UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/713,218	02/28/2007	Robert M. Sapolsky	STAN-462 (S05-322)	3367

77974 7590 11/01/2016
Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
1900 University Avenue
Suite 200
East Palo Alto, CA 94303

EXAMINER
MONTANARI, DAVID A

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
11/01/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ROBERT M. SAPOLSKY, NATHAN C. MANLEY, SHEILA BROOKE, KLAUS M. DINKEL, CAROLINA D. MUNHOZ, ANGELA L. RIEPEL, and ANDREA C. NICHOLAS[1]

Appeal 2014-001993
Application 11/713,218
Technology Center 1600

Before FRANCISCO C. PRATS, JOHN G. NEW, and TAWEN CHANG, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134(a) involves claims to methods of delivering therapeutic proteins to the central nervous systems of mammals. The Examiner rejected the claims for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

---

[1] Appellants state that the "real parties in interest are the Board of Trustees of the Leland Stanford Junior University, by virtue of the assignments recorded reel and frame 020412/0626." Br. 1.

STATEMENT OF THE CASE

The sole rejection before us for review is the Examiner's rejection of claims 13–15, 17, 20–24, and 26–33 under 35 U.S.C. § 103(a) as being unpatentable over Fathman,[2] Yebenes,[3] Beerens,[4] Falcone,[5] and Sagar.[6] Non-Final Act. 3–7.[7,8]

Claims 13, 17, and 21, the independent claims on appeal, illustrate the appealed subject matter and read as follows (Br. 12–13):

---

[2] US 2003/0091548 A1 (published May 15, 2003).

[3] Justo Garcia de Yebenes and Maria Angeles Mena, *Neurotrophic Factors in Neurodegenerative Disorders: Model of Parkinson's Disease*, 2 Neurotoxicity Res. 115–137 (2000) ("Yebenes").

[4] A.M.J. Beerens et al., *Protein Transduction Domains and their Utility in Gene Therapy*, 3 Current Gene Therapy 17–34 (2003) ("Beerens").

[5] Marika Falcone et al., *A Critical Role for IL-4 in Regulating Disease Severity in Experimental Allergic Encephalomyelitis as Demonstrated in IL-4-Deficient C57BL/6 Mice and BALB/c Mice*, 160 J. Immunology 4822–4830 (1998) ("Falcone").

[6] Divya Sagar et al., *Mechanisms of Dendritic Cell Trafficking Across the Blood-brain Barrier*, J. Neuroimmune. Pharmacol., pp. 1–21, published online Aug. 6, 2011 ("Sagar"). The Sagar article does not include page numbers; accordingly we cite to the first page as if it were page 1, and cite to the remaining pages as if numbered consecutively.

[7] Non-Final Rejection entered July 13, 2012.

[8] The Examiner also entered an objection to claims 15, 22–24, 26–29, 32, and 33, which Appellants contend is improper. Non-Final Act. 2–3; Br. 3–4. We will not review that objection. *See* MPEP § 706.01 ("The practical difference between a rejection and an objection is that a rejection, involving the merits of the claim, is subject to review by the Patent Trial and Appeal Board, while an objection, if persisted, may be reviewed only by way of petition to the Director of the USPTO.").

13. A method of delivering a neurotrophin to a central nervous system (CNS) of a mammal, said method comprising:

administering into the bloodstream of said mammal autologous or allogeneic dendritic cells, which dendritic cells have been genetically engineered *ex vivo* by introduction of a vector comprising a gene expression cassette that provides genetic sequences required for expression of said neurotrophin;

wherein said dendritic cells localize to an inflammatory lesion of said CNS, cross a blood brain barrier, and secrete said neurotrophin within the CNS.

17. A method of delivering a therapeutic protein comprising a protein translocation domain (PTD) to a central nervous system (CNS) of a mammal, said method comprising:

administering into the bloodstream of said mammal autologous or allogeneic dendritic cells, which dendritic cells have been genetically engineered *ex vivo* by introduction of a vector comprising a gene expression cassette that provides genetic sequences required for expression of said therapeutic protein comprising a protein translocation domain;

wherein said dendritic cells localize to an inflammatory lesion of said CNS and secrete said therapeutic protein comprising a translocation domain.

21. A method of delivering a CNS therapeutic protein to a central nervous system (CNS) of a mammal, said method comprising:

administering into the bloodstream of said mammal autologous or allogeneic immature CD11c expressing dendritic cells, which dendritic cells have been genetically engineered *ex vivo* by introduction of a vector comprising a gene expression cassette that provides genetic sequences required for expression of a CNS therapeutic protein of interest;

wherein said immature CD11c expressing dendritic cells localize to the region of an inflammatory lesion in the CNS, cross a blood brain barrier, and thereupon secrete said CNS therapeutic protein within the CNS.

OBVIOUSNESS

The Examiner's Position

The Examiner cited Fathman as teaching, as required by the rejected claims, the use of dendritic cells as genetically engineered vehicles for delivering therapeutic proteins, such as interleukin 4 (IL-4), to the nervous system of a mammal. Non-Final Act. 3–6. The Examiner cited Falcone as evidence that "the IL-4 administered by [Fathman] was known at the time of filing to be a CNS therapeutic protein." *Id.* at 5. The Examiner cited Sagar as evidence that "dendritic cells have the inherent capability of crossing the BBB [blood brain barrier] of the CNS with ease and that genetically modified dendritic cells localized to the CNS with respect to inflammation (pg. 86 col. 1 parag. 2)." *Id.*

The Examiner conceded that Fathman differs from the rejected claims in that Fathman "does not teach that the therapeutic proteins can be a neurotrophin, BDNF [brain-derived neurotrophic factor,] or block neuronal apoptosis and [also does not teach] modifying a therapeutic protein to have a protein translocation domain (PTD)." *Id.*

To address the first asserted difference between Fathman and the rejected claims, the Examiner cited Yebenes as evidence that it was known in the art that a neurotrophin, such as BDNF, "would be an obvious therapeutic protein involved in blocking neuronal apoptosis." *Id.* at 6.

To address the second asserted difference between Fathman and the rejected claims, the Examiner cited Beerens as teaching that PTDs were known to be useful "when wanting to ferry . . . much larger molecules into cells independent of classical endocytosis (pg. 18 lines 1-3)," and were known also to be "powerful tools for gene therapy, since incorporating a

PTD into a therapeutic gene can enable the spread of the therapeutic gene into non-transfected cells and thus increase the therapeutic effect (pg. 18 parag. 3)." *Id.*

Based on the references' teachings, the Examiner concluded that an ordinary artisan would have considered it obvious to modify Fathman's teachings "regarding treatment of CNS inflammatory lesions with genetically modified dendritic cells expressing a therapeutic protein such as IL-4[,] with the teachings of [Yebenes] regarding the therapeutic uses of neurotrophic proteins such as BDNF and GDNF to promote neuronal cell survival and prevent neuronal cell apoptosis in a CNS lesion." Non-Final Act. 6.

The Examiner reasoned that an ordinary artisan would have been motivated to substitute Yebenes's neurotrophins for Fathman's IL-4 because "it was known in the art that dendritic cells can serve as vehicles for therapeutic transgenes that inherently home to sites of inflammation and injury and that therapeutic proteins such as neurotrophins exhibit a therapeutic effect on CNS inflammatory lesions." *Id.* The Examiner reasoned that Beerens would have provided additional motivation to practice the claimed invention "in teaching that PTDs are powerful tools to increase the therapeutic effect of therapeutic proteins." *Id.*

The Examiner reasoned that an ordinary artisan would have had a reasonable expectation of success that a PTD on a therapeutic protein, "such as a neurotrophin, which functions intra-cellularly, as taught by [Fathman] and [Yebenes], would increase the therapeutic effect of the protein at the CNS inflammatory lesion since it was known in the art that PTDs increase therapeutic efficacy." *Id.* at 7. Further, the Examiner reasoned, an ordinary

artisan would have had a reasonable expectation of success that "a therapeutic protein such as a neurotrophin as taught by [Yebenes] would function as a therapeutic in the CNS since [Yebenes] teaches that neurotrophins enhance neuronal survival and reduce apoptosis in neuronal cells." *Id.*

Analysis

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

As to the presentation of separate arguments regarding individual claims subject to a single ground of rejection, 37 C.F.R. § 41.37(c)(1)(iv) explains as follows:

> Under each heading identifying the ground of rejection being contested, any claim(s) argued separately or as a subgroup shall be argued under a separate subheading that identifies the claim(s) by number. A statement which merely points out what a claim recites will not be considered an argument for separate patentability of the claim.

Appellants do not present their arguments under the separate subheadings required by § 41.37(c)(1)(iv). Appellants, nonetheless, present argument as to four separate groups. Br. 3. We select claims 13, 17, 21, and 33 as representative of the groups identified by Appellants.[9] 37 C.F.R.

---

[9] Appellants identify claim 23 as part of Group IV. Br. 3. Claim 23 does not, however, recite the step of freezing and storing the dendritic cells prior

§ 41.37(c)(1)(iv).

Appellants' arguments do not persuade us that a preponderance of the evidence fails to support the Examiner's prima facie case of obviousness as to those representative claims.

We begin our analysis with claims 21 and 33. Claim 21 recites a method of delivering a central nervous system (CNS) therapeutic protein to the central nervous system (CNS) of a mammal. Br. 12.

The sole positive process step required by claim 21 is administering, into the bloodstream of the mammal, autologous or allogeneic immature CD11c-expressing dendritic cells. *Id.* Claim 21 requires the administered cells to have been genetically engineered *ex vivo* by introduction of a vector comprising a gene expression cassette that provides genetic sequences for expression of a CNS therapeutic protein of interest. Br. 12.

Claim 21 also requires the administered to cells localize to the region of an inflammatory lesion in the CNS, cross a blood brain barrier (BBB), and thereupon secrete said CNS therapeutic protein within the CNS. *Id.* at 13.

Claim 33 recites "[t]he method according to Claim 21, further comprising freezing and storing said dendritic cells prior to therapeutic use." *Id.*

Turning to the cited references, Fathman discloses a method of treating autoimmune disorders in patients by delivering "a suppressive agent to the site of disease. Delivery is accomplished by introducing an expression

---

to therapeutic use, the limitation asserted as common to all claims of Group IV. Rather, claim 33, which we designate as representative, includes that feature. Br. 13.

vector encoding the suppressive agent into cells targeted for such sites, and administering the genetically modified cells to the patient." Fathman ¶ 4.

Fathman discloses that autoimmune disorders treatable by its methods include CNS-specific demyelinating diseases, such as multiple sclerosis (MS) and experimental autoimmune encephalitis (EAE). *Id.* ¶¶ 11, 29, 42.

As the Examiner found, and as required by Appellants' claim 21, Fathman discloses that genetically modified immature CD11c-expressing dendritic cells may be used to deliver the suppressive agent to the disease site. *See id.* ¶¶ 22–26.

As required by the sole method step positively recited in claim 21, Fathman discloses that the "genetically modified cells may be used for the treatment of disease in a recipient. Autologous cells or allogeneic cells may be used. The cells may be administered in any physiologically acceptable medium, normally intravascularly . . . ." *Id.* ¶ 44.

As required by claim 21, the administered cells localize to the site of the lesion in the CNS, and as required by claim 33, the administered cells may be frozen and stored before use:

> The cells may be frozen at liquid nitrogen temperatures and stored for long periods of time, being capable of use on thawing. . . . Once thawed, the cells may be expanded by use of growth factors, and the like. The cells localize at the site of lesions, where there is increased inflammation related to the relevant autoantigen. . . . [F]or demyelinating diseases lesion sites are primarily in the central nervous system.

Fathman ¶ 44.

As to claim 21's requirement for the delivered protein to be a CNS therapeutic protein, as the Examiner found, Fathman discloses that autoimmune suppressive agents "of particular interest include IL-4

[interleukin 4]." *Id.* ¶ 4; *see also id.* ¶ 14. Although Fathman does not expressly state that IL-4 is a CNS therapeutic protein, as the Examiner found, Falcone discloses that IL-4 plays a critical role in modulating the severity of EAE, which is an animal model of MS. *See* Falcone 4822.

As to claim 21's requirement for the cells to cross a blood brain barrier (BBB), we acknowledge that Fathman does not state expressly that, when its dendritic cells localize to the site of CNS inflammation, they also cross the BBB. As the Examiner found, however, Sagar discloses that dendritic cells, including immature dendritic cells, are inherently capable of crossing the BBB:

> Under inflammatory conditions of the CNS such as in MS or HIVE [HIV encephalopathy], DCs [dendritic cells] along with other circulating lymphocytes and monocytes/macrophages readily gain access to the CNS, resulting in edema, further inflammation, or demyelination. . . . In steady-state conditions, DCs are found in low numbers in the meninges, choroid plexus, and CSF . . ., possibly because the BBB limits penetration of immune cells into the brain parenchyma.

Sagar 3.

In sum, based on the discussed teachings, we are persuaded that an ordinary artisan would have had adequate reason to administer genetically modified immature CD11c-expressing dendritic cells, including previously frozen and stored cells, in order to deliver IL-4 to the CNS for the treatment of EAE or MS. That is, Fathman, particularly when viewed in light of Falcone, suggests performing processes having all of the steps and features required by Appellants' claims 21 and 33, and provides a reasonable expectation of therapeutic success when performing those processes. As

evidenced by Sagar, the administered dendritic cells would inherently localize to the lesion site, and cross the BBB, as claim 21 requires. Accordingly, given the cited references' teachings, we agree with the Examiner that the methods recited in claims 21 and 33 would have been obvious to an ordinary artisan.

Appellants' arguments do not persuade us to the contrary. Appellants contend that the claimed invention is "based on the unexpected finding by Appellants that dendritic cells that have been cultured and genetically modified ex vivo will localize to sites of injury and effectively cross the BBB, so that a therapeutic protein can be delivered to the region of the CNS injury." Br. 5. Appellants contend also that "the benefits of cryopreservation [as recited in claim 33] on ex vivo generation of CNS homing cells provides an unexpected benefit captured in the methods of the invention." *Id.* Appellants direct us to Exhibit A (Manley)[10] as evidence of the efficacy of the claimed invention. *Id.*

Appellants do not, however, direct us to any specific persuasive evidence, in the Specification or elsewhere in the record, in comparative form or otherwise, supporting the assertions in the Appeal Brief that dendritic cells' localizing to a CNS injury site and crossing the BBB were unexpected, or that prior cryopreservation of the cells unexpectedly influenced those properties in a positive fashion. It is well settled that attorney argument is not an adequate substitute for that type of evidence. *See In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

---

[10] Nathan C. Manley et al., *Characterization of monocyte chemoattractant protein-l expression following a kainate model of status epilepticus*, 1182 Brain Res. 138–143 (2007) ("Manley").

Contrary to Appellants' assertions of unexpectedness, moreover, Fathman expressly discloses that its engineered cells localize to the site of lesions, which, "for demyelinating diseases . . . are primarily in the central nervous system." Fathman ¶ 44; *see also id.* ¶ 53 ("Recent data suggest that autologous dendritic cells (DCs) also can be transduced and home to sites of inflammation."). Accordingly, as to the capacity of cultured dendritic cells to localize to the site of a CNS lesion, Appellants do not persuade us that they have advanced evidence of unexpectedness sufficient to overcome the Examiner's prima facie case of obviousness.

As to the allegedly unexpected property of cultured dendritic cells crossing the BBB, as noted above, and as the Examiner found, Sagar discloses that property is inherent in both immature and mature dendritic cells. Sagar 3–5. That Sagar, as Appellants argue (Br. 4, 6 n.1), is not prior art to the claimed invention does not negate the fact that dendritic cells inherently possess the BBB-crossing property.

As the Federal Circuit has explained, "[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991); *see also In re Woodruff*, 919 F.2d 1575, 1577–78 (Fed. Cir. 1990) (obviousness rejection affirmed where using claimed elements in the manner suggested by the prior art necessarily resulted in claim-recited effect). Thus, because Fathman, particularly viewed alongside Falcone, suggests performing processes that include all of the method steps required by claims 21 and 33, the claimed processes would have been prima facie obvious to an ordinary artisan, even if it were true that dendritic cells' BBB-crossing capacity was unknown at the time of Appellants' invention.

Indeed, because the Examiner has advanced evidence sufficient to suggest that the claimed functions of localizing to a CNS lesion and crossing the BBB were inherent results of performing the process of administering dendritic cells taught in Fathman, the Examiner has shifted to Appellants the burden of showing that those results would not have occurred inherently when practicing Fathman's process:

> [W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

In re Best, 562 F.2d 1252, 1254–55 (CCPA 1977) (quoting *In re Swinehart*, 439 F.2d 210, 212–13 (CCPA 1971)).

In the instant case, Appellants do not persuade us that they have met that burden. Nor are we persuaded that Appellants have shown that an ordinary artisan lacked motivation or a reasonable expectation of success in administering dendritic cells as taught by Fathman.

To those ends, Appellants advance Exhibits B (Creusot),[11] C (Tavaré),[12] and D (Sallusto)[13] to show that an ordinary artisan would have

---

[11] Rémi J. Creusot et al., *Tissue-targeted therapy of autoimmune diabetes using dendritic cells transduced to express IL-4 in NOD mice*, 127 Clin. Immunol. 176–187 (2008) ("Creusot").

[12] Richard Tavaré et al., *Monitoring of In Vivo Function of Superparamagnetic Iron Oxide Labelled Murine Dendritic Cells during Anti-Tumour Vaccination*, 6 PLoS ONE e19662 (2011) ("Tavaré").

[13] Federica Sallusto et al., *Rapid and coordinated switch in chemokine receptor expression during dendritic cell maturation*, 28 Eur. J. Immunol. 2760–2769 (1998) ("Sallusto").

expected dendritic cells to migrate to the lymph nodes, rather than a CNS lesion, as taught in Fathman. Br. 7.

We first note that both Creusot (published in 2008) and Tavaré (published in 2011) were published after Appellants' February 28, 2007 filing date (*see* Br. 1). Neither reference, therefore, is prior art to the claimed invention. Appellants, moreover, do not direct us to any specific disclosures in either Creusot or Tavaré that investigate or discuss the behavior of dendritic cells in response to CNS inflammation or a CNS lesion of the type exhibited in EAE or MS, the demyelinating disorders described in Fathman. Accordingly, Appellants do not persuade us that, at the time of Appellants' invention, either Creusot or Tavaré would have undermined Fathman's teachings, discussed above, that genetically modified dendritic cells migrate to the site of a CNS lesion when administered to treat EAE or MS.

Similarly, Appellants do not direct us to any disclosures in Sallusto discussing specifically the behavior of dendritic cells in response to CNS inflammation or a CNS lesion of the type exhibited by the disorders described in Fathman. Indeed, while Sallusto does teach that dendritic cells ultimately migrate to lymph nodes, Sallusto also discloses that, initially, dendritic cells migrate to the site of inflammation. *See* Sallusto Abstract ("Dendritic cells (DC) migrate into inflamed peripheral tissues where they capture antigens and, following maturation, to lymph nodes where they stimulate T cells."). Sallusto, thus, actually supports Fathman's teaching that genetically modified immature dendritic cells will migrate to a CNS lesion under inflammatory conditions.

We acknowledge, but are not persuaded by, Appellants' contentions regarding the three cited clinical trials. Br. 7–8 (citing clinical trials NCT01171469, NCT01235845, and NCT00639639). We first note that Appellants do not direct us to the documents in the record supporting the arguments made. *See id.* Thus, it is unclear on this record that any of the cited disclosures is prior art to the rejected claims, such that the cited disclosures may have undermined an ordinary artisan's view of the discussed teachings in Fathman. The absence from the record of the documents also prevents us, and the Examiner, from undertaking an independent review. Moreover, Appellants do not explain specifically why the expectation that dendritic cells would home to lymph nodes when treating cancer tumors demonstrates that an ordinary artisan lacked an expectation that, in different disorders (EAE and MS related inflammation), an ordinary artisan would have doubted that dendritic cells would localize to the site of inflammation as taught by Fathman, and supported by Sallusto and Sagar, as discussed above.

We acknowledge, but are not persuaded by, Appellants' contentions that "[m]ethods for ex vivo culture that were published in the art at the time of filing produced a default state of mature activation of dendritic cells - a state that is incompatible with migration to a CNS lesion." Br. 8; *see also id.* at 9 ("[T]he prior art at <u>the time of filing</u> does not teach one of skill in the art that dendritic cells, particularly immature dendritic cells, will localize to an inflammatory lesion of the CNS.").

We first note that representative claim 21 does not expressly require the dendritic cells to be cultured in any particular manner. Thus, to the extent Appellants seeks to distinguish claim 21 from the cited prior art on

the basis of culturing conditions, Appellants' arguments are not based on limitations present in the claims. While claim 33 requires the cells to be frozen and stored before use, Fathman discloses performing that step, as discussed above.

Moreover, contrary to Appellants' assertion, Fathman discloses that genetically modified dendritic cells, which as required by claim 21 may be immature (*see* Fathman ¶ 25), are useful in its methods, and states expressly that its modified cells will localize to a CNS lesion in a demyelinating disorder such as EAE or MS. *Id.* ¶ 44. For the reasons discussed above, the evidence advanced by Appellants does not persuade us that an ordinary artisan lacked motivation for performing Fathman's process, or a reasonable expectation that doing so would produce a useful therapeutic result.

In sum, Appellants' arguments, for the reasons discussed, do not persuade us that the evidence of record fails to support the Examiner's prima facie case of obviousness as to representative claims 21 and 33. Because, for the reasons discussed, Appellants' evidence as to secondary considerations of nonobviousness is insufficient to outweigh the evidence of prima facie obviousness, we affirm the Examiner's rejection of claims 21 and 33 under § 103(a). Because they were argued in the same groupings (Br. 3), claims 20, 22–24, 27, and 29–32 fall with claims 21 and 33. 37 C.F.R. § 41.37(c)(1)(iv).

Turning to representative claim 13, the process recited in that claim is similar to that recited in claim 21, discussed above, except that claim 13 does not limit the maturity of the dendritic cells, but does require the protein delivered by the dendritic cells to be a neurotrophin. Br. 12. As noted above, the Examiner cited Yebenes as evidence that it would have been

obvious to deliver a neurotrophin using Fathman's methods, because neurotrophins would have been expected to enhance neuronal survival and reduce apoptosis in neuronal cells. Non-Final Act. 6.

Appellants do not dispute the Examiner's characterization of Yebenes, nor do Appellants contend that an ordinary artisan would have lacked motivation to make the modification of Fathman's process posited by the Examiner. Rather, Appellants contend, "nothing in Yebenes would lead one of skill in the art to believe that an *ex vivo* genetically modified dendritic cell would localize to an inflammatory lesion of the CNS, or to cross the blood brain barrier, thereby enabling the delivery of therapeutic proteins to the CNS." Br. 10.

For the reasons discussed above, we do not find these arguments persuasive. Accordingly, we affirm the Examiner's obviousness rejection of representative claim 13. Because they were argued in the same claim grouping, claims 14 and 15 fall with claim 13. 37 C.F.R. § 41.37(c)(1)(iv).

Turning to representative claim 17, the process recited in that claim is similar to that recited in claims 13 and 21, discussed above, except that claim 17 does not limit the maturity of the dendritic cells, or require the cells to cross the BBB. Br. 12. Claim 17 does, however, require the delivered protein to include a protein translocation domain (PTD). *Id.* As noted above, the Examiner cited Beerens as evidence that it would have been obvious to include a PTD in the protein delivered by Fathman's methods, because a PTD would have been expected to improve the therapeutic efficacy of the delivered protein. Non-Final Act. 6.

Appellants "do not dispute that the use of protein transduction domains (PTDs) to facilitate delivery of PTD-fused proteins across cell

membranes into target cells was generally known in the art," nor do Appellants contend that an ordinary artisan would have lacked motivation to make the modification of Fathman's process posited by the Examiner. Br. 9–10. Rather, Appellants contend, an ordinary artisan lacked a reasonable expectation of success because

> PTDs, such as the HIV-derived Tat domain, can readily diffuse across cell membranes and also typically contain a nuclear localization sequence (NLS) to promote homing to the cell nucleus. Both of these factors would be expected to interfere with proper secretion of a PTD fusion protein following its translation by a carrier cell, and this is why the vast majority of existing PTD literature involves the use of purified PTD fusion proteins from bacteria.

Id. at 10. Appellants do not, however, direct us to any specific persuasive evidence supporting these factual assertions. We, therefore, do not find these assertions persuasive. *See In re Geisler*, 116 F.3d at 1471 (argument by counsel not an adequate substitute for evidence).

We acknowledge that the Beerens's disclosure might be viewed as somewhat prophetic:

> PTDs, although at this moment mainly used for the chemical or bacterial production of membrane permeable proteins can become powerful tools for gene therapy. By incorporating a PTD in the therapeutic gene product, the protein produced in the transfected cell might be enabled to spread to non-transfected cells, thereby creating an increased therapeutic effect.

Beerens 18.

It is well settled, however, that "[o]bviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853

F.2d 894, 903–04 (Fed. Cir. 1988); *accord, In re Kubin*, 561 F.3d 1351, 1359–61 (Fed. Cir. 2009). In the instant case, Appellants do not direct us to specific persuasive evidence suggesting that an ordinary artisan lacked a reasonable expectation that including a PTD in Fathman's delivered protein would provide the increased therapeutic effect described in Beerens.

We acknowledge, but are not persuaded by, Appellants' contention that, in contrast to the results seen in Exhibit A (Manley), Fathman's methods were directed to delivery of proteins with an extracellular effect, and, therefore, "one of skill in the art would not be motivated to utilize sequences encoding a PTD fusion protein as there is no benefit to intracellular activity in the prior art methods." Br. 10.

As noted above as to claim 13, and undisputed by Appellants, an ordinary artisan would have been motivated to use a neurotrophin as the delivered protein in Fathman's methods. As the Examiner found (Non-Final Act. 7; Ans. 24), and Appellants do not dispute, neurotrophins were known to act intracellularly as well as extracellularly. Accordingly, Appellants do not persuade us that an ordinary artisan lacked a reason to include a PTD domain when using neurotrophin as Fathman's delivered therapeutic protein. To the contrary, as the Supreme Court explained in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007), "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."

In sum, for the reasons discussed, Appellants' arguments do not persuade us that the evidence of record fails to support the Examiner's prima facie case of obviousness as to representative claim 17. Because, for the

reasons discussed, Appellants' evidence as to secondary considerations of nonobviousness is insufficient to outweigh the evidence of prima facie obviousness, we affirm the Examiner's rejection of claim 17 under § 103(a). Because they were argued in the same grouping (Br. 3), claims 26 and 28 fall with claim 17. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

For the reasons discussed, we affirm the Examiner's rejection of claims 13–15, 17, 20–24, and 26–33 under 35 U.S.C. § 103(a) for obviousness over Fathman, Yebenes, Beerens, Falcone, and Sagar.

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

AFFIRMED