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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DAVID SZYMKOWSKI,
MALU TANSEY, and LESLEY PROBERT

Appeal 2019-000427
Application 14/427,279
Technology Center 1600

BEFORE DONALD E. ADAMS, RICHARD M. LEBOVITZ, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

The Examiner rejected the claims under 35 U.S.C. § 102 and under the judicially created doctrine of obviousness-type double patenting. Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject the claims. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[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 INmune Bio, Inc. Appeal Br. 1.

STATEMENT OF THE CASE

Claims 1–3, 7–10, 12, 13, and 18 are pending and stand finally rejected by the Examiner under 35 U.S.C. § 102(a)(1) and under the judicially created doctrine of obviousness type double patenting.

A hearing was held November 5, 2019. A transcript of the hearing will be entered into the record in due course.

Claims 1 and 18 are independent and are reproduced below (indentations and paragraph breaks have been added for clarity):

> 1. A method of treating a human patient with neurological disorder comprising
>
> delivering a therapeutically effective amount of a dominant negative TNF-α inhibitor polypeptide to the brain of the human patient by peripherally administering the dominant negative TNF-α inhibitor polypeptide,
>
> wherein said dominant negative TNF-α inhibitor polypeptide comprises a variant sequence relative to wild-type TNF-α and inhibits soluble TNF-α but does not inhibit signaling by transmembrane TNF-α,
>
> whereby said patient is treated.
>
> 18. A method of inhibiting microglial cell activation in a human patient in need thereof comprising
>
> delivering a therapeutically effective amount of a dominant negative TNF-α inhibitor polypeptide to the brain of the human patient by peripherally administering the dominant negative TNF-α inhibitor polypeptide,
>
> wherein said dominant negative TNF-α inhibitor polypeptide comprises a variant sequence relative to wild-type TNF-α and inhibits soluble TNF-α but does not inhibit signaling by transmembrane TNF-α,
>
> whereby said microglial cell activation is inhibited.

ANTICIPATION BY DESJARLAIS

Claims 1–3, 7–10, 12, 13, and 18 stand rejected under 35 U.S.C. § 102(a)(1) (2013) as anticipated by Desjarlais et al. (WO 2006/113487 A1, published Oct. 26, 2006) ("Desjarlais"). Ans. 3.

Claims 1 and 18 require delivering a dominant negative TNF-α inhibitor ("DN-TNF) to the brain by "peripheral administration." The Specification discloses that "peripheral administration" means administration that is not through the cranium or perispinally, and other than directed administration to the brain. Spec. ¶¶ 6, 91. The Specification discloses examples of peripheral routes, including, but not limited to, "enteral, topical, subcutaneous, intradermal, inhalational, parenteral, intramuscular, mucosal, intra-nasal, oral, vaginal, rectal, intravenous, intraarterial, intracardiac, intraosseal, intrathecal, intraperitoneal, intravesical, and intravitreal routes." Spec. ¶ 6.

The Specification discloses that it was "novel and unexpected finding that certain dominant negative TNF-α proteins (DN-TNF) have effects on the CNS and brain when administered peripherally." Spec. ¶ 6. The Specification discloses that it was found that the DN-TNF proteins cross the blood brain barrier ("BBB") when administered by the peripheral route. Spec. ¶ 21. The Specification states that the invention "allows for the first time a method of treating a neurological disorder following peripheral, as opposed to intracranial, administration of a therapeutic DN-TNF." Spec. ¶ 22.

The Examiner found that Desjarlais anticipates the claimed invention. The Examiner found that Desjarlais describes the claimed DN-TNF. Ans. 3. The Examiner also found that Desjarlais describes treating neurological

disorders as in claim 1 by peripheral administration. *Id.* With respect to claim 18, the Examiner found that microglial activation would be inhibited upon peripheral administration of DN-TNF and thus would be an inherent outcome when the protein is administered. Ans. 3–4.

Appellant contends that one of ordinary skill in the art would not have interpreted Desjarlais to teach peripheral administration of DN-TNF to treat a neurological disorder because "a person of ordinary skill in the art at the time the present application was filed would have understood that the BBB effectively blocks peripherally administered large-molecule therapeutics from traversing into the brain in therapeutically effective amounts." Appeal Br. 8.

The Examiner based the rejection on the following disclosure from Desjarlais:

> FF1.[2]
>
> Thus, administration of an effective amount of the TNF-α variants of the present invention may be used to treat these peripheral nerve injury or demyelinating conditions, as well as Alzheimer[']s disease and Parkinson's disease.

Desjarlais ¶ 173

> FF2.
>
> The administration of the variant *TNF-α* proteins of the present invention, preferably in the form of a sterile aqueous solution, may be done in a variety of ways, including, but not limited to, orally, subcutaneously, intravenously, intranasally, transdermally, intraperitoneally, intramuscularly, intrapulmonary, vaginally, rectally, or intraocularly. In some instances, for example, in the treatment of wounds,

[2] Finding of Fact.

> inflammation, etc., the variant TNF-α protein may be directly applied as a solution, salve, cream or spray.

Desjarlais ¶ 176.

The Examiner did not identify an express teaching of delivering DN-TNF to the brain by peripheral administration to treat the neurological disorders Alzheimer's disease and Parkinson's disease (FF1), but rather relied on the general disclosure of the different routes that DN-TNF can be administered (FF2). The issue in this rejection is whether the skilled worker would have recognized that administering DN-TNF by a peripheral route is effective to treat Alzheimer's disease and Parkinson's disease.

Discussion

McCandless[3]

As evidence that one of ordinary skill in the art would have understood that Desjarlais teaches that peripherally administered DN-TNF would penetration the blood brain barrier and reach the brain to treat a neurological disorder, the Examiner cited McCandless. The Examiner cited McCandless as teaching that the blood brain barrier is disrupted in multiple sclerosis which would permit entry of DN-TNF. Ans. 15. Multiple sclerosis is a neurological disorder. Claim 1 requires treating a neurological disorder.

McCandless teaches:

FF3.

> Multiple sclerosis (MS) is an autoimmune disease of the CNS characterized by disruption of the blood-brain barrier (BBB).

[3] Erin E. McCandless et al., *IL-1R Signaling within the Central Nervous System Regulates CXCL12 Expression at the Blood-Brain Barrier and Disease Severity during Experimental Autoimmune Encephalomyelitis*, 183 J. Immunol. 613–620 (2009).

> This breach in CNS immune privilege allows undeterred trafficking of myelin-specific lymphocytes into the CNS where they induce demyelination.

McCandless 613 (Abstract)

> FF4.
>
> Multiple sclerosis (MS) is believed to be an autoimmune disease in which myelin-specific $CD4^{+}$T cells gain excessive entry to the CNS parenchyma and induce demyelinating disease (1, 2). The increased trafficking of mononuclear cells during MS exacerbations is accompanied by blood-brain barrier (BBB) disruption, as evidenced by the appearance of gadolinium-enhancing lesions on magnetic resonance imaging (3).

McCandless 613 (column 1) (footnotes omitted).

Although both these passages from McCandless describe disruption of the BBB, they do not teach what molecules can enter the brain through the disrupted BBB. Thus, they do not provide persuasive evidence that DN-TNF could enter through the BBB when administered peripherally as required by all the rejected claims.

With respect to entry of the lymphocytes through the BBB, as discussed by Dr. Tansey in the second Tansey declaration ("Tansey 2 Decl.", executed Sept. 26, 2017),[4] McCandless teaches that "the BBB 'compromise' disclosed in McCandless" that permits entry of lymphocytes, "is primarily a dysregulation of the cell trafficking function (mediated in part by chemokine expression) of the BBB." Tansey 2 Decl. ¶ 6. Dr. Tansey's statement is supported by the evidence. McCandless further teaches:

> FF5.
>
> Under normal conditions, CXCL12 is detected on the parenchymal surface of the CNS endothelium, where it serves

[4] Maria de Lourdes G. Tansey, Ph.D., Professor of Physiology at Emory University School of Medicine. Tansey 2 Decl. ¶ 1.

> to restrict the entry of infiltrating leukocytes (6–8). This polarized expression is altered in individuals with CNS autoimmune diseases with loss of perivascular CXCL12 expression and relocation of the chemokine to the luminal side of the microvasculature (7, 8). This **pathologic pattern of CXCL12 expression** is associated with enhanced activation of the CXCL12 receptor CXCR4 on infiltrating leukocytes and is unique to MS and its murine model, experimental autoimmune encephalomyelitis (EAE) (8). **Thus, the altered expression of CXCL12 at the BBB could promote inappropriate leukocyte trafficking and contribute to disease pathogenesis**.

McCandless 613 (column 1) (emphasis added).

Thus, although McCandless teaches a BBB disruption "allows undeterred trafficking of myelin-specific lymphocytes into the CNS" (FF1), this disruption is further explained by McCandless as being related to the "pathologic pattern of CXCL12 expression" (FF5). For this reason, we agree with Appellant that McCandless does not provide evidence that one of ordinary skill in the art would have reason to believe that DN-TNF could cross the BBB in effective amounts, when administered peripherally as required by all the claims, to treat multiple sclerosis, a neurological disorder.

Donahue[5]

The Examiner cited Donahue as evidence that the BBB is "broken down in Alzheimer's disease" and therefore would permit entry of DN-TNF to the brain when administered peripherally. Ans. 16. The following disclosure is relied upon by the Examiner:

[5] John E. Donahue & Conrad E. Johanson, *Apolipoprotein E, Amyloid-ß, and Blood-Brain Barrier Permeability in Alzheimer Disease*, 67 J. Neuropathol. Exp. Neurol. 261–270 (2008).

FF6.

> There is increasing evidence for blood-brain barrier (BBB) compromise in Alzheimer disease (AD).

Donahue 261.

FF7.

> There is growing evidence for BBB compromise in human AD (13–20) particularly in regions surrounded by Aß plaques or involved in CAA [cerebral amyloid angiopathy]. In a recent study of 13 patients who came to autopsy and fulfilled diagnostic criteria for AD, 4 had physiologic evidence of BBB impairment, as determined by CSF-albumin index, although none of these patients had any significant cerebrovascular disease (18). Therefore, CAA is insufficient as the sole explanation for BBB impairment in AD. Another recent study demonstrated perivascular leakage of Aß, complement, and immunoglobulins in human AD brains (20). This enhanced permeability can potentially lead to increased deposition of Aß within AD brains, thereby further worsening the disease (25).

Donahue 262.

Dr. Tansey clarified this disclosure in Donahue by citing Banks[6] as evidence that one of ordinary skill in the art would not have understood Donahue to teach that DN-TNF would have been expected at the time of the invention to cross the BBB. Tansey 2 Decl. ¶¶ 9–10. The following disclosure from Banks is pertinent:

FF8.

> Drugs that must reach deep brain targets as is the case in AD must cross the BBB. However, many drug trials fail because of inadequate trial design with one of the chief flaws being a neglect regarding BBB penetration [129]. The BBB represents

[6] William A. Banks, *Drug delivery to the brain in Alzheimer's disease: Consideration of the blood-brain barrier*, 64 Advanced Drug Delivery Reviews, 629-639 (2012) ("Banks").

> one of the greatest challenges for drug delivery to the CNS and many strategies have been devised to meet that challenge.

Banks 634 (Section 4).

FF9.

> At first it seems obvious that any disruption in the BBB would improve drug delivery to the brain. This has tempted many to propose disrupting the BBB for the purposes of drug delivery, despite the obvious problem that many of the endogenous substances that will then enter the brain from the blood are neurotoxic [130]. . . . Studies in stroke models and with osmotic opening show that the resulting disruption of the BBB is sufficient to allow therapeutic levels of drug to accumulate in the disrupted region [131,132]. However, other studies suggest that the increase in influx rate resulting from most approaches to BBB disruption is insignificant compared to the other dynamics that determine the equilibrium between brain and blood for a solute. . . . **The proposed micropunctate disruptions of the BBB proposed in AD and seen in some animal models may not be sufficient to allow drugs to reach therapeutic levels**. This is because even a disrupted BBB is usually still very restrictive in comparison to peripheral tissue beds. Additionally, the poor diffusion within brain tissue would prevent drug from reaching areas of the brain more than a few hundred microns from the lesion. Recently, Cheng et al. found that **BBB disruptions in animal models of AD and multiple sclerosis were not sufficient to alter small molecule uptake by brain [53]. Thus, for chronic diseases like AD, current pharmacologic methods of BBB disruption do not offer an acceptable cost/benefit ratio for drug delivery**.

Banks 634 (Section 4.1) (emphasis added).

FF10.

> Paradoxically, **disruptions of the BBB could actually retard the brain retention of some drugs**. Even modest disruptions of the BBB are pathologically significant and induce inflammatory responses. Tumor necrosis factor-alpha

> can increase Pgp activity leading to a further reduction of accumulation of Pgp substrates by brain [193–195].

Banks 635 (Section 5.1) (emphasis added).

Banks provides evidence that 1) BBB disruptions would not necessarily be sufficient to allow a molecule, such as DN-TNF, to cross the blood barrier; 2) that BBB disruption was not considered acceptable to deliver drugs (FF9), and 3) might even retard drug delivery (FF10).

Thus, based on the evidence in this record, we agree with Appellant that one of ordinary skill in the art would not have had reasonable basis to believe that DN-TNF would necessarily cross BBB in Alzheimer's disease.

Summary

As discussed in Banks and known in the art, drugs must cross the BBB to treat a neurological condition, such as multiple sclerosis and Alzheimer's disease. However, the BBB is a barrier to the entry of drugs into the brain (FF6; Tansey 2 Decl. ¶ 3). Thus, the broad teaching in Desjarlais that DN-TNF can be administered peripherally to treat disease (FF2) would not have been interpreted by one of ordinary skill in art to mean the treatment of a neurological disorder involving the brain because the BBB is a known obstacle to drug entry.

In those neurological diseases with BBB disruptions, one of ordinary skill in the art also would not interpreted Desjarlais to teach peripheral administration to reach the brain because the evidence of record as a whole teaches that such disruptions were not necessarily sufficient to allow an effective amount of the drug into the brain, and even might retard it (FF5, FF9, FF10; Tansey 2 Decl. ¶¶ 4–10). Anticipation "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 re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (internal citation and quotation marks omitted).

Accordingly, we conclude that, on this record, the Examiner did not provide adequate persuasive evidence to establish that Desjarlais anticipates claims 1–3, 7–10, 12, 13, and 18. The anticipation rejection is reversed.

2. REJECTIONS BASED ON US 7,687,461

Claims 1, 2, 7–10, 12, 13, and 18 stand finally rejected on the ground of non-statutory obviousness-type double patenting as obvious over claims 1–11 of U.S. Patent No. 7,687,461 B2 ("the '461 patent"). Ans. 4.

Representative claim 2 of the '461 patent is reproduced below:

> 2. A method of treating a Tumor Necrosis Factor-α (TNF-α) related disorder comprising administering to a patient in need of said treatment, an effective amount of a composition of a TNF-α protein comprising an amino acid sequence comprising amino acid substitutions R31C, C69V.Y87H, C101A and A145R as compared to the wild type TNF-α sequence of amino acids 1-157 of SEQ ID NO:13, whereby said TNF-α related disorder is treated.

The '461 patent discloses peripheral administration of a TNF protein (col. 20, ll. 48–50; col. 21, ll. 35–37; col. 52, ll. 22–53), but as found for Desjarlais, because the BBB is an obstacle to drug penetrance, one of ordinary skill in the art at the time of the invention would not have interpreted this disclosure to mean that DN-TNF could be administered peripherally to treat a neurological disorder in the brain. Accordingly, the obviousness-type double patenting of claims 1, 2, 7–10, 12, 13, and 18 in view of the '461 patent is reversed.

3. REJECTION BASED ON US 7,687,461 AND TOBINICK

Claims 1–3, 7–10, 12, 13, and 18 stand finally rejected on the ground of non-statutory obviousness-type double patenting as obvious over claims 1–11 of U.S. Patent No. 7,687,461 B2 and further in view of U.S. Patent No. 6,177,077 B1 (issued Jan. 23, 2001) ("Tobinick").

Tobinick teaches that TNF plays a central role in the inflammatory response (col. 1, ll. 61–63). Tobinick also teaches that "TNF has been shown to have a key role in the central nervous system" (col. 2, ll. 25–26). Tobinick further teaches "a need for TNF inhibitors" to treat neurological disorders, that include "multiple sclerosis . . . degenerative disorders of the nervous system, including Alzheimer's disease, Parkinson's disease and Huntington's disease." Tobinick, col. 2, ll. 26–39.

Tobinick further teaches that demyelinating neurological diseases, "the most important being multiple sclerosis" (col. 7, ll. 42–44), can be treated intravenously and subcutaneously with etanercept and infliximab (col. 7, ll. 51–63; col. 11. ll. 34–36). Etanercept is "a recombinant fusion protein consisting of two soluble TNF receptors joined by the Fc fragment of a human IgG1 molecule. Tobinick, col. 2, ll. 14–16. Infliximab is an antibody. *Id.* at 12–13. Thus, unlike the previously cited prior art, Tobinick contains express disclosure that a neurological disorder affecting the brain can be treated by peripheral administration of protein, namely a receptor protein and antibody.

Claim 1 of Tobinick is directed to "inhibiting the action of TNF for treating neurological conditions in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue." Dependent claims 3 and 4 list Alzheimer's disease and Parkinson's disease,

respectively, neurological brain diseases. Thus, claim 1 includes treating inflammation in Alzheimer's disease and Parkinson's disease. Claim 2 recites that the administering "is performed through any of the following routes: subcutaneous, intravenous, intrathecal, intramuscular, intranasal, oral, transepidermal, parenteral, by inhalation, or intracerebroventricular." The list includes peripheral routes. Therefore, Tobinick also claims that a neurological brain disorder can be treated by peripheral administration of a soluble TNF receptor.

Although Tobinick does not disclose peripherally administering the DN-TNF claimed in the '461 patent, the teaching that a soluble receptor protein (claim 1 of Tobinick), a protein fusion, and an antibody can be administered peripherally to treat a disorder in the brain caused by TNF, and specifically multiple sclerosis, provides a reasonable basis to believe that other proteins could cross the BBB, including DN-TNF, making it obvious to administer it intravenously or subcutaneously.

Appellant argues that it was unexpected that DN-TNF could cross the BBB, but Appellant did not address the express disclosure in Tobinick of proteins that are able to traverse it and effectively treat a TNF disorder in the brain. Appeal Br. 15.

Accordingly, the obviousness-type double-patenting rejection of Claims 1–3, 7–10, 12, 13, and 18 over the '461 patent and Tobinick is affirmed.

4. REJECTION BASED ON US 7,244,823

Claims 1, 2, 7–10, 12, 13, and 18 stand finally rejected on the ground of non-statutory double patenting as obvious over claims 1–36 of U.S. Patent No. 7,244,823 B2 ("the '823 patent"). Ans. 5.

Representative claim 1 of the '823 patent is reproduced below:

> 1. A variant Tumor necrosis factor α (TNF-alpha) protein comprising an amino acid sequence that has at least one amino acid substitution in the Large Domain and at least one amino acid substitution in a domain selected from the group consisting of the DE Loop and the Small Domain as compared to the wild type TNF-alpha sequence of amino acids 1–157 of SEQ ID NO:2,
>
> wherein the Large Domain substitution is at a position selected from the group consisting of 21, 30, 31, 32, 33, 35, 65, 66, 67, 111, 112, 115, 140, 143, 144, 145 and 146,
>
> wherein the Small Domain substitution at a position selected from the group consisting of 75 and 97,
>
> wherein the DE Loop substitution at a position selected from the group consisting of 84, 86, 87 and 91, and wherein said variant TNF-alpha protein is capable of interacting with the wild type TNF-alpha to form mixed trimers having at least a 50% decrease in receptor activation as compared to a homotrimer of wild-type TNF-alpha proteins as determined by a caspase assay.

The '823 patent discloses peripheral administration of a TNF protein (col. 17, ll. 26–28; col. 18, ll. 14–16), but as found for Desjarlais, because the BBB is an obstacle to drug penetrance, one of ordinary skill in the art at the time of the invention would not have interpreted this disclosure to mean that DN-TNF could be administered peripherally to treat a neurological disorder in the brain.

Accordingly, the obviousness-type double patenting of claims 1, 2, 7–10, 12, 13, and 18 in view of the '461 patent is reversed.

5. REJECTION BASED ON US 7,244,823 AND TOBINICK

Claims 1–3, 7–10, 12, 13, and 18 stand finally rejected on the ground of non-statutory obviousness-type double patenting as obvious over claims 1–36 of U.S. Patent No. 7,244,823 B2 and further in view of Tobinick. Ans. 6.

This rejection over the '823 patent and Tobinick is affirmed for the same reasons as the rejection over the '461 patent and Tobinick (*supra* at 12–13).

6. REJECTION BASED ON US 7,662,367

Claims 1–3, 7–10, 12, 13, and 18 stand finally rejected on the ground of non-statutory double patenting as obvious over claims 1–6 of U.S. Patent No. 7,662,367 B2 ("the '367 patent"). Ans. 7.

Representative claim 1 of the '367 patent is reproduced below:

> 1. A pharmaceutical composition comprising: a variant TNF-α protein that inhibits the activity of soluble TNF-α while substantially maintaining the activity of transmembrane TNF-α comprising an amino acid sequence corresponding to wild type amino acids 1-157 of Tumor Necrosis Factor Alpha (TNFα) (SEQ ID NO: 1) that has at least one amino acid substitution in the Large Domain and at least one amino acid substitution in a domain selected from the group consisting of the DE Loop and the Small Domain, wherein the Large Domain substitution is at a position selected from the group consisting of 21, 30, 31, 32, 33, 35, 65, 66, 67, 111, 112, 115, 140, 143, 144, 145 and 146, wherein the Small Domain substitution at a position selected from the group consisting of 75 and 97, wherein the DE Loop substitution at a position selected from the group consisting of

> 84, 87 and 91; a buffer; and, a tonicity agent; wherein said composition has a pH from approximately 5.0 to 8.0

The '367 patent discloses peripheral administration of a TNF protein (col. 7, ll. 18–19; col. 8, ll. 2–4; col. 38, ll. 39–47; col. 39, ll. 33–38; col. 41, ll. 5–40), but as found for Desjarlais, because the BBB is an obstacle to drug penetrance, one of ordinary skill in the art at the time of the invention would not have interpreted this disclosure to mean that DN-TNF could be administered peripherally to treat a neurological disorder in the brain.

Accordingly, the obviousness-type double patenting of claims 1–3, 7–10, 12, 13, and 18 in view of the '367 patent is reversed.

7. REJECTION BASED ON US 7,446,174

Claims 1–3, 7–10, 12, 13, and 18 stand finally rejected on the ground of non-statutory obviousness-type double patenting obvious over claims 1–20 of U.S. Patent No. 7,446,174 B2 ("the '174 patent"). Ans. 7.

Representative claim 1 of the '174 patent is reproduced below:

> 1. A method of selectively inhibiting the activity of wild-type soluble Tumor necrosis factor-α (TNF-α) in a human comprising administering to said human a molecule that inhibits the activity of soluble TNF-α substantially maintaining the activity of transmembrane TNF-α, wherein said molecule is a variant TNF-α as compared to human wild-type TNF-α (SEQ ID NO: 12), wherein said TNF-α variant comprises the amino acid modifications Y87H and A145R or I97T and A145R.

The '174 patent discloses peripheral administration of a TNF protein (col. 7, ll. 44–45; col. 9, ll. 2–4; col. 9, ll. 54–56; col. 40, ll. 8–33; col. 41, ll. 20–25), but as found for Desjarlais, because of the BBB, one of ordinary skill in the art at the time of the invention would not have interpreted this

disclosure to mean that TNF could be administered peripherally to treat a neurological disorder of the brain.

Accordingly, for the same reasons the anticipation rejection based on Desjarlais is reversed, the obviousness-type double patenting rejection of claim 1–3, 7–10, 12, 13, and 18 over the '174 patent is reversed.

8. REJECTION BASED ON US 7,642,340 AND TOBINCK

Claims 1–3, 7–10, 12, 13, and 18 stand finally rejected on the ground of non-statutory obviousness-type double patenting as obvious over claims 1–5 of U.S. Patent No. 7,642,340 B2 ("the '340 patent) and further in view of Tobinick.

Representative claim 1 of the '340 patent is reproduced below:

> 1. A composition comprising a TNF-α variant monomer, as compared to SEQ ID NO:3, said variant monomer comprising a covalently attached polymer at a first amino acid position, wherein said polymer is attached at a position selected from the group consisting of 21, 23, 31, 45, 88, 89, 111, 128 and 140, wherein said variant monomer maintains the ability to exchange and coassemble with endogenous wild-type TNF-α proteins to form inactive heterotrimers, and wherein said variant has amino acid substitutions comprising R31C, C69V and C101 A.

The rejection of claims 1–3, 7–10, 12, 13, and 18 in view of the '340 patent and Tobinick is affirmed for the same reasons as the rejection over the '461 patent and Tobinick (*supra* at 12–13).

.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–3, 7–10, 12, 13, 18	102	Desjarlais		1–3, 7–10, 12, 13, 18
1, 2, 7–10, 12, 13, 18		Obviousness-type double-patenting, ’461 patent		1, 2, 7–10, 12, 13, 18
1–3, 7–10, 12, 13, 18		Obviousness-type double-patenting, ’461 patent, Tobinick	1–3, 7–10, 12, 13, 18	
1, 2, 7–10, 12, 13, 18		Obviousness-type double-patenting, ’823 patent		1, 2, 7–10, 12, 13, 18
1–3, 7–10, 12, 13, 18		Obviousness-type double-patenting, ’823 patent, Tobinick	1–3, 7–10, 12, 13, 18	
1–3, 7–10, 12, 13, 18		Obviousness-type double-patenting, ’367 patent		1–3, 7–10, 12, 13, 18
1–3, 7–10, 12, 13, 18		Obviousness-type double-patenting, ’174 patent		1–3, 7–10, 12, 13, 18
1–3, 7–10, 12, 13, 18		Obviousness-type double-patenting, ’340 patent, Tobinick	1–3, 7–10, 12, 13, 18	
Overall Outcome			1–3, 7–10, 12, 13, 18	

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED