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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SUNIL CHADA

Appeal 2009-015169
Application 11/001,702
Technology Center 1600

Before ERIC GRIMES, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 involving claims to a method of suppressing or preventing an infection. The Examiner has rejected the

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

claims for lack of enablement. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

The Specification discloses that "[m]elanoma differentiation associated gene 7 (*mda7*) is a tumor suppressor gene. . . . The inventors have discovered that MDA-7 functions in a manner that involves certain pathways in cancer cells that are involved in pathogen infection and pathogen replication." (Spec. 5: 11-17.)

Claims 1, 2, 15, 16, 20-27, 30-35, 37-44, and 47 are on appeal. Claims 1 and 32 are representative and read as follows:

1. A method of suppressing or preventing an infection of a subject by a pathogen, comprising administering to the subject a composition comprising: (a) a therapeutically effective amount of an MDA-7 polypeptide or a nucleic acid encoding the MDA-7 polypeptide; and (b) a pharmaceutically acceptable preparation suitable for delivery to said subject, wherein the MDA-7 suppresses or prevents the infection.

32. A method of suppressing or preventing a viral infection of a cell, comprising: (a) obtaining an MDA-7 polypeptide or a nucleic acid encoding the MDA-7 polypeptide; and (b) contacting the cell with the MDA-7 polypeptide or the nucleic acid encoding the MDA-7 polypeptide; wherein the MDA-7 suppresses or prevents infection of the cell.

The Examiner states that, as a result of a restriction requirement, "examination has been limited to the elected nucleic acid encoding MDA-7, administered intravenously" (Answer 3).

Issue

The Examiner has rejected all of the claims on appeal under 35 U.S.C. § 112, first paragraph, on the basis that the "specification is not enabling for

a method of suppressing or preventing a Hepatitis C viral infection of a subject or a cell, comprising intravenous administration to said subject of a therapeutically effective amount of an adenoviral or non-viral vector encoding the MDA-7 polypeptide, or contacting a cell with said nucleic acid" (Answer 3).

The Examiner finds that the Specification does not provide an adequate basis for "correlating the anti-cancer apoptotic action of MDA-7 to suppressing or preventing viral infection" (*id.* at 4). The Examiner also finds that practicing the claimed method using "adenoviral or non-viral vectors encoding mda-7, delivered by intravenous administration" (*id.* at 5) would require undue experimentation because "adenoviral mediated gene delivery is associated with a number of significant problems . . . [and] intravenous delivery of mda-7 nucleic acid via a non-viral vector would not likely result in the cell targeting and expression of MDA-7 to any significant degree" (*id.* at 6).

Appellant contends that "one of ordinary skill in the art, in view of the teachings of the instant specification, would understand that MDA-7 induces PKR expression, that this PKR expression exerts antiviral and anticellular function, and that MDA-7 can thus be applied in the prevention or suppression of viral infection in a subject" (Appeal Br. 4). Appellant also contends that declaratory evidence and the prior art show that undue experimentation would not be required to practice the claimed method using adenoviral or non-viral vectors (*id.* at 9-11).

The issue presented in this appeal is: Does a preponderance of the evidence of record support the Examiner's conclusion that practicing the

claimed method to treat infection with hepatitis C virus, by administering MDA-7-encoding DNA via an adenoviral or non-viral vector, would require undue experimentation?

Findings of Fact

1. The Examiner finds that Bottaro[2] provides evidence that MDA-7 would not be useful for suppressing or preventing viral infection, because Bottaro "discloses methods of protecting cells from HIV-1 pathogenesis using inhibitors of PKR" (Answer 4).

2. Bottaro discloses "antagonists of double-stranded RNA dependent protein kinase (PKR). . . . [T]he PCR [sic, PKR] antagonists are administered to provide protection from the excessive cell death caused by human immunodeficiency virus type 1 (HIV-1)." (Bottaro, col. 5, ll. 35-45.)

3. The Examiner finds that the "specification is silent on providing any evidence of suppression or prevention for hepatitis C infection or any other type of viral infection in a subject. Therefore, no connection is evident between the described apoptotic effects of MDA-7 and the claimed suppression or prevention of viral infection." (Answer 5.)

4. The Specification discloses that one "mechanism whereby viruses ensure translational efficiency involves the cellular kinase known as interferon-induced, double stranded (ds) RNA-activated serine/threonine protein kinase (PKR)" (Spec. 3: 7-9).

5. The Specification discloses that PKR "mediates the antiviral actions of interferon" (*id.* at 3: 19).

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[2] Bottaro et al., US 6,326,466 B1, Dec. 4, 2001

6. The Specification discloses that "[m]any viruses inhibit PKR activity. One such example is Hepatitis C virus (HCV). . . . Other examples of viruses that inhibit PKR activity include adenovirus, EBV, poxvirus, influena [sic] virus, reovirus, HIV, polio, HSV, and SV40." (*Id.* at 3: 25-31.)

7. The Specification discloses that "Ad [adenovirus]-*mda-7* has been shown to induce and activate PKR in cancer cells, which leads to . . . induction of apoptosis" (*id.* at 15: 11-12).

8. The Specification discloses that "Ad-*mda7* apoptosis is dependent on a functional PKR pathway. These characteristics indicate that MDA-7 has broad therapeutic, prognostic and diagnostic potential as an inducer of PKR and, consequently, an enhancer of an induced immune response." (*Id.* at 34: 27-30.)

9. The Specification discloses that "[a]nother mediator of ER [endoplasmic reticulum] stress is the Unfolded Protein Response (UPR). . . . Prolonged UPR activation leads to activation of death-related signaling pathways and ultimately, to apoptotic death." (*Id.* at 4: 9-15.)

10. The Specification discloses that the "UPR is used by many endoplasmic reticulum-tropic viruses . . . to facilitate their life cycle and pathogenesis" (*id.* at 4: 15-17).

11. The Specification discloses that "pathogens other than viruses can activate the PKR and UPR defense systems" (*id.* at 4: 21-22).

12. The Specification discloses that "Ad-*mda7* transduction of lung cancer cells results in activation of the UPR. . . . In view of the fact that the UPR is exploited by viruses, these findings further support the inventors'

discovery that MDA-7 can be applied in the prevention and treatment of infections of subjects by pathogens." (*Id.* at 5: 19-25.)

13. The Specification discloses that "expression of . . . UPR-associated proteins is up-regulated after Ad-*mda7* transduction, suggesting that UPR activation was the mechanism by which MDA-7 was killing cancer cells" (*id.* at 62: 13-15).

14. The Examiner finds that Wilson[3] discloses that when adenovirus is infused directly into the blood, it targets essentially only hepatocytes, or liver cells (Answer 5).

15. Appellant has provided two declarations under 37 C.F.R. § 1.132 (dated March 16, 2007 ("First Chada Declaration") and Nov. 30, 2007 ("Second Chada Declaration")).

16. Appellant declared that Tolcher[4] "contradicts the Examiner's belief that intravenous or systemic delivery of adenoviral vectors may be dangerous," and provides evidence that systemically administered adenoviral vectors can transduce cells that are distant from the site of administration (First Chada Declaration, ¶ 5).

17. Tolcher discloses that "Ad5CMV-p53 can be feasibly administered at doses up to 3 x 10^{12} vp IV daily for 3 days every 28 days to patients with advanced solid tumors. . . . The safe, prolonged circulation of

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[3] Wilson, *Adenovirus-Mediated Gene Transfer to Liver*, 46 Advanced Drug Delivery Reviews 205-209 (2001)

[4] Tolcher et al., *Phase I, Pharmacokinetic, and Pharmacodynamic Study of Intravenously Administered Ad5CMV-p53, an Adenoviral Vector Containing the Wild-Type p53 Gene, in Patients with Advanced Cancer*, 24 J. Clin. Oncol. 2052-2058 (2006)

the intact vector, and successful transduction of *p53* into tumor cells at sites distant from Ad5CMV-p53 IV administration represents an important proof of concept." (Tolcher 2057.)

18. Appellant declared that Mhashilkar[5] discloses that "MDA-7 is actively secreted from cells. . . . Therefore, if one hepatic cell were to be transduced with an adenoviral vector with a nucleic acid encoding MDA-7, the subsequent MDA-7 polypeptide would be secreted and interact with other hepatic cells." (Second Chada Declaration, ¶ 6.)

19. The Second Chada Declaration provides data "demonstrat[ing] that increasing dosages of MDA-7 result in a linear dose-dependent decrease in the production of hepatitis C viral RNA. . . . [B]oth interferon [a positive control] and MDA-7 suppress hepatitis C infection by preventing hepatitis C replication." (Second Chada Declaration, ¶ 5.)

20. The Examiner finds that "expression of any gene of interest encoded by a simple nucleic acid, such as a plasmid . . . , would be transient and would not allow sustained suppression of a viral infection in a subject" (Answer 6).

21. The Specification discloses that methods of administering genetic material, including MDA-7-encoding DNA, to host cells via lipid-mediated transformation were known in the art (Spec. 49-51).

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[5] Mhashilkar et al., *Melanoma Differentiation Associated Gene-7 (mda-7): A Novel Anti-Tumor Gene for Cancer Gene Therapy*, 7(4) Molecular Medicine 271-282 (2001)

Principles of Law

> 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.

In re Wright, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993).

Analysis

We agree with Appellant that the Examiner has not provided evidence or sound scientific or logical reasoning sufficient to support a conclusion that practicing the claimed method would require undue experimentation. The Examiner asserts that the Specification does not adequately correlate the tumor-suppressing apoptotic activity of MDA-7 with its use in suppressing or preventing viral infection (Answer 5). However, the Specification discloses that MDA-7 induces and activates PKR (FF 7), which is inhibited by many viruses (FF 6), and which mediates the antiviral activity of interferon (FF 5). The Specification also discloses that MDA-7 activates the Unfolded Protein Response (UPR) (FF 12), which leads ultimately to apoptotic cell death (FF 9). In addition, Appellant has provided declaratory evidence showing that expression of MDA-7 causes a dose-dependent reduction in transcription of hepatitis C virus RNA (FF 19).

As evidence showing that MDA-7 is not useful for suppressing or preventing viral infection, the Examiner cites Bottaro's disclosure that PKR

antagonists can be used to protect cells from HIV-1 pathogenesis (FF 1). Considered in context, however, Bottaro's statement does not contradict the Specification's disclosure. Bottaro discloses the use of PKR antagonists to protect cells from being killed by HIV-1 (FF 2), while the Specification discloses that MDA-7 causes apoptosis (cell death) by activating PKR and UPR in cancer cells (FFs 7, 9, 12); causing apoptosis in virus-infected cells would suppress or prevent further infection by limiting the number of infectious viral particles. Bottaro therefore does not support the Examiner's rejection.

The Examiner has asserted that "cell death is not a desired outcome in any therapeutic approach and should be avoided, as taught by Bottaro" (Answer 8). This broad assertion, however, is not supported by Bottaro, or by the state of the art: a skilled worker would recognize that killing cancer cells or virus-infected cells before they can further spread the cancer or virus infection would be therapeutically effective, and in fact is the objective of most anti-cancer and anti-viral therapies.

The Examiner also asserts that practicing the claimed method using either adenoviral vectors or non-viral vectors, administered intravenously, would require undue experimentation because intravenously administered adenoviruses target essentially only hepatocytes (FF 14), and a non-viral vector would lead only to transient expression of MDA-7, which would not allow sustained suppression of viral infection (FF 20).

The Examiner has not adequately shown that these considerations would result in a need for undue experimentation. Appellant has provided evidence that MDA-7 is secreted from cells in which it expressed (FF 18)

and therefore would affect cells other than those into which an MDA-7-encoding vector was introduced. Appellant also argues that hepatitis C virus infects hepatocytes (liver cells) (Appeal Br. 11), the cells targeted by adenoviral vectors according to Wilson (FF 14). While the Examiner argues that HCV infects cells of tissues other than the liver (Answer 11), Appellant has provided evidence that adenoviral vectors are not limited to infecting hepatocytes (FF 17).

With regard to non-viral vectors, the Examiner has not provided evidence to support the assertion that only transient expression can be attained using non-viral vectors, or to show that transient expression would be inadequate to practice the claimed method. The Examiner therefore has not provided an adequate basis for disputing the Specification's disclosure that the claimed method can be practiced routinely using non-viral vectors (e.g., administered via lipid-mediated transformation).

In sum, the Examiner has not provided sufficient evidence to support a conclusion that practicing the claimed method would require undue experimentation.

Conclusion of Law

A preponderance of the evidence of record does not support the Examiner's conclusion that practicing the claimed method to treat infection with hepatitis C virus, by administering MDA-7-encoding DNA via an adenoviral or non-viral vector, would require undue experimentation.

SUMMARY

We reverse the rejection of claims 1, 2, 15, 16, 20-27, 30-35, 37-44, and 47 for lack of enablement.

REVERSED

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