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

We AFFIRM.

STATEMENT OF THE CASE

According to the Specification, “MMPs [matrix metallo-proteases] have been implicated in recovery in chronic brain injury, and inhibition of MMP activity has been shown to abrogate migration of neurogenic cells from the SVZ [subventricular zone] into damaged tissues and to retard neurovascular remodeling.” Spec. ¶ 43 (citing Zhao et al., Neurovascular

1 Appellants identify as real parties in interest, SanBio Inc. and The University of South Florida. App. Br. 2.
proteases in brain injury, hemorrhage and remodeling after stroke, Stroke Vol. 38, 748–752 (2007); and Zhao et al., Role of matrix metalloproteinases in delayed cortical responses after stroke, Nat Med. Vol. 12, 441–445 (2006). “MMPs may thus play a role in facilitating host cell migration towards injured brain areas as part of the process by which SB623 cells provide functional recovery from TBI.” Id.

According to the Specification, “the inventors have discovered that transplantation of SB623 cells remodeled the traumatically injured brain by creating a biobridge between the SVZ and the peri-injured cortex. This method of cell therapy can now be used to create similar biobridges between neurogenic and non-neurogenic sites, to facilitate injury-specific migration of cells across tissues that might otherwise pose barriers to cell motility.” Id. ¶ 44. In one experiment, “the biobridge formed by endogenous cells migrating from the SVZ to the site of [traumatic brain injury (TBI)] was isolated by laser capture microdissection.” Id. ¶ 42. “Zymographic assays of [] laser-captured biobridges from animals subjected to TBI revealed two-fold and nine-fold upregulation of matrix metalloproteinase 9 (MMP-9) expression/activity in animals that received SB623 cell transplants, compared to vehicle infused animals or sham-operated animals, at one month and three months post-transplantation, respectively.” Id.

Claim 1, the sole independent claim before us, recites:

1. A method for treating brain injury by inducing migration of endogenous neurogenic cells to a site of brain injury, the method comprising administering to the brain of a subject a therapeutically effective amount of matrix metalloprotease-9 (MMP-9).

**FINDINGS OF FACT**

**FF1.** According to Lee, “neurogenesis after brain injury is a functionally meaningful response.” Lee, 3491 (first para.). “Under normal conditions, the SVZ is an active area of persistent adult neurogenesis in the rodent brain, and neuroblasts migrate along the sagittal axis of the rostral migratory stream to populate the olfactory bulb. However, after stroke and other forms of brain injury, neuroblasts swerve away from their designated path and migrate toward damaged tissue instead.” *Id.* at 3493 (last para.). Lee posits “that neuroblasts migrate toward damaged brain by using matrix metalloproteases (MMPs).” *Id.* at 3491 (second para.).

**FF2.** Lee teaches that MMPs are rapidly upregulated after brain injury due to trauma, ischemia, and hemorrhage. *Id.* at 3494 (first full para.). With respect to the effects of this upregulation, Lee states that “the overwhelming evidence points to a detrimental effect in the acute phase after brain injury.” *Id.* at 3494. In contrast, during the delayed stages after brain injury, Lee posits that “MMPs may play beneficial roles by mediating the neurogenic response in the SVZ. By allowing neuroblasts to expand and migrate, MMPs should facilitate the endogenous recovery response in a damaged brain.” *Id.* Noting that earlier studies had shown that of the proteases in the MPP family, “MMP-9 was the most
responsive to acute brain injury” (id. at 3493 (first full para.) (citations omitted)), Lee states that “immunohistochemistry data suggest that MMP-9 plays a role in this phenomenon.” *Id.*

**FF3.** Lee demonstrates that, in a mouse model of ischemic brain injury, MMP-9 localizes with the neurogenic cells migrating in response to the injury. According to Lee, “bromodeoxyuridine-labeled and doublecortin-positive cells from the SVZ colocalize with the extracellular protease matrix metalloproteinase-9 (MMP-9) during the 2 week recovery period after transient focal cerebral ischemia in mice.” *Id., Abstract.* More particularly,

MMP-9 levels within the SVZ were higher in the ischemic hemisphere compared with the contralateral side (fig 2a, b). *Z*-stack confocal analysis of double-stained immunohistochemistry demonstrated that MMP-9 was colocalized in cells that incorporated BrdU (Fig. 2c-e) and streams of DCZ-positive structures that extended from the SVZ into damaged striatal tissue in the ischemic hemisphere (Fig. 2f-i).

*Id.* at 3493 (first full para.).

**FF4.** Lee notes that “[a]lthough colocalization of MMP-9 with these markers of neuroblast migration after stroke supports our central idea, it does not prove causality. To further test our hypothesis, we next examined mice subjected to 60 min focal cerebral ischemia . . . with . . . the broad spectrum MMP inhibitor GM6001.” *Id.* at 3493 (third para.). “MMP inhibition clearly suppressed the neurogenic migratory response induced by stroke.” *Id.* at 3493 (fourth para.), Abstract (“Treatment with the broad spectrum MMP inhibitor GM6001 significantly decreases the
migration of doublecortin-positive cells that extend from the SVZ into the striatum.”)

FF5. According to Lee, “[o]ur data here show for the first time that extracellular proteolysis via MMP is required for neuroblast migration as the brain attempts to heal itself.” Id. at 3494 (last para.). Lee further teaches that its “immunohistochemistry data suggests that MMP-9 plays a role in this phenomenon,” however:

A caveat here is that our MMP inhibitor GM6001 broadly targets the entire MMP family. What other proteases may be involved? A more careful delineation of how the full spectrum of MMP family members and other proteases interact to modulate matrix and subserve neurogenesis is warranted. A second caveat involves the precise mechanisms and consequences of neuroblast migration, it remains possible that the neuroblast migration toward damaged tissue reflects an endogenous response to inflammation. . . . [S]uppression of neuroblast profiles in our MMP inhibited brains may simply be attributable to reductions in inflammation and may be unrelated to matrix modulations and migration per se.

Id. at 3494 (second full para.).

ANALYSIS

Lee teaches that, cells of the SVZ migrate toward damaged areas of the brain in response to ischemic brain injury. FF1. Lee posits that the activity of MMP-9 plays a role in this phenomenon as part of the healing process. FF5. Lee basis this hypothesis on several lines of evidence: (1) that MMPs, and MMP-9 in particular, are upregulated in response to acute brain injury (FF2); (2) that MMP-9 colocalizes with migrating neurogenic cells in a mouse model of ischemic brain injury (FF3–5); and (3) that a
broad spectrum MMP inhibitor, GM6001, suppresses that neurogenic migratory response (FF4). *See e.g.*, Ans. 7–8. ²

We further adopt the Examiner’s findings of fact and reasoning regarding the scope and content of the prior art. *See* Final Act. 3–8; Ans. 4–17. As set forth in the Examiner’s Answer, it would have been obvious to provide MMP-9 to a patient suffering from brain injury because “Lee strongly suggest[s] and encourage[s] treating brain injury with MMP-9,” and “[s]ince delivery to the brain was well known at the time of filing, one of ordinary skill in the art would have had a reasonable expectation of success as well.” Ans. 5.

Appellants raise two arguments pertaining to all claims on appeal. Appellants first argue that “Lee’s disclosure does not direct the skilled artisan specifically and predictably to MMP-9 as a mediator of neurogenic cell migration.” App. Br. 3–7 (emphasis omitted); Reply Br. 2–9. In sum, Appellants argue that Lee: (1) merely demonstrated a correlation between the presence of MMP-9 and cell migration; (2) acknowledges that GM6001 inhibits MMPs other than MMP-9; (3) failed to show that the levels of GM6001 used were sufficient to inhibit MMP-9 in the mouse model; and (4) admits that the disclosed data may reflect the involvement of MMPs in inflammation rather than neuroblast migration. We do not find Appellants arguments persuasive for the reasons set forth by the Examiner’s Answer.

With respect to (1) and (2), we agree with the Examiner’s summation that it is not necessary for any single line of evidence be dispositive on its

² Although we decline to address the Examiner’s invitation to address enablement (*see* Ans. 11–12), we do note that the Appellants’ evidence for enablement (*see* Reply Br. 11–12) is no greater than that disclosed in Lee.
own. Ans. 8–9. “Rather, it is the accumulated weight of evidence, data and reasoning that tends to lead to scientific consensus.” Id. at 9. “That Lee hypothesizes a causative role of MMP-9 in the process of stroke-induced neuroblast migration and then proceeds to provide two independent lines of evidence supporting this hypothesis is considered to provide sufficient suggestion of same.” Id.; see also id. at 10 (“[The GM6001 data] is not considered dispositive on its own, but when taken with the strong correlation data specific for MMP-9 discussed above, along with the fact that scientists behind the Lee publication hypothesized a role for MMP-9 in the process of stroke-induced neuroblast migration, the fact that MMP inhibition clearly suppressed the neurogenic migratory response induced by stroke provides strong evidence that MMP-9 plays a causative role in this process.”).

With respect to (3), we agree with the Examiner that there is no evidence “to suggest that Lee used GM6001 improperly, or otherwise failed to achieve GM6001-mediated inhibition.” Ans. 10–11. Appellants’ arguments to the contrary are speculative and unsupported attorney argument. See Reply Br. 5–6.

With respect to (4), Appellants point to Lee’s acknowledgment that additional proteases may be involved in mediating cell migration and that “it remains possible that the neuroblast migration toward damaged tissue reflects an endogenous response to inflammation.” App. Br. 6 (quoting Lee, 3494 (second full para.)). We find supported, however, the Examiner’s response that Lee presents such caveats “as part of a legitimate and necessary scientific discussion . . . [regarding] possible alternative explanations for their results” but, nevertheless, “provide[s] ample suggestion to use MMP-9 in an effort to provide treatment to a subject

7
appeal 2017-004297  
application 14/489,934

suffering from a brain injury with a reasonable expectation of success.” Ans.
12–13. Under the proper inquiry, “obviousness cannot be avoided by a
showing of some degree of unpredictability in the art so long as there was a
reasonable probability of success.” Pfizer, Inc. v. Apotex, Inc., 480 F.3d
1348, 1364 (Fed. Cir. 2007).

With respect to “teaching away,” Appellants rely on four prior art
references in support of the argument that the art as a whole taught that
MMP-9 is involved in the pathology of brain injury as opposed to the
healing process. See App. Br. 7–8, Reply Br. 7–10. But in discussing this
art, Lee posits that although

the overwhelming evidence points to a detrimental effect [of
MPP expression] in the acute phase after brain injury . . . . what
happens during the delayed stages after brain injury may be
quite different. Our present study suggest[s] that, in fact,
MMPs may play beneficial roles by mediating the neurogenic
response in the SVZ. By allowing neuroblasts to expand and
migrate, MMPs should facilitate the endogenous recovery
response in a damaged brain.

Lee, 3494, (second and third paras.). Accordingly, and for the reasons set
forth at pages 13–14 of the Examiner Answer, we find supported the
Examiner’s determination that Lee does not teach away from the use of
MMP-9 for the treatment of brain injury.

Appellants further argue that claim 4 is separately patentable for
reciting treatment of traumatic brain injury because Lee presents evidence
based on a model of ischemic stroke; and that claim 5 is separately
patentable for reciting treatment of brain injury in a human because Lee
presents evidence derived from a mouse model. App. Br. 8; Reply Br. 10–
11. Appellants present no evidence that one of ordinary skill in the art

8
would consider Lee so limited and we do not find Appellants’ arguments persuasive for the reasons set forth at pages 14–15 of the Examiner’s Answer.

SUMMARY

For the reasons above, we affirm the Examiner’s decision rejecting claims 1–5.

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