In this case, while Plaintiffs strongly believe the claims do not involve well-known or conventional steps, if there is any question, the Court must allow proper development of the facts.

IV. CONCLUSION

For the foregoing reasons, Plaintiffs respectfully ask that the Court deny Defendants' Rule 12(b)(6) Motion to Dismiss the Second Amended Complaint.

C16

Neurology 1997;48(Suppl 5):S40–S45

Seronegative myasthenia gravis

Donald B. Sanders, MD; P. Ian Andrews, FRACP; James F. Howard, Jr., MD; and Janice M. Massey, MD

It has been 20 years since Lindstrom et al.[1] reported the results of a binding assay for acetylcholine receptor (AChR) antibodies in patients with myasthenia gravis (MG). This assay has subsequently become a major tool in evaluating patients with known or suspected MG. In the original report of Lindstrom et al., 6% of patients with generalized MG and almost 30% of those with ocular myasthenia did not have elevated binding antibody levels. In subsequent reports, from 7 to 34% of patients with MG did not have elevated binding antibodies (table 1). These patients without elevated AChR antibodies are referred to as having seronegative myasthenia gravis (SN-MG).

The clinical features of MG patients with elevated AChR antibodies (seropositive, SP-MG) and without elevated AChR antibodies (seronegative, SN-MG) are similar, although patients with SN-MG are more likely to have purely ocular myasthenia or milder disease (table 1). As in SP-MG, an autoimmune process underlies SN-MG. Evidence supporting this includes the fact that patients with SN-MG improve after immunotherapy such as plasma exchange, immunosuppression, and thymectomy.[2-4] Abnormal neuromuscular transmission can be transferred to animals by injecting immunoglobulin from patients with SN-MG.[5-9] This immunoglobulin has direct blocking effects on neuromuscular transmission when applied in vitro to nerve–muscle preparations.[10]

Several factors may affect the frequency of SN-MG in published reports. The sensitivity of the assay has a marked effect on the proportion of patients in whom antibodies are detected. A less sensitive assay identifies fewer seropositive patients and the proportion of SN-MG is therefore greater. The duration of disease at the time the assay is performed may also influence the results. Patients may have normal AChR antibody levels within the first months of symptoms and elevated AChR antibodies thereafter (see below). Immunotherapy or thymectomy before assay also reduce the frequency of elevated antibody levels,[11] although in our experience antibody levels usually remain elevated even when patients are in clinical remission (see below).

Some observations, however, identify differences between SN-MG and SP-MG. For example SN-MG is rare among myasthenic patients with thymoma.[3,12-14] The response of SN-MG to various treatments is less consistent than the response of SP-MG.[3,15] Moreover, autoimmune SN-MG is relatively common among children with prepubertal onset of myasthenia, but after puberty the incidence of SP-MG increases dramatically, whereas the incidence of SN-MG remains low.[16]

Does the absence of detectable AChR antibodies in SN-MG imply differences in pathogenic mechanisms underlying the autoimmune process, or is SN-MG an epiphenomenon related to limitations in measuring pathogenic AChR antibodies (i.e., circulating antibodies may be present in concentrations or with affinity too low to be detected by the assay, or antibodies may be directed at epitopes different from those present in the antigen used in the assay)? Answers to these questions could influence strategies for accurate diagnosis and improved management, particularly for patients with SN-MG.

Methods. To address these questions, we reviewed demographic and clinical data from all patients with autoimmune MG seen at the MG clinics at Duke University Medical Center and the University of North Carolina Hospitals since 1980. The patient population includes patients diagnosed elsewhere or before 1980 who have been reviewed by the authors between 1980 and the present, and a subgroup who were initially seen by one of the authors within 2 years of onset of symptoms. This subgroup represents a prospectively identified group of patients with recent onset of symptoms.

To examine the influence of endogenous sex hormones on MG, patients were divided into young adult and late adult groups according to their age at disease onset. The young adult group included those with onset after puberty (age 16) and before 50 years. The late adult onset group included those with onset after 50 years, which is the average age of menopause in North America.[17]

The patients have MG by classical clinical, physiologic, and pharmacologic criteria, and have had at least one test for AChR antibodies. Patients with thymoma were excluded from this analysis. In patients with SN-MG, all tests for binding AChR antibodies were normal and at least one test was performed more than 6 months after disease onset.

Antibodies that block bungarotoxin binding to the AChR (blocking Abs) or that increase the degrada-

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UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ATHENA DIAGNOSTICS, INC., et al,
Plaintiffs,

vs. CA No. 15-40075-IT

MAYO COLLABORATIVE SERVICES, LLC, d/b/a Mayo Medical Laboratories, et al,
Defendants.

BEFORE: THE HONORABLE JUDGE INDIRA TALWANI

HEARING ON MOTION TO DISMISS

THE SECOND AMENDED COMPLAINT

John Joseph Moakley United States Courthouse
Courtroom No. 9
One Courthouse Way
Boston, MA 02210
Tuesday, August 2, 2016
10:35 a.m.

Cheryl Dahlstrom, RMR, CRR
Official Court Reporter
John Joseph Moakley United States Courthouse
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P R O C E E D I N G S

THE CLERK: This is Case No. 15CV40075, Athena Diagnostics, Inc. v. Mayo Collaborative Services, et al. The Honorable Indira Talwani presiding. U.S. District Court is now in session. Will counsel please identify themselves for the record.

MR. McMAHON: My name is Emmett McMahon, your Honor, from Robins, Kaplan. With me is Manleen Singh, from my office also, for the plaintiffs, all three.

10:37 THE COURT: Good morning.

MR. KESSEL: Good morning, your Honor. Adam Kessel, from Fish & Richardson, for the Mayo defendant. With us today is Joseph Colaiano, who is legal counsel from Mayo, and my colleague, Jonathan Singer, who will be taking the lead.

MR. SINGER: Good morning, your Honor.

THE COURT: Good morning. It's taken us a little time to tee up the legal issue that you presented in the fall, but here we are. So it's defendants' motion if you'd like to start.

10:37 MR. SINGER: Your Honor, I have a slide presentation. I would be happy --

THE COURT: I'll take a copy, and you can leave one with my clerks as well.

MR. SINGER: I will go through as much or as little as you'd like.

THE COURT: I find that the problem with the presentation is my question may not track your order.

MR. SINGER: And I'll abruptly stop. I have no interest in talking about stuff that you don't want to hear, and I don't want to belabor things the Court is already familiar with. We're all sitting here knowing that your Honor has ruled in one of these cases before, not in this technology space but in the electrical arts. But the framework under the Supreme Court's law is the same. So we have the two same questions to answer.

Is there a button I need to push to get this on the screen? And then I can do it. Otherwise, I can go from the paper.

THE COURT: We're having a little problem getting it up. So you can tell me what page you're on, and we can work that way until we get the screen going.

MR. SINGER: I just have the basic framework on Page 3, which the Court is familiar with. And I'll go there. Plus we have some kind of blue stuff on here.

MR. KESSEL: I think it's the wrong input.

MR. SINGER: I can just go ahead.

So I have for your Honor the basic framework on Page 3, which the Court is already familiar with from the *Alice* case, the two questions for the Court really: whether the claims are directed to one of the ineligible concepts; and

then, if yes, is it implemented with something that makes it patentable? I'm going to turn to the first question. I think the dispute between the parties is on both questions. From what I'm able to gather from the brief, the largest part of the question really -- and it ties to both questions -- is whether or not using a labeled epitope enzyme, et cetera, gets the plaintiffs' patent over the hurdle.

THE COURT: So let me focus you on a few things. One is that, as we go through here, obviously we're standing here on a motion to dismiss rather than a motion for a summary judgment.

MR. SINGER: That's right.

THE COURT: And I read that as, therefore, the pre-claim construction; and, therefore, to the extent there are any disputed claims -- disputed terms here, I'm going to go with the plaintiffs' view of them at this 12(b)(6) stage. That's my one sort of caveat as we go through the discussion.

The other is that the task for patent lawyers seems to be a very difficult one because of the moving standards from when a patent was written versus when you then are in front of a court some years later to try to defend it. And I don't -- I, therefore, want to be very clear as we go through about what the claim is directed at. And you're sort of jumping to where the arguments are of disputes of what's innovative and what isn't. But I want to be very precise as to what exactly you

contend and what they contend the patent is directed at.

MR. SINGER: Okay, all right. As to your first question, I don't think there's any claim term in dispute. There wasn't raised in the briefing. But I think your Honor has stated it correctly, that if there is something that's in dispute, I think some of the cases that the parties have cited, it gets resolved at this stage in the plaintiffs' favor on the motion.

As to the point about what the patent is directed to, and sort of the timing and origins of that, I remember that from actually the first time -- that I was here with you, which was not the last time we were here. It was the time before that. And it is the case -- and you'll see that on Slide 5. There's no need to belabor it. But these patents do -- they are pre-Mayo, if you will. So they have, I think -- and it's I suppose no fault of the lawyers pursuing them -- they have the problem that pre-Mayo patents have, which is they relate to a discovery. It may be -- discovery in this case, if we go forward, may show it to be a novel discovery of an association of a disease with a naturally occurring protein in our body, in this case an autoantibody, and really that's what the patent is directed to.

THE COURT: Is there any way to read the patent, in your view, that it is directed at patenting any kind of composition of matter?

MR. SINGER: Well, the claims are method claims.

THE COURT: So --

MR. SINGER: Actually --

THE COURT: Because, as I read the argument, it seems that some of the discussion is that we, at the end of the day, might have a new -- I'm not sure of the right term -- complex that's going to come out at the end of it. But as I'm looking at that, is that what I'm looking at, or am I looking solely at the method?

10:43 MR. SINGER: I actually think, your Honor, you could actually look at it either way. You can look at it as a method -- and I think that's the -- frankly an easier way to look at it because the claims are method claims. And when we look at the claims, if we ever get them up on screen -- no big deal -- but we can look at them. But you can look at them as method claims, right, of the association, right, of the disease with the presence of the autoantibody that was discovered, or if you feel it's more appropriate to look at them as detecting the autoantibody, you can look at it that way, that they're really

10:44 directed to either, right, the presence of the autoantibody, kind of like in the --

THE COURT: That's simply saying the same thing. They're directed at detecting or diagnosing this. But they're not directed at producing a new composition.

MR. SINGER: That is correct, right. So it's not, in

essence -- if you will, there's no claim to, for example, in the *Myriad* case, the cDNA. There's no claim to that.

But the reason I articulate it that way is, if you look at some of the authorities, some of them look at it as a method, right, a method of, in this case, diagnostic efforts. But -- and then others look at them as directed at the thing you are detecting as the thing.

So as -- in the *Ariosa* case, for example, the presence of the fetal DNA, or the discovery of the fetal DNA in the mother's serum, there were claims in there that were both directed to method of detecting and diagnostics claims. What they said was, well, in essence, you can look at it either way. What they're really directed to is the fetal DNA because you are telling the person to detect the fetal DNA. And you can look at it that way.

And here I don't think it's any different. You're looking at detecting in the human blood the presence of these autoantibodies through conventional techniques. They may not like it, but that's what the claims cover, conventional techniques.

THE COURT: Is -- I know you've quoted parts of the specification to say that all they're using is conventional techniques. But is that an appropriate question for me on a 12(b)(6)?

MR. SINGER: It is. I think we cited some cases where

that -- when the specification states, right, that the techniques used are conventional, that is a permissible grounds for granting the 101 motion. Let me see if I have them here. I can tell you which ones they were. I kind of catalogued the cases as to which ones were 12(b)(6) and which ones were not. I've got three 12(b)(6) cases, if you will, where it was granted: The *Esoterix* case here in Boston; the *Cleveland Clinic* case in Ohio; and then the *Genetic Tech* case versus *Merial*, which was affirmed at the Federal Circuit. Each of those relies on the conventional nature of the technology and the admission that the technology is, in fact, conventional.

THE COURT: What if I go to -- from the more general claims to the more specific claim? I think that would be Claim 9 where we're now talking about specifically about the --

MR. SINGER: The I125.

THE COURT: You say I125 or 125I?

MR. SINGER: However you'd like to refer to it, your Honor. I have that on Slide -- you can look at Slide -- Slide 9. We can look at it together.

You're right. It's 125I. I think of it either way.

THE COURT: So Claim 9 narrows it -- Claim 8 narrows it to a radioactive label, and Claim 9 narrows it to a specific radioactive label.

MR. SINGER: Right.

THE COURT: But why doesn't that force me to get into

the more specific -- that there's now some additional specific technological process that can be patented?

MR. SINGER: Well, because the inquiry is whether or not that is, one, conventional technology, right? That's the first question we have to ask. And, second, right -- this is the argument they've raised -- is even if it were conventional, does it result in anything that's distinct, right? That was the cDNA versus the isolated DNA. And the specification says and teaches -- it says that iodination -- that's the word for putting this radioactive iodine on -- is a standard technique in the art.

10:49

THE COURT: So that's 8. But what about 9? Does it matter that it's 125I, that we're now talking about this very specific process using this very specific manmade label?

MR. SINGER: Right. That is the radioactive iodine.

THE COURT: The particular one?

MR. SINGER: Yeah. That's what it is. When someone is saying use of a radioactive label and then a radioactive iodine label is standard in the art, that's what Claim 9 is.

10:49

THE COURT: Does it matter whether this -- do I need to make an inquiry as to whether this particular radioactive iodine and using -- the process using this particular radioactive iodine is standard; and, if so, is that also in the specifications or -- because it seemed to me the specifications are more generic.

MR. SINGER: Does it say I125? I don't know the answer if it does, your Honor. I know it says iodination is a standard technique.

THE COURT: Yes.

MR. SINGER: And I think what it does is point to -- I think we've pointed to reference articles that the specification quotes. Do you need to make an inquiry as to whether this is a conventional technique? I think you do in fairness to the plaintiffs. But I think the specification gives us the answer in that, well, it doesn't say 125, the number. I think it would be a --

THE COURT: It gets me to 8. I see where 8 would track the specification. I guess my question is: Does 9 -- do I have enough information in front of me to know -- and it is appropriately done on 12(b)(6) -- to know whether 9 is not something new?

MR. SINGER: Yeah. Actually, I misspoke. So I thought the specification didn't say I125, and I remembered the sentence that said -- and I'm reading from Column 4, your Honor -- "iodination and immunoprecipitation," which is the technique described -- it's Column 4, Lines 10 through 12 -- "are standard techniques in the art, the details of which may be found in references 4 and 6." And the sentence before, it says, "preferably the label is radioactive label, which may be 125I or the like." That is the standard radioactive iodine

that is used in these techniques, as I think you can see from the context both in the specification as well as the references cited in the specification. It's the same technique used with the prior art acetylcholine. 80 percent of us who might suffer from this disease have --

THE COURT: It's the same technique generally, but it isn't using the radioactive label, is it?

MR. SINGER: It's the same technique in the R2 label.

THE COURT: Right.

10:52 MR. SINGER: That's -- you and I are on the same page.

THE COURT: We're moving to a more specific -- you can't be making the argument that there couldn't be some process in the diagnosis. You've come up with this idea. You've made this discovery that there's a correlation. It can't be that Mayo is going to say no process claim --

MR. SINGER: Oh, no.

THE COURT: -- can ever -- no method of detection or method of diagnosing is patentable at this point. So if they're doing it somewhat differently, even if it generically

10:53 is the same thing, that we're trying to test for some combination that didn't used to be there, if it's specific enough, do they get past the hurdle?

MR. SINGER: So the answer to your first question is we are not saying that no one could ever come up with something patentable. But what we are saying is that you can't use a

standard technique in the art to turn that correlation into something patentable and that the I125 is, in fact, a standard technique in the art. And I --

THE COURT: But I have to -- at this stage, the only place I get that is from what the -- what I read in the specifications.

MR. SINGER: Specification and the references incorporated therein, that's correct. That's where you have to look, right? We have no -- we have no expert declaration from them saying it's not standard, for example, that you --

THE COURT: They wouldn't be -- we're on a 12(b)(6) so --

MR. SINGER: Fair enough. Some of the cases -- just for your Honor's benefit, some of them do have expert testimony put in by one or more of the parties on 12(b)(6).

THE COURT: Which gets to the point that, if you're both trying to litigate this in a way that gets the issue decided rather than simply being a cost of litigation issue, that whatever happens here, presumably one side or the other will take it up. And the case law isn't completely straightforward enough for either side to be a hundred percent sure, whichever way I go, that the Federal Circuit isn't going to say, Well, we really don't like Mayo all that much, and we're going to move it this way or you read Mayo too broadly, you know, whichever way.

So why wouldn't it make some sense that, to the extent that this is what this issue turns on, that there's a record here as a -- which would essentially be a summary judgment record but perhaps an early summary judgment, not a late summary judgment motion, but to flesh out this issue rather than saying I need to make a what seems somewhat of a beyond my expertise decision based on reading the specifications and the paper cited in the --

MR. SINGER: At the end of the day, your Honor, if
10:55 that is what makes your Honor most comfortable, then Mayo has no objection to that. What we don't want is what you earlier referred to, and we brought it to your attention in the way that the authorities allow under a 12(b)(6) motion. We believe firmly that this is resolvable at the 12(b)(6) stage, but I don't want to put you in an uncomfortable position where you feel like you don't have enough background in the technology from experts, for example, to allow you to make a decision that you believe is going to be fully supported one way or the other on appeal. I do not want to put you in that position, and we
10:56 have no objection.

What we do have an objection to is somehow opening wide discovery so we end up spending millions of dollars to get to a result that, frankly, your Honor, we believe is inevitable. I mean, this is a standard technique applied to a discovery. These are pre-Mayo patents. The persons

prosecuting them didn't have the ability to understand the law. And the argument made by the other side is breathtaking in its breadth -- in its breadth. And that is, that adding a label to MuSK -- and I can quote from their brief -- adding a label to MuSK, a natural occurring protein and the autoantibody to that protein, that adding that label makes it patentable, that's it, that's the end, that is wrong. That is not what the law says. The law requires use of something more than conventional, and manmade doesn't get you over the hurdle.

10:57 I just -- that was addressed extensively. I don't want to leave here without hitting on that issue because you and I have discussed a lot of things. But manmade isn't the answer. That doesn't tell you really all that much in the Section 101 inquiry. If you go back to your authorities and you read the *Promethious* case, which I was involved in for ten years, for heaven's sake -- that's how long that one took -- and the *Myriad* case, which I was involved with, as was Mr. McMahon, for several years, the inquiry under 101 on the isolated DNA, which the Supreme Court found unpatentable, the

10:57 Federal Circuit said that's manmade; therefore, it's patentable. The Supreme Court said not enough because it's not distinct from the natural DNA, not sufficiently distinct from the natural DNA, that severing the bonds, right, of the DNA and isolating it out of the organism, while manmade, that was simply not enough. The cDNA was distinct. It was a distinct

any further questions after he speaks.

THE COURT: Thank you.

MR. McMAHON: Thank you, your Honor. Madame Clerk, can we have the --

MR. SINGER: It worked better without it.

THE COURT: We're having -- continuing having --

MR. McMAHON: Mine works.

THE COURT: So we would need to reboot the whole system apparently to get this up.

11:06 MR. McMAHON: Mine is up. Oh, it's not. I'm sorry.

MR. SINGER: It's on your computer.

MR. McMAHON: All right. I have paper copies, too, your Honor. I can -- thank you.

THE COURT: Thank you. Not to suggest that there's a disconnect between your cutting edge technology and mine, but we are here where we are.

MR. SINGER: I liked it better anyway. It worked out fine.

MR. McMAHON: Thank you, your Honor. What counsel is

11:07 asking this Court to do is rule that a claim that's using a laboratory-created radioactive molecule that doesn't appear in nature to form a radioactive complex that doesn't appear in nature and then detecting the radioactivity in that bodily sample that doesn't appear in nature, is really a law of nature. And I would submit that it's not even close, the

argument that they're making.

This is -- what we have to do is look at what the claims are directed to. Mayo's analysis is flawed in two very significant reasons. First, their analysis in the *Alice* Step 1 makes the same error -- and I'm going to go into these in more detail. But it makes the same error that the district court committed in *CellzDirect*. That's that case that we both advised the Court about last week. Their analysis under Step 2 is also fatally flawed because they're making the assumption
11:08 that once you use conventional techniques the analysis ends. And it doesn't.

THE COURT: So my one takeaway from the case you both just cited to me is I do have to look very carefully at what the claims are actually directed at. So I'd like to keep the discussion focused a little bit on -- I'm turning to your Page 3, and I notice these same arguments in your brief. The 125I MuSK is patent eligible, but -- you state, but this patent doesn't claim the 125I MuSK as a -- that's not what the claim is directed at, is it?

11:09 MR. McMAHON: The claim is directed at using that molecule.

THE COURT: Right. But it's not -- so you're pointing out that the -- sort of the starting point molecule compound, that our starting point is patent eligible, and your end point is patent eligible, is your point.

MR. McMAHON: Yes, your Honor.

THE COURT: But your claims are directed at a process, not at the composition. That was my question at the beginning, which was, is this a patent -- are the patent claims directed at composition or at a process? And they're directed at the process of detect -- of diagnosing. That's what the claim is.

MR. McMAHON: A process of diagnosing -- a process -- no. The last step actually of the claim --

THE COURT: I understand there are various steps of the process. My question is: What are you claiming though?

MR. McMAHON: We are claiming a process of detecting iodine -- radioactive iodine in a complex that was also created through that process.

THE COURT: But you're not claiming the creation of that complex?

MR. McMAHON: No. We're claiming the use of that, and that's what's important. And that is the very same reason why this *CellzDirect* case ruled in the way it did. The court said you've got to look at the process that's involved.

THE COURT: Wasn't that claiming producing something? Isn't that what that claim was directed at? And you're not claiming producing something.

MR. McMAHON: Well, no, we are. We're producing -- just as -- well, I think an argument that could be made that we're even producing more than in *CellzDirect*. In this case

right here, what the steps create, they produce a complex from the body.

THE COURT: So this is where I started in on, you know, the difficulty here is we're -- the patents are written before the laws, it makes it a little bit -- or before some of these cases, it's a little bit confusing. But I look at -- I'm looking through the claims, and the claims don't talk at all -- you may be right that this is the end product, that you have now produced something; and it may be that the thing that you have now produced might have been patent eligible. But it seems that I have to look at what you were -- what the patent claimed, and what the patent was claiming was not a method of producing something. What the patent was directed at was diagnosing something. Is that -- isn't that a difference?

MR. McMAHON: Well, that's true in a general sense. But just as in *CellzDirect* where the Court said we have to -- the reversal happened because the district court did exactly as Mayo is suggesting in its brief when they start -- the district court just concluded that a law of nature was involved, and then it stopped with Step 1 and went to Step 2.

THE COURT: We are clearly -- we have a law of nature that's involved in the sense that there is an antibody -- that this MuSK antibody is correlating in this 20 percent of this -- people suffering from M.G. So you have some law of nature, and now we're going to add a process about it, and your process is

involved in trying to detect and diagnose. I don't disagree that we need to move to Step 2. But the question is: Is there an inventive concept there in that Step 2 process?

MR. McMAHON: Yes.

THE COURT: And --

MR. McMAHON: Because the process is using something that -- the word "inventive concept" is unclear and vague, and I think what the proper analysis is isn't something that is a law of nature, a natural phenomenon or an abstract idea. If that's the case in Step 1, then -- I mean, that is actually the first step in *Alice*.

THE COURT: That's Step 1.

MR. McMAHON: But this claim does not involve -- I mean, what we're doing here is we're -- the practitioner -- if we could turn to my Page 7, your Honor, I have the whole claim set forthright there.

THE COURT: I tried to do this so I appreciate this.

MR. McMAHON: All right. Thank you. And going back, what I've done is I've highlighted what Mayo claims is the law of nature. That's Claim 1. Then their analysis stop. If we look at this claim, look at the very end. Now, that's not a step, the last three lines, that someone performs, but it's a statement of what is happening, I guess you would say. It says, Wherein the presence of iodine 125 is indicative that the mammal is suffering from this disease. So this is not -- if

you look at that step -- or that last clause there and you look at the first step where we're using a radioactive MuSK and then creating the MuSK complex, none of these things appear in nature.

THE COURT: I don't think my test is does it appear in nature. My question here -- we've gotten past Step 1. We're at Step 2. The question is: Have you now taken that law of nature, and have you now added an inventive concept that improves the process somehow or does something to transform it into a patent eligible? And what they're saying -- they're not stopping at Step 1. They're moving to here, and they're saying, at Step 2, everything you're doing, everybody was doing before. It's just a common --

MR. McMAHON: And that's the flaw in their argument, your Honor, because they just make the statement -- and they're asking this Court to identify some legal -- some principle of nature and say, Oh, that's involved in the claim, and then we'll move to Step 2. And that's exactly the error that the *CellzDirect* case did.

I would say that the -- first of all, the analysis should end at Step 1 because the court -- and that's what *CellzDirect* said. It said -- the court erred because it just jumped to Step 2 without looking at the claim as a whole. We have to look at Claim 9, not just the yellow part that Mayo has outlined for Step 1, but we have to look at the entire claim

and see what is that claim directed to. And if the answer is -- if the answer is that it's not directed to a law of nature, a natural phenomenon or an abstract idea, then the analysis stops.

And that's my point. That's exactly the error that *CellzDirect* found, and that's what they're asking you. When you look at the brief, their opening brief, they do not -- "they" meaning Mayo -- does not address this claim as a whole for Step 1. They just identify this Claim 1, which is only about 25 or 30 percent of the entire Claim 9. And then they say, Yup, that answer gets us to Step 2. But that's wrong. We have to look at what --

THE COURT: So what you want me to do is to just say, Well, we have a patent that is out there because we -- I mean, it's the innovative thing that's described in sort of the overall picture of the patent. And the sort of what we've done, what we're doing here, is we've come up with a way of diagnosing these 20 percent of people. You're saying that's not where we look. We go to each claim; and as to that claim, we analyze whether there's some extra process in there that's added that would then not make it a law of nature that the claim is directed at. That doesn't seem to follow the two-step analysis. It seems to conflate the entire second step into the first step.

MR. McMAHON: *CellzDirect* case said, on Page 15, it

THE COURT: You mean their motion should be denied.

MR. McMAHON: Pardon me?

THE COURT: You meant their motion should be denied.

MR. McMAHON: Their motion should be denied. Thank you.

If I could turn then to -- I ask the Court -- first, I think the Court understands the assay. But we do have here in Page 9 -- as I'm flipping to Page 9, let me stop at Page 8. What we've done is a diagram here to help the Court in reviewing what happens in those claims. And I think we understand, but what we've marked in red and orange is the matters in this method or this process that don't appear in nature.

And, again, the question is, for Step 1, is this process directed to a law of nature? And I would say there's no question that it is not directed to because they're creating this -- they're creating a molecule. So we've got MuSK. It's not just one label. They --

THE COURT: You're ending up with a molecule, but what are you -- what's the claim directed at? It's not directed at creating this molecule. That's --

MR. McMAHON: Well, making -- if we look at the end of the claim, it's directed at detecting or determining that the iodine based -- they're not looking for the complex that appears in nature. They're looking for the iodine. And, also,

we should remember though that the Supreme Court still said, When someone invents or they discover this concept, they are the ones that are in the unique position to draft the claim, and that's what this claim does. It's based -- it doesn't claim, as -- an analogy to the *Myriad* -- to the Mayo v. *Promethious* case would be to say -- for these inventors to just claim an auto-body -- a MuSK auto-body that's used to diagnose disorders and then maybe make a diagnosis.

But they've done more than that. It's really directed at using these new molecules to find -- to locate iodine. I mean, this claim doesn't even -- the relation, again, of the iodine 125 to the disease is not a natural phenomenon or a law of nature. And that's what the claim is directed to. That's what the inventors were telling the practitioner to do.

THE COURT: So this is a -- it is a pure legal question for me to determine what the claim is directed to, correct?

MR. McMAHON: With the understanding of what the claim terms mean, yes.

THE COURT: Is there any dispute what the claim terms mean at this point?

MR. McMAHON: We haven't had the claim construction process, but I haven't seen one yet.

THE COURT: As you're reading each other's briefs, there's no disagreement there?

MR. McMAHON: Yes.

THE COURT: So I -- so my first step here is to determine what the claims are, in fact, directed to. And your point is they're not directed to a law of nature, and I should just end at Step 1.

Assuming I find that they're directed there, I would then move to Step 2, which is to say, is there an additional innovative -- additional part -- elements to this process that has created an innovative concept sufficient for -- to make it patent eligible? Assuming I get there and I'm at Step 2, what's your response -- I understand you disagree with me that we get there. But if I get there, what is your response to their assertion that this iodine labeling is nothing new?

MR. McMAHON: All right. I would have several responses to that, your Honor. First, just because the steps -- the inventor stated that the step involves a conventional test doesn't satisfy Claim 2 because, if it did, that would be inconsistent with the Supreme Court's statements where it said that cDNA is patentable subject matter, and that is created through well-known techniques. The Supreme Court also said that. It would also --

THE COURT: So you would say as to this, they're wrong in saying that the answer to the question is decided just from the specifications?

MR. McMAHON: Yes, your Honor.

THE COURT: Okay.

MR. McMAHON: But I have more reasons than that, too. Also, the specification -- just because the step was conventional, again, doesn't end the analysis. But whether -- there's a difference between being routine and being well-known, and counsel has talked about the cDNA sequencing. If I may talk a bit about cDNA because we actually had a prior life in another case.

But in the cDNA -- so we've got a strand of cDNA. It has four different types of nucleotides that can be located. You've got a strand. In those tests, all they're doing is just comparing, you know, a patient's sample with something in the -- what they call the wild type. It's out in the -- that someone -- people generally agree is in the public, and then making a diagnosis over that. That's, again, just a mental conclusion.

But, again -- I keep going back to the cDNA. They can't avoid the fact -- you can't stop the analysis just because a step is conventional. It can still be patentable. *CellzDirect* also, again, after summary judgment, but the court went and also addressed Step 2.

I was leading up to my -- if I can ask the Court to please refer to Page 9. What I've done here is I've outlined the steps in *CellzDirect* just to show what that claim actually involved -- because the Court also, in *CellzDirect,* said that

work with one little strand of DNA, so they bulk up; they replicate it and they look at it in bulk. That's just a standard, well-known, routine technique that no one would think twice about doing.

There's no showing in the record that this -- the iodine 125 marker or the radioactive markers were of that level that they were just routinely done. They can't be done with everything. That's even in the record here. So I think that if the Court is wondering, Can I125 be applied to anything, the answer is no.

11:36

I think my second point would be, your Honor, that what the Court is looking at in raising that question is a 103 question, whether or not it's obvious. We're getting far afield from the issue of are we looking at a law of nature, a natural phenomenon or an abstract idea. That's what 101 is based on.

THE COURT: Well, but 101, as I'm told to apply it, I think, gets me past that if I answer yes to that, and then I have to ask whether there's an innovative concept. I don't get to say let's wait until we look at novelty, et cetera. I do have to look at it here.

11:36

MR. McMAHON: I would say it ends with Step 1. But with Step 2, there's going to have to be discovery because the -- the only argument that Mayo is making is they rely on two articles that we say aren't even intrinsic evidence and the one

statement in the patent that said "well-known technique."

My response to that is that -- the analysis doesn't end there. That's flawed. It's contrary to what the Supreme Court said with respect to the cDNA and also with *CellzDirect* because there are still well-known techniques that were employed at Step 2, and the claims were found to be patent eligible.

THE COURT: So if I were to suggest that this should be done through early summary judgment rather than on a 12(b)(6), what discovery would the -- should the parties be engaging in to get to this particular Step 2 question, not the broader everything else, but --

MR. McMAHON: I mean, your Honor, I would urge that discovery -- I would hope the Court would allow discovery to go forward. They filed the motion for Rule 12(b)(6), and I think it was their error in doing so based on this record and their misapplication of the law. So now they'll still infringing out in the market. We filed the case in early 2015, so I would urge that discovery should go forward.

You know, if they think they can bring a motion for summary judgment quickly, let them bring it and knock it out. I mean, my request of the Court is we should be able to -- allowed to go forward by this time to prove our case. They're not going to -- again, they're --

THE COURT: So let me -- obviously, I'm going to go

back and read all of these cases, but I am -- at this point, I think the question that is -- that I'm struggling with is the Step 2 question. And having -- being there on the Step 2 question and not just saying, No, they're wrong -- if they're wrong on Step 1, then, you know, sure, we're sort of moving forward. But assuming that they're right on Step 1, I get to the Step 2 question. And then what's in front of me is can I decide this on a 12(b)(6), or should I decide this on a record?

I think the parties are -- there may be enough for me to do it on a 12(b)(6); there may not be. But it would seem that addressing that issue -- I guess to put it this way: You certainly don't want this to be a 12(b)(6) decision. And so if I were to put it that way, which is that I would be thinking they've gotten pretty close there -- I'm not sure that they get there all the way, but they're pretty close, what would the discovery be that you're saying this is not enough? I understand you're saying it's not good enough to look at the specifications. But what is it that you would want to look at?

MR. McMAHON: I think I would be -- they have the burden here. I would be interested in what they would be looking at.

THE COURT: Let's say --

MR. McMAHON: And respond to it.

THE COURT: Let's say, for example --

MR. McMAHON: We would have experts.

THE COURT: Let's say, for example, I were to say -- and I certainly have the authority to do that -- I treat their 12(b)(6) as a motion for summary judgment because they've cited this additional material. Even though they want to tell me that these articles were referenced in the patent, I treat it as a summary judgment motion. You're coming forward under 56(d) or (e), or whatever paragraph it's been moved to, and say, You need additional discovery before you can respond to their 56. What would you want?

11:40 MR. McMAHON: Well, as I stand here now, we certainly would come forward with expert opinions.

THE COURT: As to this question of whether this is just a routine -- their argument is this is a routine conventional activity, and you would have experts saying, No, what's happened here is not a routine but an improved -- a technological process that has some innovative aspects to it.

MR. McMAHON: That's what we would but if --

THE COURT: I'll give you an opportunity to frame this back and forth if that's where I get.

11:41 MR. McMAHON: Pardon me?

THE COURT: I'm trying to understand what I'm looking at whichever way I go on this.

MR. McMAHON: Well, again, that certainly -- I mean, they have the burden to knock it out, so we would be interested in what they do. But I certainly would say right now, as I

think it would be quite limited. That would be the normal sort of -- when you look at the cases, for example, that have been resolved on summary judgment, that's what they're talking about right there.

THE COURT: I don't think they've necessarily said, while that was happening that other discovery didn't go on. I haven't seen that in the --

MR. SINGER: You know, I don't know the answer to that, your Honor. I would request that only because it would be, in our view, unnecessary discovery. There's been no motion for preliminary injunction or anything like that in terms of irreparable harm. At the end of the day, the damages are going to be awarded if, in fact, they prevail; and if not, nothing will be awarded. So we don't have any irreparable harm ongoing.

So I don't see what the issue is with respect to having one further round here so that the Court can be comfortable one way or the other, telling us, Okay, this is going to be an issue that has to be tried or, no, this is an issue that is not to be tried because it is, as we would submit, resolvable on a limited record, if you will, because, again, coming back to it, we don't have far to go. I think, from our perspective, we don't have anywhere to go. The patent specification says what it says. The articles say what they say about I125 and so --

THE COURT: The reason I don't -- the reason I am uncomfortable with simply saying that as -- that this should be decided by 12(b)(6) is I think that they aren't necessarily limited to exactly how it is -- yes, the specifications can sort of amount to admissions or something, but that's one piece of the picture. It's not a conclusive bar to saying, Well, no, there's something different there. So I'm not sure it's quite as clean as you're suggesting or that they would be precluded from offering other evidence.

11:53 MR. SINGER: I wasn't meaning to suggest that, your Honor. All I'm saying is we don't think there is very far to go, if you will. If the Court is needing further information to confirm what the state of the art is and what was said in the specification, we're not talking about, Oh, gosh, we have to depose the inventors, and we have to depose Mayo's business people as to what their potential sales might be and their marketing and the millions of -- all the ancillary materials are not needed for this particular dispute to be resolved in an efficient way.

11:54 Again, we're talking about -- if you want to use the word "delay," it would be a short delay of three or four months, if you will, not taken up with discovery. We could do that quite quickly but simply to get on the Court's calendar, that being the -- as we respectfully understand the nature of a federal judge's calendar. To get the parties their guidance,

which would help immeasurably as opposed to just imposing costs and us having to pull the trigger and them saying, We didn't get what we wanted. You've got to wait. We need to do X, Y, Z. If there's something that they need that we have, we can produce it. I didn't hear anything other than they would want expert discovery.

I will only say that my interest is in resolving this efficiently and quickly. You know, Mayo is a very well-known reference lab and would like to proceed in the market with what they think is a test that doesn't infringe any valid patents. They'd like resolution from their perspective.

THE COURT: So let them have a chance. If you could let counsel have a minute.

MR. McMAHON: Your Honor, may I speak from here?

THE COURT: Wherever you prefer.

MR. McMAHON: I'm thinking that we're getting into this -- if we're going to be looking at how conventional and routine, that's the issue that Mr. Singer is focusing on, we would be interested in getting into Mayo's files. I mean, I125, again, is difficult to work with. If they say it's conventional, I'd like to see not only the expert but get some fact discovery from them and see how conventional it was for them to put it. Did they try to use other things?

So if we're going to have a wider discovery -- and I think it's very difficult for us to put a fence around a

certain amount of discovery and say we can't have the others because there's going to be overplay in it.

But, again, the conventional aspect of this, the use of the iodine, I think the experts' opinions would be good, but they should be informed by the facts, and we're going to need some of them from Mayo.

THE COURT: Okay. This is what I'm --

MR. McMAHON: Or maybe third parties.

THE COURT: This is what I'm going to do. I'm going to go back and deal with the motion that's in front of me first. But I am anticipating at this point that I'm going to suggest that the Step 1 -- that defendants have convinced me of Step 1 but that we're struggling on Step 2 on trying to make that determination.

While I'm working on my opinion, I would suggest that it would be a good idea for you to -- assuming that's where I'm coming down -- to talk about what would be an efficient way to move the case forward. And that -- the argument that plaintiffs' counsel, I think, is really -- would be a really fair argument is, no matter how much I'm -- I see this as a way that -- a question that I probably should be addressing, we don't want to be deposing the same people twice. We don't want to be having half a go-round of files and so forth. So it may be that there is a limited amount of discovery that needs to be done, but that would ensure that if the case is going forward

we're not doing an overlap of that same piece so that it isn't so narrowly targeted to this particular issue that it has a high risk of cost.

But why don't you see what -- whether there is any common ground there. I will get a decision out as soon as I can. And assuming I go in that direction, I'll have you in for a status conference, and we'll just figure out what makes sense at that point.

MR. SINGER: Okay. That's very well, your Honor. Thank you very much.

THE COURT: Thank you. And I will go back and read your PowerPoints.

MR. McMAHON: Thank you, your Honor.

THE CLERK: Court is in recess. All rise.

(Whereupon, at 11:58 a.m. the hearing concluded.)

C E R T I F I C A T E

I certify that the foregoing is a correct transcript of the record of proceedings in the above-entitled matter to the best of my skill and ability.

/s/Cheryl Dahlstrom

Cheryl Dahlstrom, RMR, CRR

Official Court Reporter

Dated: August 8, 2016

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ATHENA DIAGONISTICS, INC., ISIS INNOVATION LIMITED, and MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN e. V.,	*	
Plaintiffs,	*	
v.	*	Civil Action No: 15-cv-40075-IT
MAYO COLLABORATIVE SERVICES, LLC, d/b/a MAYO MEDICAL LABORATORIES, and MAYO CLINIC,	*	
Defendants.	*	

MEMORANDUM & ORDER

August 25, 2016

TALWANI, D.J.

Plaintiffs Athena Diagnostics, Inc., Isis Innovation Limited, and Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V., allege that two tests developed by Defendants Mayo Collaborative Services, LLC, and Mayo Clinic, infringe on Plaintiffs' patent, U.S. Patent No. 7,267,820 (" '820 Patent"). Third Am. Compl. ("Complaint") [#92]. Defendants move to dismiss Plaintiffs' complaint arguing that the '820 patent is invalid under 35 U.S.C. § 101 because the claimed method applies routine and conventional techniques to a law of nature. Defs.' Rule 12(b)(6) Mot. Dismiss (Defs.' Mot. Dismiss") [#25]. The motion is DENIED.

I. Facts

A. The ’820 Patent

The ’820 patent allows for the diagnosis of a form of Myasthenia Gravis, a chronic autoimmune disorder. U.S. Patent No. 7,267,820 col. 1 l. 13. Patients with Myasthenia Gravis experience waning muscle strength throughout the day, and symptoms include eye weakness (drooping eyelids, double vision), leg weakness, dysphagia (difficulty swallowing) and slurred or nasal speech. U.S. Patent No. 7,267,820 col. 1 l. 15-23. In 1960, it was discovered that in 80% of patients with Myasthenia Gravis, antibodies attack the acetyle choline receptor (AChR) (a neurotransmitter). In those patients, diagnosis is achieved through tests which detect the presence of AChR autoantibodies. U.S. Patent No. 7,267,820 col. 1 l. 34-36. Autoantibodies “are naturally occurring antibodies directed to an antigen which an individual’s immune response recognizes as foreign even though that antigen actually originated in the individual.” U.S. Patent No. 7,267,820 col. 1 l. 42-45. However, 20% of Myasthenia Gravis patients do not have the AChR autoantibodies despite experiencing the same symptoms and responding to the same therapies. U.S. Patent No. 7,267,820 col. 1 l. 36-40. For the 20% of Myasthenia Gravis patients who do not have the AChR autoantibodies, the ’820 patent inventors discovered that they had IgG antibodies that attack the N-terminal domains of muscle specific tyrosine kinase (“MuSK”), a receptor that is located on the surface of neuromuscular junctions. U.S. Patent No. 7,267,820 col. 1 l. 55-61.

The patent describes the method for a more accurate and speedy diagnosis of these patients. U.S. Patent No. 7,267,820 col. 3 l. 4-7. Specifically, the patent describes a method for diagnosing Myasthenia Gravis in which a radioactive label is attached to MuSK (or a fragment thereof) and is then introduced to a sample of bodily fluid. U.S. Patent No. 7,267,820 col. 3-4 l. 65-10. The method specifies that ^{125}I be used as the radioactive label. U.S. Patent No. 7,267,820

col. 4 l. 10. When ^{125}I-MuSK is introduced into the sample of bodily fluid, the MuSK autoantibodies, if present, attach to the labeled fragment. After the bodily fluid is immunoprecipitated, the presence of the radioactive label on any antibody indicates that the person is suffering from Myasthenia Gravis. U.S. Patent No. 7,267,820 col. 4 l. 8-10.

B. Infringement Allegations

Athena's test, FMUSK, uses the patented method to diagnose neurotransmission or developmental disorders related to MuSK. Compl. [#92 ¶ 16]; U.S. Patent No. 7,267,820, Claim 1. Plaintiffs allege that "Defendants, with specific knowledge of the '820 patent and the method it covers, surreptitiously and purposefully designed an alternate test to avoid paying Athena for Athena's licensed FMUSK test." Compl. [#92 ¶ 20]. Plaintiffs allege that Defendants availed themselves of the technology disclosed in the '820 patent, and developed two tests for diagnosing Myasthenia Gravis patients. Compl. [#92 ¶ 18]. Plaintiffs argue that Defendants' actions directly or indirectly, and literally or under the doctrine of equivalents, infringe the '820 patent. Compl. [#92 ¶ 24]. The claims at issue are those listed in claims 6-9 of the '820 patent. Pls.' Mem. Opp'n Defs.' Mot. Dismiss. 24 [#37]. Plaintiffs concede that they will not pursue infringement claims against Defendants based on the other claims in the patent. Pls.' Mem. Opp'n Defs.' Mot. Dismiss 8 [#37].

II. Motion to Dismiss

Defendants move to dismiss the complaint on the ground that the patent seeks to patent a law of nature, and it uses techniques standard in the art. Defs.' Mem. Supp. Mot. Dismiss 5 [#26]. Plaintiffs argue that the patent is not directed at a law of nature because the patent requires the production and use of ^{125}I-MuSK, a non-naturally occurring protein. Plaintiffs also argue that

applying various known types of procedures to a non-naturally occurring protein transforms the claim and makes it patent eligible. Pls.' Mem. Opp'n Defs.' Mot. Dismiss 14 [#37].

A. Standard of Review under 35 U.S.C. § 101

In applying § 101 at the pleading stage, the court construes the patent claims in a manner most favorable to the non-moving party. See Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat'l Ass'n, 776 F.3d 1343, 1349 (Fed. Cir. 2014), cert. denied, 136 S. Ct. 119 (2015). As a threshold requirement for patent protection, the subject matter of a patent must be patentable under § 101; otherwise, the patent is invalid. Section 101 states "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. The Supreme Court has held that this section contains an implicit exception: "[l]aws of nature, natural phenomena, and abstract ideas are not patentable." Alice Corp. Pty. Ltd. v. CLS Bank Intern., __ U.S. __, 134 S. Ct. 2347, 2354 (2014) (quoting Association for Molecular Pathology v. Myriad Genetics, Inc., __ U.S. __, 133 S. Ct. 2107, 2116 (2013)). Although "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas," these three patent-ineligible exceptions prevent "monopolization" of the "basic tools of scientific and technological work" and the impeding of innovation. Mayo Collaborative Servs. v. Prometheus Labs., Inc., __ U.S. __, 132 S. Ct. 1289, 1293 (2012).

To distinguish between patents that claim laws of nature, natural phenomena, and abstract ideas from patent-eligible inventions, the court must first determine whether the claims at issue are directed to one of those patent-ineligible concepts. Alice, 134 S. Ct. at 2355. If the concept is patent ineligible, the court then considers the elements of each claim both "individually and 'as

an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application." Alice, 134 S. Ct. at 2355 (quoting Mayo, 132 S. Ct. at 1298, 1297). "We have described step two of this analysis as a search for an 'inventive concept' – i.e., an element or combination of elements that is 'sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.'" Alice, 134 S. Ct. at 2355 (quoting Mayo, 132 S. Ct. at 1294). At step two, more is required than well-understood, routine, conventional activity already engaged in by the scientific community. Rapid Litigation Management, Ltd. v. CellzDirect, Inc., __ F.3d __, 2016 WL 3606624, *3 (Fed. Cir. July 5, 2016).

B. Step One: Are Claims Directed to a Patent Ineligible Concept?

Defendants argue that the '820 patent is directed at a law of nature: that the bodily fluid of some people with Myasthenia Gravis have autoantibodies to MuSK. Plaintiffs argue that the patent method uses a man-made, patent eligible molecule, and uses that chemical complex in an innovative and transformative manner. Pls.' Surreply Opp'n Mot. Dismiss 4 [#46]. Per Plaintiffs, the claims are not directed to MuSK, instead, the claims "[r]ecite using a man-made chemically-modified version of MuSK to form a specific complex that does not occur in nature" and are therefore patent eligible. Pls.' Surreply Opp'n Mot. Dismiss 5 [#46].

The patent describes a method in which ^{125}I-MuSK is put into a sample of bodily fluid, and then the bodily fluid is filtered so that autoantibodies attached to the ^{125}I-MuSK are detected. The presence of the ^{125}I-MuSK autoantibodies indicates the person suffers from Myasthenia Gravis. The relevant portion of the patent states:

> The invention claimed is:
>
> **1.** A method for diagnosing neurotransmission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal comprising the step of detecting in

a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK).

2. A method according to claim 1 wherein said method comprises the steps of:
a) contacting said bodily fluid with muscle specific tyrosine kinase (MuSK) or an antigenic determinant thereof: and
b) detecting any antibody-antigen complexes formed between said receptor tyrosine kinase or an antigenic fragment thereof and antibodies present in said bodily fluid, wherein the presence of said complexes is indicative of said mammal suffering from said neurotransmission or development disorders.

3. A method according to Claim 2 wherein said antibody-antigen complex is detected using an anti-IgG antibody tagged or labeled with a reporter molecule.
. . .
6. A method according to claim 3 whereby the intensity of the signal from the anti-human IgG antibody is indicative of the relative amount of the anti-MuSK autoantibody in the bodily fluid when compared to a positive and negative control reading.

7. A method according to claim 1, comprising contacting MuSK or an epitope or antigenic determinant thereof having a suitable label thereon, with said bodily fluid, immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid and monitoring for said label on any of said antibody/MuSK complex or antibody/MuSK epitope or antigen determinant complex, wherein the presence of said label is indicative of said mammal is suffering from said neurotransmission or developmental disorder related to muscle specific tyrosine kinase (MuSK).

8. A method according to claim 7 wherein said label is a radioactive label.

9. A method according to claim 8 wherein said label is 125I.

U.S. Patent No. 7,267,820. Plaintiffs argue that because ^{125}I-MuSK is not naturally occurring, the claim is patent eligible under § 101. Pls.' Mem. Opp'n Defs.' Mot. Dismiss. 11 [#37] ("Those antibody/MuSK complexes are created in the laboratory and result from the use of a non-naturally-occurring laboratory-created molecule, ^{125}I-MuSK, and therefore, the antibody/MuSK complexes formed and detected by claim 9 are not found in nature.").

While ^{125}I-MuSK and the antibody/MuSK complexes are not found in nature, this does not transform the patent at issue here to a patent eligible concept. Contrary to Plaintiffs'

argument, the '820 patent is not a composition patent directed at the creation of the ^{125}I-MuSK auto-antibody complex. Rather, the patent is directed at a method for the diagnosis of a disease. U.S. Patent No. 7,267,820, col. 1 l. 9-11 ("The present invention is concerned with neurotransmission disorders and, in particular, with a method of diagnosing such disorders in mammals."). Although the patented method uses man-made ^{125}I-MuSK, the use of a man-made complex does not transform the subject matter of the patent. The focus of the claims of the invention is the interaction of the ^{125}I-MuSK and the bodily fluid, an interaction which is naturally occurring. The purpose of the patent is to detect whether any antibody-antigen complexes are formed between the ^{125}I-MuSK receptor and the antibodies "present in said bodily fluid." U.S. Patent No. 7,267,820, Claim 2. Counter to Plaintiffs' argument, because the patent focuses on this natural occurrence, it is directed to a patent-ineligible concept. See also Electric Power Group, LLC v. Alstom S.A., __ F.3d. __, 2016 WL 4073318, at *3 (Fed. Cir. Aug. 1, 2016) ("[W]e have described the first-stage inquiry as looking at the 'focus' of the claims, their 'character as a whole.'") (quoting Enfish, LLC v. Microsoft Corp., 822 F.3d 1327, 1335-36 (Fed. Cir. 2016)).

Athena's patent is similar to the patent invalidated by the Supreme Court in Mayo. In Mayo, the Supreme Court invalidated the patent of a diagnostic test which measured how well a person metabolized thiopurine drugs. 132 S. Ct. at 1295. The patent claimed a method in which the drug 6-thioguanine was given to a person, after which the level of 6-thioguanine in the person's blood stream was measured. Id. The Court held that the patent method was directed to observing a law of nature. "Prometheus' patents set forth laws of nature- namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of thiopurine drug will prove ineffective or cause harm." Id. at 1296. While the Court

acknowledged that it took human action (the administration of a thiopurine drug) to trigger the desired reaction, the reaction itself happened apart from any human action. Id. at 1297. The Court found the claim invalid because the method sought to measure how well a person metabolizes the drug. The Court described the interactions as 'entirely natural processes." Id. Likewise, Plaintiffs' method seeks to measure autoantibodies that have attached to a receptor protein, an interaction which is a similarly natural process. In Mayo, a man-made substance was administered to a person, and the by-product of the metabolization of that man-made substance was observed. Here, a man-made substance (^{125}I-MuSK) is administered to a sample of bodily fluid, and the by-product (^{125}I-MuSK autoantibodies) is observed. Mayo, 132 S. Ct. at 1297; see also Genetic Tech. Ltd. v. Merial LLC, 818 F.3d 1369, 1376 (Fed. Cir. 2016) (finding that when the patent claim focuses on a newly discovered fact about human biology, the claim is directed to unpatentable subject matter).

Further support can be found in Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1372 (Fed. Cir. 2015), cert. denied, 136 S. Ct. 2511 (2016). The case involved the patent for a method using fetal DNA for the diagnosis of certain conditions. The inventors discovered that cell-free fetal DNA ("cffDNA") was present in maternal plasma and serum. By implementing a method for detecting the small fraction of paternal cffDNA in the maternal plasma or serum, the inventors were able to determine certain inherited characteristics. Id. at 1373. The patent method isolated and amplified cffDNA, allowing for greater efficiency in diagnosis of genetic defects. As the court noted, "[t]he only subject matter new and useful as of the date of the application was the discovery of the presence of cffDNA in maternal plasma or serum . . ." Id. at 1377. Likewise, what is new and useful here is the discovery that some patients with Myasthenia Gravis have MuSK autoantibodies in their bodily fluid.

Relying on Rapid Litigation Mgmt. Ltd., 2016 WL 3606624 at *4, Plaintiffs seek to distinguish the '820 patent from Ariosa and Mayo by arguing that the '820 patent is focused on the steps required by the claimed method, rather than on the outcome of the diagnostic test. In Rapid Litigation Mgmt. Ltd., patent inventors discovered that hepatocytes, special liver cells that are used for testing, diagnostic, and treatment purposes, could be refrozen. Refreezing of hepatocytes was a breakthrough because the cells naturally have a short life span, and can only be harvested from a limited number of people. Prior to the discovery, hepatocytes could only be frozen one time, which limited their utility. Id. at *1. The patented method importantly allowed for multi-donor hepatocyte pools, a useful research tool that allows the study of a drug's impact on a representative population. Id. The Federal Circuit found the "end result of the '929 patent claims is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze thaw cycles. Rather, the claims are directed to a new and useful method of preserving hepatocyte cells." Id. at * 4. The court found that the process' "desired outcome" was a method to produce something useful, and therefore was not directed at a patent ineligible concept. Id. The method allowed for refrozen hepatocyte cells to be used in a myriad of ways. Conversely, the desired outcome of the Plaintiffs' method is the detection of MuSK autoantibodies. It does not produce something useful beyond that diagnosis.

Plaintiffs' argument that the patent is transformed by the use of a man-made molecule is unavailing. The stated purpose of the patent is to diagnose Myasthenia Gravis, and the method is directed to a patent ineligible law of nature under § 101.

C. Step Two: Does the Inventiveness of the Claim make it Patent Eligible?

While the patent is directed to a patent ineligible concept under § 101, the patent can still be upheld if the method contains an "inventive concept." Alice, 134 S. Ct. at 2355.

Defendants argue that Plaintiffs' patent fails step two of § 101 analysis because it uses well-known techniques for identifying the presence of autoantibodies to MuSK and therefore does not contain an "inventive concept." Defs.' Mem. Supp. Mot. Dismiss 14 [#26] ("[P]rocess steps that recite techniques scientists would have already known to use in conjunction with the newfound natural law cannot supply the inventive concept."). Defendants cite to the patent specification which states that "[i]ondination and immunoprecipitation are standard techniques in the art, the details of which can be found in references (4 and 6)." Defs.' Mem. Supp. Mot. Dismiss 10 [#26]; U.S. Patent No. 7,267,820, col. 4, l. 9-12. Defendants note that the two publications referenced in the specification date from 1976 and 1985, and according to Defendants the publications describe "(1) the introduction of a ^{125}I-labeled antigen (AChR) into a bodily fluid sample, (2) immunoprecipitation, and (3) detecting the radioactive label." Defs.' Mem. Supp. Mot. Dismiss 10 [#26]. Defendants argue that the publications show that the methods described in the patent are commonly used by researchers in the field, and thus the claims do not pass step two of the analysis under § 101. Plaintiffs argue that a Rule 12(b)(6) motion cannot rely on extrinsic evidence to support the claim for dismissal, and that novelty and obviousness questions involve factual determinations that cannot be determined at the pleading stage. Pls.' Mem. Opp'n Mot. Dismiss 22 [#37].

The court cannot determine at this junction whether Plaintiffs' patented method uses standard techniques in the art, or whether it is sufficiently inventive to be patentable under the second step of Mayo. While it may later be established that the Plaintiffs' process is not deserving of patent protection because the techniques are standard in the art and therefore fail to provide an inventive concept, the court cannot resolve these factual determinations at the motion to dismiss stage. On the face of the claims and specification of the patent-in-suit, as well as on

the face of the complaint, the court cannot determine as a matter of law whether the patent provides a "combination of steps" to transform the method into a patent-eligible invention. Alice, 134 S. Ct. at 2360; see also, Mortgage Grader, Inc. v. First Choice Loan Services, Inc., 811 F.3d 1314, 1325 (Fed. Cir. 2016) ("Whether a claim is directed to statutory subject matter is a question of law. [D]etermination of this question may require findings of underlying facts specific to the particular subject matter and its mode of claiming[.]") (quoting Arrythmia Research Tech., Inc. v. Corazonix Corp., 958 F.2d 1053, 1055-56 (Fed. Cir. 1992)).

III. Conclusion

For the foregoing reasons, Defendants' Motion to Dismiss [#25] is DENIED.

August 25, 2016

/s/ Indira Talwani
United States District Court

September 6, 2016

Honorable Indira Talwani
United States District Court
for the District of Massachusetts
John Joseph Moakley U.S. Courthouse
One Courthouse Way
Courtroom 9
Boston, MA 02110

Re: *Athena Diagnostics, Inc. v. Mayo Collaborative Services, et al.*
USDC, D. Mass. Civil Action No. 1:15-cv-40075 (IT)

Dear Judge Talwani:

Defendants Mayo Collaborative Services, LLC, and Mayo Clinic (together, Mayo) respectfully submit this letter to update the Court on the parties' efforts to identify an efficient way to move the case forward, including exploring limited discovery to resolve *Mayo* Step 2 as it relates to Mayo's § 101 Motion to Dismiss, as the Court suggested at the August 2, 2016 Hearing. (Hearing Tr. at 51-52.) The parties met and conferred on this issue on September 2, 2016 but were unable to reach agreement on how best to move the case forward.

It is Mayo's position that the § 101 issue should be resolved on early summary judgment and with only limited discovery on the issue raised by *Mayo* Step 2—i.e., the conventional nature of 125I-labeled antigens. In contrast, Plaintiffs told Mayo that it is their position that full discovery should proceed on all issues with the possible exception of damages. Indeed, during the September 2 telephone conference, Plaintiffs told Mayo that they expected to file an immediate motion to compel Mayo's production of technical documents concerning its diagnostic tests, including documents relating to the operation and development of those tests.

As discussed at the August 2, 2016 hearing, Mayo respectfully requests that the Court hold a status conference to discuss these issues. (Hearing Tr. at 51-52 ("I will get a decision out as soon as I can. And assuming I go in that direction, I'll have you in for a status conference, and we'll just figure out what makes sense at that point.").) Mayo is available for a status conference at the Court's direction, and suggests that each side simultaneously file a submission not longer than three pages outlining their discovery proposal at 5pm Eastern Time two business days in advance of any scheduled status conference.

Very truly yours,

/s/ Adam J. Kessel
Adam J. Kessel

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS
EASTERN DIVISION

ATHENA DIAGNOSTICS, INC., ISIS INNOVATION LIMITED, AND MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V., Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	CIVIL ACTION NO. 1:15-cv-40075

PLAINTIFFS' SUBMISSION FOR A DISCOVERY PROPOSAL

Pursuant to the Court's September 7, 2016 Notice of Electronic Filing (Dkt. No. 106), Plaintiffs hereby submit the following discovery proposal.

1. Preliminary Disclosures

a. Defendants' Preliminary Productions. This production is the subject of Plaintiffs' Motion to Compel Interrogatory Responses, Production of Documents, and Preliminary Disclosures ("Motion to Compel") (Dkt. No. 108). As set forth in the Parties' Amended Joint Proposed Pretrial Schedule ("Proposed Pretrial Schedule") filed May 3, 2016 (Dkt. No. 68), Defendants had stipulated to producing to Plaintiffs the core technical documents related to the accused tests, including but not limited to operation manuals, literature, assays, and specifications within 14 days after the Court's ruling on Defendants' Motion to Dismiss. Within that same timeline, Defendants were to respond to Plaintiffs' pending document requests and interrogatories. Defendants did not produce their full Preliminary Production within 14 days of the Court's ruling on the Motion to Dismiss. Plaintiffs therefore filed the pending Motion to Compel on September 14. The Court will hear arguments related to this Motion to Compel on October 6 (Dkt. No. 113). Plaintiffs respectfully request the Court order Defendants to immediately produce their Preliminary Production—information that should have been readily accessible and producible since their stipulation on May 3.

b. Disclosures relating to claim construction will be triggered from Defendants' Preliminary Production. Accordingly, no later than 28 days after the date of service of Defendants' Preliminary Production per Paragraph 1(a), Plaintiffs shall serve and file Preliminary Infringement Contentions for the claims at issue in this case, currently claims 7 – 9 of U.S. Pat. No. 7,267,280 based on Plaintiffs' present understanding of Defendants' accused infringing commercial offering. Plaintiffs shall identify the accused product(s) or method(s) that allegedly infringe those claims. Plaintiffs shall also specify whether the alleged infringement is literal or falls under the doctrine of equivalents. Plaintiffs shall produce all documents supporting their contentions and/or identify any such supporting documents produced by the accused infringer. Such disclosures may be amended and supplemented up to 30 days before the date of the Markman Hearing. After that time, such disclosures may be amended or supplemented only by leave of Court, for good cause shown.

c. No later than 28 days after service of the Preliminary Infringement Contentions per Paragraph 1(b), Defendants shall serve and file Preliminary Invalidity and Non-Infringement Contentions. Defendants shall identify prior art that anticipates or renders obvious the identified patent claims in question and, for each such prior art reference, shall specify whether it anticipates or is relevant to the obviousness inquiry. If applicable, Defendants shall also specify any other grounds for invalidity, such as patent ineligibility, indefiniteness, enablement, or written description. Defendants shall produce documents relevant to the invalidity defenses and/or identify any such supporting documents produced by the

Plaintiffs. Such disclosures may be amended and supplemented up to 30 days before the date of the Markman Hearing. After that time, such disclosures may be amended or supplemented only by leave of Court, for good cause shown, except that, if Plaintiffs amend or supplement their Preliminary Infringement Contentions, Defendants may likewise amend or supplement their disclosures within 30 days of service of the amended or supplemented Preliminary Infringement Contentions.

2. Claim Construction Proceedings

a. The parties previously agreed to the timing and procedures for the Markman Hearing in paragraphs 3 and 4 of the parties' Proposed Pretrial Schedule (Dkt. No. 68). There is no reason to deviate from the parties' agreed-to timeline and procedure, and Plaintiffs request that the Court adopt it to avoid further delay. In general, the parties' agreement calls for the following sequence of events:

(i) simultaneous exchange of claim terms for construction within 7 days after service of Preliminary Invalidity Contentions,

(ii) simultaneous exchange of proposed constructions 14 days later,

(iii) meet and confer 7 days later,

(iv) filing of each party's opening claim construction briefs 21 days later,

(v) filing of each party's reply claim construction briefs 21 days later,

(vi) filing of a joint claim construction statement with the Court.

b. The "Claim Construction Hearing or "Markman Hearing" will be held at least 28 days after the filing of the parties' joint claim construction statement or at the Court's earliest convenience.

3. Fact Discovery. Plaintiffs propose the following which were agreed to in the parties'

Proposed Pretrial Schedule:

a. **Written Discovery**. Written discovery (requests for production of documents, interrogatories, and requests for admission) shall be served consistent with the Federal Rules of Civil Procedure. Responses and objections to written discovery will be due 30 days after service, per the Federal Rules of Civil Procedure.

b. **Fact Discovery**. Fact Discovery must be completed within 60 days after the Court's claim construction ruling.

c. **Phased discovery**. As the parties agreed to in their Pretrial Schedule, discovery shall not be conducted in phases. Phased discovery would delay this case further.

Moreover, there is considerable overlap between discovery of the *Alice* Step Two and other issues in the case, as discussed in Plaintiffs' Motion to Compel. (DKT No. 113, at 9).

d. **Electronically Stored Information (ESI**). Within fourteen (14) days of receipt of Defendants' Preliminary Production, the parties will either submit a stipulated agreement regarding ESI, or submit disputed positions for the Court's resolution.

4. Expert Discovery. Plaintiffs propose the following which were agreed to in the parties' Proposed Pretrial Schedule.

a. The parties' trial experts must be designated, and the information contemplated by Fed. R. Civ. P. 26(a)(2) must be disclosed no later than 60 days after the issuance of the Claim Construction Order.

b. The parties must designate rebuttal trial experts and exchange rebuttal expert reports no later than 28 days after the service of Opening Reports per Paragraph 4(a) of this Section.

c. The parties must exchange reply expert reports no later than 28 days after service of Rebuttal Reports per Paragraph 4(b) of this Section.

d. The parties must depose trial experts no later than 56 days after service of Reply Reports per Paragraph 4(c) of this Section.

Provisions Relating to the Conduct of, and Limitations on, Discovery

Plaintiffs propose the following restrictions on discovery:

1. Depositions: Each side shall have a maximum of 50 hours of fact depositions, including (1) depositions conducted under Rule 30(b)(6); and (2) third party depositions.

2. Document Requests: Document requests shall be consistent with the Federal Rules of Civil Procedure.

3. Requests for Admission: Each side may serve no more than 50 requests for admission.

Procedural Provisions

The parties agreed to certain procedural provisions in their Proposed Pretrial Schedule. Plaintiffs propose that those Procedural Provisions be adopted by the Court.

Dated: September 30, 2016

/s/ *Emmett J. McMahon*

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CERTIFICATE OF SERVICE

I, Emmett J. McMahon, hereby certify that on this 30th day of September, 2016, the foregoing document was filed electronically with the Clerk of the Court using the CM/ECF system and will be sent electronically to the registered participants as identified on the Notice of Electronic Filing.

/s/ Emmett J. McMahon

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

*ATHENA DIAGNOSTICS, INC., ISIS INNOVATION LIMITED, and MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V., Plaintiffs	*	CIVIL ACTION
vs.	*	No. 15-40075-IT
*MAYO COLLABORATIVE SERVICES, LLC d/b/a/ MAYO MEDICAL LABORATORIES and MAYO CLINIC Defendants	*	

BEFORE THE HONORABLE INDIRA TALWANI
UNITED STATES DISTRICT JUDGE
MOTION TO COMPEL HEARING
October 6, 2016

Courtroom No. 9
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Boston, Massachusetts 02210

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P R O C E E D I N G S

THE CLERK: All rise.

(Whereupon, the Court entered.)

You may be seated.

This is Case No. 15cv40075, Athena Diagnostics, Inc., versus Mayo Collaborative Services, LLC, et al.

The Honorable Indira Talwani presiding.

U.S. District Court is now in session.

Will counsel please identify themselves for the record.

MR. McMAHON: Your Honor, I'm Emmett McMahon for the plaintiffs, and with me from my same firm is Matthew McFarlane.

THE COURT: Good morning.

MR. McFARLANE: Good morning.

MS. NORTON: Good morning, your Honor. I'm Vicki Norton, representing plaintiff, Athena Diagnostics, Inc.

THE COURT: Good morning.

MR. KESSEL: Good morning, your Honor. Adam Kessell from Fish & Richardson representing the Mayo defendants, and with me is my colleague Jonathan Singer from our San Diego office.

MR. SINGER: Good morning, your Honor.

THE COURT: Good morning.

Okay. So when you were in front of me last, I foreshadowed where I was going with the motion to dismiss.

And what I was struggling at the end of my analysis with was that at the Step Two part of the analysis, defendants asserted that iodination and immunoprecipitation are standard techniques in the art. And in support of that they pointed out that the patent cited two scientific articles for that point. Plaintiffs responded that we're on a 12(b)(6), and it was inappropriate for me to dig into the weeds there. And so that was what I was struggling with.

Had defendants filed with their motion to dismiss an alternative request for summary judgment and included an expert declaration saying what I just said, I would have responded by saying plaintiffs are entitled to some limited discovery to test that expert declaration, but let's get it teed up. Because this may well be a point that is so obvious one way or the other to both sides that we can get it resolved, or not. But I could not do it from the bench based on -- or I did not feel comfortable doing it merely on the face of the pleading with plaintiffs saying, no, don't go beyond the face of this document.

So that was where we were.

And I foreshadowed that concern, I think, in the argument and suggested that if I denied the motion to dismiss that might give reason to have an early summary judgment motion to tee up that exact issue. And I asked you to then go forward to try and figure out whether there was a

way to come up with a plan for discovery.

To the extent that the response is, well, you said this before and promises were made before, and it's taking -- we're already a year into this case, or 18 months into this case. That doesn't really respond to where we were right then and where I think we are now.

I think the question is the following: They are going to be allowed in this court to make an early summary judgment addressing this particular narrow issue. And I think the question is, one, is there discovery that's needed for that; and, two, if in the course of that limited discovery there are other issues that are opened up, is there a reason that it is efficient or inefficient to allow those pieces also?

So that is where we are. I may be completely wrong on Step One and you may think I am completely wrong on Step One. But we are not relitigating that question right now.

And I guess the other thing I would put out there is if your view is that I am -- if plaintiffs' view is that I am looking at -- that you would agree that iodination and immunoprecipitation are standard techniques in the art, but you think that's the wrong question, then maybe the most efficient way to do this would be for you to agree to that statement, I can enter judgment for the defendants based on that statement, and you can go up to the Federal Circuit and

say, I'm completely wrong about the entire analysis, and not waste your clients' money on discovery.

But that is what was troubling me, is that they made that narrow statement which may be completely obvious to all of you, but it wasn't to me.

So the ball's in your court.

MR. McMAHON: Thank you, your Honor.

First, your Honor, we have requested -- we have two matters that I think are in front of the Court. One is our motion to compel. We had served discovery originally on a broader basis --

THE COURT: So you served discovery, I believe before initial disclosures, before a scheduling conference, as soon as the case was out of the gate, correct?

MR. McMAHON: I think we served them after we had a conference, yes. But in that -- we're not at this time -- our motion is not seeking -- we thought the case was going to go in a different direction.

But the motion that's in front of the Court right now is narrow. I'm going to talk to you about the rest of the case, too, but there's two matters. First, the motion to compel. It's in front of the Court. The information that is requested is going to be relevant to whether or not the techniques that are described in the claims are routine and well known.

THE COURT: No. That's not the question that's in front of me right now.

Okay. That's what you are looking for. I get it. That includes both Step One and Step Two, and that includes the entire thing.

I may be, you know -- and you may have a lot more fun with this in the front of the Federal Circuit than you are with me, but I am very simplistic here. And what I feel like what I have pulled out is that you had a new discovery. No one is disagreeing there wasn't a new discovery. You had a new discovery. But that was just a law-of-nature discovery, and then you took a routine technique and combined them.

So the fact that you now have something new going on after taking this new discovery and taking a routine technique, you now have something new going on, isn't the answer to our problem. The question is just, right now, the question in front of me, I think on this point, is this: "Was this just a routine technique that was applied back then when the patent was issued"; not, "What are they doing now in order to do this current test".

MR. McMAHON: Right.

First, I think the routine -- we're not trying to relitigate Step One. The Court's already ruled on that, and the Court in its order stated there may be fact discovery

that we're entitled to, and I think we are.

As far as the routineness that you mentioned, your Honor, what we're saying here is that if Mayo, and it looks like from what they've told us in their brief, that they have to have a third party help them with this method, if the steps for Mayo right now are not routine, then they couldn't have been routine in 2001.

THE COURT: So let's say that the person infringing your patent works out of their garage and they buy something from another person and then they do whatever they're doing, and you're saying they infringe, and they say, We bought this thing from over here, you're going to say, Because they bought it from over here, therefore, that answers everything?

MR. McMAHON: No.

Well, we're entitled to discovery on that. They've even suggested to the Court, and we think incorrectly, that the use -- that they can purchase iodine MuSK molecules as a commodity. And we would dispute that, and we think the evidence is going to show that's different. I think they've misled the Court, really, in saying in their summary plan and in their response to our motion to compel that this is -- this is supposed to be a world-renown laboratory, Mayo Clinic. and they're telling us and the Court that this is a routine test that is a commodity, and our evidence is going

to be that it's not.

THE COURT: I'm not interested in whether the test in front of me is routine. I don't think that's the question in front of me. I may be wrong, but I think the question in front of me is whether when you were getting the patent, whether what was going on there was that you had a new scientific discovery, or a new discovery of a law of nature, for which you then said, We're going to do a technique that is very standard in the art, and we're going to take the two things together and get to a new test that we're going to sell.

The fact that that is a new test, that's not the question. The question is whether what happened was that you used a standard technique that was known in the art.

MR. McMAHON: I think the cases say there's two different things. As far as -- from the Mayo case -- from the Mayo v. Prometheus case on down, that have interpreted Step Two -- and Alice -- that if the Court finds that there's a law of nature involved in Step One, then it goes to Step Two to see whether other aspects of the claim involve an inventive concept. And in determining whether or not it's an inventive concept, inquiry is made as to whether the steps were routine and conventional. Those are the two --

THE COURT: Which steps?

MR. McMAHON: The step -- the additional steps or the parts of the claim that go beyond the natural -- the natural phenomenon or the law of nature that was found in Step One.

So we've got Step One -- the Court must look at three things: Is it a law of nature? Is it a natural phenomenon, or are you looking at an abstract idea?

And then once you get -- the Court concludes that those three things -- the claims are directed to one of those three things, then you go to Step Two. And then the Alice Step Two requires an analysis: Do other parts of the claims that are not the natural phenomenon, do they involve an inventive concept?

And in determining whether or not it's an inventive concept, the courts have said repeatedly that you look at two things; whether the steps are routine, or whether they're well known or conventional.

And what we're focusing -- and that's two, both of them. They're two different things. And "routineness" has even been acknowledged in Mayo's briefs.

So our point here is that if they're claiming -- because I think we all agree the iodine MuSK molecule as well as the complex that's created later are not natural. Those are the things that we have to make inquiry about. Is the use of those in the steps an inventive concept? And

that's where the inquiry must be directed to, routineness and conventional, well known.

THE COURT: I don't have the different chemicals or substances here in front of me. But if I recall, this MuSK deals with a narrow area that was not being determined on a test that was being done for this disease, right?

MR. McMAHON: Yes.

THE COURT: And if you can give me again the name for the other --

MR. McMAHON: AChR.

I think 80 percent of the patients who had the disease Myasthenia Gravis were known to express this AChR, and then the invention involving the MuSK covers 20 percent or almost 20 percent.

THE COURT: And in AChR group, there was a -- the substance that was identified, that was then tagged through iodination, and then a test was created by that tag, yes?

MR. McMAHON: Well, in that test there a label was put on bungaratoxin, alpha-bungaratoxin. The tag was put on that, and then that was put on -- and labeled to the AChR.

THE COURT: So putting on an iodine label is what was done in that case, and that is what is done in the MuSK case, correct?

MR. McMAHON: Well, they're different.

In this case the label's put on the target, on the

MuSK. In the earlier one, the label was put on the alpha-bungaratoxin, which was then put on to the AChR.

So our point here is even the patent would disclose there's two different ways to do the labeling. So the kind that's in the claim right now, where the MuSK -- the target is labeled, is different.

So if these are routine, for example, then why wasn't it done in the same way in both instances? I mean the patent discloses two ways to do it. And so --

THE COURT: Wait.

Are you saying that the patent discloses two ways to do it; one way is routine and one way isn't routine?

MR. McMAHON: No. No.

I'm saying the fact that there are two different ways to label substance, one is directly on the target and one there has to be a reason why it's put on something else, the alpha-bungaratoxin, the snake venom --

THE COURT: But the reason why it's put on something else was your discovery, but the putting the label on is known in the art?

MR. McMAHON: Using labels was known in the art.

THE COURT: That's --

MR. McMAHON: Putting labels on the MuSK or directly on the target, that has to be -- that's subject to discovery here. I mean, the claims did it differently than

the prior art. The fact that they did it differently would tend to indicate, even from the specification, that it's not routine. I mean, if the routine -- why wouldn't the inventors put it on -- the label on the bungaratoxin and then the MuSK? I mean there's reasons why these are done differently, which would tend to indicated that they're not routine, it's not routinely done.

Certainly I-125 was known.

Labeling directly on to the MuSK or on to the target was different than how it was done with the AChR.

So I would suggest there, even in the patent, it's showing you different ways to do it, which would suggest labeling the MuSK directly was not a routine practice.

And then we have -- what I'm saying, you talked -- it's common sense, and, I think it's -- the courts have routinely allowed post-filing activity to determine what was the state of the art at the earlier time the patent was applied for. And we've cited those in our reply briefs.

It happens, for example, with obviousness. The inquiry is always, What was obvious at the time the patent was invented?

Well, the Supreme Court has said the courts are even required to look at these things called the nonobvious --

THE COURT: We're not doing the obviousness inquiry right now.

MR. McMAHON: No, your Honor, but what I'm saying -- well, it's been suggested earlier that this analysis of 101 has implications of 103.

THE COURT: It may well have implications for that, but that's not the analysis we're doing right now.

The problem -- I think the problem here is that the -- I may be wrong in accepting defendant's argument here, but I'm not -- my problem with not saying they prevail on the motion to dismiss was an evidentiary one. It wasn't that I disagreed with their argument if those were the facts. It was that I did not know if those were the facts.

And I guess what I'm saying here is it may be most efficient, while you disagree with that characterization, if the only fight is about the fact that they made that argument using exhibits, and you said, well, I shouldn't be looking at those exhibits on a motion to dismiss, then you should get my decision on that out and you should argue it to the Federal Circuit where you will get fresh eyes on it.

What you're saying to me now doesn't seem to comport with the analysis I think I need to do in Step Two.

MR. McMAHON: I think that the statement in the patent didn't even address routineness.

And my point is that if the Courts said it's "well known" or "conventional," those are two different things.

So --

THE COURT: It's "standard techniques in the art." That's the question, right?

MR. McMAHON: Yes, your Honor.

But that doesn't mean it's routine. I mean, just because something is standard in the art doesn't mean -- and if you're using things that are standard in the art together with one -- you know, a claim that might otherwise be non-patentable subject matter, the Diamond v. Diehr, D-I-E-H-R, the Supreme Court said you still -- it still can be patentable. Just because something is conventional doesn't automatically take the claims out of Section 101.

But I'm suggesting here, and the courts have stated -- have you used these terms, both of them, "well known" or "conventional," either one, and "routine." And they're different.

The analogy I made before in earlier days was for lawyers to cite a case to the Court. I mean, it's going to be routine to Shepardize it. It's something that is done --

THE COURT: I think that's only yours and my generation. I don't think they Shepardize anymore.

(Laughter.)

MR. McMAHON: Yes. I'm aging myself here.

But we're going to check it and make sure it's right. Everybody knows that. These are routine things that are done that you know you have to do, and you don't think about

it.

With the DNA, as I mentioned, the DNA cases, if you want to study the DNA, you have to amplify it. Everybody knows it. It's a rote decision. We have to do that.

My point is right here that's not the case. It's not routine here, and even the patent shows that.

Because why wasn't the -- again, what I discussed before, that the labeling, it was done differently with the AChR.

So if it's not routine, if decisions are being made -- design decisions are being made that are not rote, that are not routine, then that's going to take it out of Section 101.

THE COURT: All right.

Do you want to respond?

MR. SINGER: Your Honor, I guess I'll just be very brief.

I mean, I think you've got the two issues that needed to be decided by the Court correct, and I will just go back to the patent, just to ground us, what it actually says, and it's column 4, lines 10 to 12, "Iodination and immunoprecipitation are standard techniques in the art, the details of which may be found in references (4 and 6)." And those are the two references that you were earlier talking about.

In terms of addressing the best way to do this, I think you outlined it. We would be -- we can prepare an expert declaration explaining what the patent says to give you whatever further information you need, and we tried to give you as much as we could on the motion to dismiss. We accept your decision there. And we could prepare it quickly and file it. They could take a deposition. They could give you their disagreement from another expert, which I think, to be perfectly blunt, is conflating obviousness and anticipation and relying on the actual discovery to transform standard techniques into something new.

The issue here is -- you've got it right -- the application of standard techniques to this novel discovery doesn't make this patentable under 101 because they are standard techniques. We shouldn't conflate and turn routine into easy or hard. It might be hard to do a standard technique; it might be easy to do a standard technique. They remain standard techniques, and I think that is the best way to put this to bed.

THE COURT: Let me ask plaintiffs' counsel, recognizing your disagreement about the import of this point, is there any disagreement as to the truth of this statement, "iodination and immunoprecipitation are standard techniques in the art, the details of which may be found in references (4 and 6)" of the patent?

Because I wasn't willing to take, even though it was in the patent and asserted in the patent and they argued, therefore, an admission, I took the position that that was beyond the motion to dismiss and something to be determined on summary judgment.

So the question is, is there a dispute of fact as to that statement?

MR. McMAHON: That statement isolated I can't dispute, but --

THE COURT: Okay.

So then where we are is if that statement isolated is not in dispute, then I should be granting their motion either as a motion to dismiss or as a motion for summary judgment, and you should appeal my decision. Because that is the basis on which they did not get the motion to dismiss, was on the basis of my understanding your opposition being that I could not make that determination on a motion to dismiss.

MR. McMAHON: What I'm saying is the application of that concept in this particular instance to the MuSK was different. Just because it's something that -- every invention -- most inventions are adding something that's already been known in the art.

Now, what I would like -- I think, if I may, your Honor, turn over the question about the labeling with the

bungaratoxin, etc., is something that Mr. MacFarlane is more steeped in, so I would like to have him address those questions for you.

But it's the application, so -- and even that sentence right there again does not address the issue of routineness that is required by the Court.

THE COURT: But those are the arguments that you made in opposition to the motion to dismiss. And at the end of day you may be right. I'm only doing my best attempt at this, and my best attempt at this is I disagree. And what held me up from granting the motion to dismiss is that sentence, whether that sentence was accepted, was correct, or not. And on your challenge on a motion to dismiss is I can't take as true anything other than the statements in the complaint, and the complaint, taking those statements as true, it simply says, Here's the patent. It didn't say every sentence in the patent is true, so, therefore, I gave you the benefit to dispute that. But if that is not disputed, then I don't think you should be wasting time and money to flesh this whole thing out.

MR. McMAHON: Well, I am going to let Mr. MacFarlane, because I think he can provide some helpful explanation beyond what I did on what the patent is talking about with respect to the two different concepts and what ordinary people would read from this.

MR. McFARLANE: Your Honor, thank you.

I just want to make clear the patent says what it says. The statement that you read, those words are there, and I can't stand here and tell you that those words are untrue.

THE COURT: Okay. So I got that the patent says what it says, but even if the patent says what it says, it may be wrong, and so, just to be clear, there is no disagreement that this is correct?

MR. McFARLANE: About the words?

THE COURT: Yes.

MR. McFARLANE: But the key application here is the fact that those words relate not to a statement in a vacuum. Those statements relate specifically to the claims.

When we go to the claims, the claims specifically relate to one things, that's MuSK. MuSK is what's being iodinated, and MuSK is what the subject of the immunoprecipitation is, right. So you're looking at MuSK in the claims. It's not the fact that you can iodinate, and it's not the fact that you can immunoprecipitate.

THE COURT: But that's where I might be wrong about Step One, but that's where, when I take this apart, that's where I got to the point that I am. And what you're saying here is conflating Step One and Step Two.

MR. McFARLANE: Actually it's not, and I would like to explain why that's the case.

THE COURT: Okay.

MR. McFARLANE: So if we get to Step Two, we've actually already made the conclusion that there is this law of nature, and so I'm putting that in my rear-view mirror. We're not looking to see whether there's a law of nature here at all.

What we're trying to do is understand whether what is called for in the claims converts the things we've already decided is a law of nature into an application, something that can be called an invention under 101. That's all we're trying to do.

And what defendants are saying, which is justified, there's a statement in the patent that says something was routine and known in the art.

MR. KESSEL: "Standard."

MR. McFARLANE: I'm sorry. It doesn't say -- I'm going to keep doing that. It doesn't say "routine." It says a standard technique known in the art.

But the fact of the matter, like Mr. McMahon said, is that almost every invention stands on a foundation of standard techniques known in the art. That's how the art progresses. It uses standard and known techniques to create new inventions.

And the fact of the matter is is that the law is on our side with regards specifically to Step Two, okay.

In the AMP case, which we cite in our brief, in Footnote 2 of the reply, the Federal Circuit clearly held if you take a chemical and modify it, that modified chemical, its use and method is necessarily not conventional.

Conventional is the standard for which you are looking at Step Two. Step Two is routine and conventional. Conventional cannot be the result of using a man-made chemical or a nonobvious chemical in a new process. That's what the AMP case says. That's the law, your Honor.

So this is a squarely step-two proposition, that we're saying the fact that the iodination of MuSK, right, relating that statement that you read to the claims, that iodination of MuSK is a nonobvious, novel, chemical, that's man made, that's used in a subsequent process. And that use under AMP is necessarily patent eligible under Step Two, and that's the law.

And this is consistent with how the Supreme Court has held and upheld the Diamond v. Diehr case. In that case, there is -- basically the law of nature was a crystal clear application of a mathematical convention of essentially a law of nature, the Arrhenius equation, and basically the court in that case said, You can take this well-known technique, which is curing rubber using a kiln, and essentially apply the law of nature to those known steps, and every one of those known steps was known in the art.

And that was -- if you want to take a combination of things that everybody knew and put it together, that was it. I mean, people have been curing rubber for a hundred years.

THE COURT: But that was a patent on the new substance. You don't have a patent on the new substance.

MR. McFARLANE: That was a patent utilizing a law of nature to create something that hadn't been created before.

THE COURT: But you're not patenting what you created.

MR. McFARLANE: You're patenting the steps of actually making the thing. That was the invention, was actually the steps of the process to create the cured rubber.

THE COURT: But you weren't patenting the creation of this new substance.

You were saying, We have a discovery. We're going to use the same tests that's been used in other situations, and now we have a test to test for that naturally occurring.

MR. McFARLANE: Well, respectfully, your Honor, I think the claims actually do incorporate a new chemical entity. The new chemical entity is the labeled MuSK.

THE COURT: They have that happening as part of the process, but that -- it wasn't claiming that new chemical. That isn't what you were claiming in the patent.

MR. McFARLANE: But, your Honor, respectfully, in the AMP case -- and the AMP case was actually a method claim as well. That was a method that was utilizing a new chemical, and that's essentially what's happening here.

And with respect -- I think one of the things to be clear about that one statement, and I just want to be clear about this because this is important, it's not like that one statement can possibly be dispositive here, okay. If you take one statement out of the patent, that can't be representative of what the state of the art was at the time of the invention.

And, in fact, if you look in the patent at Figure 1 -- and I'll just direct the Court's attention. It's on the third page of the patent.

It basically shows in Figure 1a, the various steps that the inventors had to take in order to even do that step of iodination, okay?

So I'll walk you through Figure 1a, because I think this is really important for how the Court should look at what the invention was in the context of conventional or perhaps standard techniques in the art.

In Figure 1a, what the inventors are showing you is that MuSK, as it exists in a cell, actually sits in a membrane. And so the long line all the way to the left with the circles on the top going through two parallel lines,

that's sitting in the membrane of a cell.

And in the case of iodination, that's the technique that's standard in the art, it's very difficult to iodinate a protein that sits in a membrane. It's very, very difficult even today, and that would not be something that would be a standard technique in the art.

And so in order to actually get to the final result, which is reported in the patent, of iodinated MuSK, what they had to do was create new chemical entities, new constructs. So these shortened versions of MuSK to the right were the ones that could actually accept the iodination, right. So they had to take an extra step. That extra step is part of the Court's analysis with regard to whether this was a routine and conventional effort. Because that's an important aspect of whether it could be iodinated in the first place.

THE COURT: Where is that in the claims?

MR. McFARLANE: Well, in claim 7 there is basically a requirement that the MuSK -- and I will read it directly. It says, "Contacting MuSK or an epitope or an antigenic determinant thereof having a suitable label thereon."

"Having a suitable label thereon" means that the label actually attaches to the chemical that you want to label and that the chemical as labeled has the same functionality that it would have had if the label wasn't present.

And it's a fact question that I think is kind of complex to sit here and say that it would have been routine to iodinate a chemical that's sitting in a membrane, because, as a matter of fact, that's a very difficult thing to do.

And these are the types of facts that would need to come out in order to understand whether as a matter of Step Two there was any consideration of routineness. There are many more facts in the patent that need to be brought to bear.

And so, your Honor, respectfully, the comparison between iodinating the toxin for the acetylcholine receptor test is extraordinarily different from iodinating the MuSK for the MuSK test. And because of that difference, it's just not an apples-to-apples comparison to say that iodination is necessarily a standard technique in the art that would render claim 7 through 9 invalid.

THE COURT: So if you were presenting this to me after discovery, what would you anticipate showing me?

MR. McFARLANE: Am I going to be successful in that? I mean, am I going to actually be able to find the facts that are necessary to prove what it is? I mean, I'm trying to figure out what it is.

THE COURT: Well, one of the ways that I was thinking of proceeding as we entered in here today was to

suggest that you revisit your initial disclosures, both sides, and that you disclose the witnesses and documents, and I would add experts, that you would use to support your contention regarding Step Two, and I was going to suggest that both sides do that. And then that we allow depositions of -- you produce those documents that you would use to support your claim on Step Two, and that you can depose those fact witnesses, and you can depose those experts. And then we can have summary judgment with what they think is supporting their defense and you think is supporting your claim.

And I sort of envisioned that that's where this would have gone, which is to say, well, I thought all we needed was an expert, and that's what was discussed at the hearing, that you have a right to present your claim, your argument for why that meets Step Two.

But when your come in and you say they hold all of that information, then you've lost me. Because it doesn't seem that that answer is an answer. Well, you might have some gravy by saying, Hah, hah, they're doing this too. It seems that the substance of what you're saying is information that you have.

Am I wrong about that?

MR. McFARLANE: So to respond to that, it's certainly not gravy. And I think the way that we would ask

the Court to consider this question is as follows: Think about the sources of information that we can turn to, factual information, not just an expert's opinion, that would dictate to the Court whether something was, in fact, as applied to the claim, a standard technique known in the art.

One, we might turn to the inventor. We might say, What did the inventor actually do to get to the invention? And that seems to be fair game.

Two, we might turn to Athena and its agents who designed the test in the first place that's commercially available. And so we might say: Well, how did you actually get to the step of applying the iodine to the MuSK in a way that made the test functional? And there might be clues in the routineness of that application to show there were difficulties if --

THE COURT: You got the patent before you tried to put it out to market, so sort of what happens in actually trying to do it doesn't seem to make it.

The question is, at the time you got the patent, what had been discovered and what was known at the time? Why isn't that the question?

MR. McFARLANE: Because, respectfully, your Honor, there is the first time that that molecular entity had been created was in the patent, and, in fact, that's why claim 7

is such a novel claim, and claim 8 and 9.

THE COURT: But why isn't the information you would need to make that argument to say, The first time this happened was then, and this was very different, and that's why we have the patent on it. Why does it say, Well, and now we've done something even more different since then?

MR. McFARLANE: No. That's actually not what we're saying. What I'm saying is it's a very different question.

The question you're posing is whether something that's a general technique, as applied generally and known within the field, is something that's a standard technique that would render this claim invalid because it failed Step Two.

And what I'm saying is something a little bit different -- actually, it's a lotta bit different.

It's basically saying that you have to focus on: Well, what is it about the claim, right, that makes the claim, the application in the claim, routine?

And by looking at just what they did in the patent, that's not getting to what's looking at the claim. It's only getting to part of the question. And the part of the question is the answer, right? Claim 7 is not limited to I-125 MuSK. Claim 7 covers labels, labels generally. And the question of claim 7, and claim 8 for that matter, is not so much whether what was specifically done in the patent is sufficient to show that it was standard technique and known

in the art. It's a collection of how are these techniques applied to the specific instances of labeling MuSK to show that that would be something that would be routine in the field.

And if you look at the --

THE COURT: So if I challenge the patent -- I'm sorry for cutting you off.

MR. McFARLANE: No problem.

THE COURT: But I do get to do that.

(Laughter.)

MR. McFARLANE: Yes. It's your prerogative.

THE COURT: If I challenge the patent the moment it's been issued, the way you're saying this, you would have a much weaker claim than when you have eight years of data to show what happened afterwards as we're trying to put it together.

MR. McFARLANE: I am not saying that at all, your Honor.

What I'm saying is that I have less information about whether the technique that's used and claimed in the patent is actually routine and conventional under a Step-Two analysis.

THE COURT: Why?

MR. McFARLANE: Because there's a whole body of -- the expert's not just going to be opining on what the

inventors did in order to get to the invention. That's a too-limited view of the world if the conclusion -- if the factual conclusion is going to be it's routine and conventional. We're asking for a survey. We're asking for all of the information that's going to go into the conclusion that something was, in fact, a standard technique as applied to the subject matter of the claim.

THE COURT: At the time the patent issued.

Why is it after the patent issued? I don't understand that.

MR. McFARLANE: Because if there was information generated later on that shows conclusively that something was difficult to do 10 years later, 15 years later, it was necessarily difficult to do at the time of the patent. Just because the information might not exist at the time of the patent as to its difficulty, the later information is just as relevant to the level of difficulty at the time of the invention.

And I can --

THE COURT: I'm not following that.

Let's assume it was difficult, and let's assume it's entirely difficult that what the patent here -- there were all these pieces, but in reality doing all of these pieces is complicated or difficult.

Why does that make it more appropriately patented?

MR. McFARLANE: Because the question of whether something is routine hinges on whether something was easy to achieve or not. The routineness and conventionality of the test, or with any application, is directly proportional to how difficult it is to actually make it functional in an inventive context.

It's hard, if not impossible, to disentangle the idea of how difficult something is with regard to how routine and conventional it is for Step Two. The whole point of Step Two is to essentially say, Well, what have you done to convert this law of nature into something that's deserving of a patent?

THE COURT: At the time that you're getting the patent.

I'm not following why the appropriate discovery or the appropriate information in front of me has to do with information that wasn't there at the time the patent issued. I'm lost.

MR. McFARLANE: If something isn't routine today then I can presume it wasn't routine at the time of the patent. Because, generally speaking, things don't become less routine. They become more routine as they're applied, as they're used, as familiarity with techniques become more prevalent in the field.

So if I can show -- and what we, I think, can show and

based on what Mr. McMahon told you, I think we have a very good chance of showing, that there are some difficulties in applying the very same standard techniques known in the art to MuSK. And those very same difficulties exist today. And the fact of the matter is it couldn't have been routine at the time of the invention and not routine today. Science doesn't move backwards. It only moves forward. Unless science takes a great step backwards, and we can't assume that.

This is just all to show that there's information that needs to be taken out of the patent and brought to bear if you're just focusing on the patent.

But our position is there's far more information than just the information that led up to the invention that's going to be relevant and bear on the fact of routineness and conventionality with respect to Step Two.

And that's the real function -- that's the real question here. It's the Step-Two question.

It's not necessarily the question as to -- you know, you framed it, your Honor, "In the patent is the statement correct"?

But, respectfully, I think that that's not quite the right question. The right question is: Are the steps that are recited in claims 7 to 9 sufficient to take the law of nature, which we've already decided is there, and convert it

into an application that can be deemed an invention?

And that, respectfully, is a different question than the one you posed.

THE COURT: So when the patent is being issued in the first instance, the information available is the information that's in the patent?

MR. McFARLANE: Correct.

THE COURT: And a decision is being made at that time that the patent is valid or invalid.

Our problem today is that the law changed along the way.

But let's assume that that wasn't the circumstance. You're saying to me that the determination of a patent's validity ultimately will be sort of a larger universe than what was present in the patent?

MR. McFARLANE: Correct, your honor.

And as we laid out in our reply brief, that's what happens routinely in a patent case. You know, the Patent Office has the information before them to make a determination in the first instance about whether a patent should be valid or not. But later, when more information is actually brought to bear in a court case, we have the benefit of after-filing information. And it's not so much --

THE COURT: If you had come in here -- or if you

want to come in here and say that although the Patent Office was told that this piece was routine, we have, you know, four experts lined up here who say, No, this wasn't at all routine, and this is what was going on at the time and it wasn't routine at all at the time. That additional information, it would seem to me, there is no reason why you would exclude it.

But to say, We're going to prove our case by seeing what happened for the next ten years, that seems different than the notion of how a patent is or is not issued.

MR. McFARLANE: Right.

So a patent's validity is established by many factors, and some of those factors occur after a patent is filed. So we pointed out in our reply in the context of obviousness. So obviousness, just like Section 101, is going to limit the validity of patents that don't meet the qualifications of that doctrine.

So if there is a charge of obviousness, one defense to that charge is for the patentee to show, Wait a second, there's other evidence out there that shows that the patent itself was not obvious.

THE COURT: But that's different because what you're saying is how does one know something is obvious? One knows something is obvious because many different people could get to that same conclusion.

But this isn't a question of whether it was obvious. This is a question of whether there was a standard technique that was applied to this new information.

MR. McFARLANE: Respectfully, the parallel is almost identical in my mind, your Honor.

Basically the whole idea of what you're saying is that the question is not obviousness here. The question is routineness. I mean, that's the standard we're applying to Step Two.

And what the Court is asking now is, At the time of the invention, was it routine?

And all I'm saying is that there is limited information that's actually in the inventive application in the file and in the patent itself and that more information is brought to bear on that question.

The same is true with obviousness. If I show ten years down the road that people licensed my invention, people copied my invention, people said that my invention was great, well, that's evidence that came later after the patent was filed that the patent, in fact, was not obvious because look at all of this praise, look at all of this satisfaction of the need in the art. That's information that comes after the patent was filed.

The exact same parallel was happening here.

We have a statement in the patent specification that's

a general statement that applies broadly in a very, very large field, and the claims that talk about a chemical that had to be made in the laboratory using constructs of DNA that have not been made before, using iodinated 125 in an application that had not been made before, to create a chemical that had not been made before, in a series of steps that had never been put together before. Are we saying that one statement is enough to negate the inventive aspect of those additional features of the claim?

My answer would be no.

But their answer is yes, and that's where we are now.

All I'm saying is let's look two years later, three years later, four years later, ten years later. What happened? Well, what happened?

We have additional tests that basically said -- and publications, this is true -- or suggest. I'm sorry. I should say "they suggest"-- that actually it's not that easy to put I125 on MuSK, okay. We have evidence now from the defendants that they have to go to a third party in order to get their I125 MuSK.

Something that is difficult to obtain or difficult to make yourself is evidence that it's just not routine, and I'm just saying that this is something that should be considered in the body of evidence when reaching a factual conclusion.

THE COURT: Is there a disagreement as to the facts that plaintiffs' counsel just stated?

MR. SINGER: That the later -- I'm not sure. He said a lot.

THE COURT: The last bit about that it's difficult to obtain, difficult to make yourself, that it's not just -- it's just not routine to make yourself, and that you're client, in fact, goes to a third party to get the I125 MuSK.

MR. SINGER: We do. I'm informed we do. That's what we do.

But in terms of is it easy versus hard, that, you know, I don't know whether we agree or disagree. I don't think it's relevant.

THE COURT: Well, but that's the point. If you don't disagree as to that fact in the patent, and they're willing to present to me the argument -- to stipulate to the facts that you've made to me, then rather than spending everybody's time on experts and discovery, tee up that issue on agreed-upon facts for purposes of my motion, and I may be convinced by that information, or I may not.

But it's a legal-- the question here is a question that is not, I don't think, ultimately disputed facts.

The question here is: What's the correct way to apply Step Two?

And you're saying, and I have been accepting that, the

correct way to apply Step Two is that so long as the iodination is a standard technique, then there's nothing new here, and I just didn't get to that fact.

And you're saying, No, clearly a whole lot more is going on and you have to take that into account.

And so I think the more efficient way here may be to see if you can agree to stipulated facts for purposes of this motion. And, you know, it may be that the only way you're going to be able to do it is with the understanding that if this isn't resolved, that this motion -- that we move past those stipulations and start clean.

But for purposes of this motion, it seems to me we should be able to tee this issue up. And either I agree with the defendants on it, and then you can have it revisited; or I agree with you on it, with the plaintiffs on it, and then we can have the full-blown discovery.

But it doesn't seem like you should be charging your clients if the real problem here is not the facts but my understanding of the law.

MR. SINGER: Your Honor, we are prepared to try to do that. I think your approach gives us the chance not to spend millions of dollars to find out the answer to a question which I think fairly the patent already answers.

THE COURT: If you will stipulate -- for purposes of this motion, if you will stipulate to the assertions

they're making about what happened after the patent, then we can tee the argument up, and I can try to make a determination here of whether I should be viewing that or not. If I view it as the motion is denied, defendant's motion is denied, and you proceed without prejudice to fleshing out what those actual facts are. If you prevail on that point, even with all of their facts assumed to be true -- I mean, it's essentially --

MR. SINGER: That's what happens on summary judgment anyway.

THE COURT: Well, no, only the disputed facts.

MR. SINGER: That's true. Fair enough.

THE COURT: I guess what I'm saying is let's suppose that you have a complaint that alleged -- and maybe the complaint does and I have not properly focused on it -- but let's assume we accept their facts as to the complexity of what happened afterward --

MR. SINGER: Your Honor, we're prepared to try to do that. I think that is a -- if that's the path forward that would help the Court.

I would just simply comment that if you look at the Supreme Court's law, "easy" versus "hard," "complexity" versus "non-complexity," that's not the answer. I mean, nuclear power is complicated. It's conventional as we look at it today.

THE COURT: So let me suggest the following, because maybe I have given short shrift to your complaint.

As I said at the beginning, I denied the motion to dismiss as Step Two, having viewed that assertion in the patent as being something that wasn't properly in front of me on a motion to dismiss.

So with your concession that that statement in the patent is correct, if I were to essentially reconsider the motion to dismiss and go back and look at what the answer is in the complaint, assuming those facts are true -- I just didn't get past your defense of, You can't look beyond the -- you can't -- those things aren't properly in front of you as an evidentiary matter. So I accepted that.

I didn't look at your further arguments that even if those are in front of you as an evidentiary matter, that's still not correct on Step -- that doesn't get you there on the Step-Two analysis based on a set of facts.

Whether those facts are in the complaint or not, I don't know, and I don't know whether you know offhand since that complaint is months ago.

But my suggestion would be to let me consider that. This is a legal fight. There is not a factual fight, I don't think, for the most part, or at least -- my concerns here at this point are a legal argument, fall into a legal argument.

So let's do this: Why don't you go back and look at the complaint that's in front of me. If you're prepared to make this argument that you're making to me on Step Two based on taking as true all the facts in the complaint, I would suggest we -- I do this as essentially a reconsideration of the motion to dismiss, and I either do -- get off of my concerns on the Step Two and we move on to discovery on it if the motion for reconsideration is denied, or I reject the argument but taking your facts as you have them, rather than getting hung up on this, my concern about whether this is evidence properly -- whether this is properly in front of me.

If when you review your amended complaint you think, no, there are other facts that we can tee up together -- you know, maybe there's stipulated facts for that additional -- I just think it would be a more efficient way to get this question in front of me properly and either go one way or another.

MR. McMAHON: Well, your Honor, I appreciate the Court's concern about handling the case efficiently for all the parties concerned, and I understand where you're going with this.

I still would like the Court, I guess, to rule on the motion to compel, because we do think if this is going to be teed up as a summary judgment motion, again it's our

position that the -- after the fact showing nonobvious -- nonroutineness, that would be relevant to this inquiry and ought to be in the motion. So for my record I need to know if the Court's going to grant that or deny that.

But our position is we wouldn't want to go through -- I want to make clear that I am not waiving our right to have that discovery, because we think it's a fact issue.

THE COURT: Well, what I'm proposing right now is that rather than giving you the discovery to go into that, that we're essentially giving you your facts. And whether we do it as a motion to dismiss or a stipulated record, I am trying to do it giving you your facts. So I don't think that you need discovery if I'm going to try to resolve the legal issue, assuming your facts are, in fact, so.

MR. McMAHON: I stand before you, your Honor, as a frustrated lawyer. I haven't had a document from them yet. To assume I am going to get a stipulation from them that they had difficulties and that their development process was nonroutine, if they'll stipulate to that, perhaps we can run with it; but if he is not, I don't know that we're going to have a stipulation.

THE COURT: Well, my point is a stipulation without prejudice to tee the issue up. So that rather than fighting -- I mean, let's assume you take discovery and at the end of the day I say, Well, you're right, that this

routine issue is a question, routineness, based on what they did, that this is relevant. I would probably then say it is a disputed fact, and so disputed facts goes to you.

So I'm simply saying, let's get the facts going to you on these facts, let's tee it up with that additional thing.

Some of you have flown in here. Are you here for a few more hours, because if there is any -- if you have the time to go outside and see if there's something that we can do along these lines that you can work with each other on, I am happy to have you back in here in a few hours.

MR. SINGER: I'm the limiting factor on that, your Honor, but I am willing, for purposes of getting a reconsideration motion, to stipulate that the Mayo -- I think they're trying to argue it was complex or complicated. If it's without prejudice and it will help the Court, I am willing to stipulate to that. I wouldn't use the word "routine," because that's just circular. The tests are conventional, standard, routine.

But I will stipulate it's complicated and requires, you know, effort by individuals. If that is the fact that they're trying to argue in the face of the patent articulating what it articulates, if that's really what we're trying to get at.

I mean, it seems to me, just from the perspective -- and we have -- you know, I mean it's interesting to hear

about the AMP cases. I was counsel for Myriad the second time around when they tried to get over the hurdle, and the exact same arguments you're hearing today is what we made and which were rejected. I mean, the discovery of the BRCA gene was the first story on the NBC Nightly News. It required enormous effort. It was enormously complicated.

The Supreme Court said that's irrelevant. The question is whether or not in implementing the natural law the techniques are standard or not.

THE COURT: And they're saying it's not standard --

MR. SINGER: -- because it's complicated.

THE COURT: Well, no.

They're saying there was an additional step that went in that wasn't -- that doesn't normally go.

MR. SINGER: Right, I understood that, that there's some shortened version of the MuSK protein which is not in the claims. I mean, when one looks at the claims that are actually here, it mirrors the paragraph I read to you. It's the same exact paragraph.

THE COURT: I guess what I would like to see, if you can work it out, because I think it would be the most efficient way to address this, is I would like to see if there are facts, rather than conclusions or labels, whether there are facts that you can either agree or already are in the amended complaint, and if they are in the amended

complaint, that's the simplest. Because, as I said, I did not drill back down as I was thinking through this argument. I got caught up on your argument that what was in front of me wasn't properly in front of me, and I agreed. And I -- I didn't know whether it was properly in front of me, and I wasn't prepared to make a decision based on just taking that sentence in the patent.

MR. McMAHON: Your Honor, counsel now is raising some issues that involve claim construction, and, you know, what's in the claims or what's not in the claims. And there's always a risk when we go into summary judgment and I have claim construction decided. And this again gets us -- I hate to be the thorn here, but there are additional problems.

And when we get into claim construction, every court that I've ever seen has local rules for going through the claim construction process. It requires full disclosure of a party's prior art, their defenses. We've produced our stuff. And the whole reasoning -- and it can't be amended without good cause. And the whole reason is so the person will be afforded due process when they're committing to certain constructions.

So we have -- if claim construction is going to be implicated, I don't know how we're going to deal with that. I think the rest of the case may be prejudiced. It's not

going to be efficient if we have to go back and revisit claim construction seriatim as new issues come down the road.

So that's my one point.

And then the other point, I guess, is I mean we're willing to go out and make the effort that the Court wants. I would still ask that the Court rule either one way or the other on my motion to compel, if it's denied or not. I would just like a ruling on that, if I may, please.

THE COURT: So I can tell you that I am certainly not allowing the motion to compel in full. I would like to try to find a way to tee up -- I have enough concern about the Step Two and where we are in the Step Two that I want to -- and that's what I said. I know you didn't think what I said at that last hearing should change what had been previously agreed, and I understand the frustration.

But to me the landscape is somewhat different here than when we spoke in the abstract about what was going to happen with the motion to dismiss.

Where we stand is that you got by the motion to dismiss at the time by a sliver, and by a sliver that at this point you sort of concede that I was kind of wrong on. And so I need to have -- I may be wrong on my Step-Two analysis and how I'm thinking about it, and I'm willing to look at it again. But I come here having gotten you past the motion to

dismiss by a sliver, and then to have you come up and say, well, that means we have to have full discovery because that's what was agreed to six months, ago doesn't convince me.

MR. McMAHON: I'm not relying on the agreement. I realize we are beyond that, Judge, and I appreciate the Court's concerns. So I'm not saying because we had the deal.

I'm just saying that if claim construction is going -- there is a risk. We will try to do what the Court is suggesting. I'm not sure if we're going to get agreements, but if we don't, then I guess there are going to be disputed issues of fact.

But I think that there is going to be some claim construction issue that's going to be involved here, too, that I need to flag, and that's a concern to us.

THE COURT: The part I don't understand here is I had a case that was important to me as a litigant, and I prevailed beating back a motion to dismiss. And after a few years of costly discovery, I lost on the exact legal issue on summary judgment. And years later I spoke with the judge and I said, Why did you rule those two different ways?

And the Judge said to me, "I thought you'd settled it in between."

And it gave me sort of this feeling of...

That's not the way I view what's going on here. I am not trying to set this up so that one side or the other has to worry about the cost of discovery or the time of litigation or litigation strategies. I am trying to figure out if at the end of the day you are going to lose this case on invalidity, wouldn't you rather know at the beginning? And maybe the answer is no because you think that if the cost is high enough then you get to where you're going. But I am not part of that. I am a part -- my looking at this is to see if this is a long-shot defense, obviously you keep moving forward on everything.

But this is a very close-call defense, and so it seems from my point of view that we need to try to resolve that question.

If you had said to me -- and I highlighted this I think when we were hear last time -- if you said to me, "I don't want to have to depose that same expert twice." That's a logic to me on what's the value, what's the burden, what's the cost.

But if you simply want to say, No, we want to deal with the whole case at once, and they want to deal with a little piece of it, we somehow have a right to deal with the whole case at once, that doesn't convince me.

Now, you may be right that we can't resolve this question without claim construction and we can't -- you

know, and at some point maybe the whole thing breaks open.

But at this point I am on the verge of saying they get this because I buy this argument of all you're doing here is applying this iodination to a new idea.

Your colleague has been fairly persuasive to say, Well, no, there's something more going on here. So I'm sort of saying, Let's tee that up then.

MR. McMAHON: I understand, your Honor.

My request to you is that in order for us to make this submission, we need to know -- we think the discovery is going to indicate that at the current time right now, Mayo, with it's expertise, does not itself view these steps as routine.

THE COURT: Okay, let's assume that's true. I mean--

MR. McMAHON: I don't know that they'll do that.

THE COURT: -- you're using "routine" as the legal conclusion. I don't want to assume a legal conclusion as true.

But let's assume the facts -- find a way to articulate that as facts, and let's assume it's true. Let's give it to you, and let's get this issue off the deck here one way or the other.

MR. SINGER: And, your Honor, we're willing to do that, of course without prejudice. And I don't, as I said

for the circularity, right, the "routine" word being a legal standard.

Whatever formulation would work for your Honor, we would be willing to stipulate to.

THE COURT: What you would do after going to summary judgment, what the plaintiffs would be saying to me is: These are disputed facts, and taking the record in favor of the non-movant, you must take as such and such facts.

So let's take those facts. I just don't think this is a factual dispute case at this point.

MR. SINGER: We agree.

I agree, your Honor.

MR. McMAHON: Your Honor, you're suggesting stipulating to facts without prejudice. I'm not sure --

THE COURT: I'm suggesting agreeing that -- you know, whether you say, These are disputed facts that would be, therefore, taken by the Court on a motion for summary judgment. That's, I guess, really what it comes down to.

So if the discovery is only going to get you to disputed facts, you get your version of those disputed facts for purposes of summary judgment. That's what I'm talking about using.

MR. McMAHON: I understand.

THE COURT: Is it helpful to go out in the hall and

talk about this and come back in a few hours?

You said that doesn't work for you?

MR. SINGER: I'm sorry, your Honor, I have to be home. It's my youngest son's birthday. So I was hoping to get back at least for the birthday dinner.

MR. McMAHON: If counsel would stipulate to non-conventionality --

MR. SINGER: We're not going to stipulate --

I thought the Court was saying we're not going to be using legal conclusions.

We will stipulate to facts that would show complexity, if that's what -- that's my understanding of what the plaintiff is arguing, that this is complicated, it requires the use of an additional -- I didn't quite understand it -- additional or shortened protein, if you will. It requires effort, and that today it is still complicated.

Those are the kind of facts we're willing to stipulate to because I thought that's what I was hearing in argument. I don't think any of that would prevent judgment being entered in defendant's favor here.

THE COURT: So the fast way about this is to the extent these facts are alleged in your complaint, that takes care of a lot of the back and forth.

MR. KESSEL: Your Honor, just to fill in the blank there, the complaint just says that the methods are useful

and they involve a man-made chemical to detect this antibody. There's no other material in there.

THE COURT: Okay.

MR. McFARLANE: And, your Honor, there's no requirement for like a Rule 9(d) --

THE COURT: And I not suggesting there is. I am just saying it would be a simple way to do it.

MR. McFARLANE: It would be, but, I mean, this would be the most unusual case to have to plead.

THE COURT: I'm not suggesting you have to plead. I'm not in any way suggesting that. I'm simply saying that I'm trying to get your facts. I'm trying to decide this case giving you your facts for purposes of this question. And if you can, giving you your facts for purposes of this question, you can beat this back, then we've taken the issue off the table until the final summary judgment motion.

If we can't, even accepting your facts, if I'm convinced otherwise, why have your client spend all the money?

I'm giving you your facts for this purpose, and I was trying -- I was just making reference to the complaint only as quick-hand -- a shortened way of not having to work it out with each other.

MR. McMAHON: We'll do that.

I mean, I understand what you're saying, your Honor.

That's -- We'll try that. I don't think I'm going to have -- we're going to get agreement. And I understand that you're saying, Well, then that could create a factual issue. So it may be that we're kicking the can down the road, so to speak, without the discovery.

Because if he's not going to stipulate that -- they don't want to use "conventional." I don't know if there's another word to use.

THE COURT: The questions isn't adjectives or adverbs. The questions are facts. We do X. We don't do Y. We buy this from some other place. We don't buy it ourselves.

MR. McMAHON: My point is they had to go somewhere else, because in our view -- your Honor, please understand I am just trying to advocate my point. I'm not trying to be argumentative.

The Mayo Clinic claims to be top notch in the world. If they have to go to another source, what I am saying is they may be -- I think our discovery that we've requested is likely to show, for example, frustration, memos: Hey, this doesn't work. I mean, we need... Were certain efforts tried and others dropped?

I think we're allowed to get in to see the picture.

And I don't know if I can construct fictitious facts, you know, to ask him to stipulate. I don't have a basis.

So I think in putting this exercise together, which I understand the goal may be very helpful for all the parties in the end, but I'm still saying that there's something that's going to be lacking without the discovery, and I don't know how to deal with that.

THE COURT: I'm sure there is going to be lots of discovery that would be interesting to have, but that's not the question here. So if you're saying, Did they try this themselves, that's a fact question, yes or no. You could say, Did they try this themselves? Yes, we tried this. We ended up hiring somebody else.

Those are facts.

We ended up hiring somebody else because we were frustrated and...

I think you're getting into arguments with me rather than facts.

I don't want to -- if this were a summary judgment motion at the end of all of this and if you came back and said, It's a disputed fact as to whether they were frustrated or not, that's not going to be material here, all right?

MR. McMAHON: And I know I shouldn't be talking to counsel in front of the Court.

Will they tell us, for example, the identity of the third party, the supplier?

THE COURT: Why?

I mean what you're saying is "I want information that could be helpful to me for other tactical reasons." And I'm saying to you, I just want you to give me the facts that you're arguing that are relevant to this point.

MR. McMAHON: All right.

Well, I think the identity could help us in understanding what happened and how they designed it. It's our view that there's only one person in the world that this comes from, and they're telling the Court it's a "commodity." So are they telling someone else how to make it? Did they set this out and try to design it themselves, or did they go to the one supplier in the world?

THE COURT: So let me make another suggestion on how you can tee this up or how I can have you tee this up.

They file a motion for summary judgment today, two weeks from today, based on essentially the argument that they made in their papers. And you can oppose it either with the information that you have saying, We're doing -- this is all of these steps, here's what we do, this is what we do.

If you think it's critical that you need this other material, if you think that's good enough to beat back the summary judgment, because based on your arguments whether they also make something complicated or not just makes it a

disputed fact, it doesn't -- on summary judgment you don't have to win, you don't have to win the facts, whether I believe the facts. All you have to do is get those facts in play. So if you do an opposition to get the facts in play and you say what you're saying to me now, Here's the thing, it's shortened, and so on.

If you're contending you have to know something from them in order to beat back summary judgment, that's a different point.

But it seems to me what you're saying is they have the legal argument wrong and my understanding is wrong, and that it's at least disputed as to what happens and how complicated this all is.

MR. McMAHON: So would it help -- I mean, we're talking about converting their motion. Do they need to file a new one? We can take the Rule 12 motion, convert it to a Rule 56. Is that what the Court is suggesting?

THE COURT: Yes.

And take that with the part that I didn't understand, which is that you take as true that statement in the patent, and then we convert it to a summary judgment and you oppose it.

MR. McMAHON: So there is no need for them to have to file --

THE COURT: There probably isn't, if they're saying

to me it's undisputed that this is a -- this iodination is a known technique.

MR. SINGER: Your Honor, that's acceptable to us with the concessions made at the hearing today.

I think we can just renew our motion under 56, and they can oppose I guess with a declaration of some kind.

THE COURT: I don't know that you even need to renew it or -- I guess it is. It's been denied. You need to renew. But you can renew it as a 12(b)(6) based on this clarification. I convert it to a 56 to give you an opportunity to respond as a 56.

MR. SINGER: I assume we get a reply brief? I suppose that's all we would need.

THE COURT: Yeah, and it may be more valuable to the plaintiffs as well if you do a short opening brief so they don't have to track through four layers of my decisions and your prior briefs to get to what they're responding to, but what the argument is that you're making based on the pleadings and the patent.

MR. SINGER: That's fine as well.

Two weeks is fine. We can do it in two weeks.

THE COURT: Does that make sense then? Then we don't have to have a stipulation. Then you're putting forward an opposition that says, No, that's the wrong focus of the analysis. Here's why this is different under Step

Two.

MR. McMAHON: Yeah.

Your Honor, I assume we will have an opportunity to respond with an expert then, too, right?

Okay. I understand what the Court's doing.

I just want the record to be clear. I'm still urging -- if you're going to rule against me, then rule against me, please, your Honor, on the motion to compel. I just want my record to be clear that this is some, you know, information that we want. We'll -- but I understand what you're saying, too, that we can address it in a Rule 56 motion.

I'm just unclear on what the resolution of our discovery motion is, and I would like that clear for the record, if I may, for the Court to rule on.

THE COURT: It's denied.

MR. McMAHON: Thank you.

So then if we have no expert, then they won't reply with an expert either?

THE COURT: I don't think you need an expert at this point because you have conceded the point there, which is that a certain iodination is standard in the art, and you're making the argument that you're doing something different and in addition to what that was about, and that that's properly in front of me on Step Two.

I --

MR. McMAHON: All right.

THE COURT: So it is a -- I think just so that the record is clean, I think it is a renewed motion to dismiss, and I will then convert it to a summary judgment motion, allowing you to respond to it. And if I deny it at this stage, then I anticipate us going to the full discovery and, as appropriate, have competing summary judgment motions at the end, if that's where we are.

MR. SINGER: Very well, your Honor.

Two weeks from today is the 20th. Do you want to set an entire briefing schedule, or would you like us to work it out?

THE COURT: I would assume you can work that out.

MR. McMAHON: We can work that out.

THE COURT: Usually the rule is three weeks thereafter.

MR. McMAHON: We can work that out. I can assure you of that.

MR. SINGER: Thank you.

THE COURT: Okay.

MR. McMAHON: Thank you.

THE CLERK: Court is in recess. All rise.

(Proceedings adjourned.)

C E R T I F I C A T E

I, James P. Gibbons, Official Court Reporter for the United States District Court for the District of Massachusetts, do hereby certify that the foregoing pages are a true and accurate transcription of my shorthand notes taken in the aforementioned matter to the best of my skill and ability.

/s/James P. Gibbons October 13, 2016
James P. Gibbons

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS
BOSTON DIVISION

ATHENA DIAGNOSTICS, INC., ISIS INNOVATION LIMITED, AND MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V., Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	Civil Action No. 4:15-cv-40075-IT

DEFENDANTS' RENEWED RULE 12(B)(6) MOTION TO DISMISS THE THIRD AMENDED COMPLAINT

Pursuant to Fed. R. Civ. P. 12(b)(6), Defendants, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories and Mayo Clinic (hereinafter, "Mayo"), hereby move to dismiss Plaintiffs Athena Diagnostics, Inc.'s, Isis Innovation's, and Max-Planck-Gesellschaft zurForderung der Wissenschaften e. V.'s Third Amended Complaint because all asserted claims of U.S. Patent No. 7,267,820 are invalid as directed to patent-ineligible subject matter under 35 U.S.C. § 101. The claims of this patent are directed to routine and conventional methods of applying a law of nature (specifically, the natural cause of a disease), and are thus unpatentable under the Supreme Court's 2012 decision in *Mayo v. Prometheus*.

In further support of this Motion, Mayo relies on its Memorandum of Law filed herewith, together with the Declaration of Adam J. Kessel and associated exhibits.

WHEREFORE, Mayo respectfully requests that this Court grant this Motion and dismiss the Second Amended Complaint, with prejudice.

CERTIFICATE OF COMPLIANCE WITH L.R. 7.1(a)(2)

I hereby state that counsel for Defendants complied with the requirements of Local Rule 7.1(a)(2) by attempting in good faith to resolve the issues presented in this motion. Plaintiffs made clear at the October 6, 2016, hearing in this matter that they oppose dismissal of this action, thus satisfying the Parties' obligation to meet-and-confer.

/s/ Adam J. Kessel
Adam J. Kessel

REQUEST FOR ORAL ARGUMENT

Pursuant to Local Rule 7.1(d), Mayo respectfully requests oral argument to address this motion as such argument will assist the Court in addressing the issues raised herein.

Dated: October 20, 2016

/s/ Adam J. Kessel

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CERTIFICATE OF SERVICE

I hereby certify that DEFENDANTS' RENEWED RULE 12(B)(6) MOTION TO DISMISS THE THIRD AMENDED COMPLAINT is being filed through the Court's electronic filing system on October 20, 2016, which serves counsel for other parties who are registered participants as identified on the Notice of Electronic Filing (NEF). Any counsel for other parties who are not registered participants are being served by first class mail on the date of electronic filing.

/s/ Adam J. Kessel
Adam J. Kessel

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS
BOSTON DIVISION

ATHENA DIAGNOSTICS, INC., ISIS INNOVATION LIMITED, and MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V., Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	Civil Action No. 4:15-cv-40075-IT

DEFENDANTS' MEMORANDUM OF LAW IN SUPPORT OF THEIR RENEWED RULE 12(B)(6) MOTION TO DISMISS THE THIRD AMENDED COMPLAINT

declined to take that statement as an admission, (*id.* at 18:1-7), and denied Mayo's motion to dismiss, (ECF No. 103 at 11).

At the October 6, 2016, hearing on Plaintiffs' Motion to Compel (ECF No. 108), the Court explained that its reluctance to grant Defendants' Motion to Dismiss was based on whether Plaintiffs' statements in Column 17 of the patent could be treated as a binding admission for Rule 12(b)(6) purposes: "what held me up from granting the motion to dismiss is that sentence, whether that sentence was accepted, was correct, or not. . . . But if that is not disputed, then I don't think you should be wasting time and money to flesh this whole thing out." (Ex. D at 17:20-19:20.) In response, Plaintiffs admitted to the Court that "[c]ertainly I-125 was known" and iodination and immunoprecipitation are standard techniques in the art—"that statement isolated I can't dispute." (*Id.* at 13:8, 18:8-9.) With that, the Court directed Mayo to renew its motion to dismiss focusing on *Mayo* step two: "So then where we are is if that statement isolated is not in dispute, then I should be granting their motion either as a motion to dismiss or as a motion for summary judgment, and you should appeal my decision." (*Id.* at 18:8-18, 58:7-21.)

B. The Asserted Discovery Underlying the '820 Patent: Naturally-Occurring Autoantibodies to the Naturally-Occurring MuSK Protein Cause Myasthenia Gravis and Other Known Neuromuscular Disorders

MG is a long-known neuromuscular disorder characterized by the weakness and rapid fatigue of skeletal muscles. (Ex. A, '820 patent at 1:13-23.) In the 1960s, decades before the filing date of the '820 patent, researchers found that a type of naturally-occurring antibody caused about 80% of MG cases. Pinpointing the cause of the remaining 20% of MG cases was the research interest of the named inventors of the '820 patent. According to the patent, the inventors' research found that many patients with MG who do not generate autoantibodies to AChR instead generate autoantibodies directed against a naturally-occurring protein in the body

called MuSK.[2] The inventors' research thus discovered a pre-existing natural relationship between a particular naturally-occurring bodily substance—the presence of autoantibodies to MuSK—and the incidence of MG and related disorders. The Court found that this discovery, embodied in all of the asserted claims, failed *Mayo* step one. (ECF No. 103 at 5, 9.)

C. The '820 Patent Discloses Using Only "Known" Techniques to Apply the MuSK Discovery

After describing their discovery of this natural correlation between autoantibodies to MuSK and the incidence of MG in a patient, the '820 patent's inventors describe how that correlation can be used to diagnose MG by detecting autoantibodies to MuSK in a bodily fluid: "The isolation and purification of this anti-MUSK autoantibody will give rise to a useful product which may be exploitable as an indicator of neurotransmission diseases." (Ex. A, '820 patent at 2:61-4:12.) Significantly for purposes of this motion, the patent only describes using routine biological techniques to do so: "The actual steps of detecting autoantibodies in a sample of bodily fluids may be performed in accordance with immunological assay techniques ***known per se in the art***. Examples of suitable techniques include ELISA, radioimmunoassays and the like." (*Id.* at 3:33-35 (emphasis added).) The patent describes two of these techniques known per se in the art—one ELISA technique and one radioimmunoassay technique. On a general level, each technique involves the conventional steps of (1) introducing the antigen into a bodily fluid sample, and (2) detecting for any autoantibody-antigen complexes that subsequently form. (*Id.* at 3:38-43.)

The first example of a technique "known per se in the art"—the ELISA example—involves using a labeled secondary anti-human antibody to detect autoantibody-MuSK complexes. (*Id.* at 3:33-35, 3:38-53.) The patent explains that anti-human antibodies, like IgG

[2] The inventors did not discover MuSK. (Ex. A, '820 patent at 1:49-2:5, 4:15-16.)

and IgM antibodies, can be used for this purpose. As was previously well-known, anti-human antibodies recognize features common to all human antibodies, including autoantibodies. (*Id.* at 3:43-47.) Accordingly, an anti-human antibody will bind to autoantibodies, creating a complex of the autoantibody/antigen/labeled secondary antibody. (*Id.* at 3:47-56.) The label on the anti-human secondary antibody can be used to detect autoantibodies to MuSK in the sample since they are bound together. (*Id.* at 3:57-65.)

The patent identifies various types of standard, well-known tags and labels that could be used with this conventional technique. For example, it describes enzymatic tags, including horseradish peroxidase (HRP). (*Id.* at 3:47-53.) Enzymatic tags are detected when they react with a substrate to cause a detectable change—like a color change. (*Id.*) In the case of HRP, reaction with o-phenylenediamine produces a color change detectable at the wavelength A492. (*Id.* at 8:41-43.) The patent also identifies other standard labels, including a heavy metal, a fluorescent or luminescent molecule, and a radioactive tag. (*Id.* at 3:57-65.) Each of these labels would provide a detectable signal indicating the presence of the autoantibody/antigen/labeled secondary antibody complex, and thus the autoantibody of interest. (*Id.*)

The second example of a technique "known per se in the art"—the radioimmunoassay technique—also involves creating a MuSK complex, but differs in terms of what part of the MuSK complex is labeled. (*Id.* at 3:33-35, 3:66-4:12; *see also id.* at 8:22-27, 10:49-67.) In this other "known" and "standard" technique, a labeled antigen is used. The patent identifies radioactive labels, like ^{125}I (i.e. radioactive iodine), as suitable for use in this conventional technique. (*Id.* at 4:2-12.) The labeled antigen is put into contact with a bodily fluid to facilitate formation of autoantibody-antigen complexes. Then, antibodies (including autoantibodies) are precipitated from the fluid. Finally, the label associated with the antigen is detected. (*Id.*)

Because the label is on the antigen, it will only be detected if it has bound to an autoantibody and precipitated with it. Thus, detecting the MuSK antigen's label after precipitation is the same as detecting autoantibodies to MuSK. (*Id.*; *see also id.* at 10:48-61.) Therefore, detecting the label indicates that the patient is suffering from a MuSK-related disorder. (*Id.* at 4:2-9.)

The Plaintiffs admit that the patent teaches that using such immunoprecipitation assays and iodination—labeling by adding an iodine atom to a given molecule—of antigens are "***standard techniques in the art***," as detailed in prior art references 4 and 6 as cited in the '820 patent. These publications, dating from 1976 and 1985, both describe detecting autoantibodies using a labeled antigen and illustrate that "[i]odination and immunoprecipitation are standard techniques in the art." (*Id.* at 4:10-12 (citing references 4 and 6; 11:19-22, 26-29 (citations for references 4 and 6); *see also id.* at 10:50-53.) More specifically, they describe (1) the introduction of a ^{125}I-labeled antigen (AChR) into a bodily fluid sample, (2) immunoprecipitation, and (3) detecting the radioactive label. (Ex. B at 1055; Ex. C at 1247.)

These publications show what the patent admits—that immunoprecipitation methods are routine and can be applied to any natural law that is based on the detection of autoantibodies. Indeed, the methods described in these articles are premised upon the natural law underlying the majority of MG cases—the presence of autoantibodies to AChR. The only difference between those methods and the methods described in the '820 patent is the identity of the antigen: AChR vs. MuSK. (*Compare* Ex. B at 1055 and Ex. C at 1247, *with* Ex. A, '820 patent at 10:48-67 (describing immunoprecipitation method using ^{125}I-labeled MuSK).) These publications and the '820 patent both teach that an antigen can be iodinated using standard techniques, and commercial reagents, before being used in a diagnostic immunoprecipitation method.

D. The ’820 Patent Only Claims Diagnostic Methods Based on the Detection of Naturally-Occurring Autoantibodies Using “Standard” Techniques

The patent’s twelve claims recite methods of diagnosing neurotransmission or development disorders related to MuSK based on the presence of autoantibodies to MuSK[3] in a bodily fluid sample. These claims can be divided into three general categories: (1) methods for diagnosing a disease by detecting naturally-occurring autoantibodies in a bodily fluid sample (claims 1 and 10-12); (2) the ELISA example known per se in the art that uses a labeled secondary antibody (claims 2-6); and (3) the radioimmunoassay technique known per se in the art that uses a labeled antigen (claims 7-9). Mayo originally moved to dismiss on the basis that all claims of the ’820 patent are invalid under § 101. (ECF No. 26.) In response, Plaintiffs represented that only claims 6-9 are at issue in this case. (ECF No. 37 at 18-19.) While Mayo still believes that all claims of the ’820 patent are invalid under § 101 for the reasons previously set forth, (*e.g.*, ECF No. 26 & ECF No. 40), Mayo only addresses claims 6-9 at this time due to Plaintiffs’ representations.

Claims 7-9 involve the radioimmunoassay technique known per se in the art. Claim 7 describes the conventional steps required to precipitate an antibody from a fluid sample using a labeled antigen, in this case MuSK, and to then monitor for the label associated with the resulting autoantibody/MuSK complex. (*Id.* at 12:62-13:5.) The label would indicate the presence of the autoantibody, and thus identify disease. (*Id.*) Claims 8 and 9 further refine the type of label on the MuSK antigen introduced to the sample—namely, a conventional radioactive label like ^{125}I. (*Id.* at 13:6-9.) Plaintiffs admit that “[c]ertainly I-125 was known.” (Ex. D at 13:8.)

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[3] The claims refer to MuSK, “epitopes” of MuSK, and/or “antigenic determinants” of MuSK. These latter two terms of art simply refer to the specific portions of the MuSK protein that the antibody interacts with. (ECF No. 11, ¶ 14; Ex. A, ’820 patent at 5:9-11 (“As aforementioned any protein which binds to the autoantibody may also be used such as an epitope or fragment of the MuSK protein itself.”); *see also id.* at 5:32-38.)

Claim 6 involves the ELISA example known per se in the art that uses a labeled, secondary anti-IgG antibody, as described in Claim 3 from which it depends. (*Id.* at 12:47-49.) Claim 6 merely adds the common sense idea that the intensity of the sample's signal could be compared to the signal of both positive and negative controls to indicate the relative amount of the autoantibody in the sample. (*Id.* at 12:57-61.)

E. There Is No Dispute about the Meaning of the Claims

Over the course of this litigation, including in the year since Mayo initially filed its Motion to Dismiss, Plaintiffs have not raised any arguments that might require claim construction before the Court would be able to determine patentability under § 101. In fact, when questioned by the Court at the initial hearing on Mayo's motion to dismiss, Plaintiffs' counsel stated that there were no disagreements with respect to claim construction.

> THE COURT: Is there any dispute what the claim terms mean at this point?
>
> MR. McMAHON: We haven't had the claim construction process, but I haven't seen one yet.
>
> THE COURT: As you're reading each other's briefs, there's no disagreement there?
>
> MR. McMAHON: Yes.

(Ex. E, Aug. 2, 2016, hearing transcript at 32:20-33:1.)

found that the claims recited "an ***improved process*** for preserving hepatocytes" with significant benefits over prior art preservation methods, including that the samples "no longer exhibit unacceptable loss of viability" in storage. *Id.* at 1051-52 (emphasis added). Contrary to the prevailing wisdom at the time, the improved process involved "multiple freeze-thaw cycles" and was, as a result, "far from routine and conventional." *Id.* at 1049, 1051.

Much like *BRCA1*, and in stark contrast to *CellzDirect*, the claims here lack any transformative application of the law of nature nor do they improve an existing prior art process. Instead, as the patent explicitly states, the claims cover routine, conventional, and "standard" methods used without any meaningful alteration to detect the autoantibodies to MuSK that correlate to a patient having MG.

B. The'820 Patent Claims Fail Because They Lack an Inventive Concept

1. The Process Steps of Claims 6-9 Are Well-Known and Conventional

As held by the Court, each claim of the '820 patent sets out a patent-ineligible law of nature—the relationship between (1) the presence of naturally occurring autoantibodies in bodily fluids directed against the MuSK protein, and (2) neurotransmission and developmental disorders related to MuSK. Although remaining Claims 6-9 include more than generic steps to detect a natural law, they do not contain enough to clear the patent-eligibility hurdle.

At the core of Plaintiffs' case, the radioimmunoassay claims (claims 7 through 9) lack an inventive concept because the additional process steps of immunoprecipitation and iodination are, as described in the patent, nothing more than "standard techniques in the art." ('820 patent at 3:66-4:12.) As described above, the additional process steps in these claims specify that the autoantibodies are detected through the use of a labeled antigen. The steps in claim 7 include (1) contacting a labeled MuSK antigen with a patient's bodily fluid sample to generate complexes of the autoantibody and labeled MuSK, (2) immunoprecipitating those complexes, and (3)

monitoring for the label. Claim 8 refines claim 7 by requiring the use of a radioactive label, and claim 9 further refines that label to a particular one—^{125}I; they do not add any additional steps to claim 7.[5]

The ’820 patent in fact directs the reader to two scientific publications that describe previous use of each step of this technique, only with a different ^{125}I-labeled antigen. (’820 patent at 4:9-12 (citing references 4 and 6), 11:19-22, 26-29 (citations for references 4 and 6); *see also id.* at 10:50-53.) Reference 4 describes this technique in section (b) of the *Acetylcholine receptor assay* description, which involves (1) contacting a serum sample with AChR containing a ^{125}I-label, (2) precipitation, and (3) “count[ing]” the label. (Ex. C at 1247.) Reference 6 describes the same thing: immunoprecipitating autoantibodies using a ^{125}I-labeled antigen and monitoring for the radioactive label. (Ex. B at 1055.)

Based on ’820 patent itself, anyone wishing to detect the presence of autoantibodies that target a specific antigen would have known that it could be done by (1) contacting a bodily fluid sample with the labeled antigen, (2) precipitating the antibodies in the sample, and (3) monitoring for the label. Thus, claims 7-9 “do nothing more than spell out what practitioners already knew”—how to detect autoantibodies in a bodily fluid sample by using a radiolabeled antigen that would complex with the autoantibody, precipitate along with it, and signal its presence. *See In re BRCA1*, 774 F.3d at 764; *see also Genetic Techs. Ltd. v. Bristol-Myers Squibb Co.* (*BMS*), 72 F. Supp. 3d 521, 532 (D. Del. 2014) (finding claims invalid where “[a]ccording to the patent itself, all of the techniques . . . were previously well known methods”); *see also Mayo*, 132 S. Ct. at 1298 (“Purely ‘conventional or obvious’ ‘[pre]-solution activity’ is

[5] Claim 7 also includes a “wherein” clause that amounts to a restatement of the underlying natural law and therefore does not qualify as an inventive concept. *Mayo*, 132 S. Ct. at 1297.

normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law.").

The simple fact that scientists may modify MuSK by adding a label to it before using it in the methods of claims 7-9 does not amount to an inventive concept or otherwise confer patent eligibility. As another court put it, "[t]he question is not whether any aspect of the patent involves non-natural processes; it is what the patent is directed to and—if the patent is directed to a patent-ineligible concept—whether the non-natural processes provide an additional inventive concept of enough heft to make the patent valid." *Genetic Veterinary*, 2015 WL 1505669, at *14. Here, the use of a radiolabeled antigen does not provide any "heft" because, as set out above, the use of radiolabeled antigens in immunoprecipitation techniques was routine and well-known before the inventors' discovery: "certainly I-125 was known." (Ex. D at 13:8.) Similarly, another court found "there is nothing inventive about adding a detectable label to the probe, in order to identify when hybridization has occurred." *Esoterix Genetic Labs. LLC*, 2016 WL 4555613, at *9. That court relied heavily on representations in the specification that: "[t]hose skilled in the art are familiar with the preparation of probes with particular specificities," "[s]uch hybridization probes are well known in the art," and that "[s]uitable assay labels are known in the art." *Id.*

The '820 patent's written description thus shows—both by calling out the claimed immunoprecipitation methods as "known" and "standard" and by citing articles employing the use of an ^{125}I-radiolabeled antigen to detect autoantibodies—that the claimed methods for detecting autoantibodies and diagnosing disease add nothing that was not already well known and routine in the art. Because the method steps in claims 6-9 precisely track those well-understood, routine and conventional immunoprecipitation techniques, they do not amount to an "inventive concept" under the *Mayo* framework, and the claims should be found patent

ineligible. *See BMS*, 72 F. Supp. 3d at 531-32 (concluding method claims ineligible on a motion to dismiss where patents state "outright" that the steps were routine and conventional); *Esoterix Genetic Labs. LLC*, 2016 WL 4555613, at *9 (claims invalid under § 101 because "adding a detectable label to the probe" was well known in the art and did not provide an inventive concept).

With respect to the ELISA claim (Claim 6) that Defendants continue to hold in reserve, none of the additional process steps captured in the claim—which concern the use of labeled anti-human antibodies to detect autoantibodies to MuSK—contain a patent-worthy inventive concept because they describe standard techniques that even the patent teaches were "known per se in the art." ('820 patent at 3:33-65.) To illustrate, claim 3 (from which claim 6 depends) builds off of claim 2's step of "detecting" autoantibody-antigen complexes by specifying that "an anti-IgG antibody tagged or labeled with a reporter molecule" is used to detect the complexes. (*Id.* at 12:47-49.) But the patent itself explains that the use of anti-IgG antibodies for that purpose is common in describing the techniques "known per se in the art" for detecting autoantibodies from a sample:

> Detection of autoantibody-antigen complexes is preferably carried out using a secondary anti-human immunoglobulin antibody, typically anti-IgG or anti-human IgM, which recognizes general features common to all human IgGs or IgMs, respectively.

(*Id.* at 3:43-47.)

Rather than adding another step to the method, claim 6 tells one that the strength of the sample's signal can indicate the relative amount of autoantibodies in the sample by comparison the signals of both positive and negative controls. Thus, claim 6 adds to claim 3 only a patent-ineligible mental process of comparing data to determine relative amounts of autoantibodies, which does not supply the "inventive concept" necessary to confer patent eligibility. *See In re*

BRCA1, 774 F.3d at 763 (explaining that "an abstract mental process of 'comparing' and 'analyzing' two gene sequences" is a patent ineligible abstract idea); *PerkinElmer, Inc. v. Intema Ltd.*, 496 F. App'x 65, 68, 70 (Fed. Cir. 2012) ("These exceptions make ineligible, for example, mental processes. . . . The claims thus recite the mental process of comparing data to determine a risk level . . . No action beyond the comparison is required.").

2. Plaintiffs Admit that the Techniques Claimed in the '820 Patent Were Standard Techniques in the Art

As noted by the Court, "the basis on which [Mayo] did not get the motion to dismiss" was that the Court had concluded that it could not determine as an evidentiary issue based solely on the pleadings whether iodination and immunoprecipitation were standard techniques in the art. (*Id.* at 18:11-18.) However, Plaintiffs themselves admitted that the claimed methods are standard techniques in the art during the October 6 hearing. (Ex. D at 17:20-18:9.) When the Court asked whether labeling was known in the art, Plaintiffs' counsel answered, "Certainly I-125 was known." Plaintiffs further admitted that labeling with radioactive iodine and immunoprecipitation are standard techniques.

> THE COURT: Let me ask plaintiffs' counsel, recognizing your disagreement about the import of this point, is there any disagreement as to the truth of this statement, "iodination and immunoprecipitation are ***standard techniques in the art***, the details of which may be found in references (4 and 6)" of the patent?
> . . .
> MR. McMAHON: ***That statement isolated I can't dispute***, but –
> . . .
> MR. McFARLANE: Your Honor, thank you. I just want to make clear the patent says what it says. ***The statement that you read, those words are there, and I can't stand here and tell you that those words are untrue.***
>
> (Ex. D at 17:20-18:9, 20:1-4 (emphasis added).)

Critically, Plaintiffs' admission that the iodination and immunoprecipitation examples of the specification were standard techniques in the art means nothing more remains in claims 7-9. As illustrated below, the limitations of claims 7-9 track the specification nearly verbatim but for

the addition of narrowing specificity in the claims. (*Compare* Ex. A, '820 patent at 4:2-12 *with id.* at claims 7-9 (emphasis added).)

> **Specification**
>
> This method comprises contacting MuSK or an epitope or antigenic determinant thereof having a suitable label thereon, with said bodily fluid, immunoprecipitating any antibodies from said bodily fluid and monitoring for said label on any of said antibodies, wherein the presence of said label is indicative of said mammal suffering from said neurotransmission or developmental disorder. Preferably, the label is a radioactive label which may be ^{125}I, or the like. ***Iodination and immunoprecipitation are standard techniques in the art, the details of which may be found in references (4 and 6).***
>
> **Claim 7**
>
> A method according to claim 1, comprising contacting MuSK or an epitope or antigenic determinant thereof having a suitable label thereon, with said bodily fluid, immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid and monitoring for said label on any of said antibody/MuSK complex or antibody/MuSK epitope or antigen determinant complex, wherein the presence of said label is indicative of said mammal is suffering from said neurotransmission or developmental disorder related to muscle specific tyrosine kinase (MuSK).
>
> **Claim 8**
>
> A method according to claim 7 wherein said label is a radioactive label.
>
> **Claim 9**
>
> A method according to claim 8 wherein said label is 125I.

Therefore, because Plaintiffs admit that its patent correctly states that immunoprecipitation and iodination with ^{125}I were standard techniques, that should end the inquiry, as the Court suggested. (*Id.* at 18:8-18 ("then I should be granting their motion either as a motion to dismiss or as a motion for summary judgment, and you should appeal my decision.").)

This is especially so because Plaintiffs have consistently made iodination of MuSK with ^{125}I the "core" and "critical" aspect of the asserted claims. Indeed, Plaintiffs built their entire

argument against Mayo's motion to dismiss on the premise that iodination with ^{125}I was the sole aspect of the asserted claims that conferred patent eligibility: "The claims at issue here depend on a man-made chemical that does not occur naturally—MuSK bound to a radioactive iodine isotope, ^{125}I. Although MuSK exists naturally in the body, ^{125}I-labeled MuSK does not and Mayo does not even dispute that ^{125}I-labeled MuSK would be patent eligible." (ECF No. 46 at 7.) For instance, Plaintiffs represented that: "Claim 9 is representative of claims 7-9 at issue in this case." (ECF No. 37 at 4.) Plaintiff described claim 9 as focusing on iodination of MuSK with radioactive ^{125}I: "The method of representative claim 9 requires the purposeful creation of a non-naturally-occurring radioactive molecule, ^{125}I-MuSK. . . . Those facts are not in dispute." (ECF No. 37 at 11; *id.* at 13 "Claim 9, for example, calls for the transformation of MuSK by the purposeful laboratory creation of a specific radiolabeled molecule.") Plaintiff didn't say this just once; in fact, they argued iodination with ^{125}I was a "core subject matter" and a "critical" step of claims 7-9. (ECF No. 46 at 4 ("a critical further step required to practice the invention: forming a complex of 125I-MuSK and anti-MuSK antibodies ("…contacting 125I-MuSK and anti-MuSK antibodies …")."); *id.* at 7-8 ("the core subject matters of the asserted claims are various man-made compounds: labeled MuSK, 125I-MuSK and labeled-MuSK/antibody complexes."). Thus, by Plaintiffs' own admission that "[c]ertainly I-125 was known" and iodination and immunoprecipitation are standard techniques in the art, "[t]hat statement isolated I can't dispute," ***no alleged inventive aspect of the claims remains***.

IV. CONCLUSION

For the reasons stated herein, Mayo respectfully requests that the Court grant this Renewed Motion to Dismiss and declare each asserted claim of the '820 patent invalid.

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS
EASTERN DIVISION

ATHENA DIAGNOSTICS, INC., ISIS INNOVATION LIMITED, AND MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V.,

Plaintiffs,

v.

MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC,

Defendants.

CIVIL ACTION NO. 1:15-cv-40075

Leave to file overlength brief granted on November 14, 2016 (D.I. 135)

PLAINTIFFS' MEMORANDUM OF LAW IN OPPOSITION TO DEFENDANTS' RENEWED RULE 12(B)(6) MOTION TO DISMISS THE THIRD AMENDED COMPLAINT

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I. INTRODUCTION

The Court denied Defendants' first motion to dismiss because Defendants had offered insufficient evidence that claims 7-9 of U.S. Patent No. 7,267,820 (the "'820 patent") are invalid under Step Two of the test laid out in *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347 (2014). Even when given a second chance, far from offering the required clear and convincing evidence to support their position, Defendants have filed a virtual mirror image of their first motion, once again asserting that general statements in the patent unbounded by actual claim elements prove the claims' invalidity.

Defendants rely on statements that, at most, might support a claim that certain immunoassay techniques, per se, are standard techniques in the art, but that is not the issue. The issue is whether it was conventional or routine to contact a patient's bodily fluids with ***suitably labeled MuSK or a labeled MuSK epitope or antigenic determinant***, as part of the claimed method of diagnosing neurotransmission disorders. It was not. The labeled MuSK components of the claims do not exist in nature, rendering the recited contacting step an inventive concept and, therefore, patent eligible subject matter under *Alice* step two. The weight of evidence from the '820 patent, supported by Plaintiffs' expert declaration, confirms that the recited steps of asserted claims 7-9 constitute an inventive concept.

By its invitation to the parties to build a factual record beyond the pleadings on this single issue, the Court has signaled its intent to convert the motion to dismiss to a motion for summary judgment under Rule 56. Defendants bear the burden of establishing the absence of disputed issues of material facts, yet Defendants have not demonstrated an undisputed record that can support summary judgment. And on the record now created by Plaintiffs' factual submissions in opposition, Defendants are unable to meet their ultimate burden of proof as to invalidity.

Instead, the facts presented below overwhelmingly support the conclusion that claims 7-9 embody a distinct "inventive concept" that transforms any law of nature thought to be present in the claims into a patent-eligible application.

First, at the time the invention was made, the step of "detecting" autoantibodies to a MuSK epitope was neither well-understood nor routine. As explained in the accompanying Declaration of Anthony De Tomaso, Ph.D., a considerable amount of additional information and experimentation related to the accessibility of the epitope was required to detect MuSK autoantibodies, especially because of the technical challenges involved with the effective use of a membrane-associated protein like MuSK.

Second, the step of "contacting" MuSK or a MuSK epitope or an antigenic determinant thereof with a suitable label was not routine because of the novel solutions implemented to label that membrane-bound protein in a way that could be used to detect MuSK autoantibodies. These are steps that others working in the field had not been previously engaged in, and cannot reasonably be considered conventional activity already engaged in by the scientific community. The claims' requirement for a labeled MuSK or a labeled MuSK epitope or antigenic determinant thereof having a suitable label thereon is also not conventional as a matter of law. A process that requires the use of a novel non-naturally-occurring patent-eligible element is necessarily a patent-eligible process. *Ass'n for Molecular Pathology v. United States PTO*, 689 F.3d 1303 (Fed. Cir. 2012), *aff'd in part, rev'd in part on other grounds*, 133 S. Ct. 2107 (2013) ("*AMP*"). What is more, case law relating to "routine" methods for manipulating and analyzing DNA is inapplicable for the more complex chemistry of the protein-protein interactions required to perform the "contacting" step of claims 7-9.

that it could not resolve those "factual

determinations" and that "[o]n the face of the claims and specification of the patent-in-suit, as well as on the face of the complaint, the court cannot determine as a matter of law whether the patent provides a 'combination of steps' to transform the method into a patent-eligible invention." *Id*. at 10-11. The Court clarified at the October 6 hearing on Plaintiffs' motion to compel discovery that it was singularly focused on whether iodination and immunoprecipitation were "standard techniques in the art." *See* Ex. A[1] at 18: 1-5, 11-18 (explaining that the language in the patent was "something to be determined on summary judgment"). Defendants filed a renewed Motion to Dismiss the Third Amended Complaint on October 20, 2016. D.I. 131.

III. COUNTERSTATEMENT OF FACTS

The '820 patent inventors were the first to establish that myasthenia gravis ("MG") patients negative for AChR autoantibodies could have autoantibodies to MuSK. DD[2] ¶¶ 58, 59, 63. The inventors did this by developing specific immunoassays they believed would identify MuSK autoantibodies. DD ¶ 62. Claims 7-9 cover a method requiring at least three steps: (i) "detecting" autoantibodies to MuSK in a bodily fluid, (ii) "contacting" a MuSK epitope[3] having "a suitable label thereon" with a bodily fluid, and (iii) "immunoprecipitating" any antibody/MuSK epitope complexes. '820 patent, claims 7-9; DD ¶ 84.

Although the specification states "[i]odination and immunoprecipitation are standard techniques in the art," '820 patent, 4:10-11, none of those steps are routine when applied to new proteins. DD ¶ 36. Proteins are far more complex than DNA, the subject matter of many "routine" and "conventional" laboratory techniques under *Alice* Step Two. DD ¶¶ 32, 33.

[1] "Ex. __" refers to exhibits of the concurrently-filed Declaration of Matthew B. McFarlane in Support of Plaintiffs' Opposition to Defendants' Renewed Rule 12(b)(6) Motion to Dismiss.
[2] "DD__" refers to the concurrently-filed Expert Declaration of Anthony W. De Tomaso, Ph.D.
[3] This memorandum uses the term "(labeled) MuSK epitope" to represent the phrase "MuSK or an epitope or antigenic determinant thereof (having a suitable label thereon)" for convenience and clarity only, with no intent to limit the scope of the claims.

Because of that complexity, even common techniques used for a new protein is experimental and empirical, not routine. DD ¶ 34, 35. It is unwise to assume that any "standard technique" will work the same for different proteins, and in practice, getting known methods to work in a new context is not a routine task. DD ¶¶ 35, 36, 38. This is especially true for interactions between antibody and antigen, as even small changes in protein folding or the physical effects of a label can destroy the ability to bind in an assay. DD ¶¶ 41, 42, 44, 78, 82. Moreover, proteins like MuSK, that are associated with the cell's membranes, require special handling to perform the methods called for in the claims—in other words, performing iodination and immunoprecipitation on MuSK in its native state would not be routine. '820 patent, 7:55-8:8; DD ¶¶ 35, 62, 103-105.

The '820 patent inventors took novel approaches to create an inventive process for detecting autoantibodies relevant to MG in the bodily fluid of a mammal, as the MuSK autoantibody assays of claims 7-9 are different from the acetylcholine receptor (AChR) autoantibody assays of the prior art in significant ways. DD ¶¶ 57, 61, 62, 79-81, 83, 90, 97, 98, 106. Those creative solutions constitute an inventive concept that satisfy *Alice* Step Two. *See* DD ¶ 112.

IV. LEGAL PRINCIPLES

A. Defendants have the burden of proving invalidity by clear and convincing evidence.

Determining patent eligibility under 35 U.S.C. § 101 presents an issue of law, but that "legal conclusion may contain underlying factual issues." *Accenture Glob. Servs. v Guidewire Software, Inc.*, 728 F.3d 1336, 1340-41 (Fed. Cir. 2013). The Court has already found that *Alice* Step Two in this case hinges on the "factual determination" of whether "Plaintiffs' patented method uses standard techniques in the art, or whether it is sufficiently inventive to be patentable

under the second step of *Mayo*." D.I. 103 at 10. Yet Defendants offer no facts beyond what has already been held insufficient.

The Court must consider subsidiary facts to determine whether the elements of the asserted claims pass *Alice* Step Two, and Defendants therefore have the burden of producing facts that prove invalidity by clear and convincing evidence. *See Microsoft Corp. v. i4i Ltd. Partnership*, 564 U.S. 91, 95, 131 S. Ct. 2238, 2242 (2011) (holding that 35 U.S.C. § 282 requires invalidity defenses to be proved by clear and convincing evidence).

B. *Alice* Step Two is satisfied if the claims include an inventive concept that transforms claims directed to a law of nature into a patent-eligible application.

Recognizing that "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas," the Supreme Court has confirmed that "a process is not unpatentable simply because it contains a law of nature." *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66, 132 S. Ct. 1289, 1293 (2012) (citing *Diamond v. Diehr*, 450 U.S. 175, 187 (1981)). Courts "must examine the elements of the claim to determine whether it contains an 'inventive concept' sufficient to 'transform' the claimed abstract idea into a patent-eligible application." *Alice*, 134 S. Ct. at 2357 (citing *Mayo*, 132 S. Ct. at 1294). *Alice* Step Two requires that claims must be considered "as a whole," *Diehr*, 450 U.S. at 187, and claim elements must be considered "both individually and as an ordered combination to determine whether the additional elements transform the nature of the claim into a patent-eligible application." *Alice*, 134 S.Ct. at 2355; *BASCOM Global Internet Servs. v. AT&T Mobility LLC*, 827 F.3d 1341, 1349 (Fed. Cir. 2016) (same).

An inventive concept does not "consist of well understood, routine, conventional activity already engaged in by the scientific community." *Mayo*, 132 S.Ct. at 1298. But a claim covering a "new combination of steps in a process" may represent an inventive concept "even though ***all***

the constituents of the combination were well known and in common use before the combination was made." *Diehr*, 450 U.S. at 189 (emphasis added).

The Court must assess whether the claims "focus on a specific means or method that ***improves the relevant technology***." *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299, No. 2015-1080 et al., 2016 U.S. App. LEXIS 16703, at *28 (Fed. Cir. 2016) (citations omitted); *BASCOM*, 827 F.3d at 1350 (confirming that the "inventive concept inquiry requires more than recognizing that each claim element, by itself, was known in the art," thus an "improved process" was a "specific method" that satisfied *Alice* Step Two). "A claim element is not conventional just because it appears in the prior art." *Veracode, Inc. v. Appthority, Inc.*, 137 F. Supp. 3d 17, 46 (D. Mass. 2015) (citation omitted). And applying various known types of procedures to a patent-eligible composition of matter "is ***not merely applying conventional steps to a law of nature.***" *AMP*, 689 F.3d at 1336 (emphasis added).

Finally, the lack of preemption is also strong evidence that claims pass *Alice* Step Two, if "additional features" are present that "ensure the claims are more than a drafting effort designed to monopolize" the law of nature. *DDR Holdings LLC, v. Hotels.com, L.P.*, 773 F.3d 1245, 1259 (Fed. Cir. 2014) (citations and quotations omitted); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1052 (Fed. Cir. 2016) (noting the relevance of non-infringing alternatives to whether claims will "lock up the natural law in its entirety").

V. ARGUMENT

A. The Court should deny Defendants' Renewed Motion to Dismiss.

Defendants once again urge the Court to consider broad, general statements in the '820 patent specification as evidence that claims 7-9 rely on standard, routine and conventional steps to apply a natural law. Those broad, general statements do not apply to the principal focus of the claims at issue: whether it was standard or routine to contact a patient's bodily fluids ***with***

"MuSK or an epitope or antigenic determinant thereof having a suitable label thereon" to create an "antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex" as part of a method of diagnosing neurotransmission disorders like MG.

Indeed, Defendants completely ignore all the novelty and complexity required to prepare labeled MuSK and incorporate that man-made chemical into a detection method for autoantibodies to MuSK—methods and approaches outlined in the '820 patent specification. Defendants' position presents methods and techniques to the Court in an overly simplified form isolated from critical inventive elements embodied in the claims. When properly considered, the information in the patent specification confirms that Defendants fail to present facts that establish the lack of an inventive concept in claims 7-9 of the '820 patent by clear and convincing evidence, and the motion to dismiss should be denied.

1. Defendants ignore key aspects of the claimed invention and trivialize the contributions of recited claim elements.

Repeating the tactics of the original Motion to Dismiss, Defendants assail the claimed methods as "known," "well-known," and standard," but in each instance, fail to consider the claimed invention as a whole. For example, Defendants' description of an "ELISA" as a technique "known per se in the art" for its "ability to detect autoantibody-MuSK complexes" (D.I. 132 at 4) ignores the fact that no MuSK autoantibody detection had ever taken place before the invention and that the ELISA technique does not use a labeled MuSK. DD ¶¶ 64, 66, 70, 88. Similarly, Defendants assert that the "radioimmunoassay technique" is "known" and "standard," with suitable labels like ^{125}I available for use in a "conventional technique." D.I. 132 at 5. Again, that description does not apply to the measurement of MuSK, which had not been done before the inventors' specific contributions to enable, for the first time, the very measurements that Defendants diminish as conventional. The portions of the '820 patent Defendants ignore are the

ones that explain the various steps that the inventors took to arrive at the invention actually claimed—a specific method for detecting MuSK autoantibodies in a bodily fluid.

Production of "MuSK or an epitope or antigenic determinant thereof having a suitable label thereon" required several steps that were neither well-known, nor standard, nor conventional for MuSK. The inventors attached a suitable label to cloned fragments containing a MuSK epitope to produce man-made, non-naturally occurring chemicals. '820 patent, 7:55-8:8. Those cloned labeled MuSK reagents were advantageous because a membrane-bound protein like MuSK is difficult to work with when still in the membrane. '820 patent, Fig. 1; Ex. A at 24:22-25; 25:1-6 (detailing issues surrounding iodination). Their use in creating an antibody/labeled MuSK epitope complex as required by the claims could not have been a well-known, routine, conventional activity performed by researchers in the field given that the inventors were the first to do it.

2. Because "MuSK or an epitope or antigenic determinant thereof having a suitable label thereon" is a patent-eligible chemical species, a method using that species is not conventional as a matter of law and satisfies *Alice* Step Two.

A method requiring the use of a patent-eligible product satisfies *Alice* Step Two as a matter of law. In *AMP*, the Federal Circuit considered the patent-eligibility of a method claim that required growing a transformed eukaryotic host cell containing an altered *BRCA1* gene. 689 F.3d at 1310. The claim was held to be patentable because even though methods of measuring the growth rate of cells was known, the host cells were man-made, transformed and had enhanced function and utility. Moreover, the court further determined that applying "known" types of procedures to novel patent-eligible compositions—even if those compositions were themselves created using known types of steps—constitutes more than just "conventional steps." *Id.* at 1336. Specifically, it held a claim was patent eligible, regardless of the recitation of known

types of steps, because that claim recited use of a novel cell into which a gene had been inserted, and which was therefore patent eligible:

> By definition . . . performing operations, ***even known types of steps, on, or to create, novel, i.e., transformed subject matter*** is the stuff of which most process or method invention consists. All chemical processes, for example, consist of hydrolyzing, hydrogenating, reacting, etc. In situations where the objects or results of such steps are novel and nonobvious, they should be patent-eligible. It is rare that a new reaction or method is invented; much process activity is to make new compounds or products using established processes. ***Thus, once one has determined that a claimed composition of matter is patent-eligible subject matter, applying various known types of procedures to it is not merely applying conventional steps to a law of nature***.

Id. (emphasis added). *AMP* thus confirms that even if the assay techniques described in the '820 patent were "standard" or "known" types of techniques their use was not "conventional" as applied to claims requiring the use of a labeled MuSK epitope—*i.e.*, structurally-altered, man-made molecules with enhanced function for detecting autoantibodies. *Id.*

Consider, for example, Claim 9, which covers a method requiring "immunoprecipitating" a labeled MuSK-antibody complex in which the label is ^{125}I. Ex. A at 13:8-9. In claim 9, MuSK is covalently attached (chemically bonded) to ^{125}I through iodination. Labeling allows an anti-MuSK antibody/^{125}I-MuSK complex to be detected by monitoring radiation. These antibody/MuSK complexes are created in the laboratory and result from the use of a non-naturally-occurring laboratory created molecule, ^{125}I-MuSK. The antibody/MuSK complexes formed and detected are man-made. Therefore, even if the asserted claims require the use of standard types of techniques, those steps were not "conventional" as applied to the man-made molecules described in the asserted claims. *AMP*, 689 F.3d at 1301.The patent's statement that "iodination and immunoprecipitation were standard techniques in the field," and that ^{125}I was

"known," cannot amount to clear and convincing evidence that the ***claims*** lack an inventive concept under *Alice* Step Two.

3. *Diamond v. Diehr* remains controlling precedent that compels this Court to reject Defendants' argument.

Diehr is particularly instructive to the *Alice* Step Two analysis of claims 7-9 of the '820 patent, because a "new combination of steps in a process may be patentable even though all the constituents of the combination were ***well known and in common use*** before the combination was made." 450 U.S. at 188 (emphasis added). In *Diehr*, the Supreme Court held patent eligible a process claim for curing rubber designed to solve a technological problem in the industry even though the claim employed a natural law—a "well-known" mathematical equation. *Id.* at 188-93. The use of a thermocouple, a then well-known tool,[4] to "record constant temperature measurements inside the rubber mold—something the industry had not been able to obtain," were additional steps that "***transformed*** the process into an inventive application of the formula." *Alice*, 134 S.Ct. at 2358 (citations and internal quotations omitted) (emphasis added). Therefore, claim elements, even "well known" claim elements, can be combined to create an inventive process. *Mayo*, 132 S.Ct. at 1298 (explaining that the "overall process" in *Diehr* was "patent eligible because of the way the additional steps of the process integrated the equation into the process as a whole").

Following *Diehr*, the Federal Circuit has found patent eligibility when the claims, viewed as a whole, combine to transform or improve upon a process—regardless of whether specific techniques used to achieve that process were "known" or "standard." *Rapid Litig. Mgmt. v.*

[4] The Court may take judicial notice of U.S. Pat. No. 2,000,489 to Lederer, issue date May 7, 1935, which states in its specification, "Thermocouples and appropriate electrical measuring instruments have been employed for the measurement of temperatures and, in recent years, such systems have been frequently employed for maintaining a constant and convenient supervision upon the temperature of gas engines used on aircraft." U.S. Pat. No. 2,000,489, at 1:7-13.

CellzDirect, Inc., 827 F.3d 1042, 1051-52 (Fed. Cir. 2016) (concluding that, while the method's "individual steps of freezing and thawing were well known," the overall "process of preserving hepatocytes by repeating those steps was itself far from routine and conventional"). *Diehr* and *CellzDirect* completely undercut Defendants' position that the techniques as applied in the steps of the '820 patent claims were well-known and conventional. Rather, those techniques, when applied to a process of detecting autoantibodies to MuSK involved in MG, created a new process and improved ability to diagnose MG in patients. Although autoantibodies had been measured in MG patients since 1960, '820 patent, 1:24-26, only AChR autoantibodies could be measured, sufficient to identify 80% of patients. *Id.*, 1:34-36. The inventors created and claimed a detection method for ***other*** MG autoantibodies using a different approach and requiring different reagents. *Id.*, 2:61-65.

In contrast, method claims held ineligible by the Federal Circuit in recent life science cases have recited method steps at a high level of generality, such as amplifying, sequencing, and hybridizing, without any recitation of a specific chemical reagent beyond patent-ineligible, DNA fragments indistinguishable from naturally occurring DNA.[5] *E.g.*, *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1373, 1377 (Fed. Cir. 2015 (discussing expert testimony that PCR amplification was well-known and produced a naturally-occurring DNA sequence); *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp.*, 774 F.3d 755, 764 (Fed. Cir. 2014) (discussing routine DNA hybridization, amplification and sequencing techniques in claims that covered naturally occurring DNA sequences).

Importantly, Defendants are unable to point to any decision in which a court has held patent ineligible a method claim reciting the specific use of a novel, man-made patent eligible

[5] Methods for manipulating and using proteins in laboratory processes tend to be far more complex than methods involving DNA. *See infra*, § IV.B.2.b.; DD ¶¶ 27-34, 45.

reagent.[6] This is not surprising because many innovations in the life sciences involving "novel and useful structure[s] created with the aid of knowledge of scientific truth" would be denied patent protection because standard techniques were used to create those structures. *Mayo,* 132 S. Ct. at 1294. This would run counter to the goal of the patent laws, which grant an inventor rights to improvements to "existing technological process[es]" even while using techniques well known in a particular field. *Alice*, 134 S. Ct. at 2358.

4. Defendants' motion to dismiss should be denied.

Here, the combination of novel elements (*e.g.*, an antibody/labeled MuSK complex) with other elements ***in the claims*** reflects an inventive concept because nothing in the '820 patent specification discloses that specific combination as well-understood, routine or conventional activity already engaged in by the scientific community. *Diehr* remains binding precedent, and its directive to view the claims "as a whole"—regardless of whether particular techniques used in the process were "known" or "standard"—requires this Court to consider the assay methods as applied to the asserted claims at issue. Thus, the proper issue before the Court is whether it was standard or routine to contact a patient's bodily fluids ***with suitably labeled MuSK or a labeled MuSK epitope or antigenic determinant thereof***, as part of a method of diagnosing neurotransmission disorders. Defendants' narrow focus on whether iodination and immunoprecipitation were "well known" and "standard," or "well understood, routine, [and] conventional," only invites error. And that narrow focus leaves Defendants without any factual evidence to support their arguments as to *Alice* Step Two.

[6] In *Esoterix v Qiagen*, the court held invalid a kit claim reciting a labeled nucleotide. No. 14-cv-13228-ADB, 2016 U.S. Dist. LEXIS 117447 (D. Mass. Aug. 31, 2016). The claim did not recite any specific method steps and instead referred to a "number of exemplary labels . . . known in the art" all of which could be employed to apply the invention. *Id*. at *27.

This Court has acknowledged that a factual question remains as to whether the claims constitute an inventive concept and has been presented with competing interpretations as to what the claims describe and require. In basing their arguments on an incorrect analysis of *Alice* Step Two, Defendants cannot establish with clear and convincing evidence that the claims fail *Alice* Step Two—especially given that the Court must construe the patent claims in a manner most favorable to Plaintiffs. *See Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat'l Ass'n*, 776 F.3d 1343, 1349 (Fed. Cir. 2014). Plaintiffs' motion to dismiss should be denied.

B. Defendants are not entitled to summary judgment.

Fed. R. Civ. P. 12(d) "allow[s] district courts the leeway to consider documents outside the complaint . . . by converting a defendant's Rule 12(b)(6) motion into a Rule 56 motion." *Foley v. Wells Fargo Bank, N.A.*, 772 F.3d 63, 72 (1st Cir. 2014) (internal citations omitted). "This conversion need not be express, but the court must give both sides 'a reasonable opportunity to present all the material that is pertinent to the motion.'" *Id.*

1. The Court has already signaled its willingness to convert Defendants' motion.

The Court invited the parties to build a complete factual record beyond the pleadings. Ex. A at 57:16 (contemplating that "on summary judgment" Plaintiffs would "do an opposition to get the facts in play"); *see also id*. 5:7-9; 27:8-11; 60:3-6 (explaining that the Court "will then convert [Defendants' renewed 12(b)(6) motion] to a summary judgment motion"). The Court's directive was consistent with its earlier advisement—acknowledged by both parties—that the parties would submit expert declarations in support of their positions. *See* Ex. B at 41:12-16 ("As to this question of whether this is just a routine . . . this is a routine conventional activity, and [Plaintiffs] would have experts saying, No, what's happened here is not [] routine . . ."); 47:20-

25 (Defendants' counsel explaining the "assumption" that expert declarations will be filed); D.I. 115 at 1 (asserting Defendants' belief that discovery should consist of expert declarations).

To present the court with the facts and information it requires to analyze *Alice* Step Two, Plaintiffs rely on the Expert Declaration of Anthony W. De Tomaso, Ph.D. ("DD") in support of the sufficiency of claimed elements under *Alice* Step Two, and urges the Court's consideration of the same, even though Defendants have not submitted further evidence in their moving papers. To consider this declaration and the facts and information it presents, the Court must convert Defendants' motion into a motion for summary judgment. Fed. R. Civ. P. 12(d); *see Collier v. City of Chicopee*, 158 F.3d 601, 603 (1st Cir. 1998) (upholding "constructive notice" of Rule 12(d) conversion when a non-movant appends materials outside the pleadings to the opposition and "urges the court's consideration of them"); *Rubert-Torres ex rel. Cintron-Rupert v. Hosp. San Pablo, Inc.*, 205 F.3d 472, 476 (1st Cir. 2000).

2. Defendants are not entitled to summary judgment because there are disputed facts material to whether the steps of the claimed methods constitute an inventive concept.

On a motion for summary judgment, defendants bear the burden of establishing the absence of disputed issues of material fact. *Borges v. Serrano-Isern*, 605 F.3d 1, 5 (1st Cir. 2010) (citations omitted). Defendants have not met this standard.[7] Plaintiffs' *Alice* Step Two analysis focuses on three active method steps required by claims 7-9: (a) detecting MuSK autoantibodies, (b) contacting MuSK having a suitable label, and (c) immunoprecipitating antibody/MuSK

[7] The Local Rules of this Court require that "[a]ffidavits and other documents setting forth or evidencing facts on which the motion is based ***shall be filed with the motion***." LR 7.1(b)(1) (emphasis added). If the Court permits Defendants to file a reply brief, *see* L.R. 7.1(b)(3), Defendants' should not be permitted to raise any new arguments within the brief regarding *Alice* Step Two. *Graham v. Sabol*, 734 F. Supp. 2d 194, 199 n.4 (D. Mass. 2010) (stating that a "reply brief is not an opportunity to raise new arguments").

epitope complexes. Each of those steps, individually and in ordered combination, constitute an inventive concept, and as a result, Defendants' motion for summary judgment must be denied.

a. The step of "detecting . . . autoantibodies to an epitope of . . . MuSK" was neither well-understood nor routine at the time of the invention.

Methods of detecting autoantibodies to MuSK were not well-understood at the time of the invention. It was the inventors who first characterized the detection method for autoantibodies to MuSK and disclosed those methods in the '820 patent. DD ¶¶ 59, 88. The AChR autoantibody detection assay first introduced in 1976 was well-understood at the time of the '820 patent invention. DD ¶ 57, 88. The AChR autoantibody detection assay cannot detect autoantibodies to MuSK. DD ¶ 88. The detection methods disclosed and claimed in the '820 patent require a set of chemical reagents that are completely different from the existing AChR autoantibody detection method. DD ¶¶ 61, 88. And those methods represent a significant advance over the failure of existing assays to detect autoantibodies indicative of MG in the 20% of MG patients seronegative for AChR autoantibodies. DD ¶ 59.

Thus, Defendants are wrong to suggest that the AChR autoantibody detection method in the prior art is functionally equivalent to the MuSK autoantibody detection method of claims 7-9. This conclusion is not supported by the facts. AChR autoantibodies had been detected in the prior art by binding AChR to a labeled snake venom protein, α-bungarotoxin, that binds specifically and tightly to the AChR. DD ¶¶ 57, 58, 59, 61, 63, 88, 90. Even if there was recognition in the field that a labeled toxin had utility, this was irrelevant because a MuSK-binding toxin was not known to exist. DD ¶¶ 57, 61, 90, 106. Instead, the '820 patent describes and claims a fundamentally different ***toxin-free*** method that had not been used in the field of detecting autoantibodies in MG before: detection using labeled MuSK epitope. DD ¶ 105.

For largely the same reasons, the MuSK autoantibody detection method of claims 7-9 were also not routine. The '820 patent reports special, creative steps the inventors took to detect MuSK autoantibodies, including breaking up the MuSK protein into smaller parts. DD ¶¶ 62, 79, 80, 97, 98. Dr. De Tomaso concludes that those additional steps, when performed for the first time, were more experimental than routine, and could not have been routine before the inventions had been made. DD ¶ 91. In fact, several years after the "detecting" step was claimed as a part of the complete invention, some in the field remained skeptical that MuSK autoantibodies were in fact responsible for MG, suggesting that the step was neither well-understood nor routine at the time of the invention. DD ¶¶ 65, 92.

b. The step of "contacting" MuSK or a MuSK epitope or an antigenic determinant thereof "having a suitable label thereon" was neither routine nor conventional activity already engaged in by the scientific community at the time of the invention.

At its core, the "contacting" step of claims 7-9 points to a protein-protein interaction: "contacting" a labeled MuSK epitope with a MuSK autoantibody. Interactions between proteins are complex because each protein folds into a unique three-dimensional structure, or "conformation." DD ¶ 33. Specific binding between labeled MuSK epitope and MuSK autoantibody requires that each have the proper conformation. DD ¶¶ 82, 98.

The development of the MuSK autoantibody assays required a major rethinking of the standard AChR-based approach for two reasons stemming from protein complexity. First, while techniques used to label proteins may be, generally speaking, standard types of techniques, the ability to label a specific protein having a unique three-dimensional structure depends upon the availability and accessibility of the target labeling site in the particular protein. DD ¶¶ 40, 82, 98. In other words, the ability to label depends upon the specific characteristics of each particular

protein. DD ¶ 98. The inventors had to create new, man-made antibody/labeled MuSK epitope complexes that could be detected. DD ¶¶ 62, 63, 67, 88.

Second, MuSK is a transmembrane protein, meaning that a part of it resides in the cell membrane. DD ¶ 94; *see also* '820 patent, Fig. 1a. When synthesized *in vitro*, transmembrane proteins will usually only fold correctly when they are inserted into a membrane during protein synthesis. DD ¶ 78. To overcome this difficulty, the inventors synthesized portions of the MuSK protein, including portions of the extracellular domain, *i.e.*, the part of MuSK residing outside the cell. '820 patent, Fig. 1; DD ¶¶ 79, 80. As these pieces are not native structures, there was no guarantee that those synthesized protein fragments would assume the proper three-dimensional shape to bind MuSK autoantibodies, indicating that the approach was not routine. DD ¶¶ 81, 82.

The labeling process also required extensive experimentation. Labeling proteins synthesized *in vitro* adds complications because the protein must fold correctly for the antibody to recognize its binding site, or epitope. DD ¶ 101.There is no guarantee that any protein can be labeled. DD ¶¶ 44, 101, 102. And once a protein is labeled, this modification can affect binding to an antibody. DD ¶ 45, 98. For example, iodination ('820 patent, col. 4, line 14) chemically modifies a protein at particular amino acid side chains. DD ¶ 44. However, that modified site may also be part of the epitope, and labeling may mask the epitope from antibody binding, or change the protein folding such that the epitope no longer exists. *Id*. In other words, while labeling a protein and using it as a target for immunoprecipitation from serum of patients may be considered common types of practice, there is absolutely no guarantee that correct epitope would be retained in the labeled protein. *Id*.

Nor would it have been routine to rely on MuSK fragments, as a person of skill would necessarily need to determine the fragment of MuSK bound by autoantibodies, as well as: (1)

conditions supporting a three-dimensional structure that make the epitope accessible to the antibody; (2) conditions supporting specific binding between antibody and MuSK epitope, minimizing non-specific binding; and (3) a suitable detection method to report that binding. DD ¶ 97, 98. The claimed method took experimentation to apply to MuSK protein fragments, and the outcome was not guaranteed. *Id*. Even if standard techniques well-known in the field were used, the application of those types of techniques to MuSK epitope binding was neither well known, nor routine, nor conventional activity among those practicing in the field. DD ¶ 98.

Because of the requirement for a specific conformation, proteins like antibodies and MuSK are simply not analogous to DNA, the source of case law Defendants rely upon to support its *Alice* Step Two arguments. *E.g.*, D.I. 132 at 13 (citing, *inter alia*, *Genetic Techs. Ltd. v. Bristol-Myers Squibb Co.*, 72 F. Supp.3d 521, 532 (D.Del. 2014)); *see Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) ("Although a close relationship exists between a DNA construct and the protein it encodes, the two are not equal."); DD ¶¶ 27-36, 45. All DNA molecules share a common "backbone" structure having the identical chemical composition, with differences appearing in the "non-backbone" portion: the linear sequence created by four bases A, C, T and G. DD ¶¶ 29, 30. Provided the linear sequence of bases is known, techniques for isolating, detecting, amplifying, labeling or analyzing one DNA sequence or gene can be readily applied to another DNA sequence or gene. DD ¶ 30.

In contrast, the chain of twenty different amino acids that make up a protein do not share a common backbone, and proteins fold into a specific three-dimensional shape that differs depending on sequence and local chemical conditions. DD ¶¶ 32-36. Because of the complexity of proteins, the "contacting" step is necessarily not routine, and as narrowly applied to a labeled MuSK or MuSK epitope, that step should satisfy the inventive concept requirement of *Alice* Step

Two. *See Rutgers v. Qiagen, N.V.*, No. 15-cv-7187, 2016 U.S.Dist. LEXIS 24736, at *10-11 (D.N.J. Feb. 29, 2016) (recognizing that proteins are "molecular machines whose activity is highly dependent on its surrounding environment" and noting that "the special characteristics of proteins as compared to those of DNA may support patent-eligibility") (internal citations omitted).

c. The step of "immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex" was neither routine nor conventional activity performed by others in the field at the time of the invention.

The complexes listed in this element are not naturally occurring because they are causing an antibody to be bound to the MuSK or MuSK fragment having a suitable label, which is not naturally occurring. Covalent attachment of the label to MuSK or a MuSK fragment creates a new, man-made chemical that is eligible for patenting, and methods using that chemical are not conventional as a matter of law. *See AMP*, *supra*.

Moreover, each immunoprecipitation protocol is unique and dependent on the unique properties of the antigen and the specific binding properties of the antibodies. DD ¶¶ 63, 108, 109. Antibodies that work for some methods might not work for immunoprecipitation. DD ¶ 109. Each new immunoprecipitation assay is inherently experimental, and only becomes routine after the conditions for its proper application to that new epitope have been established. DD ¶¶ 24, 76. Defendants completely ignore the new, improved process.

A court must consider whether an "arrangement of known, conventional pieces" constituted an inventive concept under *Alice* Step Two. *BASCOM Glob. Internet Servs. v. AT&T Mobility LLC*, 827 F.3d 1341, 1350 (Fed. Cir. 2016). In *BASCOM*, the Federal Circuit found error in the district court's narrow focus on whether the individual elements were "well-understood, routine, conventional activit[ies]," at the expense of determining whether an

inventive concept could be found in the "arrangement of known, conventional pieces." *Id*. ("The inventive concept inquiry requires more than recognizing that each claim element, by itself, was known in the art."). Instead, the court viewed the "specific method" of the claims as describing an "improved process." *Id.*

In line with *Diehr*, *AMP*, *CellzDirect* and now *BASCOM*, district courts have similarly rejected invalidity assertions where a claimed process recites ***specific or precise improvements***—regardless of whether the constituent elements required the use of well-known techniques. *See, e.g.*, *Exergen Corp. v. Kaz USA, Inc.*, No. 13-10628-RGS, 2016 U.S. Dist. LEXIS 39506, at *9 (D. Mass. Mar. 25, 2016) (noting that claim steps "known in the art" and "previously utilized" were an inventive concept because the claims "solve[d] a different problem"); *Vanda Pharms., Inc. v. Roxane Labs., Inc.*, No. 13-1973-GMS, 2016 U.S. Dist. LEXIS 113521, at *34-35 (D. Del. Aug. 25, 2016) (finding that "while it may have been conventional to investigate for side-effects, [defendant] has not proven by clear and convincing evidence that the precise test and the discovered results were routine or conventional," acknowledging that "the individual steps may have been well known"); *Ameritox, Ltd. v. Millennium Health, LLC*, 88 F. Supp. 3d 885, 912 (W.D. Wis. 2015) ("there is nothing that supports a finding that the combination of the steps is routine and conventional"). Similarly, courts have held that claims that recite a "particular approach" to solving problems in the prior art, or "particular solutions" through identified features to be patent eligible even though those claims were directed to patent-ineligible abstract ideas. *01 Communique Lab., Inc. v. Citrix Sys.*, 151 F. Supp. 3d 778, 792 (N.D. Ohio 2015); *ContentGuard Holdings, Inc. v. Amazon.com, Inc.*, 142 F. Supp. 3d 510, 517 (E.D. Tex. 2015).

The '820 patent specification is clear that the methods of claims 7-9 represent ***both*** a new process and a particular solution to a problem not addressed by others (a method of detecting MuSK autoantibodies in the bodily fluid of seronegative MG patients), which represented an improvement over existing assays which failed to detect autoantibodies indicative of MG in the 20% of patients seronegative for AChR autoantibodies. This conclusion is squarely supported by Plaintiffs' immunologist and expert in self-recognition mechanisms. *See* DD ¶ 105. Defendants' claim that claims 7-9 lack and inventive concept is only possible by ignoring those new, specific improvements, and because the law compels their consideration, Defendants should be denied summary judgment.

In addition, the lack of preemption remains an important clue as to the presence of an inventive concept. *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1259 (Fed. Cir. 2014) (holding claims patent eligible that "do not attempt to preempt every application of the idea of increasing sales by making two web pages look the same," but instead recited "a specific way to automate the creation of a composite web page"). The novel process described by claims 7-9 also does not warrant any preemption concerns, undercutting Defendants' argument. In short, because the claims are limited in requiring a "suitable label thereon," they leave open methods for detecting MuSK autoantibodies using different methods—for example, devising an immunoprecipitation using a labeled secondary antibody to identify autoantibodies that have bound to MuSK. DD ¶ 110; *see CellzDirect,* 827 F.3d at 1052 (noting that preemption is "certainly the 'concern that undergirds . . . § 101 jurisprudence'" and acknowledging that the district court's findings regarding non-preemption was "in accord" with its finding of patent eligibility) (citing *Alice*, 134 S. Ct. at 2358)).

3. *Esoterix* clarifies why the asserted claims contain an inventive concept, and Defendants' reliance on that case is misplaced.

Defendants cite to *Esoterix Genetic Labs. LLC v. Qiagen Inc.*, to support their argument, D.I. 132 at 14, but that case only serves to highlight the difference between the routine, conventional steps in that case and the inventive process recited in claims 7-9 of the '820 patent. No. 14-cv-13228-ADB, 2016 U.S. Dist. LEXIS 117447 (D. Mass. Aug. 31, 2016) ("*Qiagen II*"). In an earlier issued opinion ("*Qiagen I*"), the court invalidated a claimed method for determining whether certain drugs were likely to be effective in treating cancer in certain patients. *Esoterix Genetic Labs. LLC v. Qiagen Inc.*, 133 F. Supp. 3d at 360. A particular protein, EGFR, had been associated with the growth of cancers. *Id*. at 352. Two drugs, gefitinib and erlotinib, were especially effective at inhibiting EGFR, but many patients could develop resistance to them. *Id*. The inventors discovered that certain mutations within EGFR greatly increased the sensitivity of the protein to the drugs. *Id*. at 352-53. Thus, by determining whether a patient's EGFR contained the mutations, doctors could predict the likelihood that a patient would respond to the drugs. *Id*. at 353.

At *Alice* Step Two, the plaintiffs in *Qiagen* conceded that treatment of the cancer by EGFR inhibitor such as gefitinib and erlotinib was conventional, but claimed "that it was not previously conventional to administer these drugs only to patients with these particular genetic mutations." *Id*. Thus, the court found that the steps did not transform or "even alter, a known method of treating these cancers. Rather, it identifies a law of nature that explains why such treatment is more effective in a certain population of patients, and tells scientists and doctors that they can 'apply' that law of nature by testing for the relevant gene mutations using methods well-known in the art." *Id*.

Qiagen I is inapplicable because asserted claims require contacting MuSK "having a suitable label thereon." This element embodies a novel, improved process—manufacturing a man-made molecule for the detection of MG symptoms in new patients—completely absent in *Qiagen I.* As that court acknowledged, the plaintiffs in that case discovered a new correlation but the claims at issue did not cover or embody that improvement. *Id*. at 358 ("the inventors of the '468 Patent did not invent a new treatment for such cancers, or fundamentally alter an existing treatment."). In stark contrast, the inventors here altered the ability to diagnose MG patients by creating man-made molecules for the detection and treatment of previously-undiagnosable patients.

In *Qiagen II* the court invalidated a patent covering the same underlying invention in *Qiagen I*: "the discovery that a naturally-occurring genetic mutation correlates to an increased likelihood of effectiveness of certain cancer drugs." *Qiagen II* at *27. Turning to *Alice* Step Two, the court reasoned that there was "nothing inventive about adding a detectable label to the probe, in order to identify when hybridization has occurred." *Id*. However, the patent specification made clear that, with regards to the specific probe, "[a] number of exemplary labels are known in the art and *all such labels may be employed in connection with the present invention*." *Id*. (emphasis added). Here, the claims require a "suitable label thereon," the MuSK *protein* and are therefore limited to a new, man-made antibody/labeled MuSK complex, in contrast to the variety of "exemplary labels," described in the *Qiagen II* patent as applied to DNA.[8] Defendants conveniently ignore this glaring difference.

[8] In addition, applying labeling technology to DNA as described in *Qiagen II* could accurately be described as "routine" and "conventional," whereas the process required by the asserted claims here with respect to a protein required far more experimentation to produce a novel, improved process. DD ¶ 105.

4. Defendants have failed to meet their burden of proof.

Instead of providing the Court with any evidence that the *process* described in the asserted claims is conventional, Defendants have merely pointed to the patent specification for their entire argument that the steps are "well-understood, routine, [and] conventional." Merely defining particular steps isolated from a complete method as "standard techniques" is both improper and insufficient. Moreover, the Court explicitly rejected Defendants' bare reliance on the patent specification already. *See* D.I. 103 at 10, 11. And pointing to statements of counsel that only confirm what the words of the patent say without reference to the claims cannot provide clear and convincing evidence that the claims fail *Alice* Step Two, especially in light of the evidence Plaintiffs now provide. *See Kenexa Brassring*, No. 12-10943-FDS, at *21 (finding that defendants had "not put forth clear and convincing evidence" that patents failed *Alice* Step Two, where the defendants left the court to "assume" its assertions as to factual issues); *Ameritox, Ltd. v. Millennium Health, LLC*, 88 F. Supp. 3d 885, 914 (W.D. Wis. 2015) ("When, as here, Millennium is asking the court to infer that the combination of elements is conventional, it must supply some evidence to convince the trier of fact to accept its version of events. Since those facts are lacking here, Millennium's position is necessarily rejected.").

VI. CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request that: (i) the Court deny Defendants Renewed Motion to Dismiss, or (ii) convert Defendants' motion under Fed. R. Civ. P. 12(d) to a motion for summary judgment under Rule 56, and either deny Defendants' motion or grant summary judgment in favor of Plaintiffs that claims 7-9 of the '820 patent are patent eligible under 35 U.S.C. § 101.

Dated: November 14, 2016

Respectfully submitted,

/s/ Matthew B. McFarlane

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CERTIFICATE OF SERVICE

I, Matthew B. McFarlane, hereby certify that on this 14th day of November, 2016, the foregoing document was filed electronically with the Clerk of the Court using the CM/ECF system and will be sent electronically to the registered participants as identified on the Notice of Electronic Filing.

/s/ Matthew B. McFarlane

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS
EASTERN DIVISION

ATHENA DIAGNOSTICS, INC., ISIS INNOVATION LIMITED, AND MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V., Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants.	CIVIL ACTION NO. 1:15-cv-40075 **PLAINTIFFS' LOCAL RULE 56.1 STATEMENT OF MATERIAL FACTS BEYOND REASONABLE DISPUTE**

Pursuant to L.R. 56.1, Plaintiffs hereby submit their statement of material facts beyond reasonable dispute in support of their opposition to Defendants' Renewed Motion to Dismiss under Rule 12(b)(6), D.I. 131, which, as set forth in Plaintiffs' opposition should be converted to a motion for summary judgment pursuant to Fed. R. Civ. P. 12(d):

1. U.S. Patent No. 7,267,820 (the "'820 patent") discloses and claims methods for detecting MuSK autoantibodies in a bodily sample. Ex. A,[1] 12:31-35.

2. Using the methods disclosed and claimed in the '820 patent, the '820 patent inventors were the first to establish that myasthenia gravis ("MG") patients negative for acetylcholine receptor ("AChR") autoantibodies could have MuSK autoantibodies. Ex. A, 2:46-50, 2:61-65; DD[2] ¶¶ 59, 60, 64.

[1] "Ex.__" refers to exhibits attached to the concurrently-filed Declaration of Matthew B. McFarlane in Support of Plaintiffs' Opposition to Defendants' Renewed Rule 12(b)(6) Motion to Dismiss.

[2] "DD__" refers to the concurrently-filed Expert Declaration of Anthony W. De Tomaso, Ph.D.

3. Claim 7 covers a method requiring at least three steps: (i) "detecting" autoantibodies to MuSK in a bodily fluid, (ii) "contacting MuSK or an epitope or antigenic determinant thereof[3] having a suitable label thereon" with a bodily fluid, and (iii) "immunoprecipitating" any MuSK autoantibody/labeled MuSK epitope complexes. Ex. A, 12:62-13:5; DD ¶ 85.

4. Claim 8 covers a method requiring at least three steps: (i) "detecting" autoantibodies to MuSK in a bodily fluid, (ii) "contacting" a radioactively-labeled MuSK epitope with a bodily fluid, and (iii) "immunoprecipitating" any MuSK autoantibody/radioactive MuSK epitope complexes. Ex. A, 13:6-7; DD ¶ 85.

5. Claim 9 covers a method requiring at least three steps: (i) "detecting" autoantibodies to MuSK in a bodily fluid, (ii) "contacting" a ^{125}I-labeled MuSK epitope with a bodily fluid, and (iii) "immunoprecipitating" any MuSK autoantibody/^{125}I-MuSK epitope complexes. Ex. A, 13:8-9; DD ¶ 85.

6. The inventors described using antibodies to the MuSK autoantibodies in diagnostic kits. Ex. A, 5:6-14.

7. While "[i]odination and immunoprecipitation are standard techniques in the art," Ex. A, 4:10-11, none of those steps are routine when applied to new proteins. DD ¶¶ 28, 36, 44.

8. All DNA molecules share a common "backbone" structure having the identical chemical composition, with differences appearing in the "non-backbone" portion: the linear sequence created by four bases A, C, T and G. DD ¶¶ 29, 30.

9. Provided the linear sequence of bases is known, techniques for isolating, detecting, amplifying, labeling or analyzing one DNA sequence or gene can be readily applied to another DNA sequence or gene. DD ¶¶ 29, 30.

[3] As used in this L.R. 56.1 statement, the claim element "MuSK or an epitope or antigenic determinant thereof" is referred to "MuSK epitope" for convenience only, and is not intended to limit the scope of that claim element.

10. In contrast, proteins consist of twenty different amino acids that can fold into a specific three-dimensional shape that differs depending on sequence and local chemical conditions. DD ¶¶ 32-36.

11. Chemically, proteins are far more complex than DNA. DD ¶¶ 32, 33.

12. Because of the complex chemistry of proteins, even common techniques used for a new protein is experimental and empirical, not routine. DD ¶ 34, 35.

13. Any "standard technique" may not work the same for different proteins, and in practice, getting known methods to work in a new context is not a routine task. DD ¶¶ 35, 36, 38.

14. Small changes in protein folding can destroy the ability of an antibody to bind to an antigen in an assay. DD ¶¶ 41, 42, 44, 78, 82.

15. Transmembrane proteins in their native state like MuSK require special measures to perform iodination and immunoprecipitation techniques. Ex. A, 7:55-8:8 & Fig. 1; DD ¶¶ 35, 62, 103, 104.

16. The acetylcholine receptor (AChR) autoantibody detection assay first was first published in 1976 and had been in widespread use at the time the inventions of the '820 patent had been made. DD ¶ 57, 88.

17. AChR autoantibodies had been detected in the prior art by binding AChR to a labeled snake venom protein, α-bungarotoxin, that binds specifically and tightly to the AChR. DD ¶¶ 57; Ex. I; Ex. P.

18. The MuSK autoantibody assays of claims 7-9 are different from the AChR autoantibody assays of the prior art in that the assays of claims 7-9 do not involve the use of a labeled toxin. DD ¶¶ 57, 61, 79-81, 83, 90, 106.

19. The AChR autoantibody assay described by Lindstrom et al. 1976 does not use a labeled AChR. DD ¶ 57; Ex. I.

20. The ELISA technique described in the ’820 patent does not use a labeled MuSK. Ex. A, 8:34-46; DD ¶¶ 63, 69-71, 107.

21. The ELISA technique described in the ’820 patent detected MuSK autoantibodies in a bodily fluid, but was difficult to standardize. Ex. A, 8:34-46, 10:12-49; 107

22. The cloned MuSK fragments shown in Fig. 1 of the patent are man-made, non-naturally occurring chemicals. Ex. A, 7:55-8:8 & Fig. 1.

23. The AChR autoantibody detection assay cannot detect autoantibodies to MuSK. DD ¶ 88.

24. The MuSK autoantibody assays of the ’820 patent require different chemical reagents than the AChR autoantibody detection method of Lindstrom et al. 1976. DD ¶¶ 61, 88; Ex. I.

25. The AChR autoantibody detection method in widespread use after is publication by Lindstrom et al. 1976 failed to detect autoantibodies in about 20% of MG patients. Ex. A, 1:36-40; DD ¶ 59; Ex. I.

26. The MuSK autoantibody detection methods described and claimed in the ’820 patent detect autoantibodies in the 20% of patients who do not possess AChR autoantibodies. Ex. A, 2:61-65; 10:40-47.

27. The method of claims 7-9 claim a toxin-free method. DD ¶ 105.

28. The method of claims 7-9 relies on detection using labeled MuSK epitope, an approach that had not been used previously in the field of detecting autoantibodies in MG. DD ¶ 105.

29. There are ways of detecting MuSK autoantibodies that do not use a labeled MuSK epitope. DD ¶¶ 110, 111.

30. There are ways of detecting MuSK autoantibodies that do not require creation of a MuSK autoantibody/labeled MuSK epitope complex. DD ¶¶ 110, 111.

31. Specific binding between a labeled MuSK epitope and a MuSK autoantibody requires that each have the proper conformation. DD ¶¶ 82, 98.

32. Claims 7-9 cover detectable man-made antibody/labeled MuSK epitope complexes that had not been described before the inventions disclosed and claimed in the ’820 patent. Ex. A, 12:62-13:9; DD ¶¶ 62, 63, 67, 88.

33. Iodination creates a covalent bond, often between a radioactive iodine atom and the amino acid side chain tyrosine. Ex. A; 4:9-11; DD ¶¶ 40, 44, 100.

34. Each immunoprecipitation protocol is unique and dependent on the unique properties of the antigen and the specific binding properties of the antibodies. DD ¶¶ 63, 108, 109.

Dated: November 14, 2016

Respectfully submitted,

/s/ Matthew B. McFarlane

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CERTIFICATE OF SERVICE

I, Matthew B. McFarlane, hereby certify that on this 14th day of November, 2016, the foregoing document was filed electronically with the Clerk of the Court using the CM/ECF system and will be sent electronically to the registered participants as identified on the Notice of Electronic Filing.

/s/ Matthew B. McFarlane

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS
EASTERN DIVISION

ATHENA DIAGNOSTICS, INC., ISIS INNOVATION LIMITEDAND MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V., Plaintiffs, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES, AND MAYO CLINIC, Defendants.	Case No. 4:15-cv-40075 JURY TRIAL DEMANDED

EXPERT DECLARATION OF ANTHONY W. DE TOMASO, PH.D.

I, ANTHONY W. DE TOMASO, hereby declare and state under penalty of perjury:

1. My name is Anthony W. De Tomaso. I have been asked by counsel for Plaintiffs Athena Diagnostics, Inc. ("Athena"), Isis Innovation Limited and Max-Planck-Gesellschaft zur Forderung der Wissenschaften E.V. (together, "Plaintiffs") to provide technical information necessary to fully comprehend the elements of claims 7-9 of U.S. Patent No. 7,267,820 (the "'820 patent"), and in particular, my opinion concerning whether those additional elements as set forth in the claims constitute well-known, routine and conventional techniques known in the field at the time the claimed invention was made.

2. I am prepared to testify before the Court under oath consistent with these opinions.

3. As set forth below, I provide these facts and opinions based on my review of certain documents as informed by my more than 25 years of experience as an immunologist specializing in the molecular mechanisms of self-recognition and non-self-recognition. I am personally familiar with the technical issues discussed in this declaration.

4. I expressly reserve the right to amend or supplement this declaration at any time to consider additional facts and, as necessary, to respond to opinions that may be made by any other expert witness in this case.

A. QUALIFICATIONS

5. I attach a current version of my CV as Exhibit A to this declaration. My CV contains a list of publications I have authored in the past.

6. I earned my B.S. in Biological Sciences from Stanford University in 1987, and my Ph.D. in Cell Biology from Washington University in St. Louis in 1994, under the supervision of Dr. Robert Mercer, Professor of Cell Biology and Physiology. I was a postdoctoral fellow at Stanford University School of Medicine with Dr. Irving Weissman.

7. I am currently an Associate Professor of Molecular Cellular and Developmental Biology at University of California, Santa Barbara, and been a faculty member there since 2009. Before that, I was an Assistant Professor (Research) of Biological Sciences at Stanford University from 2006-2008.

8. My day-to-day responsibilities as Professor involve conducting active research in Immunology, Stem Cell Biology and Regeneration. I currently supervise 3 graduate students and 3 postdoctoral fellows. I have been the recipient of the Ellison Scholar in Aging Award, the Santa Barbara Cottage Hospital Special Research Award, and this year, a Mathers Foundation Award. Last year, I was also elected a Visiting Fellow at Kings College, Cambridge.

9. I have had over 25 years of experience in immunology methods including the techniques described and referred to in the ’820 patent, including ELISA, immunoprecipitation, radioimmunoprecipitation and radioimmunoassay, techniques requiring antibody manipulation and antibody-epitope binding. (As I discuss in more detail below, an epitope is the specific target of an antibody which resides on a larger antigen.). I consider myself to be an expert in these techniques, and have spent considerable time conducting my own experiments using them, as well as supervising my lab personnel. Over the last 20 years I have studied the

molecular mechanisms of self/non-self-recognition. This is a fundamental process and the essence of immune function, and it is also the process that fails during autoimmune disease, when the immune system begins to attack self-tissues. My experience is particularly relevant for this case from a scientific standpoint, as it involves the detection of autoantibodies, and in addition, the techniques in '820 patent are at the core of the work I have done for more than two decades.

10. I am being compensated at the rate of $350 per hour for the time I spend in this matter, which is my standard hourly rate for consulting work. My compensation does not depend on the content of my opinion nor the outcome of this litigation.

11. I have not testified by deposition or in court in the last four years in any case.

12. In addition to my 25 years of experience with the immunology-related techniques described in this declaration and their implementation in a variety of laboratory examinations, I also considered and cited the materials listed in Exhibit B to this Declaration.

B. BACKGROUND TO MY OPINION

1. My Understanding of the '820 Patent Claims and an "Inventive Concept"

13. I am not an expert in patents or patent law, and have been assisted by counsel for Plaintiffs in obtaining a basic understanding of patents to provide a useful opinion regarding the nature of the elements of the claims of the '820 patent.

14. The inventors of the '820 patent were the first to associate autoantibodies to MuSK with neuromuscular disease and the first to detect the

presence of autoantibodies to MuSK in human patients with neuromuscular disease such as myasthenia gravis ("MG"). The '820 patent inventors also identified that the epitope to which the autoantibodies specifically bound was on the extracellular portion of the MuSK protein. As discussed further below the identification of the region of MuSK to which autoantibodies bound was an important development in the claimed invention.

15. I have been told by counsel for Plaintiffs that this case concerns aspects of claims 7-9 of the '820 patent.

16. Claim 7 is a dependent claim. I understand this to mean that all elements of another claim referred to are incorporated into dependent claim itself. This is in contrast to an independent claim, like claim 1, which stands on its own. In this case, I understand that Claim 7 includes all elements of claim 1. Likewise, dependent claim 8, includes all elements of claim 7 (and claim 1), and claim 9 includes all elements of claims 1, 7 and 8.

17. Incorporating the elements of claim 1, claim 7 covers the following method, with the underlined elements specified in claim 7:

> A method for diagnosing neurotransmission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK), <u>comprising contacting MuSK or an epitope or antigenic determinant thereof having a suitable label thereon, with said bodily fluid, immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid and monitoring for said label on any of said antibody/MuSK complex or antibody/MuSK epitope or antigen determinant complex, wherein the pr e of said label is indicative</u>

of said mammal is suffering from said neurotransmission or developmental disorder related to muscle specific tyrosine kinase (MuSK).

18. The elements of claim 8, incorporating elements from claims 1 and 7, covers the following method with the underlined elements specified in claim 8:

> A method for diagnosing neurotransmission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK), comprising contacting MuSK or an epitope or antigenic determinant thereof having a suitable radioactive label thereon, with said bodily fluid, immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid and monitoring for said radioactive label on any of said antibody/MuSK complex or antibody/MuSK epitope or antigen determinant complex, wherein the presence of said radioactive label is indicative of said mammal is suffering from said neurotransmission or developmental disorder related to muscle specific tyrosine kinase (MuSK).

19. The elements of claim 9, incorporating elements from claims 1, 7, and 8, covers the following method with the underlined elements specified in claim 9:

> A method for diagnosing neurotransmission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK), comprising contacting MuSK or an epitope or antigenic determinant thereof having a suitable radioactive label thereon, wherein said label is 125I, with said bodily fluid, immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid and monitoring for 125I on any of said antibody/MuSK complex or antibody/MuSK epitope or antigen determinant complex, wherein the presence of 125I is indicative of said mamm fering from said

neurotransmission or developmental disorder related to muscle specific tyrosine kinase (MuSK).

20. I am not a lawyer, but I understand from counsel that the patent law permits an inventor to obtain a patent for an invention, which is defined as a "new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." Despite this broad definition in the statute, I understand that the courts have set aside certain subject matter that is not eligible for patenting. I am aware of recent cases from the Supreme Court that have defined laws of nature, natural phenomena and abstract ideas as patent-ineligible subject matter.

21. I understand that the Supreme Court has established a two-part test for determining whether the invention in a claim is eligible for patenting. In the first step, "*Alice* Step One," the court determines whether the claims of the patent are "directed to" one of the prohibited classes of subject matter. In the second step, "*Alice* Step Two," the Supreme Court has said that a court must examine the elements of the claim to determine whether it contains an inventive concept sufficient to transform the claim into a patent-eligible application. I understand that this means the patent in practice amounts to significantly more than a patent upon the natural law itself, and an application of the natural law can be patented.

22. I have been informed that performing the *Alice* Step Two analysis often requires examining facts that tend to demonstrate whether or not the elements of the claim, either alone or in combination, add enough to the law of nature to be patent eligible. I have been told that the Supreme Court teaches the courts that an element, or a combinatio lements, fails to meet Step Two if the

steps in the claims involve well-understood, routine, conventional activity already engaged in by the scientific community. I therefore understand that if the elements of the claim, aside from the law of nature, are not well-understood, are not routine, or are not conventional activity not previously engaged in by the scientific community, those elements are likely to transform the law of nature into a patent-eligible application, in other words, those elements will constitute an "inventive concept."

23. I understand that the courts have not established a special definition for "well-understood," so I will assume that it has its ordinary meaning: known to others practicing in the field.

24. I understand that "routine" is also not specially defined, but as a scientist, I believe that "routine" and "experimental" are roughly opposites. Those tasks I consider to be routine in the lab, weighing a salt, or performing a calculation to get the right concentration in a buffer, are those tasks I believe to be essentially automatic. Scientists generally consider setting up and running an established biochemical reaction to be routine—where the starting reagents are known, the conditions of the reaction are known, and the products are known.

25. I believe that "conventional activity already engaged in by the scientific community," means something more than just well-known. As a practicing biomedical scientist, I use techniques that others have developed and used in other contexts all the time. But the use of an existing technique in a new context or to solve a new problem is not "conventional" if no other scientists in the field have engaged in that specific activity.

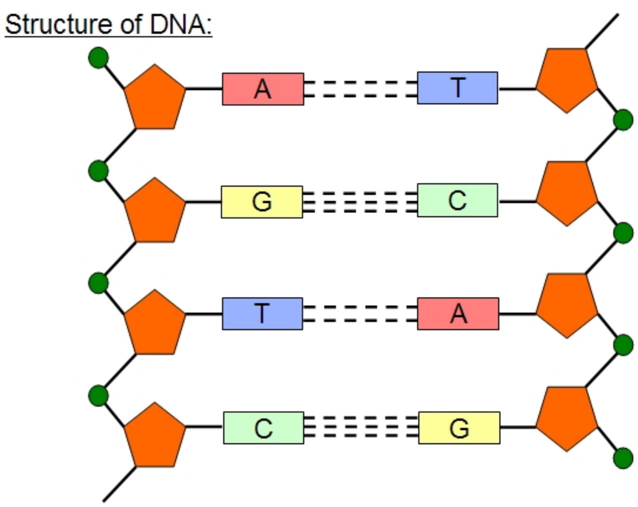
26. I have been asked to give my opinion, based on my experience in the field of immunological techniques, and based also on my review of materials that I found through my own research and have been provided to me by counsel, about whether the elements of claims 7-9 of the '820 patent contain an inventive concept as that requirement has been explained to me by counsel based on the case law.

2. Standard Techniques for Working with Proteins Are, as a General Rule, Not Routine, Because Proteins Are Far More Complex than DNA

27. I understand from counsel that several court cases assessing *Alice* Step Two to determine whether an inventive concept is present in the claims have dealt with method steps relating to manipulating DNA. I understand that the courts have concluded that standard techniques like the biochemical reaction commonly used to create multiple copies of a DNA molecule (i.e., "amplify" DNA), the polymerase chain reaction ("PCR") are routine methods that do not themselves create an inventive concept. The same is probably true for methods for detecting DNA molecules, or other techniques that manipulate DNA in a way that allow a scientist to analyze DNA molecules. This is largely because the structure of DNA is relatively simple and common among all DNA molecules. The two distinguishing characteristics of DNA are the length of a DNA molecule and its sequence.

28. As I will explain in more detail below, the same is decidedly not true for proteins, which are far more complex, and many "standard techniques" (like iodination and immunoprecipitation) are not routine in their application for any given protein.

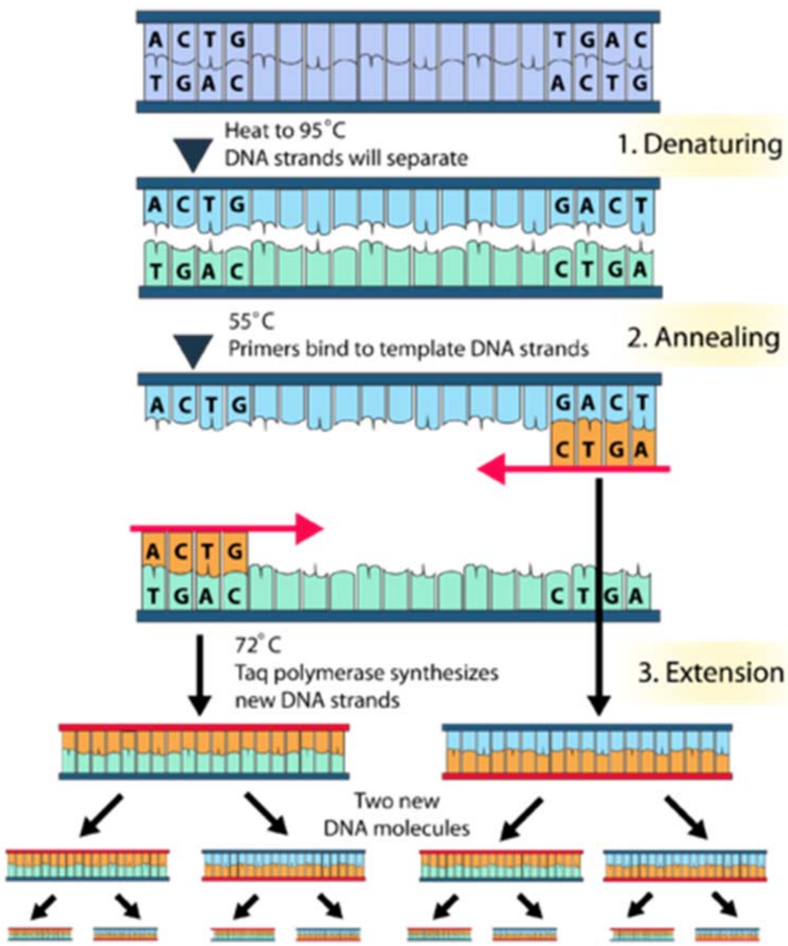
29. All DNAs share a common sugar-phosphate "backbone" structure having the same chemical composition (a scaffold of phosphodiester bonds), and the effects of variations of the non-backbone portions (the four purine and pyrimidine bases of DNA: adenine (A), cytosine (C), thymosine (T) and guanine (G)) on its physical properties are well characterized. Provided the linear sequence of bases is known, techniques used for detecting, amplifying, labeling or analyzing one DNA sequence or gene can be readily applied to another DNA sequence or gene because of base-pairing rules, in which, stable, double-stranded DNA found in the nucleus of the cell as chromosomes, T always pairs with A, and C always pairs with G.



DNA structure, showing the sugar (orange) and phosphate (green) "backbone" that is common to all DNA molecules. The variable bases (A, T, C, and G) are shown forming base-pairs with one another. Variability in DNA stems solely from the sequence of bases along the linear chain.

30. Because of the base-pairing rules, a scientist can design short segments of DNA (called "probes" or "primers") that will bind to single-stranded DNA. A probe can be easily labeled with a variety of reporter molecules, as the labeling chemistry will be the same regardless of the probe's length and sequence. Probes will bind to the complementary DNA sequence in a process called hybridization; this method can be used to identify a specific sequence of DNA.

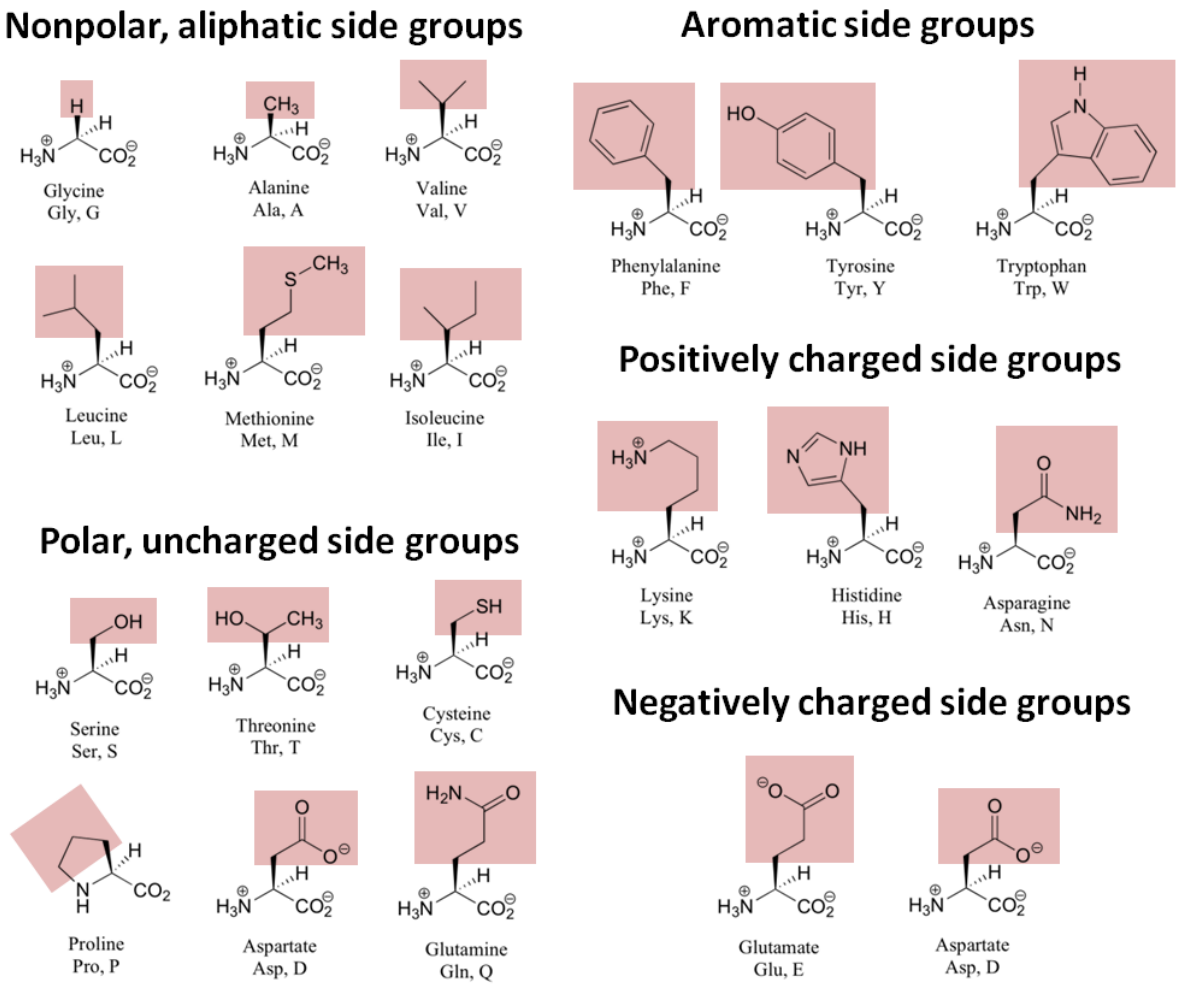
31. PCR takes advantage of the ability of probes to hybridize to DNA sequences. The method is shown in the figure below. By choosing DNA sequences flanking a region of interest, probes can be designed to bind and prime synthesis of DNA ("primers") by an enzyme called polymerase, which incorporates free nucleotides (the four chemical building blocks of DNA containing the bases). The DNA synthesized between the two primers becomes a fragment, and by separating the strands of DNA ("denaturing"), more primer can bind ("annealing"), and more



DNA fragments are synthesized ("extension"). Each cycle produces a doubling in the number of DNA fragments produced, and importantly, each DNA fragment bears an identical sequence. This is the method ich PCR literally amplifies a DNA

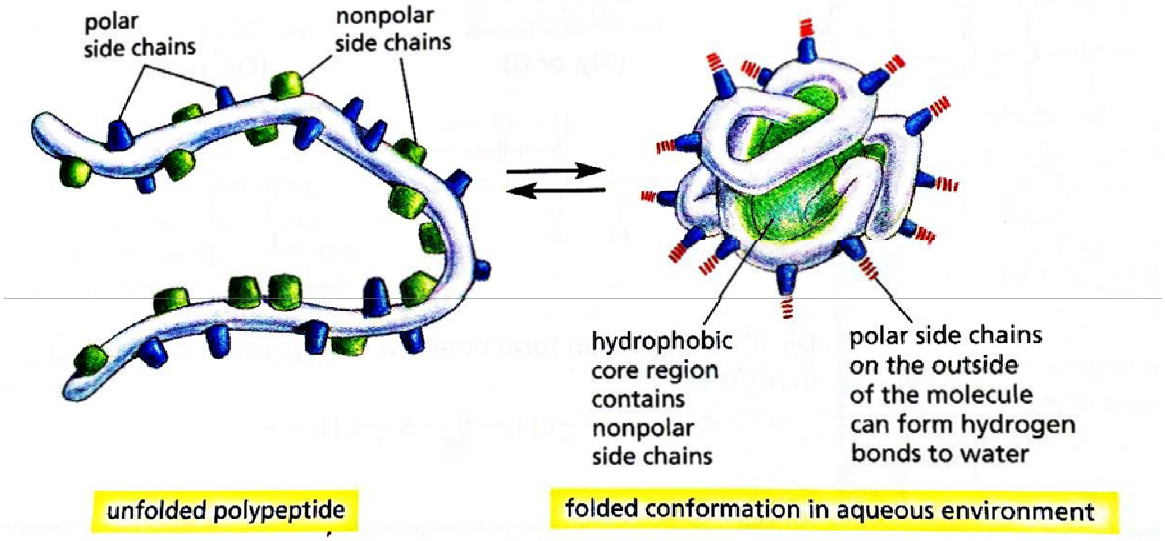
sequence to produce many copies, making that DNA sequence easier to detect, manipulate and analyze. The basic chemistry of PCR is applicable to any DNA segment because the chemistry is almost entirely independent of the actual DNA sequence being amplified. Analyzing the results of a PCR reaction is fairly straightforward—this involves confirming using standard techniques that a PCR product has been produced and has the predicted size and sequence. PCR thus involves routine methods applicable to all DNAs.

32. But the situation is quite different in the context of detecting a newly discovered protein using new starting materials which are also proteins. In contrast to DNA molecules, which share a common backbone and contain only 4 different types of building blocks, proteins contain 20 different types of building blocks (amino acids) that have "side groups" with very different chemistries.



33. Proteins may contain hundreds or thousands of amino acids linked together and folded into a specific complex three-dimensional shape—its "conformation"—which is critical for that protein's function. The amino acid sequence will largely dictate the conformation. As shown in the sketch below, the amino acid chain of a small protein (polypeptide) will fold in water so that amino acids having "polar" side chains are on the external surface (because they like to interact with water), while different "nonpolar" side chains will be on the interior

(because they don't like the water, and prefer the hydrophobic interior which will become relatively water-free).

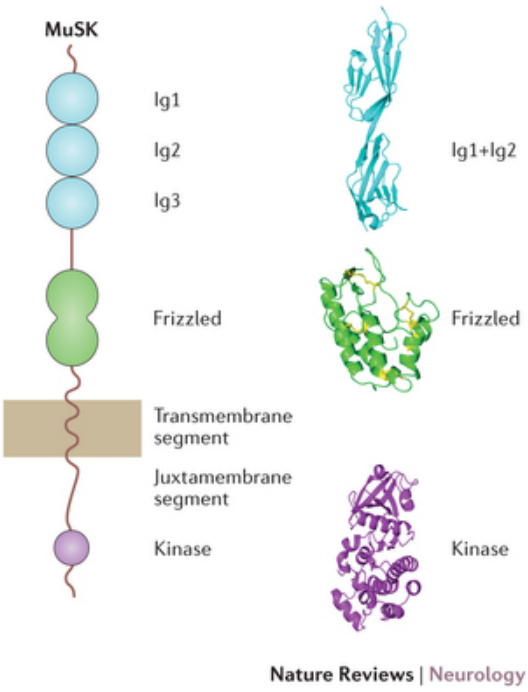


Molecular Biology of the Cell, 5th Edition, Fig. 3-5.

34. As a result, applying one type of reaction or detection method from one protein to another was no longer routine because the conditions (*e.g.*, reagents, starting materials and protein to be detected) used in a known type of reaction for one protein no longer exist. How a common technique is used in a new assay for a new protein is not routine, it is experimental and empirical.

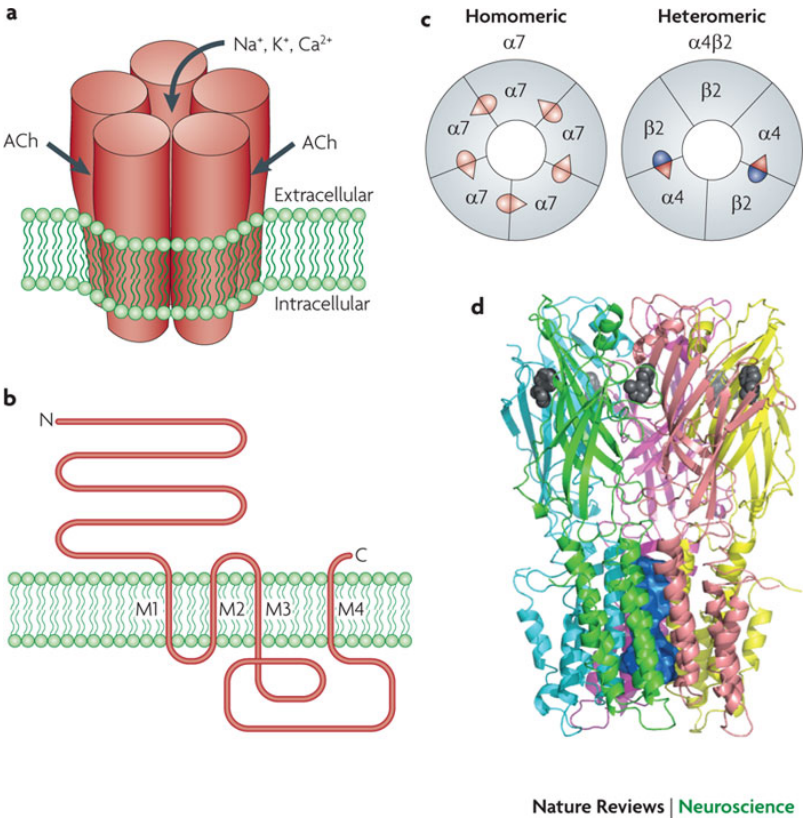
35. In fact, proteins come in so many different configurations and sizes that it is unwise to assume that any standard technique will work the same for different proteins. Take, for example, muscle-specific receptor tyrosine kinase ("MuSK"). Human MuSK is an 879-amino acid protein that contains a transmembrane segment, meaning that it passes through the cell membrane of a muscle cell. On the cell cytoplasm side of the membrane, MuSK has a kinase region

(purple) responsible for modifying other proteins in cells. On the exterior side, MuSK has two "domains," three-dimensional structures observed in many different proteins: three immunoglobulin domains ("Ig," blue) and a frizzled domain (green). *See* Gilhus et al. (2016); Valenzuela et al. (1995). In contrast, the acetylcholine receptor ("AChR") on muscle cells is a massive complex of five subunits (over 2,000 amino acid residues) associated together in the cell membrane to form a functional receptor. Each subunit has a particular structure with its own domains: for example, AChR subunits have four transmembrane regions vs. one for MuSK. Changeux (2010). Overall, the structure of the two proteins is different, both on a macro level (different overall size, different domains) and a micro level (different amino acid sequences). These two different proteins are shown together on the next page.



Structure of the MuSK protein showing the location of important domains (kinase, Frizzled, Ig), and the location of the protein relative to the muscle cell membrane.

Gilhus, et al. (2016) Nature Rev. Neurol. 12:259-69 (Box 3).



Structure of the AChR complex: (a) assembly of the five subunits into a receptor sitting in the cell membrane; (b) the linear polypeptide for a single subunit showing the location of the four transmembrane regions; (c) top-down view of arrangement of different subunits; and (d) a ribbon model showing the large extracellular portion of the protein complex formed by five subunits associated to form a functional receptor.

Changeux (2010) Nature Rev. Neurosci. 11:389-401 (Fig. 1).

36. The "standard techniques" at issue in this case are not "routine" when applied to new proteins. At best, those techniques represent a rough blueprint of what could potentially be done with a new set of starting reagents. But the specific details of any new application of those techniques still need to be worked out. In other words, the outcome of the technique or procedure is far from certain until those details are understood for each new application. The ability to troubleshoot, adapt new techniques, and get something to work is the process that separates excellent scientists from average ones. I have spent my career developing a new model organism that few had ever worked on, and know firsthand how idiosyncratic each new application of a standard technique can be. It is my opinion that getting known types of methods to work in a new context is not a routine task.

37. In fact, the '820 patent provides a definitive demonstration of my point that the standard techniques disclosed are far from routine when applied to a new system. The inventors noted that an Enzyme-Linked ImmunoSorbent Assay ("ELISA") assay they developed to detect MuSK autoantibodies did not work as robustly as the inventors would have preferred. '820 patent, col. 10, ll. 48-50, and compare Figure 6 with Figure 7. An ELISA is a standard, routine assay used for decades to detect antibody binding, that is, when the ELISA is working correctly. When the ELISA is not working correctly, the assay is useless. In my opinion, if ELISA was routine, it would have worked satisfactorily to detect autoantibodies to MuSK. But the inventors reported less than ideal results with the ELISA. '820 patent, col. 10, ll. 48-50.

38. The ELISA example above illustrates my point. There are many well-known and standard laboratory techniques and strategies that a scientist can use for a given application, but selecting the appropriate techniques and getting those techniques and strategies to work properly in each case involves finding the exact right combination of conditions. And this is especially true for different proteins given their inherent complexity and uniqueness.

39. Proteins can be labeled during synthesis using radioactive amino acids. In addition, once a protein has been synthesized, it can be labeled using multiple reagents, for example, a radioactive atom like iodine or an easily detectable molecule like biotin or a fluorescent molecule. Biotin is detected using a secondary reagent that is coupled to another molecule called streptavidin. The Biotin/Strepavidin interaction is highly specific, and in turn stepavidin can be labeled with an enzyme or fluorescent molecule.

40. Labeling a protein after it has been synthesized usually involves oxidation of an amino acid side chain followed by covalent addition of the label. “Covalent” refers to a bond between atoms that is a relatively strong and stable bond. While the techniques used to label a protein are, generally speaking, standard techniques, the ability to label a specific protein depends on the availability and accessibility of the target amino acid in that protein, and thus is a unique characteristic for each protein studied. In other words, there is no guarantee that any protein can be labeled, no matter what the source.

41. In addition, labeling a protein adds another potential complication because the protein must fold correctly, and the presence of the label could affect conformation of that protein.

42. Protein folding is an immensely complicated process that cannot always be replicated experimentally. For example, one calculation suggests that there could be 5×10^{47} possible folding configurations for a 101-amino acid-length protein. Zwanzig *et al*. 1992. Even small changes in protein folding can destroy the ability of a protein (i.e., an antibody) to bind to another protein (an antigen).

43. Other proteins, called chaperones, may assist in the folding process during protein synthesis in a cell, but when proteins are made in a test tube (in vitro), protein folding occurs without the aid of these additional proteins. As a result, protein folding in vitro may be quite different from natural protein folding in a cell. In experiments where proper folding has been quantitated, often 70% of the protein is not in its native state. See Vabulas et al., 2010.

44. For example, iodination, one "standard technique" used in the '820 patent, requires modification of an aromatic ring, found on a tyrosine residue. However, the same tyrosine residue may also be part of the epitope, and labeling may mask the epitope from binding, or change the protein folding such that the epitope no longer exists. In other words, while labeling the protein and using it as a target for immunoprecipitation from serum of patients may be considered common practice, there is absolutely no guarantee that any of the steps in between would replicate the native state of the target protein.

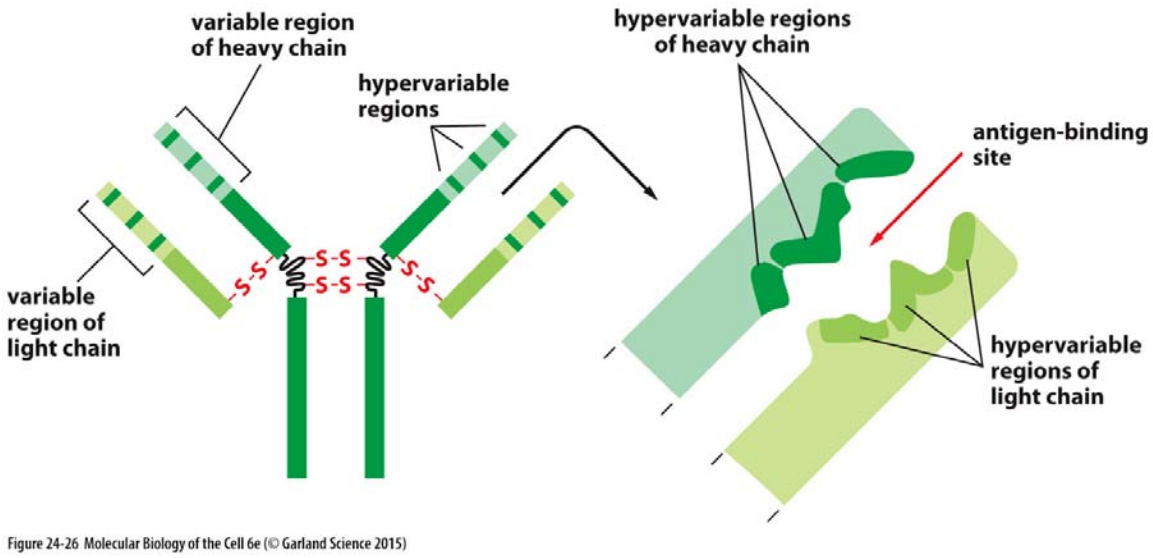
45. This is completely different than labeling nucleic acids. Nucleic acids can also be labeled during synthesis, via incorporation of a labeled nucleotide, or following synthesis by chemical modification of the backbone and addition of a tag, analogous to protein labeling. However, in both cases the techniques are much less idiosyncratic: for example, nucleic acids have only 4 variants (bases) versus 20 (amino acids) for proteins. More importantly, labeling of nucleic acids does not usually affect binding assays. This is because binding of nucleic acids occurs between the base pairs and forms a common structure (a double helix), and also occurs when the molecules are denatured, thus conformational issues in both labeling and formation of complexes are less of an issue. In other words, labeling a new nucleic acid and using it in a binding assay is usually straightforward and independent of the sequence of that nucleic acid, while doing so with a new protein is not: it requires identifying the correct labeling strategy, the correct biochemical conditions to maintain the epitope and promote specific binding. Each of these variables is unique to the interaction being studied.

3. Antibodies and Autoantibodies: Background, Origins and Detection Methods

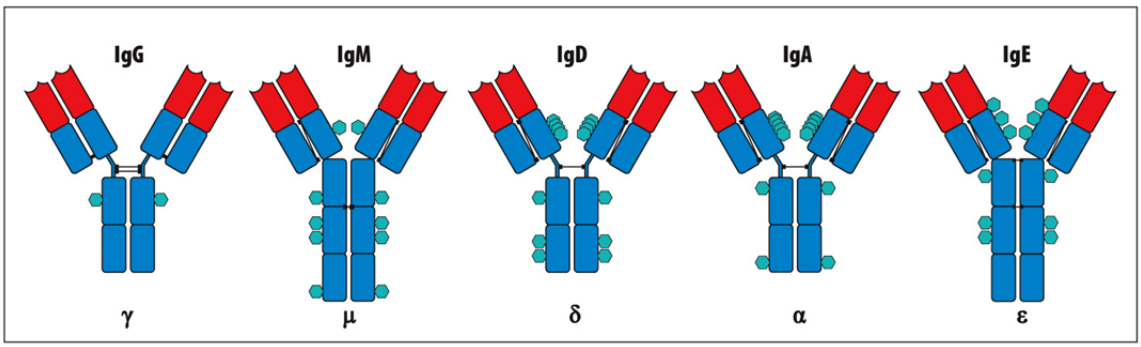
46. Cells in our blood, called B-cells, make antibodies. In turn, B-cells belong to the adaptive immune system. Adaptive immunity operates via an anticipatory strategy, whereby the body makes trillions of unique antibodies via random re-arrangement and mutation of the heavy and light chain genes. Each B-cell makes a single heavy and light chain with a unique specificity, which will bind an epitope. In a healthy individual there are trillions of B-cells in circulation, each with a unique specificity.

47. Because antibodies are randomly generated in each B-cell, they can potentially bind anything. Some B-cells will produce antibodies that bind to epitopes in that person, called self-epitopes, which can lead to autoimmune disease. Thus B-cells must go through an education process, often referred to as tolerance, during which B-cells producing auto-reactive antibodies are removed, via killing of those B-cells. When this education process fails, antibodies to self-epitopes are found in the body, and this can lead to autoimmune disease. B-cells that have never encountered a complementary epitope produce the antibody only on the cell surface, while those that have encountered the epitope begin to secrete the antibody into the blood serum. Thus, detecting antibodies in the serum means that those B-cells were stimulated at some point.

48. Under normal conditions, the immune system makes antibodies to detect foreign substances in our bodies. Antibodies are very large proteins of the Immunoglobulin superfamily of proteins. Each antibody consists of two identical heavy chains and two identical light chains. Both heavy and light chains can be subdivided into two sections, the constant regions and the variable regions. The variable regions of each heavy/light chain pair further contain a “hypervariable region,” containing “CDRs,” short for complementarity determining region. The CDRs in a hypervariable region binds to a complementary three-dimensional molecular structure, called an epitope (see figures below). The structure that the epitope resides on is called an antigen.



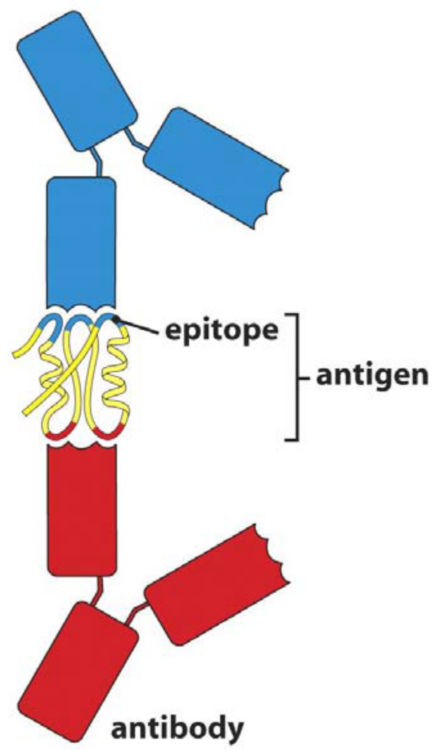
49. There are 5 heavy chain constant regions (IgM, IgD, IgE, IgG, IgA; Figure 3) that can be matched with any variable region. While the variable part of the heavy and light chain makes up the specificity of the antibody, the constant region of the heavy chain directs the structure and function of that antibody. A heavy chain variable region can be combined with a different heavy chain constant region in a phenomenon called class switching. Class switching results in a B-cell



switching the class of antibody it produces. IgM or IgD classes of antibody are found on the cell surface of an unstimulated B-cell. Following stimulation, the B-cell begins to secrete antibodies. Some classes of secreted antibodies such as IgM and IgA exist as complexes containing multiple copies of the antibody. Following stimulation, IgM is the first secreted form, and consists of 5 copies of the 4-chain antibody. During an

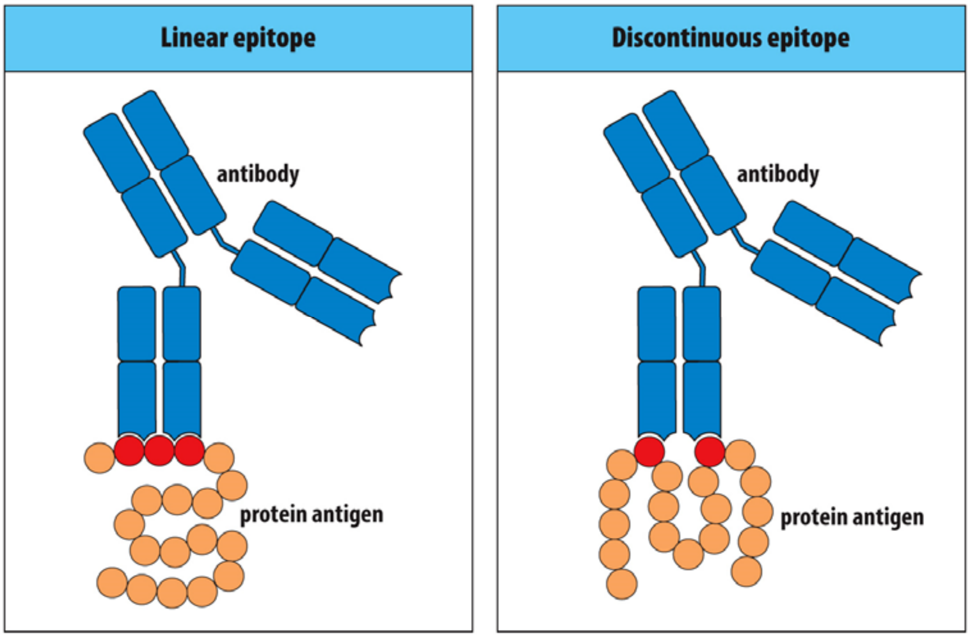
infection, the immune system gathers information on the nature of the threat, and following the initial stimulation can switch out the constant region of the antibody. Each constant chain has different properties that help in binding and initiating the correct response to tagging of the pathogen by the antibody. IgG are the most common antibodies in human blood serum. An antigen may be foreign, like an invading bacterium, the proteins on the outside of a virus-infected cell, or almost any substance with which the immune system comes into contact. In summary, an antigen stimulates an immune response, which generates antibodies binding directly to an epitope.

50. An epitope can be thought of as a shape. The antibody has a complementary shape, and the two bind to each other, reminiscent of how two puzzle pieces fit together. This binding can be highly specific, and antibodies can be so specific that they can discriminate between enantiomers (mirror images) of a single molecule, which have the same chemical composition but different three-dimensional shapes. For example a specific antibody will recognize an epitope containing the amino acid D-alanine, but not to an epitope containing L-alanine, the mirror image of D-alanine—in other words, the only difference between the epitope is a relatively small change in the arrangement of the atoms in the D-alanine molecule in



space, or the configuration of atoms. In contrast, other antibodies may bind epitopes common to more than one molecule, and do not display this high level of specificity. As described below, each antibody is made randomly and has a unique specificity, which can range from low to high.

51. Epitopes are three-dimensional shapes in space and may be part of a protein that is properly folded, in its native state. Thus the shape (conformation) of the protein defines the three dimensional structure of the epitope. Epitopes can be formed by a molecule or a combination of molecules. For example, an epitope can be a physical feature of a protein formed from a linear sequence of amino acids in the protein (called a continuous epitope) or from a physical feature of a protein formed by amino acids throughout the protein (called a discontinuous epitope), in which folding of the protein places discontinuous amino acids near each other in space to form a single three-dimensional structure, the epitope.



52. The immune system can also make antibodies that bind specifically to DNA, sugars, and even to non-biological substances. Antibodies can thus be thought of as highly specific tags. Under normal conditions, the immune system makes antibodies to detect foreign substances in our bodies. The foreign substance is often called an antigen, and the portion of the antigen the antibody binds to is called the epitope. When a human is infected with an antigen, it often makes antibodies to many epitopes on that antigen. Once the antibody binds the epitope, a number of immune mechanisms can be used to destroy the tagged (*i.e.*, antibody bound) structure. In summary, an antigen stimulates an immune response, and the resulting antibodies bind directly to a portion of the antigen, called the epitope.

53. The portion of the antibody that binds to its complementary epitope is called the complementarity determining region, or "CDR." When the CDR of an antibody binds to its epitope, this is called specific binding. However, when

antibodies are used experimentally *in vitro*, they often bind to molecules in a non-specific manner, i.e., to structures other than the epitope recognized by the CDR. The structural basis for this phenomenon is often unknown, but each antibody has its own background level of non-specific binding.

54. Non-specific binding may be due to the fact that the epitope is mimicked by some other structure. Or, regions of the antibody proteins outside of the CDR may bind to the target. When an antibody binds to something, it is critical to determine if binding is specific or non-specific. In other words, if an antibody binds to something in an experiment, it does not necessarily mean that the CDR and was binding to its epitope. This is a critical point—additional verification steps are necessary to determine whether any antibody has bound specifically to its target.

55. Autoantibodies (antibodies against self-epitopes in the body) have been long known to be associated with certain pathophysiological conditions. These are from B-cells that have somehow escaped selection (see paragraph 47, above) and have encountered their complimentary epitope in an individual. The reason this breakdown occurs is not well understood. Those antibodies are often called autoantibodies. Autoantibodies can be any of the five antibody classes described above. *See* ’820 patent, col. 1, ll. 42-48. When autoantibodies bind their target, an immune response can be induced that could destroy the tissue that has been tagged. Or, in other cases, the mere fact that a massive antibody has bound to an epitope might affect the ability of that molecule to function properly because of its physical size.

4. The Methods Disclosed in the ’820 Patent

56. Myasthenia gravis (“MG”) is an autoimmune disease whereby the immune system begins to attack neuromuscular junctions. Early studies found that this disease was due to autoantibodies to the acetylcholine receptor (“AChR”). Studies had shown that MG could be passively transferred in animal models, i.e., the disease could be initiated in an unaffected individual animal by transfusion of serum from another animal containing antibodies to AChR.

57. Based on the knowledge that autoantibodies to AChR existed, scientists developed a confirmatory test, in which blood samples could be assayed for AChR autoantibodies in patients exhibiting symptoms consistent with MG. As described in Reference #6 of the ’820 patent, a paper by Lindstrom et al. from 1976, an immunoprecipitation-based test was developed to determine whether samples contained AChR autoantibodies. According to the Lindstrom paper, the immunoprecipitation was run using a radioactively labeled snake toxin, α-bungarotoxin, that bound to AChR. Lindstrom et al., 1976. In this assay, AChR from human muscle cells were incubated with ^{125}I-labeled toxin and serum from MG patients. The antibody/acetylcholine receptor/^{125}I-toxin complexes were precipitated after a goat-anti-human secondary antibody bound. Even still, the authors noted the presence of non-specific binding, and included a second step using an inhibitor of toxin binding to the AChR, benzoquinonium, to estimate non-specific binding. The assay in the ’820 patent for MuSK does not have a parallel procedure, as no toxin was known to bind specifically to MuSK and likewise, no chemical could be used to block toxin binding to MuSK.

58. However, only 80% of patients with MG have autoantibodies to AChR according to the assay that Lindstrom developed. '820 patent, col. 1, ll. 34-36. Again, the Lindstrom AChR autoantibody assay was a confirmatory assay—patients exhibited MG symptoms, but the test failed to detect AChR antibodies in 20% of the patient population, and it was unclear why. '820 patent, col. 1, ll. 36-42. In the case of the '820 patent, the inventors hypothesized that SNMG patients might have autoantibodies that differed from the AChR autoantibodies present in the majority of MG patients. '820 patent, col. 1, ll. 49-53.

59. Until the inventors ultimately established through experiment and observation that the 20% segment—called "seronegative myasthenia gravis" or "SNMG"—could be explained by the presence of autoantibodies to other targets like MuSK, questions remained in the field about whether the AChR assay could detect all populations. The fact that positive measurements could be made in the 20% of patients negative for the AChR autoantibody test is evidence alone of the advance that the claimed methods of the '820 patent provided to the field of diagnosing MG.

60. In earlier studies, the inventors determined that there was a strong possibility that SNMG patients might have autoantibodies to another protein found in the neuromuscular junction, known to be important in clustering acetylcholine receptors on muscle cells near nerve terminals to promote fast transmission of nerve impulses into muscle contraction. Muscle-specific receptor tyrosine kinase ("MuSK") was a candidate target for those other autoantibodies, but several other candidate proteins were known to exist at the neuromuscular junction and could have been the autoantibody target.

61. But questions remained about how to measure those autoantibodies, if they existed, which at the time was not known. One thing was clear: the AChR autoantibody assay could not be used, since it was unable to detect the other autoantibody species. AChR autoantibodies specifically bind to an epitope associated with AChR. In addition, the AChR autoantibody assay could not be modified to detect the other autoantibody species, as no toxin was known that would bind to MuSK or any other potential target as tightly and with the same specificity that α-bungarotoxin bound to AChR. So the question remained about what could be used as a labeled target for the autoantibodies hypothesized to exist.

62. To test the hypothesis that MuSK was the specific target of the autoantibodies, the inventors developed specific multi-step methods that they believed would specifically identify MuSK autoantibodies. But testing direct MuSK-antibody binding was difficult because MuSK in its native state is associated with muscle cell membranes. It is difficult to manipulate membrane-associated proteins in assays like ELISA and immunoprecipitation. Therefore to test the hypothesis, the inventors created fragments of the MuSK protein (see Figure 1a, '820 patent) and tested which of those fragments would be present in serum from SNMG patients (*see* Figure 2b, '820 patent); the fragments present would be the likely location of the MuSK autoantibody epitope. In my opinion, it would be very difficult to perform either iodination and immunoprecipitation using MuSK in its native state, associated with a muscle cell membrane.

63. Having identified the likely location of epitopes for MuSK autoantibodies, the inventors designed two assays to detect MuSK autoantibodies:

an enzyme-linked immunosorbent assay (ELISA) and a immunoprecipitation assay that involved radiolabeling the MuSK epitope. Each assay involved detecting the potential binding of antibodies to the MuSK epitope, either by amplifying a chemical signal obtained from a enzyme-labeled anti-human antibody (ELISA) or detecting the presence of a labeled MuSK protein fragment after reaction with an anti-human antibody (immunoprecipitation). Again, and as described in more detail below, both approaches differed significantly from the existing assay for detecting AChR autoantibodies, using different reagents and different strategies for determining specific binding between autoantibody and MuSK target. The inventors also described using antibodies to the MuSK autoantibodies in diagnostic kits. ''820 patent col. 5, l. 6-14.

64. The occurrence of autoantibodies to MuSK in MG patients was not known before the '820 patent. Prior to the assays disclosed and claimed in the '820 patent, there was no test for detecting autoantibodies to MuSK in a mammal, and there was no disease known to be associated with MuSK.

65. Even after the inventors developed and published the assay disclosed in the '820 patent, doubts about that solution persisted in the scientific community. One paper published in 2004, at least three years after the invention, literally asks, "Are MuSK autoantibodies the primary cause of myasthenic symptoms?" Selcen et al. 2004. This paper is significant, in my opinion, because it is co-authored by Andrew G. Engel, a researcher with Mayo who has performed original research in myasthenia gravis for more than four decades.

66. The ’820 patent discloses a method to detect a specific IgG antibody in the blood serum. At any one time, there are many, many different IgG antibodies in the serum that differ only in their CDRs. One way to detect a specific autoantibody from the multitudes of antibodies in the serum, analogous to finding a needle in a haystack, is to show specific binding to a self-epitope. There are multiple assays to assess the binding of an antibody to an antigen. In immunoassays generally, the antibody that binds the antigen is often called the primary antibody. Most of those assays use a secondary reagent to detect the autoantibody, like a secondary antibody called for in the ’820 patent. Secondary antibodies are all specific for an epitope on one heavy chain constant region, for example, human IgG. Secondary antibodies are often generated by immunizing another animal, for example, injecting sheep with human antibody constant regions to generate the secondary antibody referred to as sheep-anti-human IgG. A secondary antibody like that one will be specific for an epitope found on all human IgG.

67. To detect and measure MuSK autoantibodies obtained from individual patients, the inventors of the ’820 patent had to design and synthesize a reagent containing the MuSK epitopes recognized by autoantibodies from those different patients, and to design a method to produce a detectable, labeled, complex containing the MuSK autoantibodies and the MuSK reagent.

68. Many immunoassays are designed to detect the presence of an antigen using primary and secondary antibodies purified in the laboratory. In the specific case of measuring autoantibodies in a patient serum sample, the autoantibody ***is*** the primary antibody because it binds to the self-antigen in the patient. Secondary

antibodies are very useful experimental tools because they can be modified and labeled in different ways to detect the presence of human IgG. Secondary antibodies can be labeled radioactively, or coupled to a fluorescent molecule, an iron bead, or an enzyme that can be assayed.

69. The '820 patent describes techniques for detecting the presence of a particular primary antibody (specifically, autoantibodies involved in MG) in blood serum: the Enzyme-Linked ImmunoSorbent Assays (ELISAs), and Immunoprecipitation. '820 patent, col. 3, line 33-col. 4, line 12.

70. There are seven basic steps in the ELISA assay, and to detect autoantibodies at least the following steps would be performed:

1) coat the well of a microtiter plate with the antigen (here, MuSK), equivalent to the description in the '820 patent of "immobilized on a solid support" (col. 3, line 38);

2) use reagents to prevent non-specific binding;

3) add the human serum, which may contain a primary antibody to the antigen (col. 3, ll. 38-43) ("A sample to be tested is brought into contact with the antigen and if autoantibodies specific to the protein are present in a sample they will immunologically react with the antigen to form autoantibody-antigen complexes which may then be detected or quantitatively measured.");

4) wash the plate using reagents which will disrupt non-specific binding but not specific binding of the primary antibody;

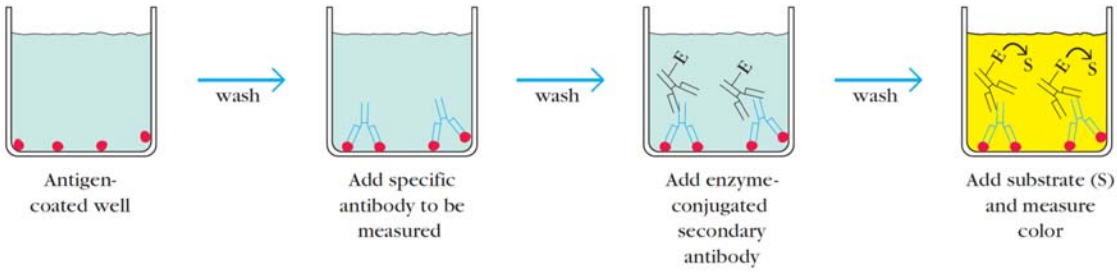
5) add an enzyme coupled anti-human IgG to detect the presence of IgG in the plate (col. 3, ll. 43-53) ("Detection of autoantibody-antigen complexes is preferably carried out using a secondary anti-human immunoglobulin antibody, typically anti-IgG or anti-human IgM, which recognizes general features common to all human IgGs or IgMs, respectively. The secondary antibody is usually conjugated to an enzyme such as, for example, horseradish peroxidase (HRP) so that detecting of autoantibody/antigen/secondary antibody complexes is achieved by addition of an enzyme substrate and

subsequent calorimetric, chemiluminescent or fluorescent detection of the enzymatic reaction products.");

6) wash the plate using reagents which will disrupt non-specific binding but not specific binding of the secondary antibody; and

7) add a substrate that reacts with the enzyme and produces a colored product, indicating the presence of IgG specific for the antigen in the serum (col. 3, ll. 43-53) (same as above).

Kuby, Immunology, 7th ed. (2009) at 660-661. As noted in this description, the '820 patent discloses only some of the principal steps in the method, but undoubtedly those steps, and perhaps others, would have been necessary to produce satisfactory results. A schematic for an ELISA is shown below, with the antigen (red) coating a well, and then an antibody binding to the antigen. A secondary antibody has an enzyme that converts a substrate into a color (yellow) for detection. In some instances protein A, a protein that binds to the non-epitope binding portion of the MuSK autoantibodies may also be labeled with an enzyme and used in an ELISA assay. '820 patent at col. 8, ll. 34-46.



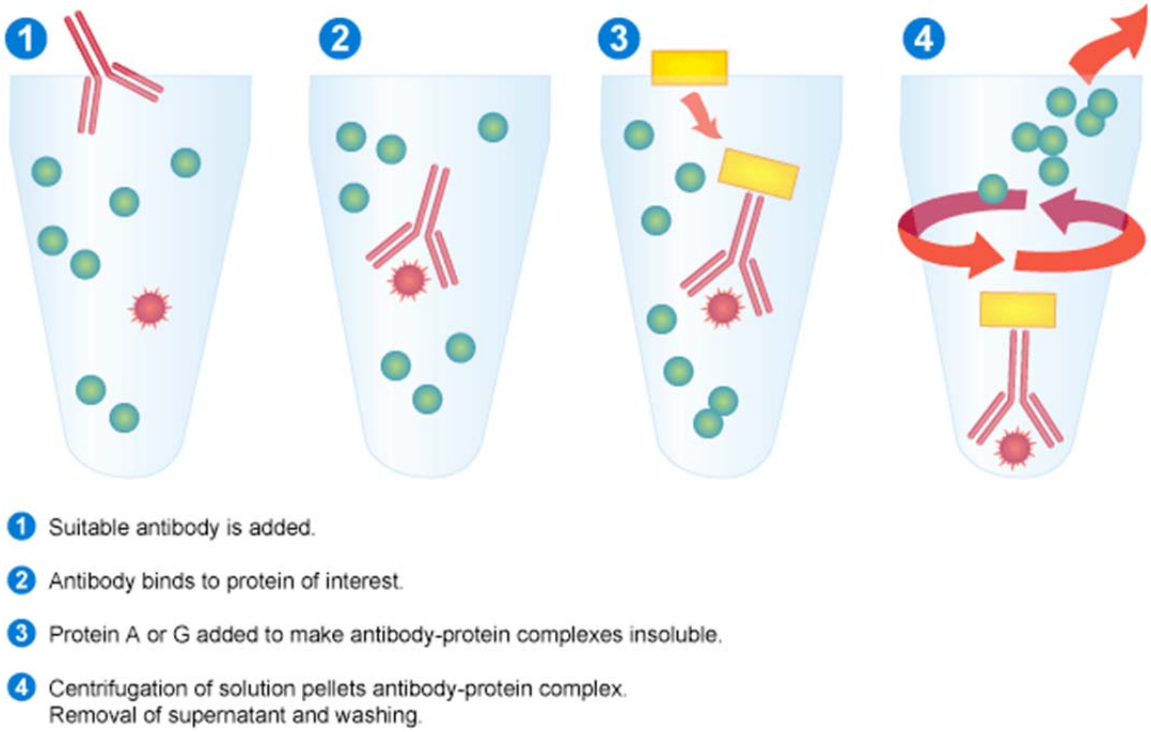
71. Claims 7-9 of the '820 patent do not encompass ELISA or other methods that do not use a labeled MuSK or labeled MuSK epitope. Those other methods can be used to detect autoantibodies to MuSK.

72. There are five basic steps in an immunoprecipitation experiment, and to use immunoprecipitation to detect autoantibodies in patient serum, at least the following steps would be performed:

> 1) mixing the patient serum (which may contain the primary antibody/autoantibody) with the antigen (here, MuSK or a MuSK epitope) in the presence of reagents which will disrupt non-specific but not specific binding of the primary antibody ('820 patent, col. 4, ll. 2-5) ("This method comprises contacting MuSK or an epitope or antigenic determinant, . . . with said bodily fluid, . . ."); (see also col. 10, ll. 55-57);
>
> 2) binding a secondary antibody (col. 4, ll. 5-6) (". . . immunoprecipitating any antibodies from said bodily fluid, . . ."); (see also col. 10, ll. 57-59);
>
> 3) isolating the secondary-primary-antigen via centrifugation (same); (see also col. 10, ll. 59-60);
>
> 4) washing the complex in reagents that disrupt non-specific binding (see also col. 10, ll. 59-60); and
>
> 5) detecting a label that co-precipitates with the antigen (col. 4, ll. 6-7) (". . . monitoring for said label on any of said antibodies. . ."); (see also col. 10, ll. 60-67).

Kuby, Immunology, 7th ed. (2009) at 656. A schematic diagram of the immunoprecipitation technique is shown below. In step 1, the sample contains a mixture with a protein of interest (red), and an antibody (Y-shape) is added. In the context of the '820 patent, the red protein is man-made labeled MuSK fragment containing an epitope to which the autoantibody will bind. The "antibody" added, in this case, will be the serum sample, which contains the autoantibody. Binding of autoantibody to the epitope is shown in step 2, and a second agent is added to the complex to allow it to be separated from the mixture. In the case shown below, the second agent is a protein that makes the complex insoluble, but in the method

disclosed in the '820 patent, the second agent is a secondary antibody that binds to the autoantibody. Finally, in step 4, the complex is separated by centrifugation—rapid spinning to separate components of the solution by weight. With all the complex at the bottom of the tube, the rest of the solution is removed, leaving only the labeled precipitated complex behind for further detection—confirmation that the antibody-antigen binding may have specifically occurred.



73. Note that the '820 patent describes different ways of incorporating the suitable label, or labeling MuSK, an epitope of MuSK, or an antigenic fragment of MuSK with different labels that would co-precipitate with the antibody/MuSK complex, allowing for detection of the complex. See '820 patent, col. 3, line 46-col. 4, line 13.

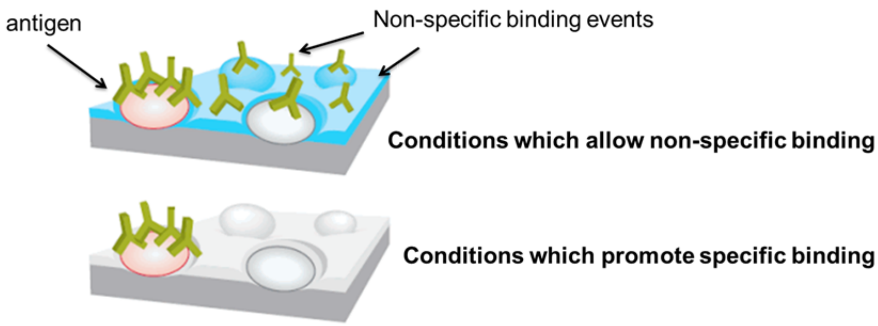
74. In one instance, covered by claim 9, the antigen was labeled: a ^{125}I-labeled extracellular fragment of the M otein. That ^{125}I-labeled MuSK

contacted an unlabeled primary antibody, and was immunoprecipitated with an unlabeled secondary antibody. '820 patent, col. 10, ll. 50-53 ("For this test, the purified extracellular domain of MuSK is iodinated using ^{125}I . . .").

75. In another case, antigen (MuSK) was obtained from antigen (MuSK) was obtained from COS cells (a well-characterized cll line derived from monkey kidney fibroblasts). '820 patent, col. 8, ll. 25-26. The MuSK antigen was then mixed plasma from seronegative or control plasma and the complex was immunoprecipitated using unlabeled rabbit-anti-MuSK antibody raised against the cytoplasmic domain of rat MuSK. The immunoprecipitates were analyzed by Western blotting. '820 patent, col. 8, ll. 24-32 (citing Ref. 12, 13 for an immunoprecipitation method). A similar method disclosed involves obtaining the antigen (MuSK) from detergent-treated C2C12 myotubes that had been fused for five days. '820 patent, col. 8, ll. 25-26.

76. Although the '820 patent does not specifically mention it, it is well recognized among those in the field that the bane of all assays using antibodies in the laboratory, including ELISA and immunoprecipitation, is non-specific binding. Each antibody and each antigen often displays a unique non-specific binding profile. This is countered by empirically changing the reagents and methods used to block these interactions, such as washing steps. Ultimately, the conditions used are often unique to the antibody/antigen pair under study. Thus, in and of themselves, these assays alone do not prove that a detected interaction between antibody and antigen is specific or non-specific, and often other control experiments are also done. In fact, in the '820 patent, the inventors noted that the ELISA results are not consistent

enough to make a reliable test, whereas the immunoprecipitation protocol appears consistent. ’820 patent, col. 10, ll. 48-67.



-modified from EMD Millipore

77. There are published studies using immunoassays that claimed the detection from serum where the results were later found to be incorrect and due to non-specific binding. An example in my field that is highly analogous of the methodology in the ‘820 patent dealt with the presence or absence of antibodies from the serum of hagfish.[1] Using an anti-immunoglobulin secondary antibody, two papers from two different labs, using equivalent techniques, claimed the detection of hagfish immunoglobulins using anti-immunoglobulin antibodies. Hanley et al. 1990; Varner et al. 1991. A year later, however, one of those labs recognized a significant error: the antibody used in the immunoassays bound non-specifically to another unrelated protein. Hanley et al. 1992. It is now known that hagfish do not have immunoglobulin genes in their genome. Pettinello & Dooley 2014. This example shows that two careful, reputable teams of scientists can be led to believe incorrect results because of non-specific binding. The lesson here, that all

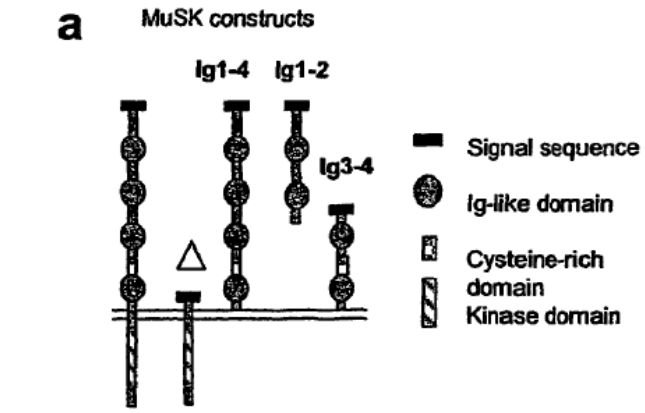
[1] Hagfish, because of its place in the animal kingdom from an evolutionary perspective, provides an important data point to assess the evolution of immune system components, like antibodies.

immunologists working with antibodies take to heart is to take all necessary measures to understand and minimize non-specific binding to yield results that can be properly interpreted.

78. MuSK is a transmembrane protein, which spans the cell membrane. When synthesized in vitro, transmembrane proteins will usually only fold correctly when they are co-translationally inserted into a membrane. To overcome this, the inventors synthesized portions of the extracellular domain, as described above.

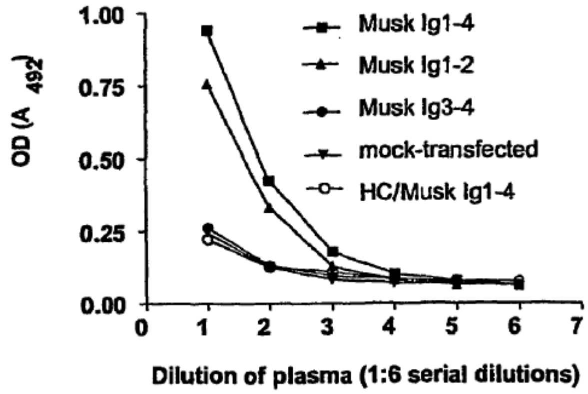
79. In the '820 patent, the authors used three different synthesized pieces of the extracellular domain of the MuSK protein (the entire extracellular domain, as well as the proximal and distal halves of the extracellular domain) to demonstrate specific binding. '820 patent, Fig. 1.

FIG. 1.



80. In Figure 2B, the patent shows that an epitope resides in the first immunoglobulin domains of the MuSK protein, as the antibody binds to the entire extracellular domain, as well as the distal half, but not to the proximal half. This experiment does not absolutely prove that this is specific binding, but it is strong

b



evidence that it is not non-specific binding, as there is clearly some selectivity in binding.

81. The strategy in the ’820 patent did not involve using natural products, as the protein fragments of the extracellular domain of MuSK were each synthesized separately in the lab. In addition, there was no conventional way to make each protein product. The inventors made three pieces, and the fragments the inventors made were decided by them alone, there is no conventional way to carry out these experiments.

82. As the nature of the epitope in the MuSK protein was unknown (e.g., continuous or non-continuous, see above), there is no guarantee that the strategy taken in the ‘820 patent would work. First, it is not a given that a partial protein sequence will fold correctly, thus the epitope may not form, or be accessible to the antibody as it would be in its native state. Second, there is no guarantee that each person makes autoantibodies to the same epitope. As outlined above, antibodies are created randomly from portions of the immunoglobulin genes, and in addition there is polymorphism of the immunoglobulin genes, and each person does not have the

equivalent raw material to make antibodies, thus they can be different in each individual.

83. The data reported in the '820 patent suggest that MG is due to autoantibodies to at least two proteins expressed in the neuromuscular junction (AChR and MuSK) and further that the autoantibodies affect the maintenance of the structure neuromuscular junction. Autoantibodies to the AChR were identified via binding of the ACHR to a labeled inhibitor of AChR, a snake toxin called α-bungarotoxin, which tightly binds to AChR. In turn, the α-bungarotoxin was labeled such that autoantibodies binding the AChR could be detected because the entire complex would be isolated by immunoprecipitation.

C. MY OPINION CONCERNING WHETHER THE ELEMENTS OF CLAIMS 7-9 OF THE '820 PATENT ARE AN "INVENTIVE CONCEPT"

84. I have been asked to consider the elements of claims 7-9, both alone and in combination, to render my opinion about whether those elements amount to an "inventive concept" that allows the claims to survive *Alice* Step Two.

85. For my analysis, I have considered three different elements:

- the **detecting** step, from claim 1, covering detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK);
- the **contacting** step of claim 7, covering contacting MuSK or an epitope or antigenic determinant thereof, having a suitable label thereon, also considering the "radioactive" label of claim 8 and the "^{125}I label" of claim 9, with a bodily fluid; and
- the **immunoprecipitating** step of claim 7, covering immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid.

86. For each of these elements I considered whether the steps consist of well-understood, routine, conventional activity already engaged in by the scientific community. The MuSK autoantibody/labeled MuSK (or labeled MuSK epitope, or labeled MuSK antigenic determinant) complexes are not products of nature and did not exist before the invention in the ’820 patent. The immunoprecipitate formed in claims 7-9 of the ’820 patent by further reaction with an anti-human antibody is also not a product nature and did not exist before the invention.

1. The “detecting” step includes an inventive concept.

87. Based on my many years of experience in immunology, specifically relating to the ability to detect immune system proteins in self-recognition processes such as the creation of autoantibodies in pathological conditions like myasthenia gravis, it is my opinion that the action to detect a specific molecular species is not universal. Depending on the molecular species to be detected, there are, most likely, several different methods that can be chosen, each having a different degree of complexity and idiosyncrasy that necessitates a fair amount of experimentation to determine whether any one of those methods would be effective at accomplishing the detecting step. Specifically, in relation to claims 7-9 of the ’820 patent, the detection step would have required a significant amount of experimentation using previously characterized techniques to confirm that MuSK autoantibodies were being detected.

88. It is difficult for me to understand how the detection of MuSK autoantibodies could be well-understood at the time of the invention, given that nobody had detected MuSK autoantibodies before the inventors even though the art

had been detecting autoantibodies in MG patients' blood samples since at least 1976 when the AChR autoantibody detection assay was first introduced. Lindstrom et al. 1976. Given its own specificity, the AChR autoantibody test was not used to detect MuSK, and it remains true today that the AChR autoantibody test ***cannot*** be used to detect MuSK autoantibodies. In fact, as I describe above, the AChR autoantibody test cannot even be modified to detect MuSK autoantibodies, as MuSK autoantibody detection requires a completely different set of chemical reagents specific for that purpose. This highlights the critical nature of the labeled MuSK fragment described in the '820 patent.

89. In my mind, there is absolutely no relationship between the AChR autoantibody detection method developed in 1976 and the MuSK autoantibody detection method of the '820 patent that would render the latter "well-understood" in reference to the former. In fact, over 25 years had passed before anti-MuSK antibodies had been detected at all, despite the prevalence of the AChR autoantibody detection method.

90. The existence of an immunoprecipitation-based assay using a ^{125}I radioactive labeled bungarotoxin simply could not detect MuSK autoantibodies. To me, this is clear evidence that the "detecting" step of claims 7-9 was not well-understood for this specific interaction when the invention was made.

91. In my opinion, the "detecting" step of the claims is also not routine. It is not like the laboratory techniques recited at a high level of generality, like "amplifying a DNA fragment" using PCR, that courts have found unsatisfactory with respect to *Alice* Step Two in other cases. As I described above, the inventors had to

take special steps to detect MuSK autoantibodies. Those special steps include the creative step of breaking up the MuSK protein into smaller parts, expressing the parts, and labeling them to be useful as molecular baits to bind to anti-MuSK antibodies present in a bodily sample. In my opinion, none of those additional steps could have been routine before those inventions had been made and reported to the scientific community in 2001—a result of efforts that were far more experimental than routine.

92. And even after anti-MuSK antibodies had been reported in the literature in 2001, prominent scientists expressed skepticism that those antibodies could be responsible for myasthenia gravis. Several years later, one group noted that a deficiency in endplate AChR should follow from MuSK autoantibody-linked myasthenia gravis, yet that information has not been shown. Selcen et al. (2004). That 2004 paper noted a number of undetermined information about the relevance of MuSK autoantibodies to myasthenia gravis:

> Studies of MuSK(+) MG are still incomplete: MuSK expression at the EPs has not been examined; qualitative or quantitative assessment of the number of AChRs per EP has not been performed; immune deposits have not been identified at the EPs, EP fine structure has not been examined; the synaptic response to acetylcholine (ACh), indicated by the amplitudes of the MEPPs and miniature EP currents (MEPCs) has not been monitored by in vitro electrophysiology; and it has not been shown that immunization of animals with MuSK could induce myasthenic weakness.

Selcen et al. (2004). Each of those listed studies would ***later*** confirm that the detection methods developed by the inventors and disclosed to the public in the 2001 Nature Medicine paper could faithfully report the correlation between MuSK

autoantibodies and myasthenia gravis. Hoch et al. (2001). To me, this confirmation is further evidence of the non-routine nature of the steps in claims 7-9.

2. The "contacting" step includes an inventive concept.

93. I understand the contacting step of claims 7-9 covers the act of bringing together a bodily fluid of a mammal (e.g., a blood or serum sample of a patient) with a labeled MuSK or labeled MuSK epitope or antigenic determinant.

94. I understand MuSK to mean the entire MuSK protein: an 869-amino acid protein having the structure identified in Figure 1 of the '820 patent, or Figure 2B of Valenzuela et al. (1995). MuSK contains a significant extracellular portion (amino acids 24-495), a transmembrane portion (amino acids 496-516), and a cytoplasmic region (amino acids 517-869).

95. I understand a MuSK epitope or antigenic determinant to be a portion of MuSK that an antibody can bind to. For purposes of understanding the claims, I consider epitope and antigenic determinant to be equivalent, so I will refer to "MuSK epitope" for simplicity.

96. Based on my experience, one possible place a MuSK epitope could be found is on the extracellular portion of the MuSK protein. This is because when the protein is expressed normally and appears in the cell membrane, the extracellular portion is the part of the MuSK protein that is "visible" to antibodies, which exist outside of cells in the extracellular fluid. But I am aware of instances for proteins other than MuSK where those proteins are not expressed normally; and in those cases, cytoplasmic portions of the proteins could contain epitopes that might be recognized by antibodies. For that reason, I hesitate to limit "MuSK epitope" to the

extracellular portion of the MuSK protein, because without experimentation, it is not possible to predict where epitopes or antigenic determinants might exist. In addition, given that epitopes are present due to proper protein folding, it may be that the presence of the epitope depends on folding of the entire protein as it occurs naturally.

97. The inventors performed those experiments to establish the location of a MuSK epitope to which an antibody might bind. The results of those experiments are shown in Figures 1a and 2b of the ’820 patent. Figure 1a shows the various fragments of the full-length MuSK protein prepared for expression into COS cells. Figure 2b shows the pattern of binding to the various MuSK constructs to autoantibodies in serum samples of patients, and as reported in the patent, the “antibodies bound strongly to MuSK constructs expressing the distal immunoglobulin-like domains, Ig1-4 and Ig1-2 (see Fig. 1a), but not to the 1g3-4 membrane proximal domains.” ’820 patent, Col. 6, line 67-col. 7, line 3. This experiment identified the location of epitopes to which the autoantibodies in the patient serum tested bound. Other antibodies might bind to other epitopes.

98. The inventors had to find the conditions whereby the MuSK protein fragments folded correctly such that the epitope was accessible to the antibody, define the conditions to <u>specifically</u> bind the antibody to the epitope on MuSK, and determine a way to detect that binding. In that context, FIG 1 alone demonstrates an inventive concept because of its non-routine and non-conventional nature. A portion of the entire MuSK protein that does not exist in nature is a unique solution for that specific, new fragment, and its use in an experimental procedure is also inventive

for that reason. Not every fragment would work, the epitope could have been in the middle of the fragments used, or correct folding necessary to create the epitope could not have worked on every fragment.

99. The element requires that the MuSK or MuSK epitope have a "suitable label thereon." In my experience, a "suitable label" for any protein has two basic requirements.

100. First, the label must be detectable, meaning; the label emits a signal that technique used to report the existence of the label must be sensitive enough to detect the label's signal, which can be difficult if the label is present in small quantities. A related issue to detectability is that the label must remain bound to the protein regardless of the chemical processing steps that must be performed in the detection method. For this reason, most labels are covalently bound to the protein a researcher wishes to label. A covalent bond is a relatively strong chemical bond formed between atoms in which the two atoms share electrons. Covalent bonds are widely accepted as defining different chemical entities, and the formation of a new covalent bond is an indication that a new chemical entity has been formed. In other words, chemicals associated by covalent bonds are transformed into a new and different chemical.

101. Second, the label must preserve the functionality of the protein to which it is attached. In my opinion, a "suitable label" for MuSK or MuSK epitope is one that can be detected and preserves the ability of any autoantibody to bind to it. Whether any label is a suitable label for a given protein requires actually constructing the labeled protein and testing it in the detection method. As with most

methods involving proteins, the suitability of a label is empirically derived, and cannot be assumed.

102. Chemists have developed many different types of label for the detection of chemicals in biological samples, like proteins. However, there are any number of reasons a given label might not be a suitable label, including, among others: (i) label cannot bind to the protein (i.e., no binding site exists to form a covalent bond); (2) antibody cannot bind to the labeled protein because the label physically blocks the binding site; (3) antibody cannot bind to the labeled protein because the label changes the local chemical environment of the antibody binding site; or (4) the label is present in the sample at too low an amount to produce a detectable signal above the background noise. Therefore, the identification of a "suitable label" for any protein, including MuSK, is neither routine nor automatic, and requires experimentation to determine whether any label will be suitable to report the presence of the protein after the contacting step has been performed.

103. The choice of the label is made more difficult for a transmembrane protein like MuSK. Transmembrane proteins contain at least one region that crosses through the cell membrane. These regions are hydrophobic (repelling water) and their preferred environment is the hydrophobic environment of the cell membrane. But often, labels are hydrophilic (water-loving), and are difficult to use in hydrophobic environments. There are two generally-accepted strategies for working with transmembrane proteins to account for the hydrophobic portions: using detergents, and breaking up the protein into smaller pieces to isolate hydrophilic portions. Both strategies have plusses and minuses. Detergents

introduce an entirely new chemical environment to the detection method, and the effectiveness of the method must be established experimentally. In addition, as detergents interact with hydrophilic and hydrophobic portions of the protein, they can change conformation, which could either destroy or mask the epitope. Breaking up the protein into smaller pieces, apart from being more technically challenging, introduces the possibility that the pieces may not fold in the same way as the native protein, which might interfere with function. Again, strategies involving breaking up a larger transmembrane protein into smaller pieces to permit hydrophilic labeling must be experimentally verified to confirm that the label is suitable.

104. Given all these variables, it is my opinion that the requirement for a suitable label on MuSK or a MuSK epitope cannot be considered routine, even though the labels themselves had been well-known, standard techniques in the field applied to other proteins before the invention in the ’820 patent.

105. The “contacting” step of claims 7-9 was neither routine nor conventional for another reason: other autoantibody detection methods for myasthenia gravis before the invention did not require that the autoantibody’s target be labeled. In other words, the use of labeled MuSK—to which MuSK autoantibodies bound—was unusual given the conventional activity already engaged in by the scientific community Detection of autoantibodies to MuSK was not simply an extension of the AChR techniques, a completely novel assay had to be developed.

106. The AChR autoantibody detection method, described in more detail above, required the use of labeled α-bungarotoxin as a means of indirectly labeling

the AChR. As a transmembrane protein, AChR is difficult to work with using water-based labels. The availability of a toxin that would bind tightly to the AChR was an inventive solution that permitted development of a detection method for AChR autoantibodies. But that toxin does not bind to MuSK, and cannot be used as an indirect method of labeling MuSK to detect autoantibodies. Therefore the direct labeling of MuSK for use in detecting MuSK autoantibodies renders the "contacting" step not routine and not conventional. In other words, the development of a labeled MuSK was an inventive concept that represents an improvement over the conventional activity already engaged in by the scientific community.

107. The contacting step's requirement for using MuSK or a MuSK epitope having a suitable label is a relatively narrow approach that is not necessary to identify autoantibodies in a biological sample. In fact, the '820 patent describes another method that does not require the use of a labeled MuSK or MuSK epitope in Column 8. At lines 36-46, the patent describes an ELISA method in which unlabeled MuSK is present on a solid surface, and the step equivalent to the "contacting" step of claims 7-9 takes place between unlabeled MuSK and a bodily sample containing MuSK autoantibodies. This is quite different from the "contacting" step of claims 7-9, which requires contacting a labeled MuSK and with a bodily sample containing MuSK autoantibodies. Detection in the ELISA method requires the use of a second antibody containing a label that reports the presence or absence of the MuSK autoantibody, however the application of this second, labeled antibody takes place after the equivalent "contacting" step in the method of claims 7-9. In my opinion, the "contacting" step creates an inventive concept in claims 7-9 precisely because the

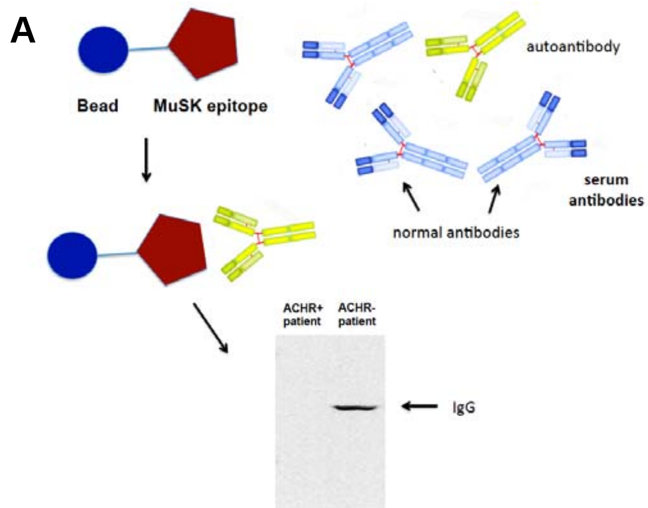
step specifies the exact requirements of the detection method. And as explained above, those requirements track with inventive solutions involving non-routine activities. Furthermore, the ELISA method did not work robustly, thus the inventors had to come up with another strategy to detect the autoantibodies. It should be noted that an ELISA assay is much easier to carry out: it uses a common format and thus is easy to scale up into a high-throughput assay, can be easily automated, and does not require the use of radioactive substances. In contrast, the test in the ‘920 patent requires multiple steps that are difficult to automate.

3. The "immunoprecipitating" step includes an inventive concept.

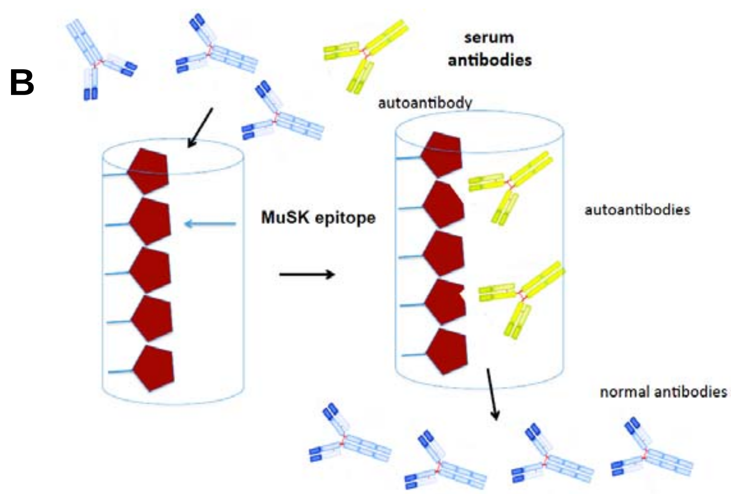
108. The complexes listed in this element are not naturally occurring because they are causing an MuSK autoantibody to be bound to the labeled MuSK or MuSK fragment to form a complex that is not naturally occurring. The immunoprecipitation step requires precipitating the complexes by binding it to a secondary antibody which binds to the MuSK autoantibody/labeled MuSK complex.

109. This immunoprecipitation step is not routine. It, like any other immunoprecipitation protocol is unique and must be worked out for that particular interaction. Many antibodies in my lab work fine for some detection methods, for example, Western Blotting or Immunofluorescence, but we have never been able to use in immunoprecipitation experiments. In my opinion, and for largely the same reasons as I discussed above, each new immunoprecipitation assay, including the immunoprecipitation steps stated in claims 7-9 of the ’820 patent is unique and is an inventive concept for those reasons.

110. There are multiple other ways to use the MuSK epitope to the detect the presence of autoantibodies. Two examples are shown below. In panel A, the MuSK fragments could be coupled to a magnetic bead, then mixed with the serum. If correct conditions were used, the anti-MuSK autoantibodies (yellow) would bind to the beads, while the normal antibodies (blue) would not. The beads would then be washed to remove non-specific binding. The autoantibodies could then be eluted and detected by Western blot using anti IgG secondary antibodies, and serum from AChR+ and AChR- MG patients could be compared. The blot shown contains a band for the AChR- MG patients, suggesting that MuSK autoantibodies play a role in that patient's disease.



Alternatively, as shown in Panel B, the MuSK epitope could be immobilized on a column and the patient serum would be poured through the column. Autoantibodies in patient serum (yellow) would bind to the MuSK while the normal antibodies in patient serum (blue) would wash through. The presence of



antibodies would then be detected by Western Blotting using secondary antibodies, as shown in A. There is no standard way to go about this, and as already demonstrated in the '820 patent, an ELISA assay was not reliable enough to use to detect the presence of autoantibodies in SNMG patients. The conditions for each assay described here would need to be specifically determined to ensure specific binding and minimize non-specific binding—as I discuss above, those qualitative characteristics are necessarily empirically derived and specific to each assay.

111. Claims 7-9 of the '820 patent do not cover the methods I describe in the preceding paragraph. As I stated above, those alternative ways of detecting MuSK autoantibodies do not use labeled MuSK or a labeled MuSK epitope, and claims 7-9 require the use of a labeled MuSK or labeled MuSK epitope. This demonstrates that there are other ways to measure MuSK autoantibodies not covered by the claims.

D. CONCLUSIONS

112. To summarize my opinion:

- The "detecting" step of the claimed methods includes an inventive concept because detecting MuSK autoantibodies could not have been well-understood until the inventors discovered them. Preexisting methods for detecting autoantibodies involved in myasthenia gravis could not detect MuSK autoantibodies, and could not be modified to do so. The inventors developed a new method for detecting MuSK autoantibodies that was far from routine to implement because the success or failure of any method to detect MuSK autoantibodies must be empirically determined for each target molecule.

- The "contacting" step of the claimed methods includes an inventive concept because of the additional non-routine steps the inventors had to take to produce a MuSK epitope or antigenic fragment having a suitable label thereon, primarily because the MuSK protein is a transmembrane protein, and MuSK would need to be broken into fragments that could be easily manipulated. It woul ave been routine to determine

whether a label was suitable, and whether a labeled MuSK epitope or antigenic fragment would bind specifically to MuSK autoantibodies with non-specific binding low enough to clearly identify when MuSK autoantibodies were present in a patient sample.

- The "immunoprecipitating" step of the claimed methods is not routine and represent an inventive concept. Each immunoprecipitation protocol is unique and dependent on the unique properties of the antigen and the specific binding properties of the antibody. But the immunoprecipitating step requires a labeled MuSK compound, which is not naturally occurring and can be patented. I understand this means that methods using the labeled MuSK compound of the claims may also be patent-eligible. Based on my 25-year experience with immunoprecipitation, that technique, while "standard" and widely known, never guarantees an outcome – the opposite of "routine," in my opinion.

Dated: November 14, 2016
Santa Barbara, California

Anthony W. De Tomaso, PhD
Associate Professor of Molecular, Cellular and Developmental Biology

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ATHENA DIAGNOSTICS, INC., et al, Plaintiffs,	)	
vs.	)	CA No. 15-40075-IT
MAYO COLLABORATIVE SERVICES, LLC, d/b/a Mayo Medical Laboratories, et al, Defendants.	)	

BEFORE: THE HONORABLE JUDGE INDIRA TALWANI

HEARING ON MOTION TO DISMISS

THE SECOND AMENDED COMPLAINT

John Joseph Moakley United States Courthouse
Courtroom No. 9
One Courthouse Way
Boston, MA 02210
Tuesday, August 2, 2016
10:35 a.m.

Cheryl Dahlstrom, RMR, CRR
Official Court Reporter
John Joseph Moakley United States Courthouse
One Courthouse Way, Room 3510
Boston, MA 02210
Mechanical Steno - Transcript by Computer

the more specific -- that there's now some additional specific technological process that can be patented?

MR. SINGER: Well, because the inquiry is whether or not that is, one, conventional technology, right? That's the first question we have to ask. And, second, right -- this is the argument they've raised -- is even if it were conventional, does it result in anything that's distinct, right? That was the cDNA versus the isolated DNA. And the specification says and teaches -- it says that iodination -- that's the word for 10:49 putting this radioactive iodine on -- is a standard technique in the art.

THE COURT: So that's 8. But what about 9? Does it matter that it's 125I, that we're now talking about this very specific process using this very specific manmade label?

MR. SINGER: Right. That is the radioactive iodine.

THE COURT: The particular one?

MR. SINGER: Yeah. That's what it is. When someone is saying use of a radioactive label and then a radioactive iodine label is standard in the art, that's what Claim 9 is.

10:49 THE COURT: Does it matter whether this -- do I need to make an inquiry as to whether this particular radioactive iodine and using -- the process using this particular radioactive iodine is standard; and, if so, is that also in the specifications or -- because it seemed to me the specifications are more generic.

MR. SINGER: Does it say I125? I don't know the answer if it does, your Honor. I know it says iodination is a standard technique.

THE COURT: Yes.

MR. SINGER: And I think what it does is point to -- I think we've pointed to reference articles that the specification quotes. Do you need to make an inquiry as to whether this is a conventional technique? I think you do in fairness to the plaintiffs. But I think the specification gives us the answer in that, well, it doesn't say 125, the number. I think it would be a --

THE COURT: It gets me to 8. I see where 8 would track the specification. I guess my question is: Does 9 -- do I have enough information in front of me to know -- and it is appropriately done on 12(b)(6) -- to know whether 9 is not something new?

MR. SINGER: Yeah. Actually, I misspoke. So I thought the specification didn't say I125, and I remembered the sentence that said -- and I'm reading from Column 4, your Honor -- "iodination and immunoprecipitation," which is the technique described -- it's Column 4, Lines 10 through 12 -- "are standard techniques in the art, the details of which may be found in references 4 and 6." And the sentence before, it says, "preferably the label is radioactive label, which may be 125I or the like." That is the standard radioactive iodine

that is used in these techniques, as I think you can see from the context both in the specification as well as the references cited in the specification. It's the same technique used with the prior art acetylcholine. 80 percent of us who might suffer from this disease have --

THE COURT: It's the same technique generally, but it isn't using the radioactive label, is it?

MR. SINGER: It's the same technique in the R2 label.

THE COURT: Right.

10:52 MR. SINGER: That's -- you and I are on the same page.

THE COURT: We're moving to a more specific -- you can't be making the argument that there couldn't be some process in the diagnosis. You've come up with this idea. You've made this discovery that there's a correlation. It can't be that Mayo is going to say no process claim --

MR. SINGER: Oh, no.

THE COURT: -- can ever -- no method of detection or method of diagnosing is patentable at this point. So if they're doing it somewhat differently, even if it generically

10:53 is the same thing, that we're trying to test for some combination that didn't used to be there, if it's specific enough, do they get past the hurdle?

MR. SINGER: So the answer to your first question is we are not saying that no one could ever come up with something patentable. But what we are saying is that you can't use a

standard technique in the art to turn that correlation into something patentable and that the I125 is, in fact, a standard technique in the art. And I --

THE COURT: But I have to -- at this stage, the only place I get that is from what the -- what I read in the specifications.

MR. SINGER: Specification and the references incorporated therein, that's correct. That's where you have to look, right? We have no -- we have no expert declaration from them saying it's not standard, for example, that you --

THE COURT: They wouldn't be -- we're on a 12(b)(6) so --

MR. SINGER: Fair enough. Some of the cases -- just for your Honor's benefit, some of them do have expert testimony put in by one or more of the parties on 12(b)(6).

THE COURT: Which gets to the point that, if you're both trying to litigate this in a way that gets the issue decided rather than simply being a cost of litigation issue, that whatever happens here, presumably one side or the other will take it up. And the case law isn't completely straightforward enough for either side to be a hundred percent sure, whichever way I go, that the Federal Circuit isn't going to say, Well, we really don't like Mayo all that much, and we're going to move it this way or you read Mayo too broadly, you know, whichever way.

So why wouldn't it make some sense that, to the extent that this is what this issue turns on, that there's a record here as a -- which would essentially be a summary judgment record but perhaps an early summary judgment, not a late summary judgment motion, but to flesh out this issue rather than saying I need to make a what seems somewhat of a beyond my expertise decision based on reading the specifications and the paper cited in the --

MR. SINGER: At the end of the day, your Honor, if that is what makes your Honor most comfortable, then Mayo has no objection to that. What we don't want is what you earlier referred to, and we brought it to your attention in the way that the authorities allow under a 12(b)(6) motion. We believe firmly that this is resolvable at the 12(b)(6) stage, but I don't want to put you in an uncomfortable position where you feel like you don't have enough background in the technology from experts, for example, to allow you to make a decision that you believe is going to be fully supported one way or the other on appeal. I do not want to put you in that position, and we have no objection.

What we do have an objection to is somehow opening wide discovery so we end up spending millions of dollars to get to a result that, frankly, your Honor, we believe is inevitable. I mean, this is a standard technique applied to a discovery. These are pre-Mayo patents. The persons

prosecuting them didn't have the ability to understand the law. And the argument made by the other side is breathtaking in its breadth -- in its breadth. And that is, that adding a label to MuSK -- and I can quote from their brief -- adding a label to MuSK, a natural occurring protein and the autoantibody to that protein, that adding that label makes it patentable, that's it, that's the end, that is wrong. That is not what the law says. The law requires use of something more than conventional, and manmade doesn't get you over the hurdle.

10:57 I just -- that was addressed extensively. I don't want to leave here without hitting on that issue because you and I have discussed a lot of things. But manmade isn't the answer. That doesn't tell you really all that much in the Section 101 inquiry. If you go back to your authorities and you read the *Promethious* case, which I was involved in for ten years, for heaven's sake -- that's how long that one took -- and the *Myriad* case, which I was involved with, as was Mr. McMahon, for several years, the inquiry under 101 on the isolated DNA, which the Supreme Court found unpatentable, the

10:57 Federal Circuit said that's manmade; therefore, it's patentable. The Supreme Court said not enough because it's not distinct from the natural DNA, not sufficiently distinct from the natural DNA, that severing the bonds, right, of the DNA and isolating it out of the organism, while manmade, that was simply not enough. The cDNA was distinct. It was a distinct

work with one little strand of DNA, so they bulk up; they replicate it and they look at it in bulk. That's just a standard, well-known, routine technique that no one would think twice about doing.

There's no showing in the record that this -- the iodine 125 marker or the radioactive markers were of that level that they were just routinely done. They can't be done with everything. That's even in the record here. So I think that if the Court is wondering, Can I125 be applied to anything, the answer is no.

I think my second point would be, your Honor, that what the Court is looking at in raising that question is a 103 question, whether or not it's obvious. We're getting far afield from the issue of are we looking at a law of nature, a natural phenomenon or an abstract idea. That's what 101 is based on.

THE COURT: Well, but 101, as I'm told to apply it, I think, gets me past that if I answer yes to that, and then I have to ask whether there's an innovative concept. I don't get to say let's wait until we look at novelty, et cetera. I do have to look at it here.

MR. McMAHON: I would say it ends with Step 1. But with Step 2, there's going to have to be discovery because the -- the only argument that Mayo is making is they rely on two articles that we say aren't even intrinsic evidence and the one

statement in the patent that said "well-known technique."

My response to that is that -- the analysis doesn't end there. That's flawed. It's contrary to what the Supreme Court said with respect to the cDNA and also with *CellzDirect* because there are still well-known techniques that were employed at Step 2, and the claims were found to be patent eligible.

THE COURT: So if I were to suggest that this should be done through early summary judgment rather than on a 12(b)(6), what discovery would the -- should the parties be engaging in to get to this particular Step 2 question, not the broader everything else, but --

MR. McMAHON: I mean, your Honor, I would urge that discovery -- I would hope the Court would allow discovery to go forward. They filed the motion for Rule 12(b)(6), and I think it was their error in doing so based on this record and their misapplication of the law. So now they'll still infringing out in the market. We filed the case in early 2015, so I would urge that discovery should go forward.

You know, if they think they can bring a motion for summary judgment quickly, let them bring it and knock it out. I mean, my request of the Court is we should be able to -- allowed to go forward by this time to prove our case. They're not going to -- again, they're --

THE COURT: So let me -- obviously, I'm going to go

back and read all of these cases, but I am -- at this point, I think the question that is -- that I'm struggling with is the Step 2 question. And having -- being there on the Step 2 question and not just saying, No, they're wrong -- if they're wrong on Step 1, then, you know, sure, we're sort of moving forward. But assuming that they're right on Step 1, I get to the Step 2 question. And then what's in front of me is can I decide this on a 12(b)(6), or should I decide this on a record?

I think the parties are -- there may be enough for me to do it on a 12(b)(6); there may not be. But it would seem that addressing that issue -- I guess to put it this way: You certainly don't want this to be a 12(b)(6) decision. And so if I were to put it that way, which is that I would be thinking they've gotten pretty close there -- I'm not sure that they get there all the way, but they're pretty close, what would the discovery be that you're saying this is not enough? I understand you're saying it's not good enough to look at the specifications. But what is it that you would want to look at?

MR. McMAHON: I think I would be -- they have the burden here. I would be interested in what they would be looking at.

THE COURT: Let's say --

MR. McMAHON: And respond to it.

THE COURT: Let's say, for example --

MR. McMAHON: We would have experts.

THE COURT: Let's say, for example, I were to say -- and I certainly have the authority to do that -- I treat their 12(b)(6) as a motion for summary judgment because they've cited this additional material. Even though they want to tell me that these articles were referenced in the patent, I treat it as a summary judgment motion. You're coming forward under 56(d) or (e), or whatever paragraph it's been moved to, and say, You need additional discovery before you can respond to their 56. What would you want?

11:40 MR. McMAHON: Well, as I stand here now, we certainly would come forward with expert opinions.

THE COURT: As to this question of whether this is just a routine -- their argument is this is a routine conventional activity, and you would have experts saying, No, what's happened here is not a routine but an improved -- a technological process that has some innovative aspects to it.

MR. McMAHON: That's what we would but if --

THE COURT: I'll give you an opportunity to frame this back and forth if that's where I get.

11:41 MR. McMAHON: Pardon me?

THE COURT: I'm trying to understand what I'm looking at whichever way I go on this.

MR. McMAHON: Well, again, that certainly -- I mean, they have the burden to knock it out, so we would be interested in what they do. But I certainly would say right now, as I

stand here, I expect we would have an expert declaration. I think this still though, your Honor, can be resolved on Step 1 and we don't get -- we don't need to go there because I think that if looking at the conventional issues -- because when you look at the plain language of a claim, they're detecting iodine in the 125 for Step 1 is not a law of nature, not a natural phenomenon. I think it ought to end right there, and we should proceed with the entire case.

To me, I just think it would be wrong for anyone to -- 11:42
for the Court to conclude that this claim in its entirety, as *CellzDirect* required to be looked at, is directed to a law of nature. Detecting radioactivity in a human is just not a law of nature. They could file a 103 motion if they think they can prevail on that or 102, but this is clearly -- this is not -- I don't even think it's close, your Honor, with all respect, on -- radioactivity doesn't appear in the human body.

That's what it's directed to especially when you look -- it's unlike the claims earlier, like in the Mayo case where just a determination is made on whether or not -- they just 11:43
cite determine the amount of whatever you're looking for in the body and make a diagnosis here. There's much more here involved with the, again, looking at this -- it's a process, again, that's creating a molecule that doesn't appear. But at the end, you're detecting iodine. They're not asking for, hey, detect the amount of -- there's no question -- they're not

detecting the amount -- when you look at the claim and how it's written, which is what the Supreme Court said, they're not even asking the practitioner to determine the amount of -- whether that complex is there. That claim reads to identify the iodine or the radioactive component of that complex. That is not a law of nature.

So I would suggest, respectfully, that Step 1 should end right there, and we should go forward with the case.

THE COURT: Okay. Let me let your brother have a brief response.

If you pull up Page -- I assume you gave a copy of your -- if you pull up Claim 7 -- Page 7, Claim 9, which writes out what the method is, why isn't your brother right, that this method is directed at the final complex rather than at a law of nature?

MR. SINGER: It begins, your Honor, with the natural relationship between the presence of the autoantibody at the beginning, and that's -- it really actually is a method for Claim 1. That's a method of Claim 1. He's filled in Claim 2.

THE COURT: It references these things.

MR. SINGER: Right.

THE COURT: That's why I appreciate this as a way of reading the whole thing. The fact that it is said in Claim 1 doesn't matter. It's all now here in Claim 9.

MR. SINGER: Right. It begins with the natural

relationships, right, and it ends with the natural relationship. It is not about detecting -- this is not a new method of detecting radioactive iodine. This is a method of detecting the autoantibody in our blood to determine whether or not you have a potential to get this disease. That's what the -- you said, as I think rightly, when someone reads this patent, that's what the person of skill would read from it. And that's what this claim is. It begins --

THE COURT: I don't think I said the person of skill. I said the ordinary person, which is the wrong person, but it is the person of skill we need to --

MR. SINGER: A little patent literary license there, your Honor.

It begins with that natural law, and it ends with the natural law. The I125 -- radioactive iodine isn't indicative of anything if you have radioactive iodine in your body. It's only indicative here because it's complex to the natural phenomenon. And that's what the claim is directed to in answering Step 1. It begins with it and it ends with it.

If you look at the *Sequenom* case, you'll see. It begins with -- same thing, a method for diagnosing a maternal sera sample for particular in fetal disease. And it ends with the same thing, wherein, if you detect, right, the fetal DNA with probes, which are not natural things, right, you can make that determination. This is exactly the same, exactly the same

inquiry. It is directed to the natural law or the natural phenomenon, beginning and the end, particularly, I think -- you say we shouldn't -- we don't need to look at Claim 1, and I agree. Claim 1 is not before the Court as I understand it. But Claim 1 by itself is indisputably, right?

THE COURT: No, but the fact that Claim 1 is indisputably a law of nature doesn't solve anything here for me because I have to figure out what Claim 9 is.

MR. SINGER: Right. But I would encourage the Court, in thinking about what the claim is directed to, to think that -- to look at Claim 1, which is directed flat out to the association. Claim 9 is simply a method of Claim 1. That's what it actually says. Yes, this is a helpful way of looking at all the language that's in the claim. I agree with that. But it, nonetheless, is a method of practicing Claim 1. And Claim 1 is the natural law and natural association. And the end of Claim 9, right, is that same natural law and natural association repeated in the wherein step, and it's just a mental step at that. So I think it begins and ends with the natural law.

And, you know, I've been doing this for a long time. I find it hard to believe someone would get up here and say this isn't close even. This case is related to the natural law that was discovered. It's a pre-Mayo patent. It's understandable why it reads the way it does. I understand why.

And the inventors may deserve credit for discovering this. But the law has changed, and that's what we have to deal with.

THE COURT: Adjectives aren't going to help me either way on this. Assuming that I agree that it -- we've got a Step 1 -- we've met the Step 1 part and I'm stuck on the Step 2 and I don't think a 12(b)(6) is an appropriate way for dealing with the Step 2. What more would -- you wouldn't need any discovery for making your Step 2 argument on -- as a summary judgment matter, but they would be entitled to -- there's no reason they wouldn't be entitled to some discovery, I would think. You come in with an affidavit of an expert, they're going to want to take the deposition.

MR. SINGER: Sure.

THE COURT: So that would suggest that we would -- if we were to go that way, we would do some limited discovery or we would need some limited -- not that we would do limited -- we would need some limited discovery in order to allow that issue to be developed.

Other than my sort of making a decision ahead of time on which way I'm likely to come down on the Step 2, why not simultaneously -- without prohibiting you from filing an immediate summary judgment motion, why not also allow the broader discovery as it's going forward?

MR. SINGER: I mean, I think that's what the whole directive from the courts to try to resolve these early is

about.

THE COURT: So the problem with resolving early is that has something to do with my efficiency or inefficiency. So the question is, you know, if I'm not there able to make that decision the moment you file your papers, how much further delay do we have? And is that -- while no one wants to go through unnecessary discovery, at what point is the potential for delay something of concern?

MR. SINGER: Well, I guess, your Honor, I would look at it this way, in that a -- some portion of the life, first off, was due to the standing issue and not having the proper parties.

THE COURT: I won't take any responsibility for the delay, but we are here. I think we are where we are. I don't think it's a blame question on the delay. I think the parties have worked very well to try to figure out how to tee this up in a way that we don't get hung up on the standing issues. But we are here now. I don't think -- I don't know. It may be close to a year since you filed initially. So --

MR. SINGER: My assumption would be -- of course, it depends on your Honor's availability, but the discovery process, if you will, could be done in two or three -- I'm thinking about preparing an expert declaration and if they wanted to depose our expert and they had one and we deposed theirs, we're talking two declarations and two depositions. I

which would help immeasurably as opposed to just imposing costs and us having to pull the trigger and them saying, We didn't get what we wanted. You've got to wait. We need to do X, Y, Z. If there's something that they need that we have, we can produce it. I didn't hear anything other than they would want expert discovery.

I will only say that my interest is in resolving this efficiently and quickly. You know, Mayo is a very well-known reference lab and would like to proceed in the market with what they think is a test that doesn't infringe any valid patents. They'd like resolution from their perspective.

THE COURT: So let them have a chance. If you could let counsel have a minute.

MR. McMAHON: Your Honor, may I speak from here?

THE COURT: Wherever you prefer.

MR. McMAHON: I'm thinking that we're getting into this -- if we're going to be looking at how conventional and routine, that's the issue that Mr. Singer is focusing on, we would be interested in getting into Mayo's files. I mean, I125, again, is difficult to work with. If they say it's conventional, I'd like to see not only the expert but get some fact discovery from them and see how conventional it was for them to put it. Did they try to use other things?

So if we're going to have a wider discovery -- and I think it's very difficult for us to put a fence around a

certain amount of discovery and say we can't have the others because there's going to be overplay in it.

But, again, the conventional aspect of this, the use of the iodine, I think the experts' opinions would be good, but they should be informed by the facts, and we're going to need some of them from Mayo.

THE COURT: Okay. This is what I'm --

MR. McMAHON: Or maybe third parties.

THE COURT: This is what I'm going to do. I'm going to go back and deal with the motion that's in front of me first. But I am anticipating at this point that I'm going to suggest that the Step 1 -- that defendants have convinced me of Step 1 but that we're struggling on Step 2 on trying to make that determination.

While I'm working on my opinion, I would suggest that it would be a good idea for you to -- assuming that's where I'm coming down -- to talk about what would be an efficient way to move the case forward. And that -- the argument that plaintiffs' counsel, I think, is really -- would be a really fair argument is, no matter how much I'm -- I see this as a way that -- a question that I probably should be addressing, we don't want to be deposing the same people twice. We don't want to be having half a go-round of files and so forth. So it may be that there is a limited amount of discovery that needs to be done, but that would ensure that if the case is going forward

we're not doing an overlap of that same piece so that it isn't so narrowly targeted to this particular issue that it has a high risk of cost.

But why don't you see what -- whether there is any common ground there. I will get a decision out as soon as I can. And assuming I go in that direction, I'll have you in for a status conference, and we'll just figure out what makes sense at that point.

MR. SINGER: Okay. That's very well, your Honor. Thank you very much.

11:58

THE COURT: Thank you. And I will go back and read your PowerPoints.

MR. McMAHON: Thank you, your Honor.

THE CLERK: Court is in recess. All rise.

(Whereupon, at 11:58 a.m. the hearing concluded.)

C E R T I F I C A T E

I certify that the foregoing is a correct transcript of the record of proceedings in the above-entitled matter to the best of my skill and ability.

/s/Cheryl Dahlstrom

Cheryl Dahlstrom, RMR, CRR

Official Court Reporter

Dated: August 8, 2016

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

ATHENA DIAGNOSTICS, INC., ISIS INNOVATION LIMITED, AND MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V., Plaintiffs/Counterclaim-Defendants, v. MAYO COLLABORATIVE SERVICES, LLC d/b/a MAYO MEDICAL LABORATORIES AND MAYO CLINIC, Defendants/Counterclaim-Plaintiffs.	Civil Action No. 1:15-cv-40075-IT

MAYO'S RESPONSE TO PLAINTIFFS' LOCAL RULE 56.1
STATEMENT OF MATERIAL FACTS BEYOND REASONABLE DISPUTE

At least because the Court did not convert Defendants' Renewed Motion to Dismiss to a Motion for Summary Judgment, Plaintiffs' L.R. 56.1 Statement is procedurally improper. Local Rule 56.1 requires that a ***movant*** must include a "concise statement of the material facts of record" with their motion for summary judgment. However, Plaintiffs are not the movant here. By submitting a L.R. 56.1 Statement, Plaintiffs have effectively transformed their response to Defendants' Renewed Motion to Dismiss into a separate Motion for Summary Judgment under 35 U.S.C. § 101, with Plaintiffs as movants. If Plaintiffs desired to file such a motion, they should have requested the Court's leave to do so, rather than burdening the Court with a statement of allegedly material facts that fails to "focus the district court's attention on what is, and what is not, genuinely controverted." *Mariani-Colon v. Dept. of Homeland Sec. ex rel. Chertoff*, 511 F.3d 216, 219 (1st Cir. 2007); *see also Khan v. OneBeacon Ins. Co.*, No. 12-cv-12333-IT, 2015 WL 1475837 (D. Mass. Mar. 31, 2015) (stating that "voluminous" Local Rule

Response: Incomplete. Claim 8 covers precisely the scope of the entirety of its claim language. Defendants acknowledge that limitations involving "detecting," "contacting," "immunoprecipitating," and "monitoring" are present in Claim 8.

5. Claim 9 covers a method requiring at least three steps: (i) "detecting" autoantibodies to MuSK in a bodily fluid, (ii) "contacting" a ^{125}I-labeled MuSK epitope with a bodily fluid, and (iii) "immunoprecipitating" any MuSK autoantibody/^{125}I-MuSK epitope complexes. Ex. A, 13:8-9; DD ¶ 85.

Response: Incomplete. Claim 9 covers precisely the scope of the entirety of its claim language. Defendants acknowledge that limitations involving "detecting," "contacting," "immunoprecipitating," and "monitoring" are present in Claim 9.

6. The inventors described using antibodies to the MuSK autoantibodies in diagnostic kits. Ex. A, 5:6-14.

Response: Immaterial / Incomplete. More accurately, the patent describes the use of antibodies to the anti-MuSK autoantibodies in kits. *E.g.*, D.I. 131-1 at 5:6-7.

7. While "[i]odination and immunoprecipitation are standard techniques in the art," Ex. A, 4:10-11, none of those steps are routine when applied to new proteins. DD ¶¶ 28, 36, 44.

Response: Disputed. This purported fact improperly contains a disputed legal conclusion. As described in Defendants' briefing, the '820 patent refers to iodination and immunoprecipitation as "standard techniques in the art" and "known per se in the art." ECF No. 131-1 at 3:33-37, 3:66-4:12. The patent also admits in the "EXAMPLE" section that the inventors used routine techniques: "immunoprecipitation was performed as

described previously." *Id.* at 8:26-27.

These standard techniques are admittedly well-described in original publications and review articles and are typically employed to iodinate or immunoprecipitate proteins. If the inventors used unusual, non-standard methods that had not been described in previous published work to iodinate and immunoprecipitate MuSK, then one would expect that these novel methods would have been included in the patent application (rather than exclusively in Dr. De Tomaso's Declaration), particularly in the "EXAMPLE" section of the patent under the heading "Immunoprecipitation Experiments." Instead, the scientists refer to the methods employed for these purposes as "standard techniques in the art," "known per se in the art," and "performed as described previously."

8. All DNA molecules share a common "backbone" structure having the identical chemical composition, with differences appearing in the "non-backbone" portion: the linear sequence created by four bases A, C, T and G. DD ¶¶ 29, 30.

Response: Immaterial / Incomplete. Although the physiochemical properties among proteins are more variable than among DNA molecules, the methods for detecting autoantibodies could be viewed as more routine than PCR-based methods for measuring DNA. Because of differences in GC content and secondary structure in DNA from a single gene, among different genes within a species or between genes from different species, it is usually essential to vary DNA primers, temperature, salt concentration, pH, magnesium concentration and reaction time in order to define and optimize PCR reactions. In contrast, there are usually fewer variations in procedures for radioimmunoassays and ELISA as applied to proteins.

United States Court of Appeals for the Federal Circuit

ATHENA DIAGNOSTICS, INC., *et al. v. MAYO COLLABORATIVE SERVICES, LLC*, *et al.*, 2017-2508

CERTIFICATE OF SERVICE

I, Melissa Pickett, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

Counsel Press was retained by White & Case LLP, Attorneys for Appellants to print this document. I am an employee of Counsel Press.

On **March 22, 2018**, Counsel for Appellants has authorized me to electronically file the **Joint Appendix** with the Clerk of Court using the CM/ECF System, which will send notice of such filing to the following registered CM/ECF users:

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March 22, 2018

/s/ Melissa Pickett
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