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W&C IP
11491 SUNSET HILLS ROAD
SUITE 340
RESTON, VA 20190

EXAMINER
NOBLE, MARCIA STEPHENS

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SUBRAMANIAM SRIKUMARAN and
SUDARVILI SHANTHALINGAM

Appeal 2019-000991
Application 14/815,240
Technology Center 1600

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

Pursuant to 35 U.S.C. § 134(a), Appellant[2] appeals from Examiner's decision to reject claims 39–44. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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[1] Oral Hearing held November 5, 2019.

[2] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as "WASHINGTON STATE UNIVERSITY of Pullman, WA" (Appellant's July 3, 2018 Appeal Brief (Appeal Br.) 3).

STATEMENT OF THE CASE

Appellant's disclosure relates "generally to conditions and/or diseases associated with *M. haemolytica* in ruminants, and more particularly to novel and efficacious compositions and methods for treating or preventing conditions and/or diseases associated with *M. haemolytica* in ruminants" (Spec.[3] ¶ 2). Appellant's independent claims 39 and 42 are representative and reproduced below:

> 39. A genetically engineered ruminant animal having a genome comprising a nucleic acid sequence encoding a ruminant CD18 protein having a cleavable signal peptide with a helix-breaking amino acid residue at an amino acid positioned 5 residues upstream of the signal peptide cleavage site, wherein said nucleic acid sequence has been introduced by homozygous integration of the nucleic acid sequence into the endogenous CD18 gene thereby disrupting the expression of native CD18 having an intact signal peptide, wherein the mutant CD18 protein encoded by said nucleic acid sequence is expressed at least in the animal's leukocytes, and wherein the genetically engineered ruminant animal is resistant to, or less susceptible to, the effects of *M. haemolytica*, relative to a wild-type control animal.

(Appeal Br. 18.)

> 42. A method of providing a genetically engineered ruminant animal, comprising introduction into the genome of a ruminant animal, a nucleic acid sequence encoding a ruminant CD18 protein having a cleavable signal peptide with a helix-breaking amino acid residue at amino acid positioned 5 residues upstream of the signal peptide cleavage site, wherein said nucleic acid sequence is introduced by homozygous integration of the nucleic acid sequence into the endogenous CD 18 gene thereby disrupting the expression of native CD18 having an intact signal peptide, wherein the mutant CD18 protein encoded by said nucleic acid sequence is expressed at least in the

[3] Srikumaran et al., US 2015/0327522 A1, published Nov. 19, 2015.

> animal's leukocytes, and wherein the genetically engineered ruminant animal is resistant to, or less susceptible to, the effects of M. haemolytica, relative to a wild-type control animal.

(*Id.* at 18–19.)

Ground of rejection before this Panel for review:

Claims 39–44 stand rejected under the enablement provision of 35 U.S.C. § 112(a).

ISSUE

Does the evidence of record support Examiner's conclusion that undue experimentation would be required to practice the claimed invention?

ANALYSIS

To satisfy the enablement requirement of 35 U.S.C. § 112(a) a patent application must adequately disclose the claimed invention so as to enable a person skilled in the art to practice the invention at the time the application was filed without undue experimentation. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371–72 (Fed. Cir. 1999). It is important to recognize, however, that "nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971). In this regard, we note that "a patent need not teach, and preferably omits, what is well known in the art." *Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

On this record, Examiner finds that "the [S]pecification fails to provide specific guidance to[:] demonstrate that the in vitro findings taught by the [S]pecification will predictably result in a phenotype of disease

resistance in the genetically engineered ruminant animal," "a method that will predictably mak[e] the claimed ruminant," "the making of the claimed genetically engineered ruminant animal or the ruminant animal proper" (Ans. 6). Thus, Examiner finds that Appellant's Specification "fails to predictably enable a genetically engineered ruminant animal with a disease resistant phenotype or a method of making such a ruminant animal" (*id.*)

In defining the breadth of Appellant's claimed invention, Examiner finds that, on this record, Appellant's claims

> are fairly narrowly defined to a specific genetic modification and a specific phenotype. The breath of "ruminant animal" encompasses any ruminant animal such as cattle, sheep, goats, camels, llamas, and alpacas. However, the type of genetic modification claimed is narrowly defined to one particular type of knock-out of an endogenous CD 18 gene and a knock-in of a replacement mutant form of CD18. The phenotype conferred by this genetic modification is also narrowly defined as resistant or reduces susceptibility to the effect of *M. haemolytica*. The "effect of *M. haemolytica*" encompasses any effect conveyed by *M. haemolytica*. As such, overall the claims are fairly narrow in scope.

(Ans.[4] 5.)

Appellant discloses that "[t]ransgenic animals are those that carry a non-native gene that were introduced into the animal using similar techniques as described herein and those well known in the art" (Spec. ¶ 87; *see generally* Ans. 6). In this regard, Appellant discloses that "[g]ene replacement techniques used in the practice of [A]pplicant's invention includes, but is not limited to, the gene replacement techniques described in Kuroiwa et al., (2004)" (Spec. ¶ 89; *see generally* Ans. 6).

[4] Examiner's September 19, 2018 Answer.

This Appeal is based on the claims in Application, 14/815,240, which is a continuation of the Srikumaran '925.[5] Issued claim 1 of Srikumaran '925 is reproduced below:

> 1. A ruminant cell that is genetically engineered to contain *a nucleic acid sequence encoding a ruminant CD18 protein having a cleavable signal peptide with a helix-breaking amino acid residue at an amino acid positioned 5 residues upstream of the signal peptide cleavage site*.

(Srikumaran '925 185: 58–62 (emphasis added).) The ruminant cell of Srikumaran '925's claim 1 contains the same nucleic acid sequence encoding a ruminant CD18 protein as required by Appellant's claim 39 and 42 on Appeal.[6] Tracking the effective filing date of Appellant's claimed invention, we note that Appellant claims benefit of PCT/US10/22932, filed February 2, 2010, which claims benefit to Provisional Application 61/149,278, filed February 2, 2009. Thus, Examiner finds that the effective filing date of Appellant's Application is February 2, 2009 (Ans. 10).

Examiner recognizes that "homologous recombination in primary fibroblasts followed by somatic cell nuclear transfer was developed and was the exclusive method for producing a targeted disruption (e.g. gene knock-

[5] Srikumaran et al., US 9,102,925 B2, issued Aug. 11, 2015, filed August 2, 2011.

[6] Appellant's independent claim 39 comprises, *inter alia*, "a nucleic acid sequence encoding a ruminant CD18 protein having a cleavable signal peptide with a helix-breaking amino acid residue at an amino acid positioned 5 residues upstream of the signal peptide cleavage site" (*see* Appeal Br. 18). Similarly, Appellant's only other independent claim, claim 42, comprises, *inter alia*, "a nucleic acid sequence encoding a ruminant CD18 protein having a cleavable signal peptide with a helix-breaking amino acid residue at [an] amino acid positioned 5 residues upstream of the signal peptide cleavage site" (*id.*).

out) in the genome of livestock at the time of [Appellant's] invention" (Final Act.[7] 6; *cf.* Ans. 12 (Examiner finds that Appellant's Specification "fails to provide any specific guidance to a method of disrupting (i.e.-knocking-out) the endogenous CD18 gene in a ruminant by inserting (i.e.-knocking-in) a mutated form of the CD18 gene into said endogenous CD18 gene"); *see generally* Ans. 12–13). *See Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384 ("a patent need not teach, and preferably omits, what is well known in the art."). To be clear, somatic cell nuclear transfer refers to a method of producing a viable embryo by transferring a somatic cell nucleus, e.g., a nucleus from a cell encompassed by the Srikumaran patent, into an enucleated oocyte.

Thus, Examiner concedes, and the evidence of record establishes, that as of the effective filing date of Appellant's claimed invention, the methodology required to produce the targeted ruminant CD18 protein modification required by Appellant's claimed invention was well known in this art (*see* Final Act 6 ("homologous recombination in primary fibroblasts followed by somatic cell nuclear transfer was developed and was the exclusive method for producing a targeted disruption (e.g. gene knock-out) in the genome of livestock at the time of [Appellant's] invention"); *see also* Laible[8] 111: col. 2 ("a cell-mediated transgenesis method that could be applied in farm animals . . . emerged in 1996 with the arrival of the clone sheep Dolly, the first mammal produced by somatic cell nuclear transfer

[7] Examiner's April 2, 2018 Final Office Action.
[8] Laible et al., *Improving livestock for agriculture – technological progress from a random transgenesis to precision genome editing heralds a new era*, 10 Biotechnol. J. 109–20 (2015).

(SCNT)"); *see also* Srikumaran '925 185: 58–62 (claim 1 of Srikumaran '925 setting forth a cell comprising Appellant's claimed mutation, which may serve as the source of nuclear material for a somatic cell transfer)).

There is no doubt that Laible's 2015 post-filing date disclosure provides evidence of the state of the art prior to Appellant's filing date that supports a finding that at the time of Appellant's claimed invention, the methodology required to produce the targeted ruminant CD18 protein modification required by Appellant's claimed invention was well known in this art. *See In re Hogan*, 559 F.2d 595, 605 (Fed. Cir. 1977) ("This court has approved use of later publications as evidence of the state of art existing on the filing date of an application.").

In addition, Beever declares that Appellant's Specification, "in view of the knowledge in the art, would have enabled one of ordinary skill in the art as of the filing date to produce the genetically engineered ruminant animal of the claimed invention without undue experimentation" (Beever Declaration[9] ¶ 6). *See Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384 ("a patent need not teach, and preferably omits, what is well known in the art."). Beever further declares that "as of the filing date, zinc finger nuclease (ZFN) gene editing technology was a known and reliable technique for generating genetically engineered animals" (*id.* (citing a number of pre-filing date documents for support); *see* Ans. 23 ("Examiner does agree that as of the filing date ZFN gene editing [was a] reliable technique for generating some genetically engineered animals with

[9] Declaration of Jonathan E. Beever, Ph.D., signed October 17, 2017.

particular types of genetic modification, such targeted gene disruptions in mice and rats were established")).

Although Examiner appreciates that ZFN technology was well-known in this art at the time of Appellant's earliest effective filing date, Examiner finds that this evidence of the state of the art at the time of Appellant's invention does "not provide adequate demonstration of enablement at the time of filing because they do not . . . produc[e] a knockin ruminant as [Appellant's] claimed invention requires" (Ans. 15; *see generally id.* at 15–20). Srikumaran declares, however, that "Examiner . . . incorrectly concluded that because the ZFN technique had not been applied to a ruminant animal in 2009 that it was not possible" (Srikumaran Declaration[10] ¶ 2). In this regard, Srikumaran declares that "apart from size, mice and rats are not all that different from other mammals such as cows" and "experiments performed in rats and mice can be extrapolated to the not so evolutionarily distant ruminant animals" (*id.*). On this record, and in view of the successful results obtained in non-ruminant animals, we find that Appellant's evidence and rationale outweighs Examiner's intimation that, at the time of Appellant's claimed invention, those of ordinary skill in this art would have found that it would have required undue experimentation to produce knock-in ruminants.

We are also not persuaded by Examiner's reliance on Laible's 2015 post-filing date disclosure "that somatic cell nuclear transfer based gene targeting proved to be too inefficient to make the introduction of site specific changes into livestock genomes a routine practice" (Final Act. 7 (citing

[10] Declaration of Subramaniam Srikumaran, Ph.D., signed January 25, 2018.

Laible 114: col. 1, first paragraph); *see* Ans. 8 (citing Laible 114: col. 1, first paragraph)). Examiner made no attempt, on this record, to identify whether the inefficiencies disclosed by Laible were discovered prior to or after the filing date of Appellant's application. In this regard, we note that it is not proper for Examiner to rely upon "a later . . . publication disclosing a later . . . existing state of the art in testing an earlier . . . application for compliance with" 35 U.S.C. § 112(a). *See In re Hogan*, 559 F.2d at 605. Therefore, Examiner failed to establish an evidentiary basis on this record to support a finding that Laible supports Examiner's assertion that "somatic cell nuclear transfer based gene targeting proved to be too inefficient to make the introduction of site specific changes into livestock genomes a routine practice" (Final Act. 7).

We recognize Examiner's reliance on the Carlson's 2012 post-filing date disclosure,[11] but find that Examiner failed to establish whether Carlson's disclosure relates to "the permissible application of later knowledge about art-related facts existing on the filing date [or] the impermissible application of later knowledge about later art-related facts . . . which did not exist on the filing date" of Appellant's claimed invention. *In re Hogan*, 559 F.2d 605. Therefore, we are not persuaded by Examiner's reliance on Carlson to support Examiner's assertion that

> homologous recombination methods used to introduced a targeted insertion in mice (i.e.-knock-in) were not applicable to other mammals. As an alternative approach, homologous recombination in primary fibroblasts followed by somatic cell nuclear transfer was developed and was the exclusive method for producing a targeted disruption (e.g. gene knock-out) in the

[11] Carlson et al., *Efficient TALEN-mediated gene knockout in livestock*, 109 PNAS 17382–87 (2012).

> genome of livestock at the time of the invention. However, generation of knockout cell lines by homologous recombination was inefficient and the length of time for gestation and reproductive maturation for livestock represent significant barrier to homozygous gene inactivation or the engineering multiple loci.

(Final Act. (citing Carlson 17382: col. 1, first paragraph); *see* Ans. 8 (citing Carlson 17382: col. 1, first paragraph).)

Examiner's reliance on the post-filing date disclosures of Tywman,[12] Liu,[13] and Gao[14] suffers the same deficiency as Carlson (*see* Ans. 7–9). Furthermore, Examiner failed to establish a nexus, on this record, between Tywman's reported "side effects" associated with "experiments concentrated on the transfer of growth-related genes" and resistance, or reduced susceptibility, to the effects of *M. haemolytica* encompassed by Appellant's claimed invention (*id.* at 7).

For the foregoing reasons, we are not persuaded by Examiner's finding that "the post-filing art provide[s] adequate evidence demonstrating that a great deal of undue experimentation would have been required at the time of the invention to enable the claims" (*id.* at 10). *See In re Hogan*, 559 F.2d at 605 (Examiner's conclusion is based on "the impermissible

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[12] Twyman et al., *Gene Expression in Recombinant Animal Cells and Transgenic Animals*, Encyclopedia of Industrial Biotechnology: Bioprocess, Bioseparation, and Cell Technology 1–74 (Michael C. Flickinger ed., John Wiley & Sons, Inc.) (2013).
[13] Liu et al., *Zinc-finger nickase-mediated insertion of the lysostaphin gene into the beta-casein locus in cloned cows*, Nature Communications DOI: 10.1038/ncomms3565, www.nature.com/naturecommunications (2013).
[14] Gao et al., *Single Cas9 nickase induced generation of NRAMP1 knockin cattle with reduced off-target effects*, 18 Genome Biology 1–15 (2017).

application of later knowledge about later art-related facts . . . which did not exist on the filing date.").

In sum, the available evidence on this record supports a finding that those of ordinary skill in this art, at the time of Appellant's earliest effective filing date, would have been able to produce, without undue experimentation, a ruminant somatic cell that contains the specific CD18 modification required by Appellant's claimed invention. Examiner fails to establish an evidentiary basis on this record to support a finding that a person of ordinary skill in this art would not have been able to produce a cell (i.e., a somatic cell) that expresses the specific CD18 genetic modification required by Appellant's claimed invention without undue experimentation (*see* Srikumaran '925 185: 58–62 (claim 1 of Srikumaran '925 setting forth a cell comprising Appellant's claimed mutation, which may serve as the source of nuclear material for a somatic cell transfer); *cf.* Ans. 23 (Examiner asserts that making Appellant's "claimed ruminant . . . requires more than a targeted gene disruption because the claimed ruminant has a gene replacement, which requires gene disruption, targeted gene insertion in a manner that successfully results in expression of the inserted gene, and the development of a phenotype susceptibility or resistance to *M. haemolytica*)).

The available evidence on this record further supports Examiner's finding that "homologous recombination in primary fibroblasts followed by somatic cell nuclear transfer was developed and was the exclusive method for producing a targeted disruption (e.g.[,] gene knock-out) in the genome of livestock at the time of [Appellant's] invention" (Final Act. 6; *see also* Laible 111: col. 2 ("a cell-mediated transgenesis method that could be applied in farm animals . . . emerged in 1996 with the arrival of the clone

sheep Dolly, the first mammal produced by somatic cell nuclear transfer (SCNT)")).

For the foregoing reasons, we are not persuaded by Examiner's assertion that Appellant failed to enable a method of producing an animal within the scope of their claimed invention (*see e.g.*, Ans. 22).

In addition, Examiner failed to establish an evidentiary basis on this record to support a finding that an animal produced by somatic cell nuclear transfer using a cell engineered to contain the genetic modification required by Appellant's claimed invention, would not have been reasonably expected, at the time of Appellant's claimed invention, to exhibit the phenotype the animal was engineered to express, i.e. an animal that is resistant to, or less susceptible to, the effects of *M. haemolytica*, relative to a wild-type control animal (*see* Appeal Br. 18–19; *cf.* Ans. 22 (Appellant fails to enable "gene correction in ruminant cells that can be developed into a live ruminant animal that successfully expresses the corrected gene in a manner that predictably leads to a specific disease resistance phenotype, as the instant claimed ruminant animal and methods require")).

For the foregoing reasons, we find that the weight of the evidence on this record falls in favor of Appellant.

CONCLUSION

The evidence of record fails to support Examiner's conclusion that undue experimentation would be required to practice the claimed invention. The rejection of claims 39–44 under the enablement provision of 35 U.S.C. § 112, first paragraph is reversed.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
39–44	112(a)	Enablement		39–44

REVERSED