The opinion in support of the decision being entered today was not written
for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte TIMOTHY J. JEGLA

Appeal No. 2005-2207
Application No. 09/548,933

ON BRIEF

Before SCHEINER, MILLS and GRIMES, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a nucleic acid encoding a polypeptide monomer of an alpha subunit of a human hyperpolarization-activated cation channel, designated hHAC3.[1] The examiner has rejected the claims under 35 U.S.C. §§ 101 and 112, first paragraph, as lacking both utility and enablement. We have jurisdiction under 35 U.S.C. § 134. We will reverse these rejections.

BACKGROUND

"Cation channels are a diverse group of proteins" that are "involved in a number of physiological processes, including regulation of heartbeat, dilation of arteries, release

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[1] This appeal is related to an appeal in application serial no. 09/767,597 (appeal no. 2005-2265). We have considered the two appeals together.

of insulin, excitability of nerve cells, transduction of sensory stimuli, and regulation of renal electrolyte transport." Specification, pages 1-2. Typically composed of four heteromeric or homomeric subunits, "[t]hese channels allow the flow of various cations in and/or out of the cell under certain conditions" and "are regulated, e.g., by calcium sensitivity, voltage-gating, cyclic nucleotides or other secondary messengers, extracellular ligands, and ATP-sensitivity." Id., page 2.

Specialized cells in the heart and brain create rhythmic activity due in large part to a particular subset of cation channels: hyperpolarization-activated channels that generate a mixed sodium/potassium pacemaker current known as I_h. Id. The specification cites a number of references that reflect the level of understanding of the nature and identity of pacemaker channels at the time of the invention. Id., pages 2 and 3. For example, Ludwig[2] reports the molecular cloning and functional expression of HAC1, a murine cation channel "dually gated by hyperpolarization of the membrane and by direct binding of cyclic nucleotides" (Ludwig, pages 587 and 590). According to Ludwig, "[t]he functional properties of the HAC1 current, that is, the voltage-dependence of activation, ion selectivity, pharmacological profile and modulation by cyclic nucleotides, concur with the general criteria that characterize I_h in several neuronal and non-neuronal cells" (id., page 590). Further, "[t]he expression pattern of HAC1 indicates that it may mediate the current that is involved in control of pacemaker activity in both central nervous system and cardiac cells" (id.). In addition, Ludwig identified full-length sequences of two related brain-specific channels, HAC2 and HAC3, "indicating the

[2] Ludwig et al., "A Family of Hyperpolarization-Activated Mammalian Cation Channels," Nature, Vol. 393, pp. 587-591 (June 1998).

existence of a family of hyperpolarization-activated cation channels" (id., page 587), "members of which are characterized by six membrane-spanning segments (S1-S6), including a voltage-sensing S4 segment, and an ion-conducting pore between S5 and S6" (id.), as well as a putative cyclic nucleotide-binding domain (id.). According to Ludwig, the identification of HAC2 and HAC3 "is consistent with the diversity of I_h currents detected in different types of neurons" (id., page 590).

Similarly, Santoro[3] reports the cloning and functional expression of murine BCNG-1 (HAC2), as well as the isolation and characterization of human BCNG-2 (HAC1) and human BCNG-1 (HAC2). Santoro, pages 718 and 722-723. Santoro teaches that "[t]he distinct sequences and tissue distributions of the identified BCNG [(HAC)] genes reveal[ ] that the BCNG products represent a family of ion channel proteins, with characteristic motifs for voltage sensing and cyclic nucleotide binding . . . predominantly located in brain and in heart" (id., page 725). Santoro further teaches that the properties of mBCNG-1 (mHAC2) "closely correspond to those of the brain channel (I_h or I_q)" and "these properties are quite similar to those of the pacemaker current in the heart (I_f)" (id.). Thus, mBCNG-1 (mHAC2) "may well code for the cardiac channel" (id.). Santoro also teaches that defects in pacemaker activity can lead to both inherited and acquired cardiac arrhythmias, and that defects in pacemaker activity may

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[3] Santoro et al., "Identification of a Gene Encoding a Hyperpolarization-Activated Pacemaker Channel of Brain," Cell, Vol. 93, pp. 717-729 (May 29, 1998), especially page 717. Santoro refers to the HAC family of cyclic nucleotide and hyperpolarization-gated pacemaker channels as the BCNG family.

underlie various neurological diseases as well. Id., page 717. Finally, Santoro teaches that acetylcholine and norepinephrine exert their actions on heart rhythm through modulation of pacemaker channel activity, and that direct binding of cyclic AMP modulates pacemaker channel activation. Id.

Thus, the Ludwig and Santoro references reflect a general consensus in the art that pacemaker activity in the brain, and probably the heart, is due, at least in part, to the HAC family of hyperpolarization-activated, cyclic nucleotide-gated channels.

"The present invention provides . . . a nucleic acid encoding a human HAC3 alpha subunit, identified and cloned from human tissue" (Specification, page 8). "Functionally, hHAC3 is an alpha subunit of a voltage-gated channel that is activated upon hyperpolarization" (id., page 10). Structurally, hHAC3 "contains six membrane spanning domains (S1-6), including a voltage sensing domain (S4) and an ion-conduction pore between S5 and S6, as well as a putative cyclic nucleotide binding domain region that has a conserved amino acid sequence" (id.). Based on hHAC3's structure and function, the specification discloses that hHAC3 "is a member of the HAC family of potassium channel monomers . . . [which] have significant roles in maintaining the resting potential and in controlling excitability of a cell" (id., page 8).

When functionally expressed in Xenopus oocytes, hHAC3 monomers formed "a classic I_h channel that passe[d] both sodium and potassium" and "that open[ed] upon hyperpolarization" (id., page 63). Analysis of hHAC3 expression patterns revealed "especially high [expression] in the putamen, thalamus, caudate nucleus, medulla, occipital lobe, substantia nigra, spinal cord and fetal brain" (id.), and "moderate levels [of expression] in . . . the amygdala, cerebellum, cerebral cortex, frontal lobe,

hippocampus, temporal lobe, nucleus accumbens, heart, stomach, pancreas, pituitary gland, liver and appendix" (id.).

According to appellant, "[t]he identification and cloning of hHAC3 . . . provides a means for assaying for inhibitors and activators" of hHAC3, and "[t]hese activators and inhibitors are [ ] useful as pharmaceutical agents for treating diseases involving pacemaker dysfunctions such as familial sinus rhythm diseases, sick sinus syndrome associated with atrial fibrillation, sinus tachycardias, bradycardias and ventricular arrhythmias" (id., page 12). Modulators of hHAC3 activity "are also useful for treating other disorders involving abnormal ion flux, e.g., . . . CNS disorders such as migraines . . . [and] seizures" (id., page 9).

THE CLAIMS

Claim 1 is representative of the subject matter on appeal:

> 1. An isolated nucleic acid encoding a polypeptide comprising an alpha subunit of a cation channel, the polypeptide forming, with at least one additional hyperpolarization-activated channel (HAC) alpha subunit, a cation channel having the characteristic of activation upon hyperpolarization; wherein said nucleic acid encodes a polypeptide that has greater than 96% identity to SEQ ID NO:1.

DISCUSSION

Utility

The examiner rejected claims 1, 3-5, 7-9, 12, 22 and 23, all the claims remaining in the application, as lacking an "apparent or disclosed specific and substantial credible utility" sufficient to satisfy 35 U.S.C. § 101. Answer, page 3. The examiner also rejected all of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement. However, that rejection is merely a corollary of the finding of lack of utility (id., page 12).

Therefore, our conclusion with respect to the § 101 issue also applies to the § 112 issue.

The U.S. Court of Appeals for the Federal Circuit recently addressed the nature of the § 101 utility requirement in the context of a claim to expressed sequence tags (ESTs) - short nucleotide sequences purportedly encoding fragments of proteins of unknown structure or function. See In re Fisher, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). Revisiting Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966), the Fisher court interpreted it as rejecting a "de minimis view of utility" (Fisher, 421 F.3d at 1370, 76 USPQ2d at 1229), and held that § 101 requires a utility that is both specific and substantial (id. at 1371, 76 USPQ2d at 1229).

With respect to the requirement for a "specific" utility, the court explained that "an application must disclose a use which is not so vague as to be meaningless." Id. at 1371, 76 USPQ2d at 1230. The court identified "the nebulous expressions 'biological activity' [and] 'biological properties' . . . [and] the equally obscure expression 'useful for technical and pharmaceutical purposes'" as examples of meaningless asserted utilities. Id. Thus, "an asserted use must [ ] show that that claimed invention can be used to provide a well-defined and particular benefit to the public." Id.

With respect to the requirement for a "substantial" utility, the Fisher court explained that "an application must show that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." Id. at 1372, 76 USPQ2d at 1230.

The Fisher court held that none of Fisher's seven asserted uses were specific because "[a]ny EST transcribed from any gene in the maize genome has the potential to perform any one of the alleged uses. . . . Nothing about [the] seven alleged uses set[s] the five claimed ESTs apart from the more than 32,000 ESTs disclosed in the [ ] application or indeed from any EST derived from any organism." Id. at 1374, 76 USPQ2d at 1232. Accordingly, the court concluded that Fisher "only disclosed general uses for its claimed ESTs, not specific ones that satisfy § 101." Id.

Furthermore, the Fisher court held that none of the uses asserted by the applicant in that case were substantial because "all of [the] asserted uses represent merely hypothetical possibilities, objectives which the claimed ESTs, or any EST for that matter, could possibly achieve, but none for which they have been used in the real world." Id. at 1373, 76 USPQ2d at 1231. The court concluded that the claimed ESTs lacked "a 'substantial' utility under § 101" "because Fisher failed to prove that its claimed ESTs [could] be successfully used in the seven ways disclosed in the [ ] application" (id. at 1374, 76 USPQ2d at 1232).

The present specification discloses that hHAC3, expressed at high levels in the brain, and moderate levels in the heart, is a member of the HAC family of hyperpolarization-activated, cyclic nucleotide-gated channels, and generates a mixed sodium/potassium I_h current associated with pacemaker activity when functionally expressed in oocytes. Specification, page 63. In addition, the specification discloses that activators and inhibitors of hHAC3 channels are useful as pharmaceutical agents for treating various pacemaker dysfunctions, e.g., cardiac arrhythmias, as well as disorders involving abnormal ion flux, e.g., migraines and seizures. Id., pages 9 and 12.

The examiner concedes that "hHAC3 [ ] is structurally related to a voltage-gated cation channel family of proteins, specifically it is related to the family of hyperpolarization-activated channels (HAC)" (Answer, page 4). The examiner also concedes that "[o]ne skilled in the art [would] readily understand[ ] that hyperpolarization-gated cation channels could certainly be involved in modulation of cellular excitability" (id., page 9), and "could be associated with [the] etiology or development of migraine and epilepsy" (id.).

Nevertheless, the examiner argues that the "asserted utility of [the] HAC3 channel as a modulator of cell excitability is not specific because it is associated with a general physiological function of regulating a membrane potential in a cell" (id., page 12, emphasis ours). The examiner also argues that the asserted utility is not substantial because the identification of hHAC3 as "a novel cation channel does not unequivocally lead to the conclusion that it is directly associated with dysfunctions, disorders or conditions in which cation channels are known to be involved" (id.). We disagree with the examiner's analysis and conclusions.

First, the examiner has not explained why modulating cellular excitability or regulating membrane potential does not "provide a well-defined and particular benefit to the public." See Fisher, 421 F.3d at 1371, 76 USPQ2d at 1230. The fact that all cells have a membrane potential, and that there are many classes of channels that modulate membrane potential and cell excitability, does not mean that identifying modulators of one particular type of channel (in this case disclosed to be a hyperpolarization-activated, cyclic nucleotide-gated channel that generates a mixed sodium/potassium I_h pacemaker current) does not provide a specific, well-defined and particular benefit to the public,

especially as the examiner agrees that this type of channel "could be associated with [the] etiology or development of migraine and epilepsy" (id., page 9).

Nor are we persuaded that appellant's disclosed utility is insubstantial simply because a direct association between the HAC3 channel and epilepsy or migraine is "unsubstantiated" on the record (id.). As discussed above, there is evidence of record that those of skill in the art at the time of the invention believed that members of the HAC family of hyperpolarization-activated, cyclic nucleotide-gated channels were associated with pacemaker currents in brain and heart tissue. See e.g., Santoro, page 725, and Ludwig, page 590. Moreover, there is evidence of record that it was known in the art that defects in pacemaker activity could lead to both inherited and acquired cardiac arrhythmias, and that defects in pacemaker activity might also underlie various other neurological diseases. See Santoro, page 717.

We recognize that the Fisher court wrote in terms of Fisher's failure to "prove" or "show" that the claimed ESTs could be used in any of the ways disclosed in the specification. Nevertheless, we do not understand Fisher to relieve the PTO of its well-established "initial burden of challenging a presumptively correct assertion of utility in the disclosure." In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (citation omitted). "Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility." Id. In our view, the mere assertion that "a skilled practitioner would not reasonably expect administration of [ ] modulators of HAC3 to have any effect

on any of the 'diseases of hyperexcitability'" (Answer, page 10) is insufficient to overcome the examiner's initial burden.

We conclude that the specification discloses an asserted utility for the claimed nucleic acids which is both substantial and specific, as required by 35 U.S.C. § 101, and the examiner has not provided evidence sufficient to establish that one of ordinary skill in the art would reasonably doubt that asserted utility. We therefore reverse the rejection of the claims under 35 U.S.C. § 101, and the corresponding rejection under § 112, first paragraph.

REVERSED

Toni R. Scheiner Administrative Patent Judge	))))) BOARD OF PATENT
Demetra J. Mills Administrative Patent Judge	)) APPEALS AND)) INTERFERENCES)
Eric Grimes Administrative Patent Judge	))

Townsend & Townsend & Crew
8th Floor
Two Embarcadero Center
San Francisco, CA 94111-3834