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, dba 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

BRIEF FOR PLAINTIFFS-APPELLANTS

DIMITRIOS T. DRIVAS
ADAM R. GAHTAN
ERIC M. MAJCHRZAK
VANESSA PARK-THOMPSON
WHITE & CASE LLP
1221 Avenue of the Americas
New York, New York 10020
(212) 819-8200

– and –

EMMETT J. MCMAHON
ANDREW J. KABAT
ROBINS KAPLAN LLP
800 LaSalle Avenue, Suite 2800
Minneapolis, Minnesota 55402
(612) 349-8500

Attorneys for Plaintiffs-Appellants

November 6, 2017

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, Counsel for the Plaintiffs-Appellants certifies the following:

1. The full name of every party or amicus represented by me is:

   Athena Diagnostics, Inc., Oxford University Innovation Limited, and Max-Planck-Gesellschaft Zur Forderung der Wissenschaften e.V.

2. The name of the real party in interest represented by me is:

   Same as above.

3. All parent corporations and publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Party	**Parent corporation and publicly held companies that own 10% or more of stock in a party**
Athena Diagnostics, Inc.	Quest Diagnostics, Incorporated
Oxford University Innovation Ltd.	The Chancellor, Masters, and Scholars of the University of Oxford
Max-Planck-Gesellschaft Zur Forderung der Wissenschaften e.V.	N/A

4. The names of all law firms and partners or associates that appear for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

Emmett J. McMahon, Manleen K. Singh, Andrew J. Kabat, Lisa A. Furnald, Tara S.G. Sharp, ROBINS KAPLAN LLP,

Vicki G. Norton, DUANE MORRIS LLP,

Mathew B. McFarlane, LEICHTMAN LAW PLLC, and

Dimitrios T. Drivas, Adam R. Gahtan, Eric M. Majchrzak, Vanessa Park-Thompson, WHITE & CASE LLP.

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a)(5) and 47.5(b).

None.

Dated: November 6, 2017

/s/ Adam R. Gahtan
Adam R. Gahtan
Counsel for Plaintiffs-Appellants Athena Diagnostics, Inc., Oxford University Innovation Limited, and Max-Planck-Gesellschaft Zur Forderung der Wissenschaften e.V.

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, counsel for Plaintiffs-Appellants Athena Diagnostics, Inc., Oxford University Innovation Limited, and Max-Planck-Gesellschaft Zur Forderung der Wissenschaften e.V. certify that, to their knowledge, no appeal from this civil action was previously before this or any other appellate court.

INTRODUCTION

Claims 7-9 of Athena's U.S. Patent No. 7,267,820 (the "'820 patent") are directed to quintessentially patent-eligible subject matter: concrete steps, involving non-natural substances, in the first known laboratory techniques for detecting autoantibodies to muscle specific tyrosine kinase ("MuSK"), all in aid of diagnosing myasthenia gravis ("MG"), a serious neurotransmission-related disease. In form – specified laboratory methods – the claims are like countless others that have always been eligible for patent protection, and methods of diagnosis are surely the type of discoveries that such protection is meant to promote. The methods claimed in the '820 patent are, indeed, particularly beneficial, as treatments are available for MG, but previous diagnostic tools missed 20% of cases, a gap that the invention of the '820 patent has closed. Because the district court erroneously interpreted the claims as directed to a law of nature (the binding of autoantibodies to naturally-occurring MuSK), and as not reflecting an "inventive concept" sufficient to confer eligibility nonetheless, it held the claims invalid under the Supreme Court's recent *Alice* and *Mayo* test. This Court should reverse.

When the Supreme Court decided *Alice* and *Mayo*, it warned that lack of rigor in the application of its new two-part test for patent eligibility under 35 U.S.C. § 101 would result in the wrongful invalidation of worthy patents. Recognizing that *all* inventions incorporate natural phenomena to some degree, the

Supreme Court emphasized that only claims that truly monopolize such phenomena are ineligible under Section 101. The post-*Alice* and *Mayo* jurisprudence has been occasionally inscrutable – not surprising, given the sudden explosion of Section 101 challenges – but, in this case, on *de novo* review, it compels a finding that claims 7-9 of the '820 patent are directed to patent-eligible subject matter: detailed, non-generic laboratory techniques are not laws of nature under step one of the test, and the combination of elements in the claimed methods is inventive and useful under step two. The district court misunderstood the claims, misapplied the test, and, in invalidating the asserted claims, committed precisely the overreach that the Supreme Court feared when it redefined the test for patent eligible subject matter.

JURISDICTIONAL STATEMENT

The district court had jurisdiction over this case under 28 U.S.C. §§ 1331, 1338, and 2201. On August 4, 2017, the district court issued its final decision through a memorandum opinion and order, granting Mayo's motion to dismiss the complaint for failing to state a claim under 35 U.S.C. § 101. Athena timely filed its notice of appeal on August 18, 2017. This Court therefore has jurisdiction over this appeal under 28 U.S.C. § 1291.

STATEMENT OF ISSUES

1. Whether claims 7 through 9 of the ’820 patent claim patent-eligible subject matter under *Mayo* step one where the claims are directed to a new and useful laboratory method for the detection of anti-MuSK autoantibodies and the prior art disclosed *no* methods for detecting anti-MuSK autoantibodies.

2. Whether claims 7 through 9 of the ’820 patent claim patent-eligible subject matter under *Mayo* step two where the claims contain a number of “inventive concepts,” including (1) a process involving a new combination of steps and (2) non-naturally occurring compounds – radiolabeled-MuSK and/or radiolabeled-MuSK/autoantibody/“second” antibody complexes – which had never been described in the prior art.

3. Whether the district court properly determined the validity of claim 6 of the ’820 patent, which defendants challenged on eligibility grounds, where the reasoning it applied in invalidating claims 7 through 9 does not apply to claim 6, and where there is no separate analysis of claim 6 in the district court’s Memorandum and Order.

4. Whether the district court erred by granting Mayo’s motion to dismiss without the benefit of fact-finding, especially after the court acknowledged the existence of unresolved issues of fact concerning the patent-eligibility of claims 7 through 9 of the ’820 patent under *Mayo* step two, invited, but ignored,

submissions of fact that demonstrated a clear dispute as to step two, and declared its intention to convert the motion into one for summary judgment, but then failed to do so.

STATEMENT OF THE CASE

I. MYASTHENIA GRAVIS AND ITS DIAGNOSIS

Myasthenia gravis ("MG") is a chronic autoimmune disorder that causes variable muscular weakness. (Appx43, col. 1, ll. 13-15) Treatments that "vastly improve the length and quality of life" are available to those diagnosed with MG. (Appx43, col. 1, ll. 28-29)

Early studies associated MG with autoantibodies targeting the acetylcholine receptor ("AChR"). To diagnose MG, therefore, scientists developed a method for detecting anti-AChR autoantibodies that involved binding radioactive iodine ("^{125}I") with α-bungarotoxin ("αBTX"), which binds naturally to AChR. (Appx43, col. 1, ll. 34-36, Appx142, Appx150) AChR-detection was a limited diagnostic tool, as up to 20% of MG sufferers were "seronegative" ("SNMG"): they had MG symptoms, but no anti-AChR autoantibodies. (Appx43, col. 1, ll. 34-42, Appx153-154) The cause of MG in SNMG patients remained unidentified for more than a decade. (*See* Appx187) The inventors of the '820 patent discovered the cause, and closed the diagnosis gap.

Muscle-specific receptor tyrosine kinase ("MuSK") exists naturally as a transmembrane protein located on the cell surface of neuromuscular junctions. (Appx43, col. 1, ll. 57-59) MuSK passes through the cellular membrane of a muscle cell and relies on the membrane's chemical environment to function. (*See* Appx37, Fig. 1a, Appx46, col. 7, ll. 57-65) By 1997, MuSK was thought to play a role in transmission of biochemical signals to and from muscle cells (Appx43, col. 1, l. 62-col. 2, l. 5), but, prior to the invention of the '820 patent, no disease was associated with MuSK, and its role in adult muscle had not been elucidated. (Appx43, col.2, ll. 35-37) The inventors of the '820 patent were the first to connect MuSK and MG, hypothesizing that SNMG patients would have MuSK autoantibodies. (Appx43-44, col. 1, ll. 54-61, col. 2, l. 25-col. 3 l. 3)

The inventors' first attempt to detect anti-MuSK autoantibodies – and so to improve MG diagnosis – involved enzyme-linked immunosorbent assay ("ELISA"). (*See* Appx47, col. 10, ll. 48-50) Because ELISA proved difficult to standardize, they turned to immunoprecipitation. (Appx47, col. 10, ll. 48-50) The inventors first created a series of non-naturally-occurring MuSK fragments using recombinant DNA technology. (Appx46, col. 7, ll. 55-65, Appx37, Figure 1a, Appx618 ¶ 79) This led them to the discovery that anti-MuSK autoantibodies bound specifically to MuSK's extracellular Ig1-2 region. (Appx37, Figures 1b-c, Appx618-619 ¶ 80) Working with synthesized MuSK fragments containing the

epitope or antigenic determinant (MuSK binding site) made detection of MuSK autoantibodies through immunoprecipitation possible. (Appx47, col. 10, l. 50-52) No known toxin binds MuSK (in contrast to AChR), so to make MuSK antibodies detectable following immunoprecipitation, the inventors labeled MuSK directly, including with ^{125}I. (Appx44, col 3, l. 66-col. 4, l. 10) The inventors did not use MuSK in its native transmembrane state in their immunoprecipitation method.

II. THE '820 PATENT CLAIMS AN INNOVATIVE LABORATORY TECHNIQUE FOR DETECTING ANTI-MUSK AUTOANTIBODIES

The '820 patent issued on September 11, 2007, asserting priority to foreign application GB 0014878.3, filed on June 16, 2000. (Appx35) It is assigned to Isis Innovation Limited (now Oxford University Innovation Limited) and Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften e.V. Athena Diagnostics, Inc. is the exclusive licensee. (Appx70)

The '820 patent contains the first public description of (1) a laboratory method, of any kind, for detecting anti-MuSK autoantibodies, (2) radiolabeled MuSK and MuSK fragments, and (3) the diagnoses of MG using the laboratory technique disclosed. (Appx43, col. 1, ll. 49-53, Appx608 ¶ 59)

Claim 7 depends from claim 1:

> 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).

> 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).

(Appx48-49, claim 7) To practice the claim 7 method, a skilled person must perform specified concrete laboratory steps, including: (1) "contacting MuSK or an epitope or antigenic determinant thereof having a suitable label thereon, with said bodily fluid," (2) "immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid," and (3) "monitoring for said label on any of said antibody/MuSK complex or antibody/MuSK epitope or antigen determinant complex." (*Id.*)

Claim 8, which depends from claim 7, recites a particular type of label:

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

(Appx49) Claim 9, which depends from claim 8, requires a specific radiolabel:

"9. A method according to claim 8 wherein said label is ^{125}I."

(*Id.*) This additional limitation enables detection of a MuSK autoantibody/^{125}I-MuSK complex by monitoring radiation. (Appx47, col. 10, ll. 49-61)

The autoantibody-labeled-MuSK complexes described in the asserted claims do not exist in nature; a skilled artisan must make them in the laboratory, as first described in the '820 patent. They also require the use of *labeled* MuSK, a non-naturally-occurring, laboratory-synthesized molecule described for the first time in the '820 patent. (Appx47, col. 10, ll. 50-54) The "immunoprecipitating" limitation in claims 7-9 involves the formation of another non-naturally occurring complex: the autoantibody/labeled-MuSK complex bound to a "second" anti-IgG antibody that binds to the MuSK autoantibody. (Appx48-49)

Claim 6 of the '820 patent is directed to the ELISA method of detection. (Appx48, Appx384). It does not involve labeled MuSK or immunoprecipitation. (Appx48)

III. PROCEEDINGS BELOW AND THE DISTRICT COURT'S DECISIONS

Athena filed its Complaint in June 2015, alleging Mayo's infringement of its claimed methods. (*See* Appx50-55) Athena amended the Complaint in July and August, 2015, and July 2016. (Appx50-73) Mayo moved to dismiss the Second Amended Complaint, under Rule 12(b)(6) of the Federal Rules of Civil Procedure, on September 15, 2015. (Appx91-94) In responding to the motion, Athena represented that is was not asserting, and that there was no controversy as to, claims 1-5 and 10-12. (Appx163, Appx179-180) The district court denied the motion, which it described as involving only claims 6-9, in August 2016,

(Appx276-286), but granted a renewed version of it a year later, in August 2017. (Appx1-12) The path to dismissal was as indirect as it was long.

A. The district court denied Mayo's first motion to dismiss in light of unresolvable factual matters

During argument on Mayo's original motion, the district court signaled its view that the asserted claims of the '820 patent were directed to an ineligible law of nature under *Mayo* step one. (Appx768) As to *Mayo* step two, the court acknowledged the insufficiency of the information before it to determine whether the claims contained an inventive concept, questioning: "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?" (Appx728, *see also* Appx763) The court suggested fact-finding, followed by a motion for summary judgment, as a more appropriate procedure to "flesh out this issue rather than saying I need to make a [sic] what seems somewhat of a beyond my expertise decision based on reading the specifications and the paper cited in the [specification]." (Appx731) The court reinforced its preference for summary judgment several times, and asked the parties what discovery they would need. (Appx756, Appx758)

The court even warned Athena, without elaborating, that "[y]ou certainly don't want this to be a 12(b)(6) decision," before asking, again, what discovery Athena thought was necessary to resolve the issue. (Appx757) Correctly noting that the burden was ultimately Mayo's, Athena offered to present expert evidence

that the claims were sufficiently innovative under step two of *Mayo*, (*id*.), without, however, conceding that the claims were directed to a law of nature under step one. (Appx759) The district court ordered the parties to try to find common ground for discovery, on the assumption that it would deny the motion under step two, (Appx768-769), which it did on August 25, 2016:

> [t]he 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. . . . *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.

(Appx285-286 (emphasis added))

B. The district court allows Mayo to renew its motion to dismiss, again invites fact-finding, and states its intention to convert the renewed motion into one for summary judgment

On October 6, 2016, during argument on Athena's motion to compel discovery, the district court raised Mayo's step two arguments again, *sua sponte*, having decided that the issue turned entirely on the following statement from the '820 patent specification: "iodination and immunoprecipitation are standard techniques in the art, the details of which may be found in references (4 and 6)." (Appx318-319) The court pressed Athena about the statement's truth, to which Athena responded, "[t]hat statement isolated I can't dispute, but - -", clarifying

that, "the application of that concept in this particular instance to the MuSK was different." (Appx319) For the district court, however, it was sufficient for determining the eligibility of the claimed methods that immunoprecipitation and iodination, *per se*, were known:

> 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.

(Appx319 (emphasis added)) The court rejected Athena's arguments that it was improper to consider immunoprecipitation and iodination in *isolation*, and it took the position that, although Athena was the plaintiff facing a motion to dismiss, the burden was on Athena to have alleged facts about its use of those techniques in the asserted claims:

> 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.

(Appx320)

The court acknowledged that its analysis might be wrong, and suggested that Athena should admit the facts that the court deemed relevant and appeal:

> [I]f you [Athena] agreed 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 statements, 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 client's money.

(Appx306-307, *see also* Appx308 (Athena "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"), Appx314 (recommending the Federal Circuit's "fresh eyes.")).

The court attempted to get the parties to stipulate to the facts it believed necessary, (*e.g.*, Appx352-354), so that, if Athena was "going to lose this case on invalidity," it would know that "at the beginning." (Appx350) (By then, the case had been pending for over a year, and the district court would not grant Mayo's motion to dismiss for another year to come.) The court wished to limit the stipulations to facts about whether immunoprecipitation and iodination, "isolated," were standard techniques. (Appx319)

The parties could not agree on a stipulation. (Appx352-355) Nevertheless, the court allowed Mayo to renew its motion to dismiss, on the understanding that it would convert the motion into one for summary judgment and give Athena "an opportunity to respond as a [Rule] 56." (Appx358-360) The court reiterated: "Then we don't have to have a stipulation. Then you're [Athena] putting forward an opposition that says, No, that's the wrong focus of the analysis. Here's why this

is different under Step Two." (Appx359-360) Finally, "so that the record is clean," the court described the agreed plan as "a renewed motion to dismiss, and I will then convert it to a summary judgment motion, allowing you to respond to it." (Appx361)

C. Mayo limited the scope of its renewed motion

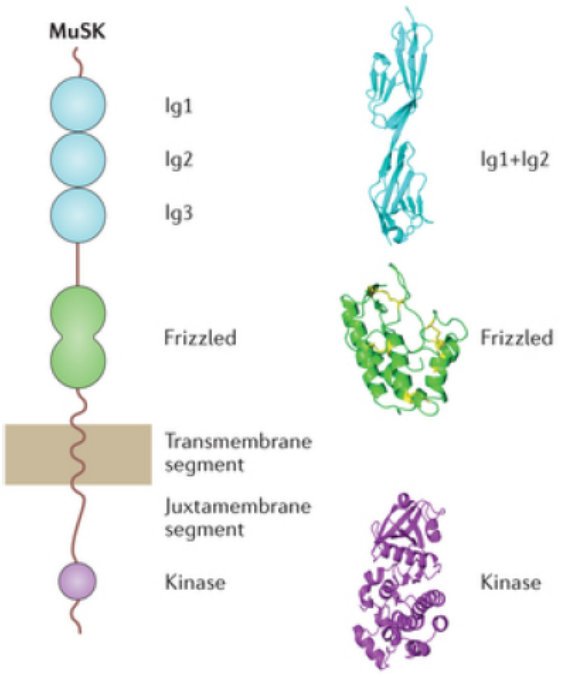
In its renewed motion, Mayo explicitly addressed claims 6-9 only, in reliance on Athena's earlier representation that it was not asserting claims 1-5 or 10-12. (Appx376) Claim 6, which depends from claims 1, 2, and 3 in successive dependencies, is directed to a method of diagnosing MG through an ELISA-based autoantibody detection. (Appx48) The ELISA method in claim 6 does not involve labeling MuSK or MuSK fragments, or immunoprecipitation. (Appx48-49)

D. Athena's opposed Mayo's renewed motion with facts related to the step two dispute

In opposition to Mayo's renewed motion, Athena relied in part on the Expert Declaration of Anthony W. De Tomaso, Ph.D. (*See generally* Appx581-633) Athena also filed a "Statement of Material Facts Beyond Reasonable Dispute," under local rules governing summary judgment. (Appx574) Through Dr. De Tomaso's lengthy, highly technical, and unrebutted declaration, Athena offered the following facts, among others:

- Due to the natural complexity of the MuSK protein structure, the iodination or immunoprecipitation methods described in the '820 patent were not routine, (*see, e.g.*, Appx592-600 ¶¶ 32-45);

- MuSK comprises 879 amino acids and exists naturally in a highly complicated transmembrane structure; on the cell cytoplasm side of the membrane (*i.e.*, inside the muscle cell), MuSK has a kinase region responsible for modifying other proteins in the cell, and on the exterior side, MuSK has two domains;



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).

(Appx594 ¶ 35)

- Prior laboratory detection methods, such as the one used to detect AChR autoantibodies, were unavailable for MuSK autoantibodies because no known toxin binds specifically to MuSK, (Appx607 ¶ 57);

- Because MuSK is a transmembrane-protein, attempts at *in vitro* synthesis and post-synthetic modifications, such as iodination, are difficult, (Appx609 ¶ 62; *see also* Appx618 ¶ 78 ("MuSK is a transmembrane protein . . . When synthesized in vitro, transmembrane proteins will usually only fold correctly when they are co-translationally inserted into a membrane"); Appx618-620 ¶¶ 79-82);

- To create a MuSK autoantibody detection method, the inventors had to epitope map the protein and synthesize non-natural MuSK fragments, (*see* Appx611 ¶ 67); and

- The synthesis of radiolabeled MuSK fragments and immunoprecipitating such complexes after interacting with MuSK autoantibodies are each independently inventive concepts because they are not routine in the art. (*See* Appx624-632 ¶¶ 93-111)

Athena did not address claim 6 in its opposition. As it had informed the district court earlier, without discovery it could not finally determine whether to pursue a claim 6 infringement case. (Appx180)

E. The district court did not convert the motion into one for summary judgment, it did not acknowledge Athena's evidence, and it ruled on grounds that neither party had briefed or argued, depriving Athena of a chance to defend

In its final decision, on August 4, 2017, the district court granted Mayo's renewed motion as a motion to dismiss, not as one for summary judgment. (Appx12) The district court identified claims 6-9 as the only ones "at issue," acknowledging Athena's decision not to pursue Mayo for infringement of the remaining claims. (Appx3)

Although only claim 9 recites ^{125}I-MuSK, it was the court's view that 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." (Appx6 (emphasis added)) Consistent with this understanding," the court found that "the focus of the *claims* of the invention is the interaction of the ^{125}I-MuSK and the bodily fluid". (Appx7 (emphasis added)) In consequence, as to *Mayo* step one, the court held that, "because the patent focuses

on this natural occurrence, it is directed to a patent ineligible concept." (Appx7) The court did not refer to claims by number in reaching this conclusion, nor did it distinguish claim 9, the only claim to recite ^{125}I-MuSK (iodination), from claims 7 and 8, which more broadly recite labeled and radiolabeled MuSK, respectively, (Appx1-7), or from claim 6, (*id.*), which does not involve labeled MuSK of any type, or immunoprecipitation. (Appx48)

As to step two, the court rejected Athena's arguments that iodination of MuSK and immunoprecipitation of radiolabeled-MuSK/autoantibody/second antibody complexes were sufficiently innovative, because, in the court's view, the '820 patent fails "to provide the precise description of the manner and process of making the invention" under *35 U.S.C. § 112(a)* – i.e., the rule governing adequate written description. (Appx11) Mayo never asserted a Section 112 defense, and written description never arose at argument, meaning that Athena had no opportunity to address it or make a 112 case. Finally as to step two, the court also held that the use of man-made ^{125}I-MuSK did not rescue the claims from law-of-nature ineligibility under *Mayo* step two, because the claims are not to ^{125}I-MuSK itself. (Appx12)

As in its step one analysis, in step two the court did not distinguish among the claims, or attempt to explain how its treatment of claim 9 iodinated (^{125}I) MuSK was relevant to broader labeled-MuSK-related claims 7-8, or how its

holding with respect to an immunoprecipitation method applied to claim 6, which does *not* involve immunoprecipitation. There is, in fact, no analysis of claim 6, or of the ELISA method it describes, anywhere in the decision. (Appx1-12)

Finally, although the district court cited pages from Athena's brief on which Athena cited Dr. De Tomaso's declaration, the court did not acknowledge the declaration's existence, let alone address its contents. (*Id*.)

F. Athena received no discovery in over two years of litigation

In one form or another, Mayo's motion to dismiss was pending for over two years. During this time, which included over eight months of inaction following the completion of renewed briefing, Athena was unable to advance its case, though it sought discovery from Mayo after the district court denied Mayo's first motion. (Appx296-301, Appx307) Mayo did not comply, causing Athena to file a motion to compel. (*See* Appx297) At the hearing on its motion, nearly 16 months after Athena filed its Complaint, Athena informed the district court that it had, as yet, received no discovery at all from Mayo. (Appx344) The court denied Athena's motion. (Appx360)

SUMMARY OF ARGUMENT

The *Mayo* test for patent eligibility has two steps. In step one, a court determines whether the challenged claim is "directed to" a law of nature or abstract idea. If it is not, then the inquiry ends and the claim is patent eligible. If it *is*, then

the court proceeds to step two, in which it determines whether the claim reflects an "inventive concept" that, notwithstanding the step one conclusion, renders it eligible. On Mayo's motion to dismiss, the district court held that the asserted claims of the '820 patent were ineligible. As to both parts of the test, the court was wrong. This Court, in its *de novo* review, giving Athena the benefit of all reasonable inferences, should find asserted claims 7-9 eligible under step one and, if necessary, step two.

Step one. Claims 7-9 of the '820 patent require a skilled person to perform non-generic, specifically defined steps in a novel method for detecting non-naturally occurring, lab-synthesized, labeled MuSK autoantibodies. As this Court recently held, innovative methods that recite concrete steps remain patent eligible post-*Mayo*, even when the method depends on the operation of a natural phenomenon. *Rapid Litig. Mgmt. Ltd. v. Cellzdirect, Inc.*, 827 F.3d 1042 (Fed. Cir. 2016). Claims 7-9 of the '820 patent recite concrete laboratory steps, and the method is certainly innovative, not least in that it is the first of any type for detecting MuSK autoantibodies, or for diagnosing MG through such detection.

The district court erroneously found the asserted claims directed to the natural phenomenon of autoantibody/MuSK binding, ignoring the concrete steps in the method, and so applied inapposite cases to reach its decision. Those cases, in which the methods recited generic steps to achieve known goals, and where the

only innovation was a purely mental process, are easily distinguished from the claims Athena asserts. In addition, nothing about the asserted claims preempts the natural law that the district court identified: researchers are free to develop inventions that take advantage of autoantibody/MuSK binding, and to develop novel methods of MuSK autoantibody detection.

Step two. Because the asserted claims reflect "inventive concepts," they are patent eligible even if this Court determined that they were directed to a law of nature under step one. The claims recite an innovative combination of steps leading to a new and useful result, which is sufficient for eligibility even if some of the steps involved known techniques. The claims also require novel, laboratory-made, labeled-MuSK complexes and labeled MuSK/autoantibody complexes, which were not only novel, as to which the known processes had never before been applied.

The district court erroneously considered only whether immunoprecipitation and iodination (a form of radiolabeling) in "isolation" were known in the art, without regard to the application of those techniques as claimed, and it did no ordered combination analysis. The court also committed a clear error of law by substituting a written description analysis under 35 U.S.C. § 112 for the "inventive concept" analysis required. Not only is written description a wholly separate issue

from eligibility, but Mayo did not raise a Section 112 defense and there was none of the fact-finding required to support the court's 112 ruling.

Procedural matters. As the district court initially and correctly determined, there was insufficient evidence on a motion to dismiss to find the asserted claims patent-ineligible. Then, despite having initially identified a factual dispute, invited the submission of relevant evidence, and decided to convert Mayo's renewed motion into one for summary judgment, the district court failed to consider Athena's factual submissions, which were properly before it on a motion to dismiss. The court also denied Athena the benefit of the inferences to which it was entitled. For these reasons, even if ineligibility could have been determined on a motion to dismiss, the court's procedure was flawed.

STANDARD OF REVIEW

Regional circuit law determines the standard of review for an appeal from an order granting a motion to dismiss for failure to state a claim. *See BASCOM Global Internet Servs. v. AT&T Mobility LLC*, 827 F.3d 1341, 1347 (Fed. Cir. 2016) (citation omitted). The First Circuit reviews such appeals *de novo* and "accept[s] as true all well-pled facts alleged in the complaint and draw[s] all reasonable inferences in [the plaintiffs] favor." *See In re Loestrin 24 Fe Antitrust Litig.*, 814 F.3d 538, 549 (1st Cir. 2016). Under First Circuit law, a party may offer, and a court must consider, evidence offered by the party opposing a motion

dismiss, provided that the evidence is consistent with the pleadings. *See Watterson v. Page*, 987 F.2d 1, 4 (1st Cir. 1993) ("Plaintiffs, moreover, introduced the documents themselves, in order to bolster their argument against defendants' motion to dismiss. . . . Like the court below, therefore, we treat the documents submitted by plaintiffs . . . as part of the pleadings."); *Demers v. Pilkington N. Am., Inc.*, No. 10-cv-296, 2010 U.S. Dist. LEXIS 121390, at *16-17 n.5 (D.N.H. Nov. 10, 2010).

Patent-eligibility under Section 101 "is a question of law," which this Court reviews "without deference." *Cellzdirect*, 827 F.3d at 1047 . Under Section 282, a court may declare a patent invalid only if evidence proves its invalidity clearly and convincingly. *See Microsoft Corp. v. i4i Ltd. P'Ship*, 131 S. Ct. 2238, 2242 (2011).

ARGUMENT

Under 35 U.S.C. § 101, a person may obtain a United States patent for "any new and useful process, machine, manufacture, or composition of matter." Courts interpret these categories broadly to reflect congressional intent that "the patent laws would be given a wide scope." *Bilski v. Kappos*, 561 U.S. 593, 601 (2010) (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). Method claims that recite specific steps to be performed in a laboratory are and have always been

patent eligible, even when the method involves a law of nature. *Cellzdirect*, 827 F.3d at 1048-49.

Courts recognize an "implicit exception" to the patent-eligible categories in Section 101: "[l]aws of nature, natural phenomena, and abstract ideas are not patentable." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116 (2013) (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012)). "The concern underlying these judicial exclusions is that 'patent law not inhibit future discovery by improperly tying up the future use of these building blocks of human ingenuity.'" *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014) (quoting *Mayo*, 132 S. Ct. at 1301). The Supreme Court cautions that this exception is limited: "too broad an interpretation of this exclusionary principle could eviscerate patent law" as "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." *Mayo*, 132 S. Ct. 1293. Courts must "tread carefully in construing this exclusionary principle lest it swallow all of patent law." *Alice*, 134 S. Ct. at 2354.

The Supreme Court has recently promulgated a two-part test for evaluating patent eligibility under Section 101. *Mayo*, 132 S. Ct. at 1294, 1296-97; *Alice*, 134 S. Ct. at 2355. To resolve a Section 101 challenge, courts must first determine whether the claim is "directed to one of [the] patent-ineligible concepts." *Alice*,

134 S. Ct. at 2355. If the answer is yes, then, at step two, courts must determine whether "the elements of each claim both individually and 'as an ordered combination' . . . 'transform the nature of the claim' into a patent eligible application." *Id.* (quoting *Mayo*, 132 S. Ct. at 1297-98).

Alice and *Mayo* have prompted an unprecedented rash of Section 101 challenges.[1] In deciding these cases, this Court and district courts have refined the test to fit different types of claims. Most importantly here, this Court has recognized the step one *eligibility* of claims to laboratory-technique-based methods, like those of the '820 patent, even when they involve the operation of a "law of nature," distinguishing such claims from those to a law or product of nature itself. *E.g., Cellzdirect*, 827 F.3d at 1047-49. Under step two, even those method claims that *are* directed to a law of nature, and even when they recite known individual steps, are nonetheless patent eligible if the combination of steps

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[1] *See* Jeffrey A. Lefstin, *et al.*, *Final Report of the Berkeley Center for Law & Tech. Section 101 Workshop: Addressing Patent Eligibility Challenges*, __ BERKELEY TECH. LAW J. __, at 22 (forthcoming 2018), available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3050093 ("We see a dramatic rise in the number of district court § 101 invalidity decisions following the *Mayo* decision, with no more than three in any year prior to 2012 to an average of 8 per year in the two years following the *Mayo* decision. That number increases 10-fold after the *Alice* decision."); Timothy B. Dyk, *Thoughts on the Relationship Between the Supreme Court and the Federal Circuit*, 16(1) CHICAGO-KENT J. OF INTELLECTUAL PROPERTY 67, 74 (2016) ("Before the Supreme Court's decisions in *Bilski*, *Mayo*, *Myriad*, and *Alice*, challenges to patentability based on 35 U.S.C. § 101 were rare. Those challenges now consume a significant portion of our docket.").

represents an "inventive concept." *See id.* at 1050-52; *BASCOM Global*, 827 F.3d at 1349-52.

The district court held the asserted claims of the '820 patent invalid under both steps in *Mayo*. (Appx5-12) As to both, the court was wrong, on the law and the facts, and this Court should reverse.

I. THE COURT SHOULD REVERSE THE DISTRICT COURT'S DISMISSAL OF ATHENA'S COMPLAINT BECAUSE CLAIMS 7-9 OF THE '820 PATENT ARE DIRECTED TO PATENT-ELIGIBLE, INNOVATIVE LABORATORY TECHNIQUES, NOT TO LAWS OF NATURE

Like the claims in *Cellzdirect*, which this Court held eligible under *Mayo* step one, the claims of the '820 patent recite patent-eligible "concrete steps" in an innovative laboratory technique for achieving a new and useful purpose. *Cellzdirect*, 827 F.3d at 1047. That purpose, detecting anti-MuSK autoantibodies, was itself innovative – no previous such detection methods existed – and allowed for the improved diagnosis of a serious neurotransmission disease. (Appx47, col. 10, ll. 49-67) In holding that the asserted claims were directed to a law of nature – antibody/MuSK binding – the district court misunderstood their nature, and misapplied the cases on which it relied.

In *Cellzdirect*, this Court reversed the district court's invalidation of claims to a method of preserving certain liver cells (hepatocytes) through cryopreservation. *Cellzdirect*, 827 F.3d at 1047. According to the district court, the invention amounted to nothing more than the observation of a natural law, that

hepatocytes can survive multiple freeze-thaw cycles. *Id.* at 1046. In reversing, this Court explained that, regardless of whether that hepatocyte property was a natural law, "[i]t is enough in this case to recognize that the claims are simply not directed to [that property]. Rather, the claims . . . are directed to a new and useful *laboratory technique* for preserving hepatocytes." *Id.* at 1048 (emphasis added).

The claims in *Cellzdirect* required "concrete steps to achieve the desired preparation" of pooled hepatocytes: (1) subjecting thawed cells to fractionation, (2) recovering viable cells, and (3) refreezing the recovered cells. *Id.* at 1046-47. Such claims, even if their steps were known and rely on a so-called natural law, are "precisely the type of claim[s] that [are] eligible for patenting," if they "'achieve a new and useful end.'" *Id.* at 1048 (citing *Alice*, 134 S. Ct. at 2534, in turn *quoting Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). The inventors did not stop at or claim their discovery of a natural property of hepatocytes; they claimed an *application* of that discovery, which they were in an "excellent position" to do as the parties having made it. *Cellzdirect*, 827 F.3d at 1048 (internal citation and quotations omitted). "Through the recited steps" in the *Cellzdirect* claims, "the patented invention achieves a better way of preserving hepatocytes." *Id*.

Crucially, the Court clarified that it is irrelevant for patent eligibility that a process merely involves a law of nature:

> The '929 patent claims are like thousands of others that recite processes to achieve a desired outcome, e.g., methods of producing things, or methods of treating disease. That one way of describing the process is to describe the natural ability of the subject matter to *undergo* the process does not make the claim 'directed' to that natural ability. If that were so, we would find patent-ineligible methods of, say, producing a new compound (as directed to the individual components' ability to combine to form the new compound), treating cancer with chemotherapy (as directed cancer cells' inability to survive chemotherapy), or treating headaches with aspirin (as directed to the human body's natural response to aspirin).

Id. at 1048-49 (emphasis in original).

"[R]egardless of whether the individual hepatocytes . . . perform in their natural way, the claims are directed to a new and useful process of creating that pool [of multi-cryopreserved hepatocytes], not to the pool itself." *Id*. at 1049. Such claims fall "squarely outside those categories of inventions that are 'directed to' patent-ineligible concepts." *Id.* at 1050.

A. Claims 7-9 of the '820 patent are not directed to a law of nature

Like the claims in *Cellzdirect*, and "thousands of others," method claims 7-9 of the '820 patent pass the first step of the *Mayo* test because each describes a *process* with "concrete steps" – "laboratory techniques," as in *Cellzdirect* – designed to "achieve a desired outcome," the diagnosis of certain neurotransmission diseases through previously unknown detection of autoantibodies to MuSK. *Cellzdirect*, 827 F.3d at 1049.

The method of claim 7 of the '820 patent requires at least the following steps: (1) "contacting MuSK or an epitope or antigenic determinant thereof having a suitable label" with "bodily fluid," (2) "immunoprecipitating [using a "second" antibody] any [labeled] antibody/MuSK complex or [labeled] antibody/MuSK epitope or antigenic determinant complex from said bodily fluid," and (3) "monitoring for said label on any of said [labeled] antibody/MuSK complex or [labeled] antibody/MuSK epitope or antigen determinant complex." (Appx48-49) Claims 8 and 9 add detail to the steps, specifying, respectively, a radioactive label, and a specific radioactive label, ^{125}I. (Appx49) The inventors of the '820 patent no more claim antibody/antigen binding *itself* than the inventors in *Cellzdirect* claimed the inherent ability of hepatocytes to survive multiple cryopreservations. *Cellzdirect*, 827 F.3d at 1049. Rather, the inventors of the '820 patent claimed a detailed method for detecting the presence of anti-MuSK antibodies using labeled-MuSK, which does not occur, or come into contact with bodily fluids, anywhere in nature.

Athena's claimed method is also "innovative" for step one purposes, as there had been no known method of any kind for detecting the presence of anti-MuSK autoantibodies, or for diagnosing SNMG patients in this manner. If anything, the '820 methods are *more* innovative than those in *Cellzdirect*, as they require (in claim 9, for example) unknown, laboratory-synthesized ^{125}I-MuSK to achieve a

novel goal (detection of MuSK autoantibodies), whereas the hepatocyte cryopreservation steps in the *Cellzdirect* method were not only known and in use – the innovation being simply repeating them a second time – but the hepatocytes were naturally-occurring and unaltered. *Cellzdirect*, 827 F.3d at 1045. The inventors discovered MuSK's link to certain neurotransmission diseases, (Appx43, col. 1, ll. 54-61, Appx44, col. 3, ll. 16-24, Appx584-585 ¶ 14), putting them in an "excellent position" to claim applications of that discovery, *see Cellzdirect*, 827 F.3d at 1048, such as in the asserted claims. These, in turn, made possible an accurate diagnosis of the 20% of MG sufferers whom earlier diagnostics had failed. (Appx43, col. 1, ll. 34-48)

Moreover, "[i]t is the *process* of [detection] that is patent eligible here, and not necessarily the end product." *Cellzdirect*, 827 F.3d at 1050 (emphasis in original); s*ee also Myriad Genetics*, 133 S. Ct. at 2119 ("Had Myriad created an innovative method of manipulating genes while searching for the [naturally occurring] BRCA1 and BRCA2 genes, it could have possibly sought a method patent."). Even if the end product of a given method *is* a product of nature, the claim can be patent-eligible; otherwise, "no one could ever get a patent on . . . any other innovative method that acts on something that is naturally occurring, simply because of the nature of the underlying subject matter. *Section 101* is not so narrow." *Cellzdirect*, 827 F.3d at 1050 (emphasis added). Here, as in *Cellzdirect*,

the "process of detection" – which is what the asserted claims cover, by their terms – is patent eligible, even if the "underlying subject matter" or end product are laws of nature.

Because claims 7-9 of the '820 patent are not directed to an ineligible law of nature, they are valid under Section 101 without regard to the second step in *Mayo*. *See Alice*, 134 S. Ct. at 2355.

B. The district court committed several errors in its step one analysis

The district court misunderstood the nature of claims 7-9 of the '820 patent and, as a result, how to evaluate their patent-eligibility under step one. According to the court, the '820 patent has the following eligibility-determinative characteristics: it is "directed at a method for the diagnosis of a disease;" "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;" and "[t]he 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.'" (Appx7) The court concluded that, "because the patent *focuses* on this natural occurrence, it is directed to a patent-ineligible concept." (*Id.* (emphasis added)) There are several errors in the district court's analysis.

First, the court's essential step – deciding that the "interaction of the ^{125}I-MuSK and the bodily fluid" is "naturally occurring" – was flat-out wrong. In

nature, MuSK is a transmembrane protein; it does not occur in bodily fluid as a full molecule. (*See* Appx37, Appx46, col. 7, ll. 57-65) ^{125}*I*-MuSK – iodinated MuSK – does not occur naturally *anywhere*, nor do the labeled epitope-containing fragments recited in the asserted claims. They must be made, in a laboratory, as described in the '820 patent. (*See, e.g.*, Appx46, col. 7, l. 57-col. 8, l. 7, Appx47, col. 10, ll. 50-55) Accordingly, "complexes . . . formed between the ^{125}I-MuSK receptor and the antibodies" are *not* "natural occurrences," even if the binding itself occurs naturally. *Myriad Genetics*, 133 S. Ct. at 2119 (because a lab technician must make it, cDNA is patent-eligible even though its nucleotide sequence is dictated by nature). The only natural occurrence even arguably related to the claimed invention is the binding of MuSK autoantibodies with certain *natural* MuSK receptor elements, but claims 7-9 require the ex-vivo contacting of indisputably *non-natural, labeled* MuSK or MuSK fragments, with bodily fluid.

Second, the district court ignored this Court's admonition to "be careful to avoid oversimplifying the claims by looking at them generally and failing to account for the specific requirements of the claims." *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299, 1313 (Fed. Cir. 2016) (citation and internal quotations marks omitted); *see also Diamond v. Diehr*, 450 U.S. 175, 189 n.12 (1981) (cautioning that overgeneralizing claims, "if carried to its extreme, make[s] all inventions unpatentable because all inventions can be reduced to underlying

principles of nature which, once known, make their implementation obvious."). The district court, which described its own approach as "simplistic," (Appx308), erroneously substituted its impressions of the "purpose" and "focus" of the *patent* for a proper review of the *claims*, corrupting its analysis. As in *Cellzdirect*, the asserted claims recite a series of "concrete steps" to achieve a useful outcome. (Appx48-49) In form, those claims are identical to the patent eligible claims in *Cellzdirect*, which are, in turn, like "thousands of others" before it. *Cellzdirect*, 827 F.3d at 1046-48. For the district court, however, once it had determined, erroneously, that binding of ^{125}I-MuSK receptors and autoantibodies were "natural occurrences," the claim details became irrelevant. (Appx7) Not only did the court ignore the form of the claims – concrete steps in a method rather than a law of nature itself of mere mental processes – but it ruled that they were *all* ineligible in light of its view that the binding of ^{125}I-MuSK with MuSK autoantibodies was a natural phenomenon: it is *not*, but, that aside, *only* claim 9 recites ^{125}I-MuSK, and claim 6 does not involve labeled MuSK of any type.

Third, the presence of a natural phenomenon within a claim does not disqualify the claim from patent eligibility. It was immaterial in *Cellzdirect* that the claims involved operation of what the district court deemed a "'natural law' – the cells' capability of surviving multiple freeze-thaw cycles," because the claims recited a "new and useful laboratory technique," not the natural law itself.

Cellzdirect, 827 F.3d at 1048. The method claims in the '820 patent are also "directed to" a laboratory technique, not to what the district court (mistakenly) considered a natural occurrence. (Appx48-49) This critical distinction, recognized in *Cellzdirect* and applicable here, is consistent with the Supreme Court's admonition that courts are to apply the Section 101 exceptions narrowly, as all inventions rely, to one extent or another, on natural laws. *Mayo*, 132 S. Ct. at 1293; *see also Myriad Genetics*, 133 S. Ct. at 2119 (because the exceptions to Section 101 are not broad enough to exclude man-made compounds, laboratory technician created cDNA is patent-eligible even though its nucleotide sequence is dictated by nature); *Diehr*, 450 U.S. at 188 ("Arrhenius' equation is not patentable in isolation, but when a process for curing rubber is devised which incorporates in it a more efficient solution of the equation, that process is at the very least not barred at the threshold by § 101."). Thus, even if the MuSK receptor/antibody binding *were* a natural law, because claims 7-9 of the '820 patent are to methods that incorporate it, they are, "at the very least not barred" from *eligibility* for protection. *Id*.

Fourth, the district court erred in distinguishing *Cellzdirect* on the basis of the number or nature of uses for the claimed methods:

> The method [in *Cellzdirect*] 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.

(Appx9) This Court did *not* decide that the claims in *Cellzdirect* were patent eligible on the strength of the number of potential uses for twice-frozen, twice-thawed hepatocytes. As discussed above, the claims were patent-eligible because they recited the "concrete steps" of a "new and useful method of preserving hepatocyte cells"; in fact, the *claims* recited only one goal, "producing a desired preparation of multi-cryopreserved hepatocytes." Contrary to the district court's understanding, "[i]t is the *process* of preservation that is patent eligible here, not necessarily the end product." *Cellzdirect*, 827 F.3d at 1050 (emphasis in original). Likewise, here, it is the *process* required for MuSK autoantibody detection that is patent eligible.

Even on its own theory, the district court's attempt to distinguish *Cellzdirect* does not hold up. The court does not explain how "detection of MuSK antibodies" is the "converse" of the "myriad" purposes of the *Cellzdirect* claims, (Appx9), and there is certainly no requirement, in Section 101 or elsewhere, that an invention have multiple utilities to be patent eligible. A method that "does not produce something useful beyond that diagnosis [of MG]" (Appx9), is useful enough and still qualifies as "a notable advance over prior art techniques," *Cellzdirect*, 827

F.3d at 1047. Until the '820 patent, there was *no* method of detecting anti-MuSK autoantibodies, (*see generally* Appx43), and previous MG diagnostic methods failed 20% of sufferers. (Appx43, col. 1, ll. 34-48)

The diagnosis of a serious disease is, moreover, surely "useful" as that term has been understood in patent law since ratification of the Constitution. *See* U.S CONST. art. I, § 8, cl. 8. There is, after all, often no treatment without it. Diagnosis is certainly not *per se* ineligible subject matter, though the district court treated it as such, (Appx9-10), an otherwise patent eligible method does not become ineligible simply because its goal is diagnosing disease. As explained immediately below, in the easily distinguishable recent cases holding diagnostic methods ineligible, the methods involved nothing more than the mental step of correlating biological or chemical facts with known diseases; the claims were not invalid simply for being directed to diagnosis. Diagnosis is a goal for a given method, no different in form, for example, from "treating disease," which this court has recently described as a traditionally *eligible* goal. *Cellzdirect*, 827 F.3d at 1049.

C. Recent 101 cases are readily distinguishable

The district court misapplied *Mayo* and *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015), the same cases that the district court in *Cellzdirect* had misapplied. *Cellzdirect*, 827 F.3d at 1048. The claims in those cases, this Court has explained, were invalid as being directed to a law of

nature because they "amounted to nothing more than observing or identifying the ineligible concept itself." *Id.* at 1048.

The claims in *Mayo*, to a method for "optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal order," required only "administering" a thiopurine drug that provided a certain metabolite to a subject, and then "determining the level" of the metabolite, "wherein" certain levels indicated the subject's need for more or less of the drug. *Mayo*, 132 S. Ct. at 1295. The claims did not tell *how* to administer the thiopurine drug, which doctors had been doing "long before anyone asserted these claims," or how to determine metabolite levels, leaving that to "whatever process the doctor or the laboratory wishes to use." *Id*. at 1297. Moreover, scientists had "routinely measured metabolites as part of their investigations into the relationships between metabolite levels and efficacy and toxicity of thiopurine drugs," *id*. at 1298, that is, the same goal recited in the patent. *Id.* at 1295. Finally, the "wherein" claim limitations simply "tell a doctor about the relevant natural laws" – the significance for treatment of various thiopurine metabolite levels. *Id*. at 1297. Thus, properly discounting the known, generic, unelaborated data-gathering steps left to the practitioner's discretion, the method was ineligible: it instructed doctors to make an inference, a purely mental step, from the data. *Id*. at 1298.

In *Ariosa*, the method was ineligible as directed to a law of nature because it "begins and ends with a natural phenomenon," the same paternally inherited cffDNA in different amounts, and because the generic steps, "amplifying" and "detecting" naturally occurring DNA in a sample, were well known. *Ariosa*, 788 F.3d at 1376-77. As in *Mayo*, the claims gave no specific direction for performing the method.

Cleveland Clinic Found. v. True Health Diagnostics LLC, 859 F.3d 1352 (Fed. Cir. 2017), provides additional helpful contrast between the ineligible claims in *Mayo* and *Ariosa*, and the eligible claims, analogous to those in in the '820 patent, in *Cellzdirect*. The claims in *Cleveland Clinic* were to methods of "assessing a test subject's risk of having atherosclerotic cardiovascular disease." *Id*. at 1356. With slight variations, the methods involved "comparing levels of myeloperoxidase [(MPO)]" in test subjects, with MPO levels from "subjects diagnosed as not having the disease." *Id*. As in *Mayo* and *Ariosa*, the methods recited no specific concrete steps, "comparing" being a mental exercise. In addition, unlike ^{125}I-MuSK, MPO is natural and occurs naturally in bodily samples. *Id.* at 1361.

This Court has likened the method in *Cleveland Clinic* to that in *Ariosa*, in that it "starts and ends with naturally-occurring phenomena with no meaningful non-routine steps in between," and distinguished the *Cleveland Clinic* claims from

the *eligible* claims in *Cellzdirect*: the claims in *Cellzdirect* were directed to a "laboratory technique," not to the underlying natural phenomenon, whereas the claims in *Cleveland Clinic* were directed to the natural relationship between MPO and cardiovascular disease itself, rather than, for example, to a "'useful laboratory technique'" for *detecting* this relationship." *Id* (emphasis added, internal citation omitted). As shown above, the asserted claims of the '820 patent are like those in *Cellzdirect*: they describe a new and innovative laboratory technique for achieving a useful goal; indeed, the techniques in claims 7-9 of the '820 patent are more innovative than those in *Cellzdirect* because, among other reasons, they involve non-naturally occurring substances in a combination of non-generic steps unknown in the art. (*See* Section I.A.1, *supra*) Those claims are, therefore, likewise distinguishable from the claims in *Cleveland Clinic*, *Mayo*, and *Ariosa*.

The methods in those cases involved generic, known, non-elaborated processes that work on, or merely observe, known natural phenomena. *See Mayo*, 132 S. Ct. at 1295 ("determining" naturally-occurring levels of known metabolites); *Cleveland Clinic*, 859 F.3d at 1361 ("comparing" naturally-occurring levels of MPO, a known, natural substance, methods for the detection of which were also known and not even claimed); *Ariosa*, 788 F.3d at 1376-77 (generically "amplifying" and "detecting" naturally-occurring DNA). In contrast, no process involving MuSK fragments or labeled MuSK was known prior to the '820 patent.

In addition, claims 7-9 of the '820 patent require the use of a indisputably non-naturally-occurring substance, labeled MuSK, whereas the claims in *Mayo* (metabolites), *Cleveland Clinic* (MPO), and *Ariosa* (DNA), all involved purely natural, unaltered substances. (*See* Appx44, col. 3, l. 66-col. 4, l. 10) The methods of claims 7-9 of the '820 patent neither start nor end with a product of nature. *See Ariosa*, 788 F.3d at 1376.

Unlike in *Mayo*, *Cleveland Clinic*, and *Ariosa*, but precisely as in *Cellzdirect*, it is impossible to read claims 7-9 as reciting a mere mental step – observation, comparison, inference – with respect to a natural phenomenon: even putting aside that the claims of the '820 patent require non-naturally occurring substances, they are directed to specific, concrete *steps* for *detection*. *See Cleveland Clinic*, 859 F.3d at 1361 (claims invalid because they are directed to the relationship between MPO and disease, rather than to "a new and useful laboratory technique" for "detecting that relationship"). No mental step would accomplish the goal of claims 7-9 of the '820 patent, which instruct a skilled person in concrete laboratory steps for determining whether a bodily sample contains MuSK autoantibodies.

Claims 7-9 of the '820 patent pass step one of *Mayo* and are patent-eligible. The Court may conclude its analysis here, and reverse.

D. Claims 7-9 do not preempt a law of nature, natural phenomenon, or abstract idea

The concern driving the *Alice/Mayo* "exclusionary principle" is "one of preemption," that is, that patent protection should "not inhibit further discovery by improperly tying up" the "building blocks of human ingenuity." *Alice*, 134 S. Ct. at 2354 (quoting *Mayo*, 132 S. Ct. at 1301). Preemption exists "when the claims are not directed to a specific invention and instead improperly monopolize 'the basic tools of scientific and technological work.'" *McRO*, 837 F.3d at 1314 (quoting *Alice*, 132 S. Ct. at 2354). In *McRO*, this Court reversed a finding of patent ineligibility in part because the "specific structure of the claimed rules would *prevent* broad preemption of all rules-based means of automating lip synchronization." *Id*. at 1315. Where the claims do not "lock up the natural law in its entirety," and it is possible to engineer around them, there is no preemption. *Cellzdirect*, 827 F.3d at 1052 (internal quotations and citations omitted).

Like the claims in *McRO*, claims 7-9 of the '820 patent describe a specific, defined process: a multi-step laboratory technique for detecting MuSK autoantibodies. That the claims involve the antibody/MuSK binding phenomenon does "not inhibit further discovery" into that phenomenon itself, nor, in fact, do the claims prevent the development of alternative MuSK autoantibody detection methods. *See McRO*, 837 F.3d at 1315-16 (because the "limitations in claim 1 prevent preemption of all processes," it "is not directed to ineligible subject

matter"). Although "pre-emption is not the test for determining patent eligibility," it is "certainly the concern that undergirds . . . § 101 jurisprudence," and its absence here accords with a conclusion that the asserted claims of the '820 patent are directed to eligible subject matter. *Cellzdirect*, 827 F.3d at 1052 (internal quotations omitted, citing *Alice*, 134 S. Ct. at 2358).

II. THE ASSERTED CLAIMS OF THE '820 PATENT ARE PATENT ELIGIBLE UNDER STEP TWO BECAUSE THEY CONTAIN INVENTIVE CONCEPTS

Should the Court find that any of claims 7-9 is directed to a law of nature, it is nonetheless patent-eligible because, under *Mayo* step two, it embodies numerous "inventive concepts," elements "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Mayo*, 132 S. Ct. at 1294. Claims 7-9 share at least two inventive concepts: (1) an innovative combination of steps leading to a new and useful process, and (2) novel, laboratory-made, labeled MuSK and MuSK fragments, and labeled MuSK/autoantibody/"second" antibody immunoprecipitated complexes. (Appx48-49) Claims 8 and 9 recite, respectively, non-naturally-occurring *radio*labeled and ^{125}I-radiolabeled MuSK as additional inventive concepts. (Appx49)

The district court committed errors of law and fact in its step two analysis. First, the court considered only whether immunoprecipitation and iodination in "isolation" – that is, without regard to the application of those techniques as claimed – were known in the art, and it did not consider the "ordered combination"

of elements at all. (*See generally* Appx10-12) Second, the court committed a clear error of law by substituting an (incorrect) written description analysis under 35 U.S.C. § 112 for an "inventive concept" analysis under *Mayo* step two. (Appx11-12) Mayo did not raise a Section 112 defense, meaning that Athena had no opportunity to address it, there was no fact finding whatsoever related to written description (or anything else), and, in any event, a court may not determine eligibility under Section 101 by reference to other potential grounds of invalidity.

A. Claims 7-9 contain a number of "inventive concepts" and are therefore patent-eligible at Mayo step two

1. *The method described in claims 7-9 is a non-generic, non-conventional arrangement of steps and is therefore an "inventive concept"*

At step two, courts consider, among other things, whether the elements of each claim "'as an ordered combination' . . . 'transform the nature of the claim' into a patent eligible application." *Alice*, 134 S. Ct. at 2355 (quoting *Mayo*, 132 S. Ct. at 1297-98). If they do, the claims are patent-eligible. *BASCOM Global*, 827 F.3d at 1350. It has been true since before *Alice* and *Mayo*, of course, that a "new combination of steps in a process may be patentable even though all of the constituents of the combination were well known and in common use before the combination was made." *Diehr*, 450 U.S. at 188-89 (finding it inappropriate to "dissect the claims into old and new elements and then to ignore the presence of the old elements" rather than analyzing the claims as a whole). The district court

did not consider whether all steps in claims 7-9 of the '820 patent were known (they were not), or, if so, whether their combination rendered the claims eligible under *Mayo* step two. It does.

In *BASCOM Global*, the "limitations of the claims, taken individually, recite[d] generic computer, network and Internet components, none of which [was] inventive by itself." 827 F.3d at 1349. But as an ordered combination, the claims described "the installation of a filtering tool at a specific location," which provided a number of previously unknown benefits. *Id.* at 1350. Thus, although "[f]iltering content on the Internet was already a known concept," this Court found a patent-eligible inventive concept because the patent described "how its particular arrangement of elements [was] a technical improvement over prior art ways of filtering such content." *Id.* Indeed, this Court has found that the mere *repetition* of known steps in a known order qualifies as an inventive concept under this standard. *Cellzdirect*, 827 F.3d at 1050-51 (that "individual steps (freezing, thawing, and separating) were known independently in the art," did "not make the claims unpatentable" because "view[ing] them as a whole," the elements were a significant improvement over prior art).

Claims 7-9 of the '820 patent satisfy *Mayo* step two because they describe an innovative, new combination of steps: (1) labeling MuSK or specific MuSK fragments, (2) combining the labeled-MuSK or fragments with a patient sample to

form a labeled-MuSK/autoantibody complex (if anti-MuSK autoantibodies are present in the patient's sample), (3) adding a "second" antibody which binds to the MuSK autoantibody to precipitate the entire labeled-MuSK/autoantibody/"second" antibody complex, and (4) detecting the presence of autoantibodies by the label. (*See, e.g.*, Appx47, col. 10, ll. 50-60) Even if the individual elements were known in the art – and neither the labeled-MuSK nor the labeled-MuSK/autoantibody/"second" antibody complexes were known in the art – the claims are still patent-eligible because they represent a new combination of steps that achieve a novel and useful purpose. Before the '820 patent there was no description of a method comprising these steps, and no test *at all* to detect MuSK autoantibodies. In addition, the methods are a significant improvement over the art in that they enable diagnosis of SNMG sufferers, a significant subset of all MG patients. Therefore, as in *Cellzdirect* and *BASCOM Global*, the combination of elements in claims 7-9 represent more than the sum of their individual parts – again, even assuming that the individual steps, as claimed, involved some known laboratory techniques – and, as a whole, contain a patent-eligible inventive concept.

Methods are patent-ineligible under step two only when they do not extend to technology beyond the natural phenomenon itself. *See Cleveland Clinic*, 859 F.3d at 1362; *Genetic Techs. Ltd. v. Merial LLC*, 818 F.3d 1369, 1378 (Fed. Cir.

2016) (finding disclosures insufficient to pass *Mayo* step two where the new and useful aspect of the claims was "a mental step . . . it merely sets forth a routine comparison that can be performed by the human mind"); *Ariosa*, 788 F.3d at 1377 (claims relied on well-known "methods like PCR to amply and detect cffDNA" and the "only subject matter new and useful . . . was the discovery of the presence of cffDNA in maternal plasma or serum"); *Univ. of Utah Research Found. v. Ambry Genetics Corp.*, 774 F.3d 755, 764 (Fed. Cir. 2014) (the patentee did not challenge the "district court's finding that the claims contain no otherwise new process for designing or using probes, primers, or arrays beyond the use of BRCA1 and BRCA2 sequences in those processes"). Here, in contrast, claims 7-9 describe a novel and useful laboratory technique, which requires novel probes, for detecting MuSK autoantibodies, independent of the correlation between MuSK autoantibodies and MG.

2 *Laboratory-synthesized labeled-MuSK and labeled-MuSK/autoantibody/"second" antibody complexes are also "inventive concepts" under Mayo step two*

Novel, man-made compositions of matter are "patentable subject matter" because such matter "is not a hitherto unknown natural phenomenon, but a *nonnaturally* occurring manufacture or composition of matter – a product of human ingenuity." *Chakrabarty*, 447 U.S. at 309 (1980) (emphasis added). When a "lab technician unquestionably creates something new," that new matter "is not a

'product of nature' and is patent eligible under § 101," even when nature dictates the new matter's essential property. *Myriad Genetics*, 133 S. Ct. at 2119. A claim that *requires* the use of a man-made molecule includes an "inventive concept" because it "ensure[s] that the patent in practice amounts to significantly more than a patent upon the natural law itself." *See Mayo*, 132 S. Ct. at 1294.

Claims 7-9 satisfy *Mayo* step two because they require the use of a man-made compounds, including labeled-MuSK. Claim 7 describes "MuSK or an epitope or antigenic determinant thereof *having a suitable label*." (Appx48-49) Claim 8 requires "a radioactive label," and claim 9 requires "^{125}I," radioactive iodine. (Appx49) These compounds do not exist in nature, and they are required for the innovative laboratory technique described in the claims. (*See* Appx47, col. 10, ll. 51-52 ("[T]he purified extracellular domain of MuSK is iodinated using ^{125}I[.]")) Thus, like cDNA in *Myriad Genetics*, another non-naturally occurring molecule, a labeled-MuSK molecule is a patent-eligible invention in its own right. *See* 133 S. Ct. at 2119. This element of claims 7-9 is therefore an "inventive concept" because it ensures that the claims amount to something "significantly more than a patent upon the natural law itself," and so the inclusion of this element is sufficient for the claims to pass *Mayo* step two. *See Mayo*, 132 S. Ct. at 1294; *Myriad Genetics*, 133 S. Ct. at 2119 (finding non-natural cDNA patent-eligible);

Chakrabarty, 447 U.S. at 309-10 (finding a man-man, non-naturally-occurring bacterium patent-eligible).

The labeled-MuSK/autoantibody/"second" antibody complex that forms during practice of the methods in claims 7-9, (Appx48), also does not exist in nature, is also an innovation of the '820 patent inventors, and so also represents an inventive concept. *Myriad Genetics*, 133 S. Ct. at 2119.

B. The district court considered the wrong facts and applied the wrong law in its step two analysis

The district court made several reversible errors in its *Mayo* step two analysis.

First, for determining whether the methods in claims 7-9 contained inventive concepts, the district court relied entirely on its view that iodination and immunoprecipitation are, in isolation, "standard techniques in the art." (Appx10-12) This was consistent with the court's view during argument: "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." (Appx319 (emphasis added)) The court clearly misunderstood the law to be that, if a claimed method involves a known technique at any point, it is ineligible: "[t]he 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." (Appx310)

At step two, courts must analyze the elements of the claim "both individually and as *an ordered combination*," *Alice*, 132 S. Ct. at 2355 (internal quotations omitted) (emphasis added), and the Supreme Court has cautioned against precisely the approach employed by the district court: it is "inappropriate to dissect the claims into old and new elements," rather than reviewing the claims as a whole, "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." *Diehr*, 450 U.S. at 188; *see Cellzdirect*, 827 F.3d at 1051-52 (a method requiring the mere repetition of known steps reflects an inventive ordered combination under step two). The "novelty" of one element in a method – the district court's sole focus here – "is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter." *Id.* at 188-89.

Second, in response to Athena's argument that the court must consider immunoprecipitation and iodination in the context of the claimed method, not in isolation, the court substituted a Section 112(a) written description analysis for *Mayo's* required step two inquiry, finding Athena's argument "unavailing" because, "[p]atent applications are required to provide the precise description of the manner and process of making the invention. 35 U.S.C. § 112(a)." (Appx11) The court then set out Section 112(a) in its entirety and concluded that, "[n]one of

the complexity to which Plaintiffs cite is described in the patent." (Appx11) The court's switch to a Section 112 analysis was not only legal error and severely prejudicial to Athena, but fundamentally wrong.

Courts may not "substitute §§ 102, 103, and 112 inquiries for the better established inquiry under § 101." *Mayo*, 132 S. Ct. at 1304 (citing Lemley, Risch, Sichelman, & Wagner, *Life After Bilski*, 63 STAN. L. REV. 1315, 1329-32 (2011) (outlining the differences between Sections 101 and 112)); *BASCOM Global*, 827 F.3d at 1350 (criticizing district court's step two analysis for looking "similar to an obviousness analysis under 35 U.S.C. § 103," and reversing finding of invalidity); *Classen Immunotherapies, Inc. v. Biogen Idec*, 659 F.3d 1057, 1064 (Fed. Cir. 2011) (the "question therefore of whether a particular invention is novel is wholly apart from whether the invention falls into a category of statutory subject matter") (quoting *Diehr*, 450 U.S. at 189-90). "[P]atent-eligibility does not turn on ease of execution or obviousness of application. Those are questions that are examined under separate provisions of the Patent Act." *Cellzdirect*, 827 F.3d at 1052 The issue before the district court was whether the asserted claims reflected an "inventive concept" that *qualifies* them for a "category of statutory subject matter" under Section 101; that the claims might be invalid for lack of written description under 112(a), or for any other reason, is a question "wholly apart". *Classen*, 659 F.3d at 1064.

The district court's reliance on Section 112 for its eligibility analysis was, moreover, not only legally inappropriate, but prejudicial to Athena. Mayo did not raise a defense under Section 112, the issue did not come up in the multiple rounds of briefing and argument, and there was neither the fact-finding nor claim construction required to resolve written description attacks. Athena had no reason to prepare, or opportunity to present, a Section 112 case. This court has recently suggested that resolving validity-related issues, including written description, in the same "litigation cycle" as eligibility might be the more efficient procedure, but it acknowledged that resolving those additional issues would require additional evidence, and that they could not be decided "as overflow from the eligibility debate." *BASCOM Global*, 827 F.3d at 1354-55 (Newman, J., concurring).

The court also got its written description analysis wrong. To satisfy 35 U.S.C. § 112(a), a "patent must contain a written description of the claimed invention[.]" *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1324 (Fed. Cir. 2008). Whether a patent contains written description adequate to support a particular claim is a question of fact. *Ariad Pharm. v. Eli Lilly*, 598 F.3d 1336, 1355 (Fed. Cir. 2010) (*en banc*); *see also Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1297 (Fed. Cir. 2014); *Ericsson Inc. v. TCL Commc'ns Tech. Holdings, Ltd.*, 161 F. Supp. 3d 438, 457 n.7 (E.D. Tex. 2015) (refusing to decide written description at claim construction stage in the absence of

required fact-finding). The test for written description "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad*, 598 F.3d at 1351. A patent is presumed valid, and overcoming the presumption requires clear and convincing evidence. *Abbvie*, 759 F.3d at 1297.

A proper Section 112 analysis here would have required, at a minimum, "an objective inquiry . . . from the perspective of a person of ordinary skill in the art," into whether the '820 patent specification contained a written description adequate to support the asserted claims. *Ariad*, 598 F.3d at 1351. But the district court conducted no fact-finding whatsoever, despite intending to convert Mayo's motion into one for summary judgment, and, indeed, denied Athena any discovery. Even if a Section 112 analysis had been legally appropriate at *Mayo* step two, therefore – it was not – the court could not properly have ruled on it. The court also misapplied the written description analysis. Citing page 11 of Athena's opposition to Mayo's motion, the court determined that "[n]one of the complexity to which Plaintiffs cite is described or claimed in the patent." (*Id*.) In the cited portion of its brief, Athena had described the "complexity" of one of the *problems* it had solved, the application of immunoprecipitation and iodination to proteins, which "are far more complex than DNA." (Appx550) The district court did not make a finding

that the specification lacks a description of the *claimed invention*, which is the only relevant inquiry under Section 112(a).

III. BECAUSE THE DISTRICT COURT DID NOT RULE ON CLAIM 6, THIS COURT SHOULD REMAND

Validity is to be determined on a claim-by-claim basis. *MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264 (Fed. Cir. 2013) ("[t]he central problem with the district court's analysis is that it fails to treat claims 15 and 19, which are not limited to fragrance products, differently from the asserted fragrance-specific claims"). When a court does not address or give reasons for the invalidity of a challenged claim, that claim is not invalid. *See, e.g.*, *Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1356-57 (Fed. Cir. 2013) (remanding a district court's decision on validity, in part because the district court's minimal discussion "fail[ed] to provide any meaningful analysis for this court's review"); *see also Osram Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 707 (Fed. Cir. 2012) ("Where, as here, the record is devoid of meaningful analysis, we will not conduct such an analysis in the first instance") (citing *Research Corp. Techs. v. Microsoft Corp.*, 536 F.3d 1247, 1254 (Fed. Cir. 2008)); *Nazomi Commc'ns, Inc. v. Arm Holdings, PLC*, 403 F.3d 1364, 1370-71 (Fed. Cir. 2005) (remanding an issue of law to the district court because it provided little to no analysis and noting that this Court "must be furnished 'sufficient findings and reasoning to permit meaningful appellate scrutiny'" because its

review "is not an independent analysis in the first instance") (quotation omitted). Likewise, when the reasons given for invalidating certain claims do not apply to other challenged claims, those other claims cannot be deemed invalid for the given reasons. *C.f. Content Extraction & Transmission LLC v. Wells Fargo Bank, N.A.*, 776 F.3d 1343, 1348 (Fed. Cir. 2014) (claims may be invalidated without direct analysis only if other "representative claims" are fully considered, *i.e.*, claims that are "substantially similar and linked to the same abstract idea.").

Here, although claim 6 was "at issue," the district court provided no analysis of it at all, merely reproducing it at the start of its opinion. (Appx1-12) (In fact, the court does not appear to distinguish among any of the asserted claims.) Accordingly, there has been no ruling with respect to claim 6, notwithstanding the court's generic granting of Mayo's motion (Appx12). *See Content Extraction*, 776 F.3d at 1348; *Plantronics*, 724 F.3d at 1356-57.

In addition, no part of the district court's analysis applies to claim 6. The district court's step one analysis, (Appx5-10), relied entirely on the court's (erroneous) view that "[t]he 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." (Appx7) ^{125}I-MuSK, specifically, appears only in claim 9 of the '820 patent. Claims 7 and 8, from which claim 9 depends, at least recite "labeled" and "radioactive label[ed]" MuSK, respectively, but claim 6 does not involve labeled

MuSK of any type. The method in claim 6 cannot, therefore, be "directed to a patent ineligible law of nature," (Appx10), according to the court's analysis. *See Content Extraction*, 776 F.3d at 1348; *Plantronics*, 724 F.3d at 1356-57. The district court's step two analysis was likewise inapplicable to claim 6, as it focused entirely on immunoprecipitation and iodination. (Appx10-12) Claim 6 involves neither of those steps. Even if claim 6 were ineligible under step one, therefore – and there was no finding to that effect – it cannot be ineligible under step two, again, according to the court's own reasoning. *See Content Extraction*, 776 F.3d at 1348; *Plantronics*, 724 F.3d at 1356-57.

IV. BECAUSE THE DISTRICT COURT ACKNOWLEDGED THE EXISTENCE OF ISSUES OF FACT, IT SHOULD NOT HAVE DISMISSED UNDER 12(B)(6)

This Court has ruled that a motion to dismiss can be an appropriate procedure for deciding patent eligibility challenges, but, in this case, it was not appropriate. In the district court's its initial view, maintained through its decision to allow Mayo to renew its motion to dismiss, and reflected in its intention to convert that motion into one for summary judgment, fact-finding was necessary to resolve at least step two. That the court changed its mind, and reversed itself by granting Mayo's renewed motion under Rule 12(b)(6), reflects a misunderstanding of the claims and the law. Its failures to acknowledge the evidence that Athena proffered, and to give Athena the benefit of the inferences to which it was entitled on a motion to dismiss, were also reversible errors.

In the First Circuit, "factual dispute[s] . . . cannot be resolved on a Rule 12(b)(6) motion." *Foley v. Wells Fargo Bank, N.A.*, 772 F.3d 63, 76-77 (1st Cir. 2014). The district court acknowledged such a dispute, as to "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," and *denied* Mayo's first motion to dismiss, recognizing that it could not resolve the question "at the motion to dismiss stage." (Appx285-286) During argument leading to Mayo's renewed motion, the court even tried to get the parties to stipulate to unestablished facts, as a "more efficient way to get this question in front of me properly." (Appx340, Appx343)

In opposition to Mayo's renewed motion, and in reliance on the district court's intention to convert the motion, Athena filed a statement of undisputed material facts. (Appx574-580) Mayo contested a number of Athena's asserted facts, including one at the heart of what the district court perceived as the essential dispute, whether iodination and immunoprecipitation are "routine when applied to new proteins," (Appx951-952), underscoring the existence of factual dispute. Athena also proffered the expert declaration of Dr. Anthony De Tomaso, who explained the science underlying the claimed methods. (*See generally* Appx581-622) All the facts in his declaration favor Athena's position that the asserted claims contain inventive concepts, including that, because MuSK is a highly-

complex transmembrane protein, (*see, e.g.*, Appx592-600 ¶¶ 32-45), iodination and immunoprecipitation were not routine as applied, (*see, e.g.*, Appx592-600 ¶¶ 32-45), that labeling MuSK directly was a novel practice not used in prior MG diagnostics, (*see* Appx607 ¶ 57), and that, to create an autoantibody detection method, the inventors had to epitope map MuSK. (*See* Appx611 ¶ 67)

Although the movant on a motion to dismiss must rely on the facts in the complaint, the non-movant "may elaborate on his factual allegations so long as the new elaborations are consistent with the pleadings." *Geinosky v. City of Chicago*, 675 F.3d 743, 745 n.1 (7th Cir. 2012); *see also Watterson*, 987 F.2d at 4 ("Plaintiffs, moreover, introduced the documents themselves, in order to bolster their argument against defendants' motion to dismiss. . . . Like the court below, therefore, we treat the documents submitted by plaintiffs . . . as part of the pleadings."); *Early v. Bankers Life & Casualty Co.*, 959 F.2d 75, 79 (7th Cir. 1992) (A "plaintiff is free, in defending against a motion to dismiss, to allege without evidentiary support any facts he please that are consistent with the complaint, in order to show that there is a state of facts within the scope of the complaint that if provided (a matter for trial) would entitle him to judgment."); *Demers*, 2010 U.S. Dist. LEXIS 121390, at *16-17 n.5.

The district court cites *In re TLI Commc'ns LLC Patent Litig.*, 823 F. 3d 607, 613-14 (Fed. Cir. 2016), presumably as authority for its decision not to

consider Athena's evidence. (Appx11) The court in *TLI Commc'ns*, a computer-system-based, "abstract idea" case, noted only that courts "must be mindful of extraneous fact finding outside the record," and found additional facts unnecessary in that case because the specification fully addressed patentee's own step two arguments. *TLI Commc'ns*, 823 F.3d at 613-14. Here, the district court *invited* additional evidence, which was *in* the record, not extraneous. That the court cited *TLI Commc'ns* in its Section 112(a) analysis, (Appx11), emphasizes the necessity of additional fact-finding here: as discussed above, (*see* Section II.B, *supra*), a written description analysis requires facts sufficient for "an objective inquiry . . . from the perspective of a person of ordinary skill in the art." *Ariad*, 598 F.3d at 1351. As Judge Newman explained in *BASCOM Global*, in those cases in which it is more efficient to evaluate 112 and 101 defenses at the same time, courts should allow patentee to present additional evidence and litigate the non-eligibility issues directly. *See BASCOM Global*, 827 F.3d at 1355 (Newman, J., concurring). In *TLI Commc'ns*, this Court explicitly did not reach the 112 issue before it. *See* 823 F.3d at 609.

Athena was also entitled to all reasonable inferences in its favor on a motion to dismiss, *see Loestrin 24 Fe Antitrust Litig.*, 814 F.3d at 549, but the court effectively reversed that benefit, taking the view that, unless Athena could "dispute" – or had alleged – that immunoprecipitation and iodination, *per se*, were

not standard techniques, it could not prevail. (Appx320) This is further evidence of the court's erroneous fixation with immunoprecipitation and iodination in "isolation" as determining step two according to its admittedly "simplistic" approach. (Appx308)

The court should have, but clearly did not, consider Dr. De Tomaso's declaration, and drawn inferences favorable to Athena from the complaint, the patent, and the declaration, all in the *motion to dismiss* context. The evidence from those sources tells a more complex, more accurate story about inventive concept, and would have resulted in a second denial of Mayo's motion.

The Court should reverse and remand.

CONCLUSION

For the foregoing reasons, this Court should reverse the district court's decision granting Mayo's motion to dismiss and reinstate Athena's complaint. This Court should also find that claims 7, 8, and 9 of the '820 patent are directed to patent-eligible subject matter or, alternatively, remand the matter to the district court for further discovery concerning the technology underlying the '820 patent.

Dated: November 6, 2017

Respectfully submitted,

/s/ Adam R. Gahtan
Dimitrios T. Drivas
Adam R. Gahtan

Eric M. Majchrzak
Vanessa Park-Thompson
WHITE & CASE LLP
1221 Avenue of the Americas
New York, NY 10036
(212) 819-8200

Emmett J. McMahon
Andrew J. Kabat
ROBINS KAPLAN LLP
800 LaSalle Avenue
Suite 2800
Minneapolis, MN 55402
(612) 349-8500

Attorneys for the Plaintiffs-Appellants Athena Diagnostics, Inc., Oxford University Innovation Limited, and Max-Planck-Gesellschaft Zur Forderung der Wissenschaften e.V.

Addendum

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

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**

PCT Pub. Date: **Dec. 20, 2001**

(65) **Prior Publication Data**

US 2004/0082010 A1 Apr. 29, 2004

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
A61K 39/395 (2006.01)
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.

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Primary Examiner—Eileen O'Hara
Assistant Examiner—Sandra Wegert
(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.

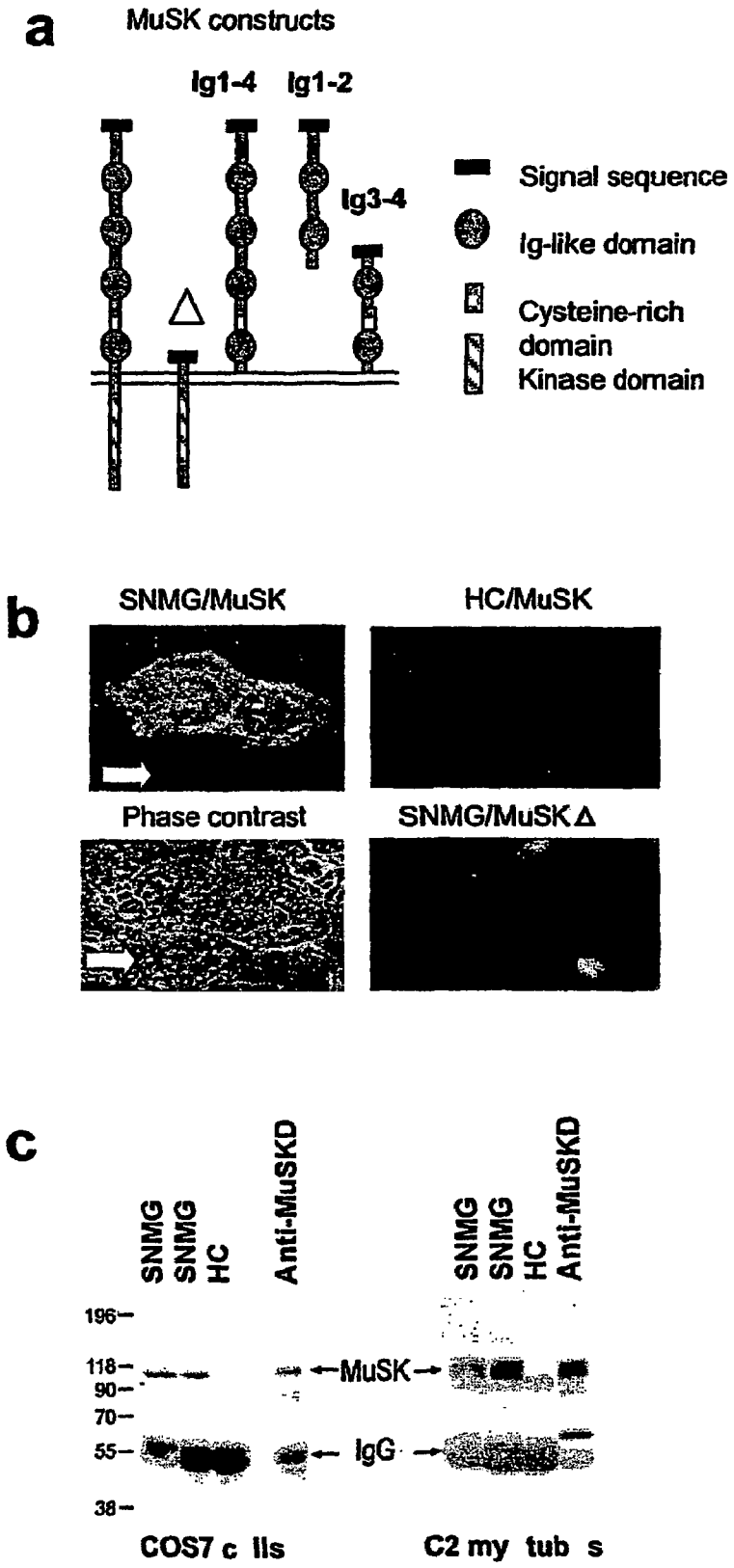
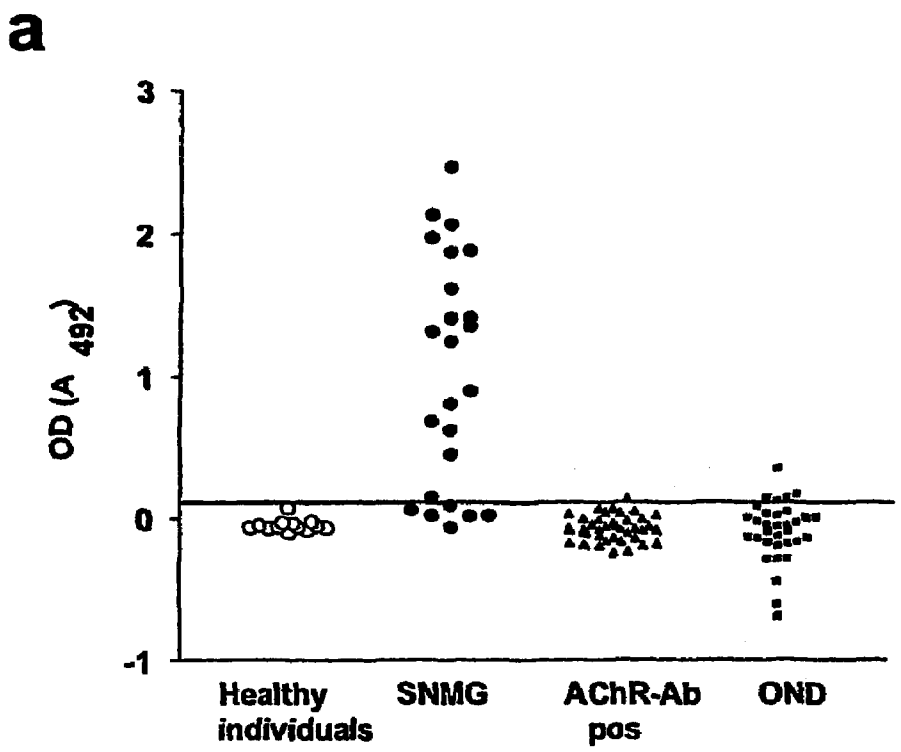

a
MuSK constructs
Ig1-4
Ig1-2
Ig3-4
Signal sequence
Ig-like domain
Cysteine-rich domain
Kinase domain
b
SNMG/MuSK
HC/MuSK
Phase contrast
SNMG/MuSKΔ
c
SNMG
SNMG
HC
Anti-MuSKD
SNMG
SNMG
HC
Anti-MuSKD
196
118
90
70
55
38
MuSK
IgG
COS7 c lls
C2 my tub s

FIG. 2.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2
1
0
-1
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SNMG
AChR-Ab pos
OND

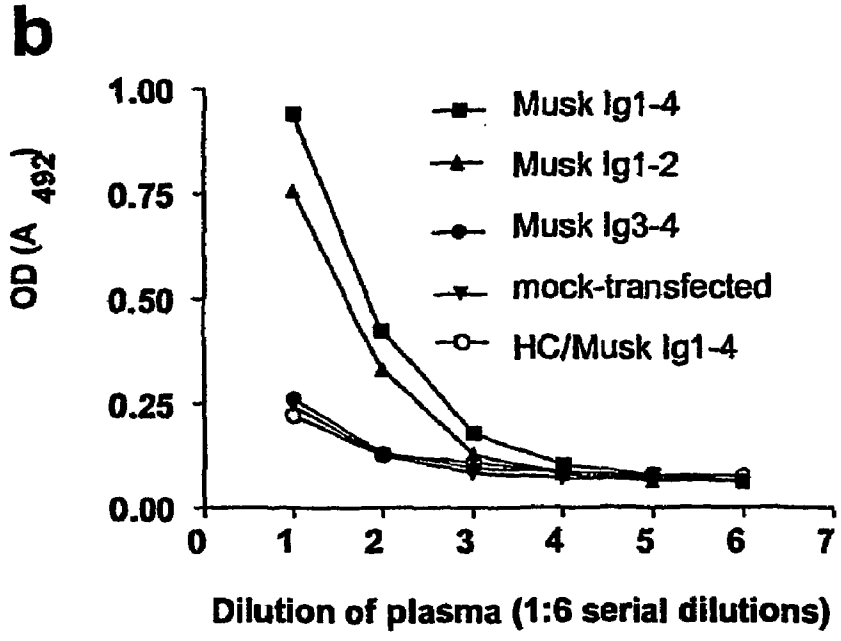
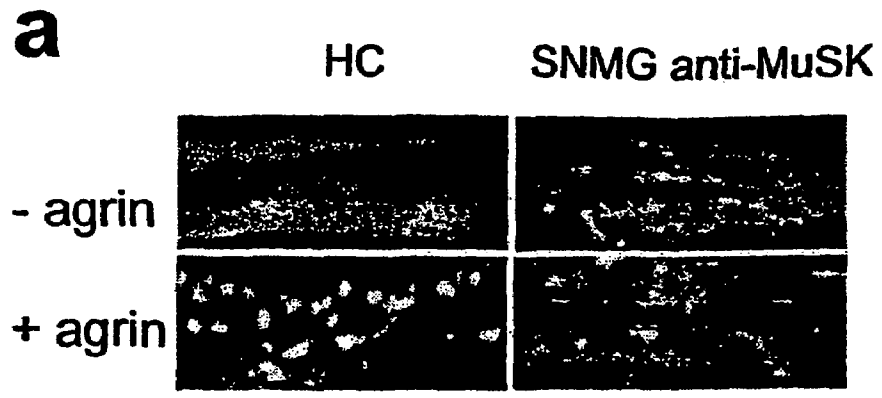

b
OD (A 492)
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
Musk Ig1-4
Musk Ig1-2
Musk Ig3-4
mock-transfected
HC/Musk Ig1-4
Dilution of plasma (1:6 serial dilutions)

FIG. 3.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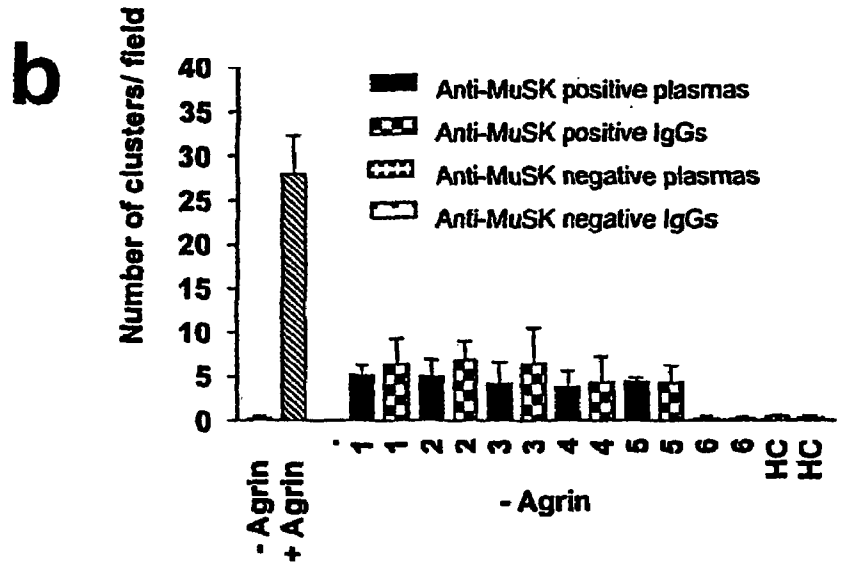
HC
SNMG anti-MuSK
- agrin
+ agrin


b
Number of clusters/ field
40
35
30
25
20
15
10
5
0
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

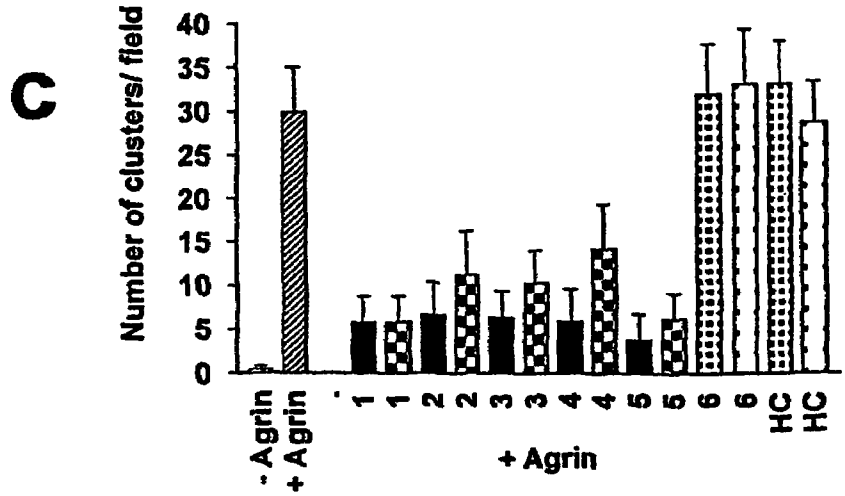

c
Number of clusters/ field
40
35
30
25
20
15
10
5
0
- Agrin
+ Agrin
1 1 2 2 3 3 4 4 5 5 6 6 HC HC
+ Agrin

FIG. 4.

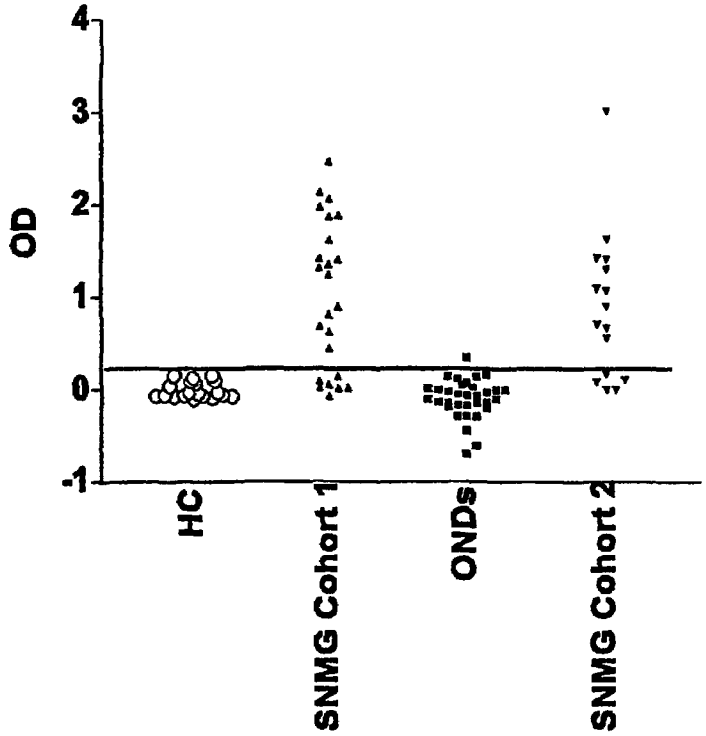

OD
4
3
2
1
0
-1
HC
SNMG Cohort 1
ONDs
SNMG Cohort 2

FIG. 5.

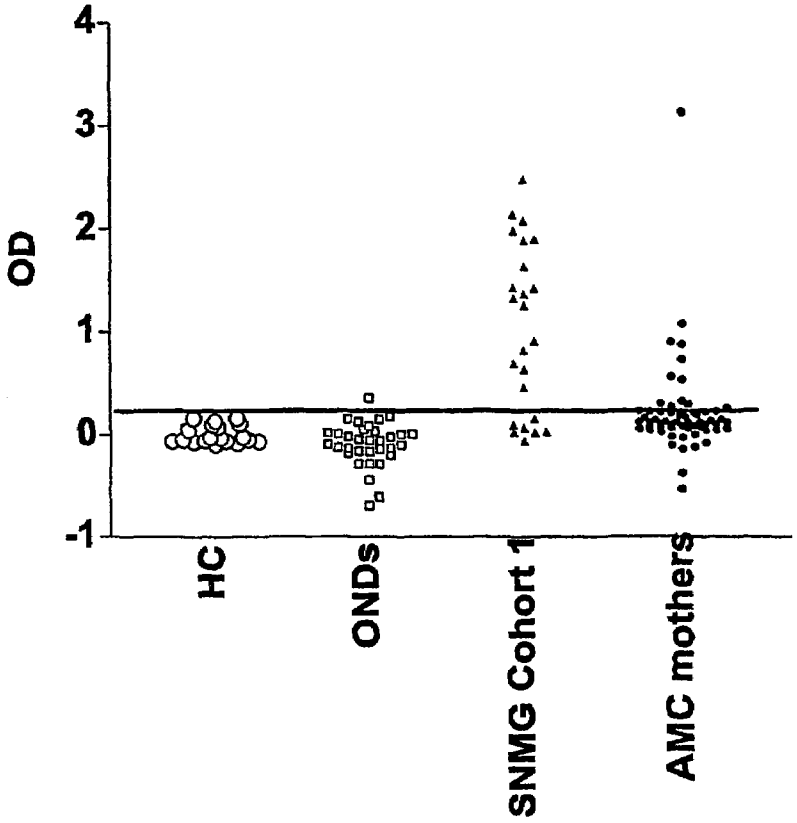

OD
4
3
2
1
0
-1
HC
ONDs
SNMG Cohort 1
AMC mothers

FIG. 6.

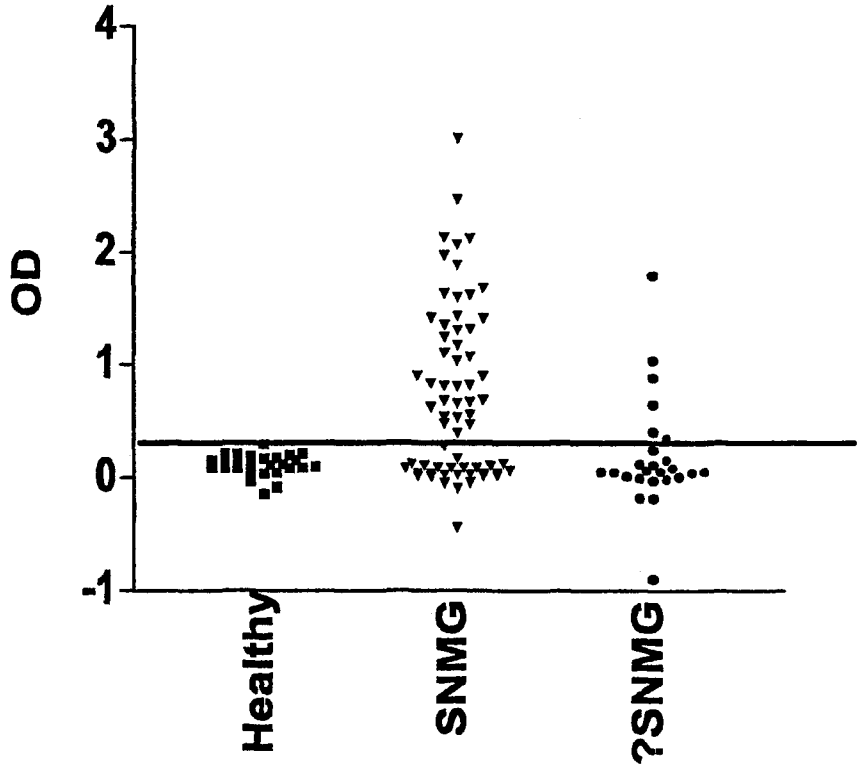

OD
4
3
2
1
0
-1
Healthy
SNMG
?SNMG

FIG. 7.

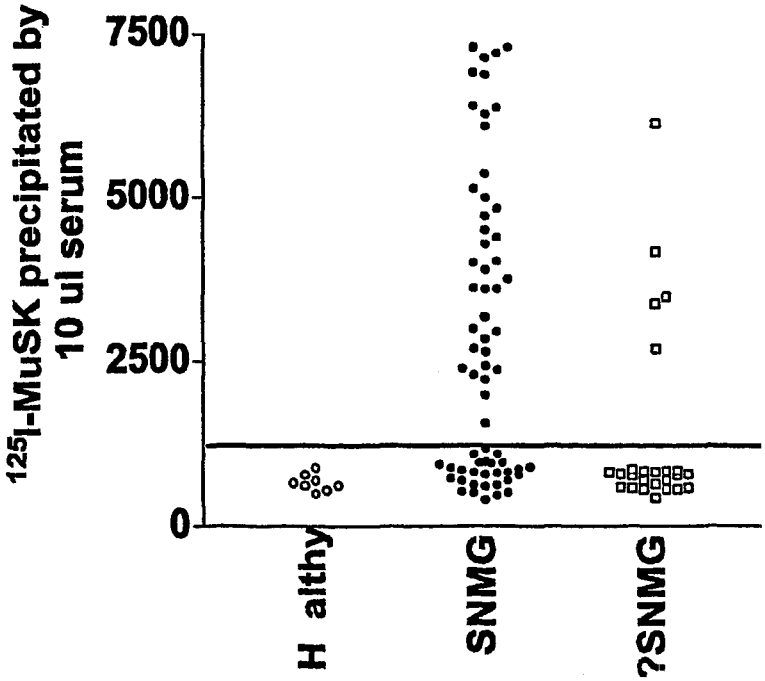
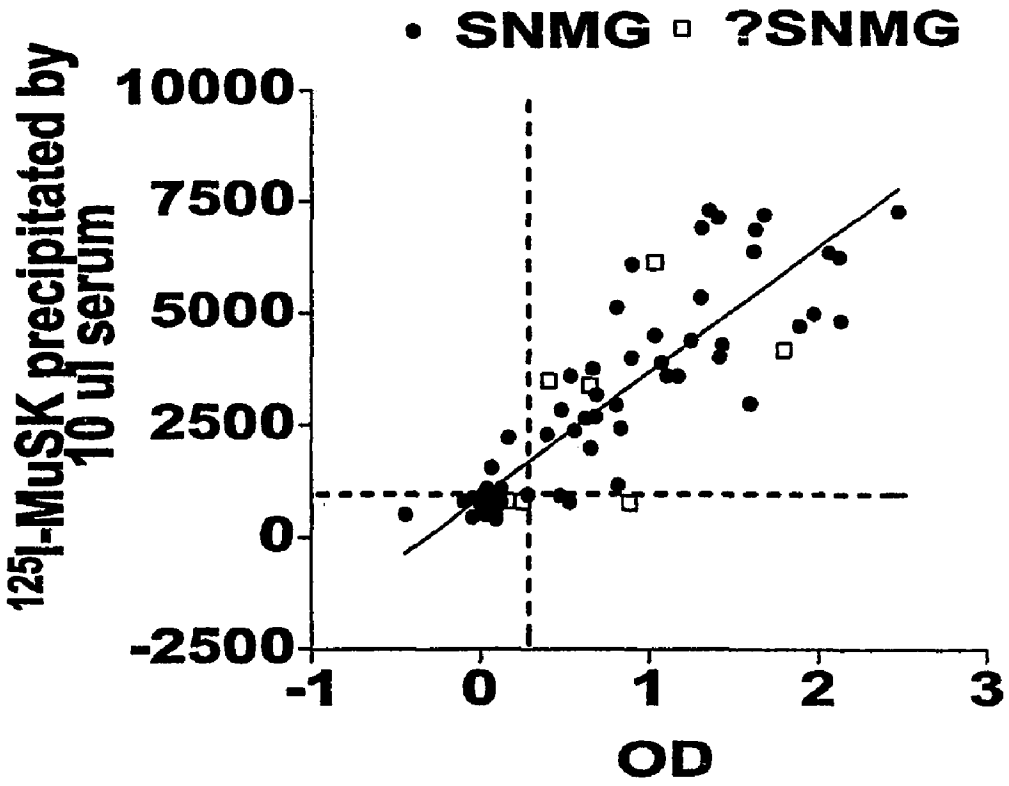

125I-MuSK precipitated by 10 ul serum
7500
5000
2500
0
H althy
SNMG
?SNMG

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).

* * * * *

United States Court of Appeals
for the Federal Circuit

ATHENA DIAGNOSTICS, INC., et al. v.
MAYO COLLABORATIVE SERVICES, LLC, et al., 2017-2508

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JONATHAN ELLIOT SINGER
Fish & Richardson, PC
12390 El Amino Real
San Diego, CA 92130
singer@fr.com

JOHN CAMERON ADKISSON
ELIZABETH M. FLANAGAN
PHILLIP GOTER
DEANNA JEAN REICHEL
Fish & Richardson, PC
60 South Sixth Street, Suite 3200
3200 RBC Plaza
Minneapolis, MN 55402
adkisson@fr.com
EFlanagan@fr.com
goter@fr.com
reichel@fr.com

Counsel for Defendants-Appellees Mayo Collaborative Services, LLC (d/b/a/ Mayo Medical Laboratories) and Mayo Clinic

November 6, 2017

/s/ *Melissa Pickett*
Melissa Pickett
Counsel Press

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/s/ Adam R. Gahtan
Adam R. Gahtan
Counsel for Plaintiffs-Appellants Athena Diagnostics, Inc., Oxford University Innovation Limited, and Max-Planck-Gesellschaft Zur Forderung der Wissenschaften e.V.