

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 56

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte RONALD M. EVANS,
EMILIANA F. BORRELLI, and
RICHARD A. HEYMAN

Appeal No. 2001-1293
Application No. 08/464,271

ON BRIEF

Before SCHEINER, ADAMS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 3-8, 12, 29, 31-41, 44, and 45, all of the claims remaining.

Claims 44 and 38-40 are representative and read as follows:

44. A method for selectively inhibiting growth or causing death of a tissue-type or cell line in an intact organism;

wherein said tissue-type or cell line comprises endogenous thymidine kinase and further comprises DNA encoding and expressing an exogenous enzyme that selectively converts a latent toxin into a cell toxin in said tissue-type or said specific cell line, where said DNA is operatively linked to a promoter specific for said tissue-type or said cell line,

said method comprising administering to said organism an amount of said latent toxin effective to trigger generation of said cell toxin by enzymatic conversion of the latent toxin; thereby selectively inhibiting growth or causing death of at least a substantial portion of said tissue-type or cell line.

38. A method according to Claim 42 wherein said exogenous enzyme is selected from non-mammalian enzymes that catalyze the conversion of the latent toxin into a cell toxin for said cell line.
40. A method according to Claim 39 wherein said viral enzyme is herpes simplex thymidine kinase.

The examiner relies on the following references:

Ledley, "Somatic gene therapy for human disease: Background and prospects. Part I," The Journal of Pediatrics, Vol. 110, pp. 1-8 (1987)

Kappel et al. (Kappel), "Regulating gene expression in transgenic animals," Current Opinion in Biotechnology, Vol. 3, pp. 548-553 (1992)

Mullen, "Metabolic suicide genes in gene therapy," Pharmac. Ther., Vol. 63, pp. 199-207 (1994)

Claims 3-8, 12, 29, 31-41, 44, and 45 stand rejected under 35 U.S.C.

§ 112, first paragraph, as nonenabled.

We affirm in part.

Background

The specification discloses a method of "establishing stable transgenic cell populations and then selectively ablating (i.e., negatively selecting for) specific cell types and/or cell lineages in such transgenic cell populations at desired stages of development or differentiation." Page 1.

According to the invention method, (C) cells that express exogenous gene (G) and thus contain enzyme (E) within the transgenic cell population, when exposed to a specific latent toxin, i.e., non-toxic drug substance that enzyme (E) converts into a

substance that is toxic to the cells (C), are eliminated from the original cell population. In this manner, the toxic potential of the cell (C) is actualized, thus allowing specific cell (C) types within the transgenic cell population to be negatively selected for, i.e., to be ablated. In addition, by controlling the amount of expression of gene (G) in cell (C), which can be done, for example, by linking the gene (G) to a "weak" or a "strong" tissue-specific promoter, and by controlling the rate, dose and/or timing of the exposure of cell (C) to the non-toxic drug compounds, it is possible to control the degree and timing of the resulting genetic ablation.

Id., page 10.

The specification discloses several exemplary tissue-specific promoters suitable for use in the disclosed method. See page 8. The specification also discloses that the exogenous enzyme can be herpes simplex virus thymidine kinase (HSV-TK). See, e.g., pages 16-17. No other examples of suitable exogenous genes or enzymes are disclosed, although the specification notes that "[o]ther enzymes which can be used in the practice of the present invention are non-mammalian, i.e., enzymes which are not native to the host cells contemplated for the generation of a transgenic cell population." Page 15.

The specification discloses that the method "makes it possible to progress from mild cellular degeneration to almost complete destruction of a specific cell line, thus providing the ability to (1) create valuable animal models with which to study lineage formation and cell function; (2) treat diseased individuals by selective ablation of disease cells, and (3) selectively ablate any cell line."

Specification, page 19.

Discussion

The claims stand or fall together. Appeal Brief, page 6. We will consider independent claim 44 as representative of the claimed method. The remaining claims will stand or fall with claim 44.¹

Claim 44 is directed to a method for killing cells of a particular tissue-type or cell line in an organism, where the targeted cells comprise endogenous thymidine kinase and exogenous DNA, linked to a tissue-specific promoter, encoding an enzyme that converts a latent toxin to a cell toxin. The only manipulative step recited in claim 44 is that of “administering to said organism an amount of said latent toxin effective to trigger generation of said cell toxin by enzymatic conversion of the latent toxin; thereby inhibiting growth or causing death of at least a substantial portion of said tissue-type or cell line.”

The examiner rejected the claims as nonenabled, on the basis that the specification “does not reasonably provide enablement for a method of selectively inhibiting the growth or causing death of all tissue types in any and all intact organisms comprising producing all transgenic organisms comprising DNA encoding and expressing any and all exogenous enzymes that selectively convert a latent toxin into a cell toxin, wherein said DNA is operatively linked to a promoter specific for any and all tissue types.” Examiner’s Answer, page 4.² The examiner thus concluded that the claims were overly broad with respect to the

¹ We will, however, consider claims 40 and 41 separately, for reasons that are explained infra.

² The examiner also concluded that the specification does not “enable methods of selectively inhibiting the growth or causing death of all tissue types in any and all intact organisms comprising using any and all methods of gene therapy.” Id. For reasons that will become clear, we need address this basis of the rejection only with regard to claims 40 and 41.

scope of: (1) the tissue types subject to ablation; (2) the organisms in which the method is carried out; (3) the exogenous enzymes expressed; and (4) the tissue-specific promoter used.

With respect to the scope of tissue types, organisms, and promoters, the examiner has not convincingly shown that undue experimentation would have been required to practice the claimed method. The specification provides a list of tissue-specific promoters that are expressed only in B-lymphocytes, specific populations of T-lymphocytes, pituitary cells, and adrenal medullary and sympathetic neuron cells. See page 8. The specification also states that the exogenous DNA can be introduced into the appropriate cells by a variety of known methods, including infection with retroviral constructs, microinjection, or transfection. See pages 11-12. Finally, the specification provides working examples showing specific killing, upon exposure to a nucleoside analog, of spleen and thymus cells (and lymphoma cells in one experiment) in transgenic mice transformed with a construct encoding HSV-TK under the control of an immunoglobulin light-chain promoter and heavy-chain gene enhancer. See pages 23-37.

The examiner has conceded that the specification is enabling for ablation of lymphoid cells in mice using the exemplified system (Examiner's Answer, page 6), but asserted that the record lacks evidence to show that "transgenic animals of any and all species [could be produced] such that specific ablation of a desired cell population can be achieved without undue experimentation." Examiner's Answer, page 6. The examiner concluded that the enabling scope of the

specification was limited to the single embodiment specifically exemplified.

Examiner's Answer, page 8.

The examiner has not shown, however, that undue experimentation would have been required to practice the claimed method in species other than mice, or to substitute other tissue-specific promoters for the exemplified lymphoid-specific promoter in order to ablate cells of other tissues. The examiner carries the initial burden of showing nonenablement. In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (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.").

In this case, the examiner relies heavily on "the unpredictability of the transgenic art." See the Examiner's Answer, page 6 (emphasis in original): "It was well known in the art that the expression of a transgene and the effects of its expression on the animal as a whole are not predictable due to numerous uncontrollable factors such as the site of integration and methylation-inactivation of the transgene. See Kappel et al., the right column of page 549." We can accept for the sake of argument that the transgenic art in general is subject to a large amount of unpredictability. Here, however, Appellants have demonstrated that this unpredictability does not prevent the claimed method from specifically ablating lymphoid cells in mice. Thus, the evidence shows that the sources of

unpredictability cited by the examiner did not prevent the method from having its intended effect in vivo.

The examiner, in considering enablement, appears not to have given appropriate weight to Appellants' demonstrated success. That is, since the claimed method has been demonstrated in mice, with a HSV-TK expression construct under the control of a lymphoid-specific promoter, the question with respect to enablement is: would undue experimentation have been required to extrapolate from that successful experiment to practice the claimed method in other organisms, with other tissue-specific promoters, or with other toxin-converting enzymes? The examiner has not presented adequate evidence or reasoning to show that it would have required undue experimentation to extrapolate the exemplified method to other organisms, to identify and obtain other tissue-specific promoters, or to substitute other tissue-specific promoters with a reasonable expectation of causing a similar effect in other tissues. Thus, we conclude that these factors cannot support a rejection for nonenablement.

However, we agree with the examiner that the specification does not provide adequate guidance to enable practice of the claimed method using any "DNA encoding and expressing an exogenous enzyme that selectively converts a latent toxin into a cell toxin" in the targeted cells. The only gene identified in the specification as encoding an enzyme meeting this limitation is the HSV-TK gene. See, e.g., page 15. The working examples disclosed in the specification all use the HSV-TK/nucleoside analog system. The specification provides no meaningful guidance with respect to other genes that meet the criteria recited in

the claims or the latent toxin(s) that the encoded enzyme would act on to convert into a cell toxin.

The only guidance provided in the specification with regard to other enzymes is that “[o]ther enzymes which can be used in the practice of the present invention are non-mammalian, i.e., enzymes which are not native to the host cells contemplated for the generation of a transgenic cell population.” Page 15. Essentially, this passage simply states that other exogenous enzymes that can be used are exogenous enzymes. This “guidance” does nothing to reduce the experimentation that the skilled artisan would have to undertake in order to practice the invention as broadly as it is claimed.

“Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Those considerations include “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” Id.

Here, most of the Wands factors tend to show that the claims are not fully enabled. Claim 44 reads on a method of using any enzyme that converts any nontoxic compound into a toxic compound. Thus, the claims are very broad; much broader than the guidance and working examples provided in the specification, which are limited to HSV-TK.

The state of the prior art does not appear to contribute significantly to the enabling scope of the disclosure. Mullen discusses “metabolic suicide genes” which appear to meet the criteria recited in the claims. However, Mullen was published in 1994, while the instant application claims an effective filing date at least as early as 1990. Thus, Mullen’s disclosure does not appear to reflect the state of the art as of the relevant date. See Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1987) (“Enablement . . . is determined as of the filing date of the patent application.”).

In addition, Mullen identifies only three metabolic suicide gene systems, one of which is the HSV-TK system. The other systems discussed by Mullen are the cytosine deaminase system and the varicella thymidine kinase system. With one exception, the references cited by Mullen with respect to these other enzyme systems were all published after 1990. The only exception concerns a “non-genetic” approach of coupling cytosine deaminase enzyme to a tumor-specific antibody; an approach very different from the claimed method. Thus, the prior art of record does not reflect that other DNAs encoding enzymes meeting the limitations of the instant claims were known in the art as of the application’s effective filing date.

The examiner has provided evidence that expression of transgenes was unpredictable. See the Examiner’s Answer, pages 5 and 6. This evidence is relevant here, where no other genes encompassed by the claims have been exemplified, or even identified. The examiner’s evidence shows that the disclosed success with HSV-TK in mice would not have been viewed by those in

the art as predictive of other enzymes being expressed at an adequate level to cause cell ablation in the presence of the appropriate nontoxic precursor compound.

Finally, the specification shows that a substantial amount of experimentation is required to carry out the experiments required to make new constructs comprising other genes and to test such constructs in vitro and in vivo to determine whether tissue-specific expression of the transgene can be achieved and whether such expression results in tissue-specific cell ablation in intact organisms. See pages 20-37 (working examples showing tissue-specific ablation using the HSV-TK system).

We can assume, based on the technical sophistication of the references, that the level of skill in the art was high. However, as we have found supra, the balance of the Wands factors indicates that the claims are not commensurate in scope with the disclosure. Therefore, we agree with the examiner that claim 44 does not meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

Appellants argue that

the sole act required in the practice of the invention, as defined by claim 44 is “administering to said organism an amount of said latent toxin effective to trigger generation of said cell toxin by enzymatic conversion of the latent toxin”. This act implicitly requires that the practitioner choose a latent toxin that is “effective” to promote the required result of being converted by the enzyme expressed in the target tissue, but it does not require the practitioner to create a transgenic animal.

That the organism to be treated already contains a tissue-type or cell line that comprises endogenous thymidine kinase and DNA encoding and expressing an exogenous enzyme under the control of a tissue specific promoter is a precondition analogous to that in

most “method of treatment” claims wherein the subject to be treated is said to be “in need of” the drug administered. In such a claim, creation of the precondition is not required of the one who would practice the treatment claim. It is respectfully submitted that the burden of creating a transgenic animal should be relegated to those who submit claims reciting acts that lead to the production of transgenic animals.

Appeal Brief, page 9 (emphasis in original).

This argument is not persuasive. Appellants argue, in a nutshell, that the only manipulative step actually recited in the claim is administering a latent toxin to a transgenic organism, and therefore that is all that must be enabled by the specification. However, it is indisputable that practicing the claimed method requires that the transgenic animal recited in the claims be available for treatment. Appellants have presented no evidence to show that a “stable” of appropriate transgenic animals are available in the art, such that they can be obtained by the skilled artisan without experimentation. Thus, it would appear from the record that the only way for a person of skill in the art to obtain a transgenic animal expressing an exogenous converting enzyme, such as that recited in claim 44, would be to make it following the guidance provided in the specification. That the claim does not expressly recite the manipulative steps required to do so is of no importance; those steps are required to practice the claimed method, even if they are not expressly recited in the claims. In order to enable the claimed method, therefore, the specification must enable those skilled in the art to make the recited transgenic organisms.

Appellants also argue that the specification is enabling “[e]ven if the claims were to be read as requiring creation of an organism containing a transgene.”

Appeal Brief, page 12. Appellants cite to a declaration submitted under 37 CFR § 1.132 as showing evidence that “the specification fully enables insertion of a transgene into an animal.” Id. Appellants also cite Palmiter³ as showing that “methods for creating a transgenic animal expressing an exogenous protein under the control of a tissue specific promoter were known to those of skill in the art.” Id. Finally, Appellants argue that “the Specification contains detailed information about types of tissue specific promoters, the cell types for which they are specific, enhancers for such promoters and the like that can be utilized in the practice of the invention methods.” Id., page 13.

This argument is also not persuasive. None of the evidence cited by Appellants – the Evans declaration, Palmiter, and the cited passages from the specification – is directed to the aspect of the examiner’s rejection on which we rely. Specifically, none of these sources provides evidence that, based on the specification and what was known in the art, a skilled artisan would have been able to practice the claimed invention with converting enzymes other than HSV-TK without undue experimentation. Therefore, none of the cited evidence overcomes the rejection for nonenablement.

Although Appellants elected to let the claims stand or fall together, we think it is appropriate to treat claims 40 and 41 separately. Claims 40 and 41 are directed to the method of claim 44, where the exogenous gene is HSV-TK. Thus, claims 40 and 41 do not share the infirmity on which we have based our

³ Palmiter et al., “Cell lineage ablation in transgenic mice by cell-specific expression of a toxin gene,” Cell, Vol. 50, pp. 435-443 (1987).

conclusion of nonenablement. As we discussed above, the remaining grounds set out by the examiner are inadequate to support the rejection. Therefore, the examiner has not shown that claims 40 and 41 are not enabled for a method of making transgenic organisms.

In addition to the “transgenic animals” analysis discussed in detail above, the examiner set out a second enablement analysis, based on the disclosed use of the claimed system in gene therapy. We do not agree that any potential problems that might be encountered using the claimed system in gene therapy support a rejection for nonenablement. The specification discloses that the claimed method can be used to “create valuable animal models.” Page 19. There is no rejection for lack of utility before us, and the examiner has conceded that the claims are enabled with respect to mice lacking lymphoid cells. See the Examiner’s Answer, page 4. Thus, the examiner does not appear to dispute that tissue-specific cell ablation would be useful in making animal models for research.

“The enablement requirement is met if the description enables any mode of making and using the invention.” Johns Hopkins Univ. v. CellPro Inc., 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998) (quoting Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991)). Since the specification describes one method of making and using the invention of claims 40 and 41, it enables these claims, whether or not the claimed method is also enabled for use in gene therapy. Therefore, we reverse the examiner’s rejection with respect to claims 40 and 41.

Summary

We affirm the rejection of claims 3-8, 12, 29, 31-39, 44, and 45, because the examiner has provided evidence to show that practicing the full scope of these claims would have required undue experimentation, and Appellants have not effectively rebutted the rejection. However, we reverse the rejection of claims 40 and 41 because they are limited to use of the HSV-TK gene in the claimed method.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED IN PART

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