

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte RICCARDO CORTESE, ELISA SCARSELLI, and
ALESSANDRA VITELLI

Appeal 2008-0763
Application 10/494,555
Technology Center 1600

Decided: January 24, 2008

Before DONALD E. ADAMS, NANCY J. LINCK, and JEFFREY N.
FREDMAN, *Administrative Patent Judges*.

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DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of screening for compounds which inhibit SR-BI activity, which the Examiner has rejected as lacking an adequate description in the Specification and as failing to enable the full scope of the claims. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Background

“It is estimated that about 3% of the world's population is infected with the hepatitis C virus (HCV)” (Specification 1). The Specification discloses that as “part of its infection cycle, HCV enters into a cell. The LDL receptor and CD81 molecule have been identified as putative HCV receptors.” (Specification 1). The Specification separately notes that, “SR-BI is highly expressed in the liver hepatocytes and steroidogenic tissues, and mediates the selective cellular uptake of cholesterol and phospholipids.” (Specification 5).

Appellants teach that the “identification of SR-BI as a site for HCV E2 binding provides a target that can be modulated to study the HCV infection cycle and to inhibit HCV replication or infection” (Specification 6). According to Appellants, the “ability of a test compound to modulate the interaction between SR-BI and HCV E2 can be performed for example, using assays employing a naturally occurring SR-BI or derivative thereof that binds HCV E2, a compound that binds to the SR-BI HCV E2 binding site, and the test compound” (Specification 6).

Statement of the Case

The Claims

Claims 4-12 and 19-22 are on appeal¹. We will focus on claim 4 which is representative and reads as follows:

¹ Claims 5-12 and 19-22 were not separately argued. These claims therefore stand or fall together with claim 4. 37 C.F.R. § 41.37(c)(1)(vii). With regard to claim 7, *see* 37 C.F.R. § 41.37(c)(1)(vii) (“A statement which

4. A method of screening for a compound that inhibits SR-BI activity comprising the steps of:
- a) contacting a cell capable of expressing SR-BI which is either a human SR-BI or a protein having at least 95% sequence similarity to SEQ ID NO: 1, with a polypeptide that binds to the SR-BI HCV E2 binding site and with a test compound, wherein said polypeptide comprises a naturally occurring HCV E2 region binding to said SR-BI; and
 - b) measuring the ability of said test compound to inhibit one or more of the following: (i) binding of said polypeptide to said SR-BI, (ii) HCV internalization, and (iii) functional surface expression of said SR-BI; as an indication of the ability of said compound to inhibit said SR-BI activity; wherein said cell is pre-incubated with said test compound prior to adding said polypeptide.

The Issues

Written Description

Claims 4-5 and 19 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that the claims are drawn to methods of screening for compounds that inhibit HCV E2 interactions with a protein that is at least 95% similar to human SR-BI and the specification does not

provide any sufficiently identifying characteristics of the variants of the SR-BI protein. The application discloses SEQ ID NO: 1, but does not identify what residues or regions within the protein are required for its HCV E2 binding activity. Thus, while the application provides a function desired by the variants (i.e. HCV E2 binding), the application does not identify any structure that correlates with that function.

merely points out what a claim recites will not be considered an argument for separate patentability of the claim.”)

(Answer 4.) Further, Appellants did show that the murine analog of SR-BI, with 80% homology to human SR-BI, “does not have the requisite binding activity” (Answer 4). The Examiner finds that the Specification does not provide an adequate written description of the claimed method (Answer 5).

We agree with the Examiner that the Specification does not adequately describe the claimed method. Describing a claim to a method requires describing the compounds used in the method.

[T]he inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods. As the district court observed, “[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment.”

University of Rochester v. G.D. Searle & Co., 358 F.3d 916, 926 (Fed. Cir. 2004).

Claim 4 requires use of an SR-BI molecule which, when expressed in a cell, will be capable of being inhibited in either binding to HCV-E2, in HCV internalization, or in functional surface expression. The Specification therefore must adequately describe that genus of compounds.

The written description requirement can be met by disclosing “complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.” *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964, (Fed. Cir. 2002).

In this case, the Specification provides the complete sequence of the 509 amino acids which comprise SR-BI in SEQ ID NO: 1 (*see* Specification 6). The Specification indicates that only 20 amino acids of the 509 amino acid SR-BI protein are required for the interaction of SR-BI and the HCV E2 protein (Specification 6, ll. 28-32).

The Specification specifically refers to a putative SR-BI binding site for HCV E2, noting that polypeptides “capable of binding to the SR-BI HCV E2 binding site contain a region able to bind to the same site as HCV E2” (Specification 9, ll. 22-23). The Specification later references this SR-BI binding site in assay development suggesting that antibodies “binding to a region distinct from the SR-BI HCV E2 binding site can be employed to detect binding using capture assay formats” (Specification 13, ll. 4-5).

However, the Specification does not describe any of the specific structural features of SR-BI which give rise to the function of HCV E2 binding. In fact, the Specification fails to identify which region, or regions, within the 509 amino acid SR-BI protein are involved in HCV E2 binding. The Specification demonstrates that the mouse SR-BI, which has 80% amino acid similarity to the human SR-BI, does not bind HCV E2 (*see* Specification 23, ll. 17-20).

The present case is therefore analogous to *Rochester*. In *Rochester*, the patent claimed a method of selectively inhibiting the enzyme PGHS-2 (also known as COX-2) by “administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human.” *Rochester*, 358 F.3d at 918. The patent “describes in detail how to make cells that express either COX-1 or COX-2, but not both . . . , as well as

‘assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product.’” *Rochester*, 358 F.3d at 927.

The court held that even if a DNA sequence might support a claim to hybridizing nucleic acids, the “same is not necessarily true in the chemical arts more generally. Even with the three-dimensional structures of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them.” *Rochester*, 358 F.3d at 925.

The concern is even more acute in the current case. Unlike the situation in *Rochester*, in which the claims involved only the use of the natural COX-2 molecule, here the claims encompass any protein that is 95% similar to the 509 amino acid SR-BI protein. That five percent variance results in a situation in which even if a 25 contiguous amino acid region is independently varied among the 20 different naturally occurring amino acids, there would be 3.35×10^{32} different possible molecules. In fact, since the variations could occur anywhere within the SR-BI protein, the actual number of different possible molecules is orders of magnitude greater than 3.35×10^{32} .

Appellants have not provided any identification of a single region or multiple regions within the SR-BI protein which are involved in HCV E2 binding. Appellants have not provided any identification of critical residues in the SR-BI protein which are essential to HCV E2 binding.

As in *Rochester*, the present application discloses the assay for screening SR-BI but fails to provide SR-BI regions other than the wild type shown in SEQ ID NO: 1 which bind to HCV E2.

As the district court pointed out: Tellingly, . . . what plaintiff's experts' [sic] do not say is that one of skill in the art would, from reading the patent, understand what compound or compounds-which, as the patent makes clear, are necessary to practice the claimed method-would be suitable, nor would one know how to find such a compound except through trial and error Plaintiff's experts opine that a person of ordinary skill in the art would understand from reading the '850 patent what method is claimed, but it is clear from reading the patent that one critical aspect of the method-a compound that selectively inhibits PGHS-2 activity-was hypothetical, for it is clear that the inventors had neither possession nor knowledge of such a compound.

Rochester, 358 F.3d at 925-26.

Just as in *Rochester*, it is "hypothetical" which amino acid modifications of SR-BI will share the claimed activity of binding to HCV E2. In the Specification, there is no description that would show Appellants possessed or had knowledge of any such specific compound.

Appellants argue that in contrast with *Rochester*, the "skilled artisan can readily determine whether a protein has at least 95% sequence identity to SEQ ID NO: 1" (App. Br. 9). However, the issue is not whether the protein is 95% identical to SEQ ID NO: 1, but rather that functional information regarding HCV E2 binding is not correlated to any specific SR-BI structure. As the court in *Enzo* noted, written description may be met with "functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such

characteristics.” *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002). It is the absence of any knowledge of structural elements within SR-BI which mediate the interaction with HCV-E2 that fails the *Enzo* description test. Here, as many as 25 amino acids in SR-BI may be altered based upon the 95% identity language. However, based upon the disclosure in the Specification, Appellants lacked possession of any method, other than trial and error, to determine whether the alterations will impact the binding to HCV-E2 (Answer 6). We find that in the absence of knowledge of which structural elements of SR-BI are involved in HCV E2 binding, Appellants did not possess subsets of SR-BI molecules in the immense genus encompassed by the 95% similarity language which would retain the binding function.

Appellant contends that while “the application does not indicate which HCV E2 amino acids bind SR-BI, the skilled artisan can readily determine which sequence of the full-length protein is involved in binding” (App. Br. 10). This argument conflates the issue of written description with that of enablement. These are separate statutory requirements. *See Rochester*, 358 F.3d at 921 (“an invention may be enabled even though it has not been described”). In this application, the enablement rejection was withdrawn by the Examiner (*see* Answer 3). Thus, the enablement arguments need not be addressed.

Appellants argue that the present situation differs from *Rochester* in that the “present application includes both examples of polypeptides that can be used in the claimed method and guidance steering the skilled practitioner towards additional polypeptides structurally related to the exemplified

polypeptides” (App. Br. 10). Appellants state that there is guidance steering the practitioner to additional polypeptides but fail to identify any such guidance in the specification of alternate SR-BI molecules which function in the screening assay (App. Br. 10).

This argument fails to appreciate the guidance required to describe a genus of more than 3.35×10^{32} different possible molecules. Without specific delineation of which regions within SR-BI are necessary for HCV E2 binding, Appellants are imposing a trial and error approach on the ordinary artisan interested in extending this invention beyond the SR-BI of SEQ ID NO: 1. *See Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000)(“The purpose of this provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.”).

With no structural guidance, the ordinary artisan is left to trial and error screening on how to distinguish which of the more than 3.35×10^{32} different possible SR-BI related molecules would be useful in the claimed screening assay. The disclosure of one species, human SR-BI, does not provide description of an entire undescribed genus of proteins that are 95% similar to SR-BI. *See Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997)(“These cases do not compel the conclusion that a description of a species always constitutes a description of a genus of which it is a part.”)

Appellants argue that

the Examiner appears to be making an argument that is relevant to only the small subgenus of proteins having one

or more mutations that happen to be in a small portion of the protein - namely the binding site. The argument fails to indicate the extent to which the entire genus of proteins with at least 95% sequence identity would not be expected to bind HCV E2.

(Reply Br. 1.) We reject this argument because Appellants fail to appreciate that the ordinary artisan lacks any guidance as to which members of large genus of 95% identical proteins will fall into the “small subgenus” with mutations in the binding site because there is no guidance as to where the binding site is located in SR-BI.

We affirm the rejection of claim 4 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description. Claims 5 and 19 fall with claim 4.

Enablement

Claims 4-12 and 19-22 stand rejected under 35 U.S.C. § 112, first paragraph², on the basis that the Specification

while being enabling for methods of screening for compounds that inhibit the SR-BI activity of binding to HCV E2 comprising the measurement of the binding of a polypeptide that binds to the SR-BI HCV E2 binding site to SR-BI, does not reasonably provide enablement for methods of screening for inhibitors of any SR-BI activity comprising the same method steps.

(Answer 7.) The Examiner reasons that

² The Examiner notes that the elected embodiment is drawn to screening for inhibition of binding of SR-BI and HCV E2 (Answer 12).

inhibition of the binding between SR-BI and the HCV E2 protein is not indicative of the ability of the compound to inhibit any SR-BI activity. This is because SR-BI is accepted in the art to perform multiple activities involving multiple binding sites, and as it has been shown that compounds affecting one SR-BI activity do not indicate that the same compound would affect other SR-BI activities.

(Answer 12.) The Examiner cites the Acton and Connelly references to demonstrate that SR-BI has activities that are not involved in binding to HCV E2 (*see* Answer 8).

The Examiner concludes that, because of the paucity of guidance and working examples on other SR-BI activities beyond the interaction with HCV E2, undue experimentation would be required to determine the effect of SR-BI inhibitors (Answer 9).

Findings of Fact

1. The Specification does not describe the structure of the SR-BI binding site for HCV E2 (*see* Specification 2, ll. 23-28).
2. The Specification teaches that SR-BI can independently bind HCV E2 and CD81 (Specification 5).
3. The Hepatitis C virus can bind to proteins other than SR-BI on the surface of cells, including the LDL receptor and CD81 (Specification 1).
4. There is only a single working example of a single compound (an antibody) which functions to inhibit the binding of SR-BI and HCV E2 (Specification 23).
5. There is no working example demonstrating any effect of any compound on HCV internalization or on functional surface expression of SR-BI.

6. SR-BI has “functional surface” activities other than binding to HCV E2, including selective uptake of HDL cholesteryl ester (*see* Connelly at 5249).

7. The “present studies as well as those reported earlier on HDL CE selective uptake indicate that a spectrum of rather distinct SR-BI-mediated activities is localized to the extracellular domain of this receptor” (Connelly at 5257).

Discussion

We agree with the Examiner that the Specification does not provide sufficient guidance to enable practice of the full scope of the claimed method without undue experimentation. The nature of the invention is such that it is in the class of invention which the Federal Circuit has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001). The claim broadly encompasses inhibition of the activity of proteins 95% identical to SR-BI other than binding of HCV E2 to SR-BI, including “(ii) HCV internalization, and (iii) functional surface expression of said SR-BI” (Claim 4). Thus, the breadth of the claims is not commensurate in scope with disclosure of the Specification.

As noted above, the Specification provides no description even of the HCV E2 binding site on the SR-BI molecule (FF 1). The Specification teaches only that SR-BI binds HCV E2 independently of CD81 (*see* FF 2). The Specification notes that HCV binds to proteins other than SR-BI on cells, including the “LDL receptor and CD81 molecule. . . . The LDL receptor has been suggested to mediate virus internalization via binding to

LDL particles that are virus associated . . . The CD81 molecule has been suggested to bind HCV E2 based on recombinant envelope protein E2 from HCV genotype 1a” (Specification 1). Therefore, the prior art, recognized by the Specification, teaches that HCV internalization can be mediated by proteins other than SR-BI, and supports the conclusion that it is unpredictable whether inhibition of HCV E2 binding will necessarily prevent HCV internalization.

The only working example in the Specification is shown in Example 5, where a monoclonal antibody functions to inhibit binding of HCV E2 protein to cells transfected to express SR-BI (FF 4). There is no working example demonstrating any effect of any compound on HCV internalization or on functional surface expression of SR-BI (FF 5).

The Examiner also notes that SR-BI has “functional surface” activities other than binding to HCV E2, including selective uptake of HDL cholesteryl ester (*see* FF 6). The prior art further notes that the “present studies as well as those reported earlier on HDL CE selective uptake indicate that a spectrum of rather distinct SR-BI-mediated activities is localized to the extracellular domain of this receptor” (Connelly at 5257). The Specification is entirely silent on guidance regarding how the presence of HCV E2 will affect these “functional surface” activities of SR-BI. Additionally, the Specification does not address how the variation included by the 95% similarity language will alter any of the different SR-BI activities by altering their domain in unpredictable ways.

We do not agree that “Step (b)(iii) is not directed to assaying for a modulator of SR-BI/HCV binding that would have an effect on surface

expression of the SR-BI. Rather, the step is directed to an inhibitor that reduces expression of SR-R1” (App. Br. 11). The Specification does not support this narrow reading of the term, noting “Compounds modulating functional surface expression at the post-transcriptional level include compounds acting on lipid rafts membrane compartments (referred to as "raft domains") to alter SR-BI activity. SR-BI activity that can be altered by such compounds include HCV binding and internalization” (Specification 3). We decline to read a limitation into the claim that inhibition of the “functional surface activities” is limited to reducing expression of SR-BI when that limitation is not present in the claim. *See In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993) (“limitations are not to be read into the claims from the specification”).

The Examiner has provided specific references which disclose that SR-BI has multiple activities unrelated to HCV E2 and that “the teachings of the reference demonstrate that compounds that inhibit one SR-BI activity would not necessarily have any effect on any other SR-Bi activity” (Answer 8). This is the essence of unpredictability in the enablement context. It is unpredictable whether a compound which inhibits HCV internalization will have any effect on SR-BI activity, since SR-BI activity is not required for interaction of HCV with cell surface proteins and since no evidence that SR-BI is required for HCV internalization has been presented.

We affirm the rejection of claim 4 under 35 U.S.C. § 112, first paragraph, as it would require undue experimentation to identify SR-BI domains involved in HCV internalization and functional surface expression. Claims 5-12 and 19-22 fall with claim 4.

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CONCLUSION

In summary, we affirm the rejection of claim 4 under 35 U.S.C. § 112, first paragraph, written description and enablement. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 5-12 and 19-22 under 35 U.S.C. § 103(a) as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

Ssc:

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