

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte GREGORY J. RIGGINS and ANITA LAL

Appeal 2007-4135
Application 10/465,572
Technology Center 1600

Decided: December 11, 2007

Before ERIC GRIMES, NANCY J. LINCK and RICHARD M. LEOVITZ,
Administrative Patent Judges.

LEOVITZ, *Administrative Patent Judge.*

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 4-9 and 15-21. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The Specification describes the identification of certain genes whose expression “is elevated in cells grown under hypoxic conditions” (Specification 8). “Cellular responses to hypoxia have important effects on the development and metastasis of tumors, angiogenesis, wound healing, recovery from ischemia, and other physiological and pathological processes.

Reduced oxygen availability can trigger a variety of cellular mechanisms including angiogenesis, cell-cycle arrest, apoptosis, and glycolysis” (Specification 1). Thus, the Specification describes the genes and their products as useful for treating conditions and diseases associated with hypoxia. One of these genes is HFARP (SEQ ID NO: 16), a gene which had already been identified in the prior art to protect endothelial cells from apoptosis (Specification 9).

Claims 4-9 and 15-21, which are all the pending claims, are appealed (Appeal Br. 2). Appellants request review of the following rejections:

1. Claims 4-9 and 15-21 under 35 U.S.C. § 112, first paragraph, as not being adequately enabled by the written description of the Specification (Answer 3); and

2. Claims 4-9 and 15-21 under 35 U.S.C. § 112, first paragraph, as lacking written description (Answer 6).

We select claims 4 and 15 as representative of the claimed subject matter for the purpose of deciding all issues in this appeal. *See* 37 C.F.R. § 41.37(c)(1)(vii)(2006). Claims 4 and 15 read as follows:

4. A method of inhibiting angiogenesis associated with retinopathy, inflammation, or skin inflammation, comprising:
administering to a subject in need thereof an antibody which specifically binds to a polypeptide comprising^[1] SEQ ID NO: 16 (HFARP) whereby angiogenesis is inhibited.

¹ The term “comprising” was not present in claim 4 in the listing of the appealed claims that accompanied the Appeal Brief. However, this omission was an error since “comprising” was added to claim 4 by an amendment during prosecution (*see* Amendment dated Jan. 12, 2006).

15. A method of treating a tumor, comprising:
administering to a subject in need thereof an antibody
which specifically binds to a polypeptide comprising SEQ ID
NO:16 (HFARP) whereby the growth of the tumor is
diminished.

CLAIM INTERPRETATION

According to claims 4 and 15, administering an antibody which “specifically binds to” HFARP results in inhibiting angiogenesis and diminishing tumor growth, respectively. The Specification states that antibodies which “bind specifically to” HFARP are “preventing physiological action of” the polypeptide (Specification 14-15). Thus, we interpret “an antibody which specifically binds to” HFARP “whereby angiogenesis is inhibited” or “whereby the growth of the tumor is diminished” to mean that the activity of HFARP is inhibited or blocked by the antibody.

DISCUSSION

ENABLEMENT REJECTION

The Examiner rejects claims 4-9 and 15-21 under 35 U.S.C. § 112, first paragraph, as not being adequately enabled by the written description of the Specification. The Examiner contends that the Specification does not adequately enable the claimed methods of inhibiting angiogenesis (claim 4) and treating a tumor (claim 15) comprising administering an antibody which specifically binds to HFARP (SEQ ID NO: 16) (Answer 3).

The Examiner cites several references to support the position that the Specification does not adequately enable the claimed invention. We find

Kim (*Biochem J.*, 346: 603, 2000) and Qiang (*Chin. Med. J.*, 117: 1364,² 2004) to be the most pertinent.

Kim describes the identification and cloning of the gene coding for hepatic fibrinogen/angiopoietin-related protein, referred to as “HFARP” (Kim, at p. 603, Abstract) – which is the same HFARP gene that is targeted in claims 4 and 15. According to Kim, HFARP codes for a secreted protein and an apoptosis survival factor in endothelial cells which may protect them from damage (Kim, at p. 603, col. 2; at p. 609, col. 2). In cell culture using human umbilical vein endothelial cells (“HUVEC”), Kim showed that HFARP did not increase cell proliferation and therefore concluded that “HFARP . . . is not an endothelial-cell growth factor *in vitro*” (Kim at p. 607, col. 2). Kim also reported that HFARP did not induce sprouting in porcine pulmonary arterial endothelial cells (“PPAEC”) (*id.*).

Based on Kim’s conclusion that HFARP is not an endothelial growth factor and does not induce sprouting activity in endothelial cells, the Examiner finds there is no “nexus” between its activity and the claimed methods (Answer 5-6).

Qiang, which is a post-filing date publication, expressed the cloned ANGPTL4 gene (another name for HFARP) in HEPG2 tumor cells and showed that ANGPTL4 inhibited their growth (Qiang, at p. 6 (“Human ANGPTL4 inhibits tumor growth in nude mouse”). This inhibitory activity is opposite to the activity upon which claim 15 is based. Claim 15 is drawn to inhibiting HFARP; Qiang teaches that persons of skill in the art would *not* want to inhibit HFARP because the protein is itself already inhibitory. Thus,

² Numbering is from p. 1 to p. 8 in the eprint file copy.

the Examiner concludes that the “specification as filed merely extends an invitation to further experimentation to determine the function of HFARP” (Answer 12).

Analysis

“To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *Genentech, Inc. v. Novo Nordisk*, A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). “When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling.” *Wright*, 999 F.2d at 1561-1562.

In the present case, we find that the Examiner has set forth a reasonable basis for finding that the scope of the appealed claims is not enabled by the general description of the Specification. In particular, Kim’s teaching that HFARP does not stimulate endothelial cell proliferation or sprouting – all characteristics expected of an endothelial growth factor which would stimulate angiogenesis (*see* Kim, at p. 607, col. 2) – would have raised reasonable doubt that an antibody that blocks its function would inhibit angiogenesis as claimed in claim 4. If HFARP does not stimulate endothelial growth – as Kim teaches – persons of skill in the art would not

have reasonably expected its blockade with an antibody to inhibit angiogenesis.

Similarly, since Qiang teaches that HFARP is inhibitory to tumors, there is reasonable basis to doubt Appellants' assertions that blocking its activity would be beneficial to treating a tumor as recited in claim 15.

Having provided a reasonable basis to doubt the scope of enablement, the burden properly shifted to Appellants to provide evidence or arguments to rebut it.

Appellants contend that "Kim does not address the *in vivo* activity of HFARP" (Appeal Br. 7). They assert Kim only teaches that HFARP is not an endothelial-cell growth factor *in vitro* (*id.*). Appellants introduce Le Jan (*Am. J. Pathol.* 162: 1521-28, 2003) – published after the application filing date – as evidence that "HFARP is an angiogenesis factor *in vivo*" (*id.*).

Le Jan induced angiogenesis in an *in ovo* (chicken egg) neovascularization assay which involved grafting Chinese Hamster Ovary (CHO) cells expressing HFARP (referred to by its alternate name, "ANGPTL4") onto a chick chorioallantoic membrane (CAM) and observing subsequent alterations in CAM vascularization (Le Jan, at p. 1524, col. 1). Le Jan stated that the expressed HFARP induced "a major reorganization of mesodermal vessels in the CAM, the formation of a spoke-wheel pattern of vascularization toward the nodule, a feature typical of active neoangiogenesis" (Le Jan, at p. 1524, col. 1). Le Jan concluded that HFARP "is an angiogenic factor" (Le Jan, at p. 1524, col. 1). Appellants assert that "Le Jan provides direct evidence supporting the application's teaching that HFARP is involved in angiogenesis" (Appeal Br. 8).

We are not persuaded by this evidence that the Examiner erred. In fact, both the HUVEC and CAM systems are models for the asserted utility. The HUVEC system, as employed by Kim, utilizes human HFARP on human endothelial cells. Le Jan's CAM system uses human HFARP (as produced by CHO cells) on chicken cells in a chicken egg. Appellants have not provided any evidence that Le Jan's system would be considered by persons of ordinary skill in the art as more reliable and more predictive of HFARP's activity in disease treatment than Kim's. We see no evidence of record that chicken eggs experience "retinopathy, inflammation, or skin inflammation" as recited in claim 4 or "a tumor" as recited in claim 15 that would make it an obviously better model than Kim's, which uses human cells.

To the contrary, we find, as the Examiner did (Answer 11), that the conflicting results of Kim and Le Jan suggest unpredictability and the necessity for further experimentation to determine whether HFARP is pro-angiogenic (Le Jan) or not (Kim).

In addition to Le Jan, Appellants provide two other post-filing date publications to confirm the teachings of the Specification: Stull (*BMC Genomics*, 6:1-20, 2005) and Hermann (*Clin. Immunol.*, 115: 93-101, 2005; Pubmed abstract only provided).

Stull is characterized by Appellants as showing "increased HFARP expression in tumors at a time consistent with angiogenesis" (Appeal Br. 10). As pointed out by the Examiner, Stull's experiments are not a direct showing that HFARP is pro-angiogenic, but merely a correlation with a stage of tumor development as determined using a microarray (Answer 14).

Thus, we do not find that this publication addresses or resolves the conflict between the direct tests described in Kim and Le Jan.

Appellants do not provide the complete Hermann article, but only an abstract. In the Pubmed abstract, Hermann states that recombinant mouse Angptl4 – which is the same protein known as HFARP – “promoted endothelial cell survival and formation of tubule-like structures.” The Hermann abstract does not explain how the activity of HFARP is assessed. Thus, we do not know how Hermann’s assay for HFARP compares to Kim and Le Jan, one of the points of contention in this appeal. In addition, because the complete publication is not available, we can not determine the basis for the statement that HFARP promoted the “formation of tubule-like structures.” Without the complete publication, we do not consider Hermann to be persuasive evidence.

Regarding Qiang’s teaching that HFARP inhibits tumor growth – opposite to the activity upon which claim 15 is based – Appellants contend that overexpression of HFARP in HEPG2 cells may have interfered with the protein’s normal function (Appeal Br. 11). They argue that when p53, a cancer protein, was overexpressed in cells, it had the opposite of its effect when present at normal physiological levels (*id.*). Thus, p53 ““as a function of its dose . . . can either protect from [cell] death or promote”” it (Appeal Br. 11, quoting from Lassus, *EMBO J.*, 15: 4566-73, 1996).

We do not find this argument persuasive because Appellants have not provided evidence that a difference in dosage explains the discrepancy between the asserted utility for treating tumors by inhibiting HFARP and Qiang’s conflicting teaching that the same protein inhibits tumor growth. To

the contrary, we find that this conflict provides further evidence of unpredictability and the need for further experimentation.

Given the conflict between the results obtained by Kim, Le Jan, Qiang, and others, it appears that the role of HFARP is unpredictable and therefore that the art itself is also unpredictable. The claims, as summarized by the Examiner, are broad, covering a wide range of disease (angiogenesis association with retinopathy, inflammation, and skin inflammation) and tumor types (Answer 3), yet there are no actual working examples – only a prophetic one (*see* Specification 29-30, Example 7). Thus, we find that undue experimentation would have been necessary to have enabled the claimed invention. *See In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) for a discussion of factors to be considered in determining whether a disclosure would require undue experimentation to enable the claimed invention (factors include the presence or absence of working examples, the nature of the invention, the state of the prior art, the predictability or unpredictability of the art, and the breadth of the claims).

In sum, after reviewing the *Wands* factors in light of the totality of evidence before us, we find sufficient evidence to conclude that claims 4 and 15 are not adequately enabled by the Specification. We affirm the rejection of claims 4 and 15. Claims 5-9 and 16-21 fall with claims 4 and 15 because they were not separately argued. *See* 37 C.F.R. § 41.37(c)(1)(vii) (2006).

Written description rejection

Claims 4-9 and 15-21 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

The Examiner contends that the Specification does not describe the structure of antibodies which bind to HFARP and inhibit angiogenesis and tumor growth (Answer 6-7). The Examiner states that “the skilled artisan cannot envision the detailed CDRs 1-3 of the heavy and light chain of the encompassed genus of antibodies for the claimed methods, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method” (Answer 7).

According to the written description requirement of § 112, first paragraph, the “specification shall contain a written description of the invention.” 35 U.S.C. § 112, ¶ 1. For antibody claims which are defined by their function, rather than the structure of the antibody itself, the Federal Circuit has adopted the USPTO Guidelines

as persuasive authority for the proposition that a claim directed to “any antibody which is capable of binding to antigen X” would have sufficient support in a written description that disclosed “*fully characterized* antigens.” Synopsis of Application of Written Description Guidelines, at 60, available at <http://www.uspto.gov/web/menu/written.pdf> (last visited Jan. 16, 2003) (emphasis added).

Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004); *see also Enzo Biochem Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002). Thus, “as long as an applicant has disclosed a ‘fully characterized antigen,’ either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.” *Noelle*, 355 F.3d at 1349.

In this case, the antibody of claims 4 and 15 is defined functionally by having specific binding affinity to HFARP “whereby angiogenesis is inhibited” or “whereby the growth of the tumor is diminished,” respectively. Consequently, we conclude that to satisfy the written description requirement, the HFARP protein must be fully characterized.

The Specification provides the complete sequence of HFARP in a sequence listing (SEQ ID NO:16). The claims specify that the recited antibody binds to SEQ ID NO:16. In our opinion, the disclosure of the complete HFARP sequence recited in claims 4 and 15 – which is its complete formula – is sufficient to fully characterize it in fulfillment of the written description requirement. The rejection of claims 4-9 and 15-21 is reversed.

CONCLUSION

We affirm the rejection of claims 4-9 and 15-21 under § 112, first paragraph, for lack of an enabling disclosure. We reverse the rejection of claims 4-9 and 15-21 for failing to meet the written description requirement of § 112, first paragraph.

OTHER ISSUES

If prosecution of this application is resumed, the Examiner and the Appellants should consider the post-filing date publication, Ito, *Cancer Res.*, 63: 6651-6657 (2003). Ito states on page 6656, column 2:

During preparation of this manuscript, ANGPTL4, which is identical to ARP4 [and also known as HFARP], was reported to have a proangiogenic effect and to be induced under hypoxic conditions (36) [which corresponds to the same Le Jan publication relied upon by Appellants]. Although we also

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confirmed that ARP4 mRNA was induced in endothelial cells under hypoxic conditions (data not shown), we could not find a proangiogenic effect of ARP4 by any *in vitro* experiments.

Ito also reported *in vivo* experiments in transgenic mice that suggested ARP4 is not a proangiogenic factor (Ito, at pp. 6656-57).

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).

AFFIRMED

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