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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte CHAI EZERZER and NICHOLAS HARRIS

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Appeal 2022-004253
Application 12/576,750
Technology Center 1600

_____

Before JEFFREY N. FREDMAN, DEBORAH KATZ, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134(a) involving claims to specific CKRD peptides. The Examiner rejected the claims as directed to non-statutory subject matter and on the grounds of obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as Symthera Canada Ltd. (*see* App. Br. 1). We have considered the Specification of Oct. 9, 2009 ("Spec."); Final Action of Aug. 11, 2021 ("Final Action"); Appeal Brief of Feb. 11, 2022 ("Appeal Br."); Examiner's Answer of May 31, 2022 ("Ans."); and Reply Brief of Aug. 1, 2022 ("Reply Br.").

Statement of the Case

Background

"Laboratory research and clinical observations indicated that the expression of specific chemo-attractant cytokines, Chemokines (CKs**),** correlated with specific autoimmune diseases." Spec. ¶ 8. "Given that CKs and CK receptors constitute a network of interacting proteins, these validated drug targets are prime candidates for treatment with multi-target, low affinity drugs." *Id*.

> The present invention is based on the experimental findings that specific amino acid sequences, originating in and abstracted from the CK regulatory domains of CK receptors, are capable of modulating immune system activity. The inventors have found that individual CK Receptor-Derived (CKRD) peptides can alter the course of an inflammatory disease induced in animals.

Id. ¶ 10.

The Claims

Claims 1, 5, 6, and 20–22 are on appeal.[2] Claim 1 is representative and reads as follows:

> 1. A CKRD peptide selected from the group consisting of: (a) a peptide consisting of the amino acid sequence of SEQ ID NO: 16, and (b) a peptide consisting of the amino acid sequence of SEQ ID NO: 16;
>
> wherein amino acid positions 5, 6, and 7 of SEQ ID NO. 16 have been replaced with His-Gly-Met or Asn-Ala-Met; and
>
> wherein the peptide of (a) or (b) binds to cytokines MIG, 1-309, Eotaxin, Eotaxin 2, Eotaxin 3, SDF1-α, SDF1-β, and MIP3- α, and has an anti-inflammatory effect.

[2] The Examiner notes that claims 2–4, 7–19, and 24–34 were cancelled and that claim 23 was withdrawn from prosecution as drawn to a non-elected group. *See* Final Act. 2.

The Rejections

I. The Examiner rejected claims 1, 5, 6, and 20–22 under 35 U.S.C. § 101 as directed to non-statutory subject matter. Final Act. 3–7.

II. The Examiner rejected claims 1 and 20–22 on the ground of nonstatutory double patenting as being unpatentable over claims 1–7 of U.S. Patent No. 8,703,911. Final Act. 18.

III. The Examiner rejected claims 1 and 20–22 on the ground of nonstatutory double patenting as being unpatentable over claims 1–5 of U.S. Patent No. 9,416,158. Final Act. 18–19.

IV. The Examiner rejected claims 1, 5, 6, and 20–22 on the ground of nonstatutory double patenting as being unpatentable over claims 1–26 of U.S. Patent No. 9,931,376. Final Act. 19.

I. 35 U.S.C. § 101

The Examiner finds that the amino acid sequences of human chemokine receptors "CXCR3 comprises WVFGSGLCK (instant SEQ ID NO:16) (the residues preceding TM3[3]), and that CCR3 comprises WVFGHGMCK (instant SEQ ID NO:2) (the residues preceding TM3) and that CCR2B comprises WVFGNAMCK (instant SEQ ID NO:5) (the residues preceding TM3)." Final Act. 4. The Examiner concludes that the "instant claims correspond to fragments of known proteins. Thus . . . the peptides correspond to domains of naturally occurring proteins which are a product of nature (natural phenomenon)." *Id*.

The Examiner cites *Ass'n for Molecular Pathology v. Myriad Genetics, Inc*., 569 U.S. 576, 593 (2013) for the proposition that "Myriad's

[3] "TM3" indicates transmembrane region 3.

claims are not saved by the fact that isolating DNA from the human genome severs the chemical bonds that bind gene molecules together." Final Act. 5 (*citing Myriad*, 569 U.S. at 593; "Nor are Myriad's claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule.")

The Examiner finds that "the peptides are from the ligand binding domains of the chemokine receptors" and therefore "the fact that the peptides bind cytokines is not deemed a markedly different characteristic because the peptide comes from a cytokine (i.e. chemokine) receptor." Final Act. 6, 8. The Examiner also finds that "Chen[4] specifically shows that agents capable of targeting chemokine/chemokine receptors have anti-arthritic effects." *Id.* at 7.

Appellant contends they find

> no examples in the Patent Office's Guidance documents in which a small fragment of a known protein, or in the present case a very small fragment of a known G protein-coupled receptor (GPCR), has been found to be a product of nature. In all of the examples finding claims to include a product of nature, the product of nature is structurally and functionally identical to nature-based product. The exemplary claims in the Guidance documents that were found unpatentable recite entire proteins, or antibodies, or cells, or chemical compounds (amazonic acid) that exist in nature. Indeed, to find the claimed peptides to be a product of nature would create an entirely new judicial exception rendering invalid numerous issued patents with claims reciting peptides that are small fragments of naturally occurring proteins, and especially those peptides

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[4] Chen et al., *Chemokines and Chemokine Receptors as Novel Therapeutic Targets in Rheumatoid Arthritis (RA): Inhibitory Effects of Traditional Chinese Medicinal Components*, 1 Cellular & Molecular Immunology 336–42 (2004).

> whose function is different from the function of the naturally occurring protein.

Appeal Br. 5. Appellant asserts that "[w]hile SEQ ID NO. 16 may represent a small fragment of this protein, its physical structure, and hence, chemical characteristics, are markedly different." *Id*.

Appellant first points out that "[i]n contrast to the structure of CXCR3, predicted as it may be . . . the structure of SEQ ID NO. 16 is: WFVGSGLCK. It is clear to see the structural differences between the claimed peptides and the GPCRs from which they are derived." Appeal Br. 7. Appellant contends that SEQ ID NO: 16 "does not exist in its claimed form, and is not a naturally occurring phenomenon or a product of nature." *Id*.

Appellant second points out that "[i]n contrast to the claims at issue in the *Myriad* decision, the claimed peptides are indeed expressed in terms of a chemical composition- the actual sequence of the peptide. The *Myriad* claims merely recited DNA encoding for the BCRA1 and BCRA2 genes, and thus, the DNA could have different amino acid sequences." Appeal Br. 8.

Appellant's third point is that

> the present claims recite a peptide with an anti-inflammatory effect. Appellant has shown by unrefuted evidence that the claimed peptides have the opposite effect of their naturally occurring counterpart proteins. The naturally occurring counterpart proteins cause inflammation, whereas the claimed peptides have an anti-inflammatory effect. An opposite effect is a markedly different characteristic.

Appeal Br. 9. Appellant notes that "[c]laim 1 of the present application recites the markedly different properties of the claimed peptides as having an anti-inflammatory effect." *Id*. at 10.

Appellant's fourth argument is based on Figures 1 and 2 of the Specification, which show that:

> In sharp contrast with the binding attributes of the naturally occurring CXCR3, the peptides recited by the present claims bind with excellent affinity to the inflammatory CKs GRO-β, IL-8, MCP-1, -2, -4, RANTES, Eotaxin, Eotaxin 2 and Eotaxin 3. Ph-p 15 also bound the constitutively expressed CKs BCA-1, Exodus 2 and TECK and the dual function CKs Fractalkine and Lymphotactin.

Appeal Br. 14. Appellant contends that "[d]ue to this unexpected binding activity of the claimed peptides, the inventors discovered that the claimed peptides would be useful as therapeutic agents in treating disorders that involve expression of CKs . . . disorders the naturally occurring CXCR3 would be incapable of treating." *Id*. at 15.

The Alice Test

The Supreme Court has long interpreted 35 U.S.C. § 101 to include implicit exceptions: "[l]aws of nature, natural phenomena, and abstract ideas" are not patentable. *See, e.g.*, *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014). We follow the United States Patent and Trademark Office published guidance on the application of 35 U.S.C. § 101. USPTO's *2019 Revised Patent Subject Matter Eligibility Guidance* ("Guidance").[5]

In determining whether a claim falls within an excluded category, we are guided by the Supreme Court's two-step framework, described in *Mayo* and *Alice*. *Id.* at 217–18 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 75–77 (2012)). In accordance with that framework, we first determine if there is a judicial exception. Although composition of

[5] *2019 Revised Patent Subject Matter Eligibility Guidance*, 84 Fed. Reg. 50–57 (January 7, 2019).

matter claims are generally eligible subject matter, claims that are directed only to laws of nature and/or natural phenomena are directed to patent ineligible concepts. *Ariosa Diagnostics, Inc. v. Sequenom, Inc*., 788 F.3d 1371, 1376 (Fed. Cir. 2015).

If the claim is "directed to" a judicial exception, we turn to the second step of the *Alice* and *Mayo* framework, where "we must examine the elements of the claim to determine whether it contains an 'inventive concept' sufficient to 'transform' the claimed abstract idea into a patent-eligible application." *Alice*, 573 U.S. at 221 (quotation marks omitted).

Analysis

Because the same issues are present in each of the claims, we focus our consideration on representative claim 1. The same analysis applied below to claim 1 also applies to the other rejected claims.

A. Statutory Category

We consider whether the claimed subject matter falls within the four statutory categories set forth in § 101, namely "process, machine, manufacture, or composition of matter." *See* 35 U.S.C. § 101. Claim 1 recites a "composition" and, thus, falls within the "composition of matter" category. Consequently, we proceed to the next step of the analysis.

B. Step one - Judicial Exception

We now determine if the claims are directed to a patent ineligible concept. The Examiner, as already noted, finds that the claimed peptides are judicial exceptions as drawn to products of nature. *See* Final Act. 4–5. Appellant, however, contends that the evidence does not support a finding that the claimed complexes are naturally occurring because they are not naturally occurring peptides. *See* Appeal Br. 5–7.

There is no dispute that the peptides themselves are fragments of larger naturally occurring proteins. Thus, for this prong, the judicial exception issue resolves to whether a peptide that is a fragment of a larger naturally occurring protein is inherently also naturally occurring. Because, as we will discuss below, we find that the "markedly different" analysis supports the conclusion that the peptides are patent eligible, we provide a more limited discussion of the judicial exception analysis.

The Examiner provides no evidence that the particular peptides recited by the SEQ ID NOs: 2 and 16 are found in nature, and claim 1 requires the peptide sequence consist of the particular recited amino acids, not the entire protein sequence of CXCR3. Meanwhile, the Specification teaches that this particular peptide was discovered by laboratory experiments in a non-naturally occurring system and was screened and created in a laboratory. *See* Spec. ¶ 143.

We analyze this factual pattern consistent with *Myriad,* where the Supreme Court explained that naturally occurring isolated DNA fell within the law of nature exception because "Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA." *Myriad,* 569 U.S. at 593. However, *Myriad* also noted that "creation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring." *Id.* at 594. Myriad explained that "[i]n rare instances, a side effect of a viral infection of a cell can be the random incorporation of fragments of the resulting cDNA, known as a pseudogene, into the genome." *Id.*, n. 8. But *Myriad* concludes that the "possibility that an unusual and rare phenomenon *might* randomly create a molecule similar

to one created synthetically through human ingenuity does not render a composition of matter nonpatentable." *Id.*

Unlike the naturally occurring isolated DNA in *Myriad*, claim 1 is more clearly expressed in terms of a chemical composition, and the binding and functional properties of the particular peptide of SEQ ID NOs: 2 and 16 as identified in the Specification represent structural differences that, in claim 1, require the peptides to have an anti-inflammatory effect as was shown "in a study of Adjuvant-Induced-Arthritis (AIA), evidence that the CK-binding peptide was modulating disease-related CKs for therapeutic effect (Examples 27 and 29). P15." Spec. ¶ 143.

More importantly, the existence of the particular peptides of SEQ ID NOs: 2 and 16 in human bodies can be analogized to unusual and rare phenomenon of a naturally occurring cDNA sequence of the BRCA1 gene. Just as it was not impossible that a cDNA of the BRCA1 gene had previously existed in nature, so too, it is not impossible that the particular peptides of SEQ ID NOs: 2 and 16 out of the 368 amino acids of CXCR3 (*see* Appeal Br. 5) were previously naturally formed by protease cleavage inside a human body.

Nevertheless, it is the Examiner's burden to show that claimed subject matter is necessarily naturally occurring and not merely an unusual and rare phenomenon. *See MEHL/Biophile Int'l. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient."). In *Myriad*, it was certain that the human genome necessarily comprised the BRCA1 DNA, while it was merely possible that the BRCA1 cDNA would be found in nature. *Myriad*, 569 U.S.

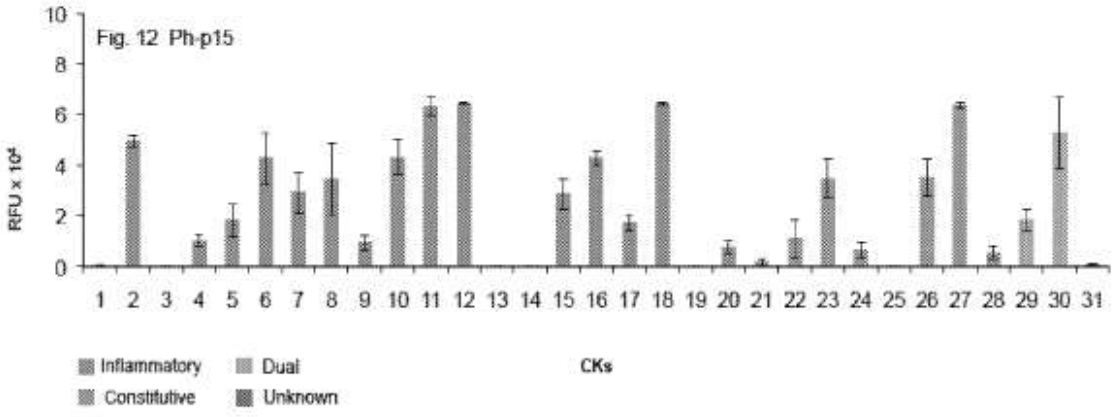
at 594. In the instant case, it is at best merely possible that the CXCR3 protein would have been cleaved into the specific peptides comprising SEQ ID NOs: 2 and 16. The Examiner has not established that these peptides necessarily existed in nature.

Therefore, we find that the mere possibility that the peptides of claim 1 might have existed as a natural phenomenon is insufficient to establish that the composition is a product of nature and therefore a judicial exception.

C. Markedly Different

In the product of nature analysis, if the claim is drawn to a compound or composition that is "markedly different" from what is found in nature, it is not a natural phenomenon and not a judicial exception. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). Specifically, the claimed composition must "[have] markedly different characteristics and have the potential for significant utility" to be eligible subject matter. *Chakrabarty*, 447 U.S. at 310.

We are persuaded that the peptides of SEQ ID NOs: 2 and 16 have markedly different characteristics than the naturally occurring CXCR3 protein based upon multiple lines of evidence. First, the binding data in Figure 12 of the Specification is reproduced below:



"Fig. 12 shows that Ph-p 15 bound with relatively high affinity (> 15,000 RFU, responses in the upper 75% range of 0-60,000RFU) to the inflammatory CKs Mig, IP-10 and 1- TACK, cognate ligands of CXCR3 from which the peptide is derived." Spec. ¶ 202. The data shows that the peptide binds to inflammatory targets. While we appreciate the Examiner's criticism that "there is no adequate comparison to any natural counterpart" (Ans. 12), the data does show that this peptide differentially binds the inflammatory targets of interest relative to other targets, supportive of a finding that the peptide differs structurally from the anti-inflammatory CXCR3 protein.

Second, while fairly apparent, the alphafold predicted three dimensional structure for CXCR3 shown in Appellant's Brief would reasonably be expected to result in a structurally different orientation for the claimed peptides as they exist embedded in the protein relative to the structure resulting from the claimed peptides in solution. *See* Appeal Br. 6. The prior cases cited by the Examiner such as *Myriad* and *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation*, 774 F.3d 755 (Fed. Cir. 2014), involve the hybridization activity that functions substantially based on the nucleotide sequence of the nucleic acid binding or hybridizing to their corresponding base pair. The cases do not address more unusual situations such as enzymatic activity or structural binding activity of nucleic acids such as ribozymes and therefore also do not address the similar concerns associated with peptides. Therefore, that the peptide differs in structure from the natural protein does support a finding that the peptide is markedly different.

Third, the peptide has an opposite effect than the naturally occurring CXCR3 protein. As Appellant shows through multiple citations, the naturally occurring CXCR3 protein is involved in increasing the amount of inflammation. *See* Appeal Br. 11–12. However, example 27 of the Specification teaches

> P5 that is derived from the CK receptor CCR3 and bound to RA-related CKs, was tested for anti-inflammatory activity in a rat model of AIA (Fig. 26). The peptide was injected intraperitoneally (IP, 3.6μg / injection) on days 7 - 11 and 14 - 18 following disease induction on day 0. The peptide had an anti-inflammatory effect from about day 13 that was maintained for the duration of the experiment. At the end of the experiment inflammation in the PS-treated group was about 60% of the disease, untreated group. Inflammation in the untreated, disease group was self-resolving from a maximal clinical score (CS) of 14 on day 19. Inflammation in the dexamethasone (Dexa)-treated group was at the base line until day 24, 6 days after the last injection, when it increased until it was almost equal that of the untreated, disease group.

Spec. ¶ 230. This provides experimental evidence that the peptide has anti-inflammatory activity and is another line of evidence showing the peptides have markedly different structures than the naturally occurring CXCR3 protein.

Based on these three separate lines of evidence, we do not find these facts analogous to *Myriad*, where there was no evidence whatsoever that the nucleic acid sequences were markedly different. Rather, we find the evidence for the claimed peptides as more similar to *Chakrabarty*, where the microorganism was found patent-eligible as markedly different.

We note the peptides of SEQ ID NOs: 2 and 16 were shown to have anti-inflammatory properties and the practical application identified in the Specification is

> to alter and modulate immune system functioning to treat autoimmune diseases specifically and inflammatory disorders in general. In some embodiments, there is provided methods of treating rheumatoid arthritis comprising administering to a subject in need thereof and therapeutically effective amount of one or more CKRD peptide or peptidic compounds of the present invention and a pharmaceutically acceptable excipient.

Spec. ¶ 119. Thus, the Specification provides evidence showing that claim 1 has the potential for significant utility.

Conclusion of Law

We conclude that claims 1, 5, 6, and 20–22 are not directed to patent-ineligible subject matter.

II.–IV. Obviousness-Type Double Patenting

The Examiner finds the ’911 patent recites “recite SEQ ID NO:5 which is WVFGNAMCK (claim 1) which corresponds to the Asn-Ala-Met modified peptide recited in claim 1b. 911 recite pharmaceutical compositions and carriers (claim 1).” Final Act. 18. The Examiner also finds that the ’158 patent recites “SEQ ID NO:5 (claim 1) which is WVFGNAMCK which corresponds to a compound of instant claim 1b. 158 recite pharmaceutical carriers (claim 1).” *Id*. at 19. The Examiner lastly finds that the ’376 patent recites “a pharmaceutical composition comprising SEQ ID NO:9 (WVFGSGLCK) or SEQ ID NO:2 (WVFGHGMCK) and a carrier (claim 1).” *Id*.

Appellant asserts that during prosecution, there were restriction requirements issued in the applications leading to the ’911, ’158, and ’376 patents and therefore the “obviousness-type double patenting rejections advanced in the Action therefore are inconsistent with the positions previously adopted by the Patent Office.” Appeal Br. 29. Appellant also

asserts that "the Action has failed to consider the additional limitations required in each of the cited patent claims; namely, a cytokine." *Id*. at 30.

We consider these rejections together because they share the same issues. We agree with the Examiner's position that no § 121 bar exists. *See* Ans. 28. "We conclude that the protection afforded by section 121 to applications (or patents issued therefrom) filed as a result of a restriction requirement is limited to divisional applications." *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.*, 518 F.3d 1353, 1362 (Fed. Cir. 2008). There is no dispute that this application is not a divisional of the other cited applications.

The Examiner bears the initial burden of presenting a prima facie case of unpatentability. In making an obviousness-type double patenting rejection, the Examiner must show that a claimed invention is "a mere variation of [the patented] invention . . . which would have been obvious to those of ordinary skill in the relevant art. . . [and] there must be some clear evidence to establish why the variation would have been obvious which can properly qualify as 'prior art.'" *In re Kaplan*, 789 F.2d 1574, 1579–80 (Fed. Cir. 1986). Accordingly, in *Kaplan*, the Federal Circuit reversed an obviousness-type double patenting rejection "because there [was] no proper evidence to show that the claim [was] for a mere obvious variation of what [was] claimed in the Kaplan patent relied on to support the rejection." *Id*. at 1581.

The claims of the '911, '158, and '376 patents each require the presence of a chemokine, an element not required by the instant claims. The Examiner provides no teaching to exclude the chemokine from the prior art to satisfy the instant claims or any reason to do so. The Examiner has

provided essentially no evidence or explanation as to why the appealed claims would have been obvious over the claims of the related patents. We, therefore, conclude that the Examiner has not met the burden required to show that the appealed claims would have been obvious in view of or anticipated by the patented claims.

CONCLUSION

In summary:

Claim(s) Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 5, 6, 20–22	101	Eligibility		1, 5, 6, 20–22
1, 20–22		Nonstatutory Double Patenting US 8,703,911		1, 20–22
1, 20–22		Nonstatutory Double Patenting US 9,416,158		1, 20–22
1, 5, 6, 20–22		Nonstatutory Double Patenting US 9,931,376		1, 5, 6, 20–22
Overall Outcome				1, 5, 6, 20–22

REVERSED