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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KARL DEISSEROTH, ALBRECHT STROH,
M. BRET SCHNEIDER, and RAAG D. AIRAN

Appeal 2018-004032
Application 12/997,140[1]
Technology Center 1600

Before DONALD E. ADAMS, JOHN E. SCHNEIDER, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method for selectively controlling growth and development of a mammalian stem cell, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

STATEMENT OF THE CASE

Appellant's Specification indicates that "[t]here are a number of challenges to successful production of a cultured neuronal tract using stem

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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 The Board of Trustees of the Leland Stanford Junior University. (Appeal Br. 3.)

cells (either adult stem cells or embryonic stem cells)." (Spec. 3.)

Appellant's invention is concerned with a method for the growth and development of a mammalian stem cell. (*Id.* at 1.)

Claims 1, 2, 7, 8, 10, 13, and 20–31 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method for selectively controlling growth and development of a mammalian stem cell *in vivo* or in a tissue *in vitro*, the method comprising:
>
> a) genetically modifying a selected type of stem cell to express a microbial opsin;
>
> b) stimulating the genetically modified stem cell with a light-based activation signal, wherein the light-based activation signal is generated by a system comprising:
>
> i) a light source;
>
> ii) a pulse generator that is configured to send signals to and control the light source;
>
> iii) a signal receiver that is configured to receive response signals from the genetically modified stem cell; and
>
> iv) a computer that is configured to modulate signals sent by the pulse generator based on the response signals;
>
> c) receiving one or more response signals from the genetically modified stem cell; and
>
> d) modulating the light-based activation signal based on the response signals, thereby selectively controlling growth and development of the genetically modified stem cell.

(Appeal Br. Claims Appendix (iii).)

The following grounds of rejection by the Examiner are before us on review:

Claims 1, 2, 7, 8, 10, 21, 22, 26–28, 30, and 31 under 35 U.S.C. § 103(a) as unpatentable over Zhang,[2] Deisseroth,[3] and Boyden 2005.[4]

Claims 1, 2, 7, 8, 10, 21–28, 30, and 31 under 35 U.S.C. § 103(a) as unpatentable over Zhang, Deisseroth, Boyden 2005, and Boyden 2007.[5]

Claims 1, 2, 7, 8, 10, 13, and 21–31 under 35 U.S.C. § 103(a) as unpatentable over Zhang, Deisseroth, Boyden 2005, Boyden 2007, McAllister,[6] and Morelli.[7]

Claims 1, 2, 7, 8, 10, 13, and 20–31 under 35 U.S.C. § 103(a) as unpatentable over Zhang, Deisseroth, Boyden 2005, Boyden 2007, McAllister, Morelli, and Takahashi.[8]

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[2] Zhang et al., *Channelrhodopsin-2 and optical control of excitable cells*, 3:10 Nature Methods, 785–792 (2006).
[3] Deisseroth et al., *Excitation-Neurogenesis Coupling in Adult Neural Stem/Progenitor Cell*s, 42 Neuron 535–52 (2004).
[4] Boyden et al., *Millisecond-timescale, genetically targeted optical control of neural activity*, 6:9 Nature Neuroscience 1263–1268 (2005).
[5] Boyden et al., US 2007/0054319 A1, published Mar. 8, 2007.
[6] A. Kimberly McAllister, *Cellular and Molecular Mechanisms of Dendrite Growth*, 10:10 Cerebral Cortex 963–73 (2000).
[7] Morelli et al., *Neuronal and glial cell type-specific promoters within adenovirus recombinants restrict the expression of the apoptosis-inducing molecule Fas ligand to predetermined brain cell types, and abolish peripheral liver toxicity*, 80 J. General Virology 571–583 (1999).
[8] Takahashi et al., *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 Cell 663–76 (2006).

DISCUSSION

Non-obviousness of Claim 1 over Zhang, Deisseroth, and Boyden 2005

The Examiner finds that Zhang teaches using microbial opsin, such as Channelrhodopsin-2 (ChR2), for photostimulation of cells and "has the capacity for excitation intensity tuning" given that the stimulation "can be readily toggled between subthreshold synaptic-like depolarizations and suprathreshold spike-generating events simply by modulating light-pulse duration or intensity." (Ans. 3, 4.) The Examiner further finds that Zhang teaches ChR2 can be targeted to cells, including stems and progenitor cells present in the adult brain, by genetically modifying a selected cell type through viral infection and that stimulation of ChR2 can be applied to neurons *in vivo*. (*Id.* at 4.) The Examiner also finds Zhang "teaches that the low light power required for activation of ChR2 makes it feasible to apply ChR2 *in vivo* to drive cellular activity and assay physiological behavior." (*Id.*) The Examiner finds in this regard that Zhang teaches the "ability to remotely read out the signals from the stimulated cells with calcium sensitive and voltage sensitive dyes" and that this coupled with the ability to depolarize cells with light "could be used for guiding stem cell differentiation." (*Id.* at 3.) From this, the Examiner concludes that "Zhang teaches guiding stem cell differentiation by precise depolarization patterns by photostimulation of ChR2 expressing stem cells" and that "activation of ChR2 can be practiced *in vivo* and that the excitation intensity through ChR2 can be tuned simply by modulating light-pulse duration or intensity." (*Id.* at 5.)

The Examiner finds that Deisseroth teaches that one can induce mammalian neural progenitor cells into neurogenesis by excitation/depolarization and that the response of the stimulated cells can be

assayed using confocal microscopy where the signal receiver is configured to receive response signals from the stem cell, as well as electrophysiologically by using electrodes. (*Id.* at 4–5.) In other words, states the Examiner:

> Deisseroth teaches that the development of NPCs into neurons can be selectively controlled by controlling the excitation of the NPCs and that the excitation state of the NPCs can be sensed by receiving signals from the stimulated cells by calcium or voltage sensitive dyes or electrodes.

(*Id.* at 5.)

In light of the foregoing the Examiner concludes that one of ordinary skill in the art

> would have found it obvious to selectively control growth and development of genetically modified mammalian *in vivo* or in a tissue *in vitro* by stimulating the genetically modified stem cells with a light-based activation signal (photostimulation of ChR2), receiving one or more response signals from the genetically modified stem cell (detection of depolarization and/or excitation by calcium or voltage sensitive dyes or with mechanical electrodes) and modulating the light-based activation signal based on the response signals (modulating the light intensity or duration to effect the required degree of excitation as evidenced by the response signals).

(*Id.*)

The Examiner relies on Boyden 2005 for its teaching of "optical control of cells" with ChR2 activation where a computer system was used to deliver light pulses and record electrical spikes representative of cellular activity. (*Id.* at 6.) According to the Examiner, Boyden 2005 "teaches the use of ChR2 in guiding stem cell differentiation," and concludes that one of ordinary skill in the art "would have found it obvious to configure the computer to modulate the light intensity or duration of the light based

activation signal to effect the required degree of excitation to induce differentiation of the stem cells into neurons." (*Id.* at 6–7.)

We disagree with the Examiner's factual findings and conclusion of obviousness. First, we disagree with the Examiner that Boyden 2005 teaches "the use of ChR2 in guiding stem cell differentiation" or that Zhang teaches "guiding stem cell differentiation" by photostimulation of ChR2 expressing stems cells with precise depolarization patterns. Boyden 2005 teaches that light pulse durations can be modulated to elicit photostimulation of neurons and control synaptic transmission. (See e.g., Boyden 2005 Abs.) In particular, Boyden 2005 states

> We found that ChR2 could be expressed stably and safely in mammalian neurons and could drive neuronal depolarization. When activated with a series of brief pulses of light, ChR2 could reliably mediate defined trains of spikes or synaptic events with millisecond-timescale temporal resolution.

(*Id.* at 1264.) And it further notes that

> subthreshold depolarizations evoked by repeated light pulses were reliably evoked over a range of frequencies. . . . Thus, ChR2 can be used to drive subthreshold depolarization of reliable amplitude.
>
> Finally, synaptic transmission was also easily controlled with ChR2. Indeed, both excitatory (Fig. 4c) and inhibitory (Fig. 4d) synaptic events could be evoked in ChR2-negative neurons receiving synaptic input from ChR2-expressing neurons.

(*Id.* at 1266.) Thus, as Boyden states "[c]ombining the best aspects of earlier approaches that use light to drive neural circuitry, the technology described here *demonstrates* voltage control significantly faster than previous genetically encoded photostimulation methods." (*Id.* at 1267 (emphasis added).)

Boyden 2005 hypothesizes future possibilities with ChR2 activation of neurons or other cell types including "guiding stem cell differentiation" from "the technology described herein," stating that it "*may* fulfill the long-sought goal of a method for noninvasive, genetically targeted, temporally based on precise control of neuronal activity, with *potential applications* ranging from neuroscience to biomedical engineering." (*Id.* at 1267 (emphasis added).) As to these applications, Boyden 2005 suggests that because of "the efficacious and safe transduction of light with a single natural biological component" it "*could* serve biotechnological needs, in high-throughput studies of activity-dependent signal transduction and gene expression programs, for example, in guiding stem cell differentiation." (*Id.* (emphasis added).) In other words, Boyden 2005's reference to using the technology in "guiding stem cell differentiation" is providing a skilled artisan with a "general approach that seem[s] to be a promising field of experimentation, [but] where the prior art g[ives] only general guidance as to the particular form of the claimed invention or how to achieve it." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). Where there is a suggestion for a general approach with no instructions on how to achieve the result, one is presented with an invitation to try that is not equated with obviousness. *Id.* On the other hand, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007): "In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* The Examiner has not provided evidence to establish Boyden 2005 provides this latter finite number of identified, predictable solutions alternative.

The Examiner's allegation that Zhang teaches "guiding stem cell differentiation by precise depolarization patterns by photostimulation of ChR2 expressing stem cells" (Ans. 5) is similarly overstated. Zhang is a review article that reviews a number of photostimulation techniques of cells and notes that ChR2 is one of them. (Zhang 785–87 and Table 1.) Zhang notes, from a review of the art, the practical considerations for ChR2-based photostimulation experiment planning for cells (*id.* at 789 (Box 1), 790). After describing observations from various past experiments, Zhang, like Boyden 2005 hypothesizes future possibilities in a section entitled "Future directions." (*Id.* at 791.) There it is stated:

> The rapid transduction of light into ionic current also has clear biotechnological implications in high-throughput studies of activity-dependent signal transduction and gene expression, *perhaps including guiding stem cell* differentiation by precise depolarization patterns and screening for drugs that modulate cellular responses to depolarization.

(*Id.* (emphasis added).) In other words, just like Boyden 2005, Zhang provides at best a promising field of experimentation, but with no reasonable expectation of success given the lack of guidance as to how to achieve the goal other than the generalized statement of "perhaps . . . by precise depolarization patterns." *Id.*

The Examiner relies on Deisseroth for its teaching that neural stem/progenitor cells (NPCs) can be induced into neural development by excitation/depolarization resulting in an increase in intracellular calcium, and thus, the Examiner concludes that one of ordinarily skill in the art would have found it obvious in combination with Zhang to selectively control the growth and development of stem cells genetically modified to express ChR2 with photostimulation. (Ans. 5.) We disagree with the Examiner's

conclusion that Deisseroth would have provided motivation or a reasonable expectation of success in this regard.

"A rejection based on section 103 clearly must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art." *In re Warner*, 379 F.2d 1011, 1017 (CCPA 1967). Deisseroth observed an increase in neuron production from neural stem/progenitor cells (NPCs) by "applying modest depolarizing levels of extracellular potassium . . . synchronously with the initiation of mitogen taper." (Deisseroth 536–37.) It also observed a similar effect on "[d]irect application of the excitatory neurotransmitter glutamate." (*Id.* at 537.) Deisseroth does not apply photostimulation and we conclude it does not fill the gap discussed above regarding the teachings of Zhang and Boyden 2005 with respect to a reasonable expectation of success of guiding stem cell differentiation with photosimulation of ChR2 expressing stem cells. We conclude that, at best, Deisseroth provides an invitation to investigate the use of other external excitation methods to determine whether similar effects would be observed.

Additionally, we agree with Appellant that the references do not teach or suggest modulating the light-based activation signal based on the response signals from the genetically modified stem cell and thereby selectively controlling growth and development of the genetically modified stem cell. (Appeal Br. 8.) At best, the references teach that one can monitor NPC cellular responses to excitation initiated with potassium or glutamate by quantifying intensity of signals of calcium sensing dyes (Deisseroth 546–47 and 549–50) and that light activation signals can be controlled by a computer and cellular response signals, such as spike rates, can be measured (Boyden 2005 1267–68). But none of the foregoing establishes a reason

why one of ordinary skill in the art would have been motivated to measure stem cell response signals from light activation and to control light-based activation signals to control the growth and development of a stem cell genetically modified to express ChR2. "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the answer depends on "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417. The fact that instruments were known to be capable of measuring signals and controlling excitation does not mean these elements were known to be used or could be predictably used for controlling growth and development of stem cells. Thus, we conclude that for this additional reason the Examiner has failed to establish a prima facie case of obviousness.

Consequently we reverse the Examiner's rejection of claims 1, 2, 7, 8, 10, 21, 22, 26–28, 30, and 31 over Zhang, Deisseroth, and Boyden 2005.

Non-obviousness of Claim 1 over Zhang, Deisseroth, Boyden 2005 and Boyden 2007

The Examiner adds Boyden 2007 to the initial rejection of 1, 2, 7, 8, 10, 21, 22, 26–28, 30, and 31 as being obvious over Zhang, Deisseroth, and Boyden 2005, to conclude that claims 23, 24, and 25 are obvious as well. (See Ans. 13.) In particular, the Examiner states:

> Hence, a person of ordinary skill in the art at the time of the invention would have found it obvious to practice the method obviated by Zhang, Deisseroth and Boyden 2005 discussed above, wherein the tissue comprising the ChR2 expressing stem cell is an *in vitro* tissue which is an artificial tissue comprising cells within an artificial matrix which can be used for *in vivo* implantation because Boyden 2007 teaches encapsulating

> LACC-expressing cells in semipermeable membranes, hollow fibers, beads and planar diffusion devices and implanting the capsule (i.e. artificial tissue) into patients

(*Id.*) Claim 23 adds that "the *in* vitro tissue is an artificial tissue." Claim 24 adds to claim 23 that cells of the artificial tissue are within an artificial matrix. Claim 25 adds to claim 23 that the artificial tissue is implanted in vivo.

In arriving at this conclusion, the Examiner makes a number of findings regarding Boyden 2007 that we find relevant to claim 1. In particular, the Examiner explains that Boyden 2007 teaches stem cells can be genetically modified to express a light activated cation channel protein (LACC) such as ChR2 and that such cells can be differentiated by activation with light. (Ans. 11 (citing Boyden 2007 ¶¶ 32, 192.)) We agree with that finding. In other words, we find that unlike Zhang and Boyden 2005, Boyden 2007 teaches guiding stem cell differentiation by photostimulation of ChR2 expressing stem cells.

Notwithstanding the foregoing, we conclude that Boyden 2007 does not cure the additional deficiency noted above.

The Examiner further finds that Boyden 2007 also "teaches modulation of the rate of replication of stem cells expressing LACC by in vivo and ex vivo methods by activating the channels by exposure to light." (*Id.* (citing Boyden 2007 ¶ 187.)) We disagree with that finding. Boyden 2007 teaches that exposing cells that have been genetically modified with ChR2 to particular light patterns can "drive differentiation or replication of, or hasten the death of, the cells expressing the light-activated channel." (Boyden 2007 ¶ 187.) While Boyden 2007 does teach that "it may be desirable to control the replication, differentiation, and death" of cells (*id.*),

it does not teach or suggest modulating the rate of replication of a cell. Moreover, it does not address any type of modulation that is based on a response signal from the genetically-modified stem cell.

Thus, just as was the case discussed above when addressing the rejection of claim 1 as being obvious over Zhang, Deisseroth, and Boyden 2005, we agree with Appellant that the Boyden 2007 also does not teach or suggest modulating the light-based activation signal based on the response signals from the genetically modified stem cell and thereby selectively controlling growth and development of the genetically modified stem cell. (Appeal Br. 9.) Thus, for this reason, we conclude that the Examiner has failed to establish a prima facie case of obviousness as to claims 1, 2, 7, 8, 10, 21, 22, 26–28, 30, and 31 as well as claims 23, 24, and 25.

Consequently we reverse the Examiner's rejection of claims 1, 2, 7, 8, 10, 21, 22–28, 30, and 31 over Zhang, Deisseroth, Boyden 2005, and Boyden 2007.

The remaining obviousness rejections

The Examiner's rejection of claims 1, 2, 7, 8, 10, 13, and 21–31 under 35 U.S.C. § 103(a) as unpatentable over Zhang, Deisseroth, Boyden 2005, Boyden 2007, McAllister, and Morelli, and the rejection of claims 1, 2, 7, 8, 10, 13, and 20–31 under 35 U.S.C. § 103(a) as unpatentable over Zhang, Deisseroth, Boyden 2005, Boyden 2007, McAllister, Morelli, and Takahashi suffer from the same infirmity just discussed. Thus, we reverse both of those rejections as well.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 2, 7, 8, 10, 21, 22 26–28, 30, 31	103	Zhang, Deisseroth, Boyden 2005		1, 2, 7, 8, 10, 21, 22 26–28, 30, 31
1, 2, 7, 8, 10, 21–28, 30, 31	103	Zhang, Deisseroth, Boyden 2005, Boyden 2007		1, 2, 7, 8, 10, 21–28, 30, 31
1, 2, 7, 8, 10, 13, 21–31	103	Zhang, Deisseroth, Boyden 2005, Boyden 2007, McAllister, Morelli		1, 2, 7, 8, 10, 13, 21–31
1, 2, 7, 8, 10, 13, 20–31	103	Zhang, Deisseroth, Boyden 2005, Boyden 2007, McAllister, Morelli, Takahashi		1, 2, 7, 8, 10, 13, 20–31
Overall Outcome				1, 2, 7, 8, 10, 13, 20–31

REVERSED