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EXAMINER	
CROUCH, DEBORAH	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/308,135	NEWMAN, STUART A.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed February 9, 2004 have been fully considered but they are not persuasive. Claims 37-50 are pending.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 37-50 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 of copending Application No. 08/993,564 for reasons of record.

Applicant has agreed to submit a terminal disclaimer once claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 of 08/993,564 are indicated as allowable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-50 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention so that it will operate as intended without undue experimentation for reasons of record.

The enablement rejection, in summary, is that the specification fails to provide sufficient guidance to make and use human/nonhuman primate chimeras. Neither the art at the time of filing, nor the present specification, provide the requisite guidance as to the methodology that would lead to the production of these chimeras without an undue amount of experimentation and with a predictable degree of success.

Applicant argues techniques were known in the art at the time of filing for the production of interspecific chimeric animals created from nonhuman embryonic cells. As evidence, applicant cites several research articles available to the skilled artisan at the time of filing. Fehilly (1984), applicant argues, demonstrates the successful production of interspecific sheep-goat chimera by embryo manipulation where either single blastomeres from 4-cell goat embryos were combined with single blastomere from 4-cell or 8-cell sheep embryos; surrounding an 8-cell goat embryo lacking a zona pellucida with blastomeres from 3, 8-cell sheep embryos or surrounding an 8-cell sheep embryo with blastomeres of 3, 8-cell goat embryos; or insertion of the inner cell mass and polar trophoectoderm from day 8 goat blastocyst into day 8 sheep blastocyst. Applicant argues that these chimeric sheep-goat embryos were then transferred into recipient ewes and does for gestation. Applicant argues that Meinecke-Tillman teaches the production of interspecific chimeric embryos by combining one blastomere from a 4-cell stage sheep embryo with two blastomeres from an 8-cell stage goat embryo, or two blastomeres from an "early" 8-cell stage sheep embryo with two blasotmeres from "late" 8-cell stage goat embryos in a pig zona pellucida.

Applicant argues that Meinecke-Tillman transferred the chimeric embryos and brought to term sheep-lamb and goat-lamb interspecific chimeras. These arguments are not persuasive. Applicant also cites Pope et al (1982), Gould (1983), Pope (1984), Fourie (1987), Pope (1997), US Patent 6,211,429 (Machaty), US Patent 6,376,743 (Yanagimachi), Homa (1994) and Herbert (1995). Applicant argues that the methods disclosed in these references could be applied to the production of human/nonhuman primate chimeric embryos without undue experimentation. These arguments are not persuasive.

It should be noted that the specification does not provide a definition of applicant's meaning of the term "chimeric animal." However, Applicant states in the response of February 9, 2004 "... interspecific chimeric animal, like the sheep-goat chimeras disclosed in the cited references, would contain cell contributions from both species throughout all of its organs and tissues" (response, page 4, lines 2-8). This definition is not supported by the teachings of the art at the time of filing which defined chimeric animal without specifying parental cell contribution to organs or tissues of the chimera. The art defined a chimeric animal as "consisting of a mixture of cells derived from more than one animal;" and "produced by a mixing of cells from the early stages of development of two different embryos" (Rossant (1982), page 1241, col. 2, parag. 1, lines 5-12). Thus, the art's definition encompasses applicant's definition but includes chimerism found in some tissues but not others, or where a tissue is composed of one parental cell type while other tissues are composed of the other parental cell type or mixtures of parental cell types. Further, as discussed in detail below, the sheep – goat chimera art does not support cell contributions from both species through out all of the animal's organs and tissues.

Using either applicant's definition of chimeric animal or the broader definition provided by the art at the time of filing, the art cited by applicant in their response does not enable any of the possible chimeric animals encompassed by the claims. The specification

fails to enable the production of a chimeric human/nonhuman animal that contains contributions from both parental cell types in all its organs and tissues. Likewise, the art fails to enable the production of a human/nonhuman primate chimeric animal that has tissue(s) composed of predominantly or only one parental cell type and other tissues composed of the other parental cell type or a mixture of both parental cell types. There is no predictability in parental cell contribution in a resulting chimera. Fehilly produced sheep x goat chimeric embryos, using the method as stated by applicant, which when implanted into surrogate mothers resulted in 8 interspecies chimeras (page 635, Table 1). Only one animal was described has having two chimeric tissues, and that one was a coat and blood protein chimera (See Fehilly, page 636, col. 20.). The other chimeras are each described as being a coat chimera, that is, these sheep-goats had coat/skin contributions from each parent, but no other chimeric tissues were described. Meinecke-Tillman teaches as applicant has described, but the animals born are not tissue chimeras. The author states "cytogenetic analysis, hemoglobin and transferring typing, blood group serology, polyacrylamide gel electrophoretic analysis of blood and muscle proteins and breeding experiments gave no indications of chimerism" (Meinecke-Tillman, page 638, col. 1, parag. 1). Thus, there is no guidance in Fehilly or Meinecke-Tillman for producing a chimeric animal regardless of parental cell contributions to the animal's tissues and organs. Both references actually support the unpredictability of producing chimeric animals of any definition in that neither reference provided direction for obtaining reproducibly a chimeric human/nonhuman primate animal whose organs and tissues were of any particular parental cell composition. Rossant (1983), cited by applicant, is not on-point with the present claims. Rossant teaches the production of chimeras of separate mouse species; obviously the mice are of the same genus. The present animals would not be of the same genus or species. Further, Rossant (1983) taught the degree of chimerism or mosiacism in adult chimeric mice varied (Rossant,

page 196, Table 2). Chimera 2 has only mosiacism in leg muscle, chimera 3 demonstrated blood, brain and leg muscle mosiacism, and other chimera demonstrated mosiacism in all tissues analyzed but the degree of mosiacism varied. Thus, Rossant (1983) does not support the enablement of the claimed invention, independent of the "definition" of chimera used, as the degree of chimerism between individual mice was unpredictable, and without any apparent means of chimerism control by the artisan. Especially Rossant (1983) supports the unpredictability of obtaining chimerism in all the organs/tissues of the chimera, the definition used by applicant. Thus, the production chimeric human/nonhuman primate animals having both human and nonhuman primate cells in all or some of their tissues/organs is not predictable without undue experimentation given the teachings in the art at the time of filing and the lack of guidance in the specification.

The additional references, Pope (1982), Gould, Pope (1984), Fourie, Pope (1997), US Patent 6,211,429 (Machaty), US Patent 6,376,743 (Yanagimachi), Homa (1994) and Herbert (1995), each teach various methods of culturing or producing by IVF primate embryos or human embryos. While these references may teach such methods, none of the methods address the unpredictability in using the chimeric embryos of the claims to produce a chimeric human/nonhuman primate animal of either applicant's or the art's definition.

Applicant argues that the specification was also enabled for the production of chimeric human/nonhuman primate animals using human and nonhuman primate embryonic stem cells as the methods of isolating and culturing these stem cells were known at the time of filing. Applicant argues that Thomson (1995) teaches the isolation of an ES cell line from the embryo of a rhesus monkey and the isolation of human ES cells (1998). Applicant argues the ES cell lines were isolated using existing techniques without undue experimentation. Applicant argues that prior to the present filing date, the isolation of ES-like cells from human embryos was known (Bongso et al (1994)). Applicant argues that

Bradley (1984) discloses techniques that can be used to produce interspecific chimeric embryos, and that Bradley also teaches that the combination of ES cells from the same or different species will result in normal development of the embryo. Applicant argues that Nagy et al (1993) teaches the use of early passage ES cells to produce mice that are completely ES cell derived by combining mouse ES cells with defective mouse embryos. Applicant argues that Goldstein (2002) discloses human embryo ES cells implanted into chick embryos to make human/chicken chimeric embryos. These arguments are not persuasive.

Neither Applicant's assertion that the chimeric animal claimed would "develop while incorporating both human and nonhuman primate cells into all of the organs of the resulting chimeric animal" (response, page 4, parag. 1, lines 2-8) nor the art's broader definition is enabled by the specification nor applicant's cited art. As taught by Fehilly et al, Meinecke-Tillman et al and Rossant (1983), as discussed above, the parental contribution to organs and tissues of sheep x goat chimeras is unpredictable when chimeric embryos are implanted in a surrogate mother. Whereas Thomson (1995 and 1998) and Bongos (1994) each teach nonhuman primate or human ES cell or ES-like cell isolation and culture, none of these references provide methodology for the production of human/nonhuman primate chimeric embryos that can produce a chimeric animal meeting either applicant's or the art's definition. Additionally, Nagy discloses the cloning of mice from mouse ES cells using mouse tetraploid embryos. These teachings are not comparable to the present claims as the animals of Nagy are same species, mouse, and not separate genus and species as presently claimed. Nagy, therefore, does not provide any guidance to the production of interspecific chimeric human/nonhuman primate animals. There is no evidence on this record that to make a human/nonhuman primate chimeric animal all one would need is access to ES cells. Goldstein produced chimeric human/chick embryos by a method not contemplated by the

specification. At no place does the specification discuss injecting human or primate embryonic cells into an embryo that already had distinct organ system formation (specification, pages 1-5). Goldstein states that human ES cells were injected into the trunk region of 1.5 to 2 day chick embryos (Goldstein, page 81, col. 1, parag. 1, lines 1-3). Goldstein distinguishes the work therein from applicant's methodology in stating "these experiments are also different from those attempting to produce true chimeric embryos where stems cells are mixed or injected into intact embryos at the blastula/gastrula stage and could potentially make a major contribution to many of the host tissues" (Goldstein, page 83, col. 2, lines 8-13). Finally, the chimeric mice produced by Bradley are chimeric for other mouse strains. Thus, these animals are not relevant to presently claimed chimeric human/nonhuman primate animals as Bradley's mice are produced by inserting a blastomere from an embryo of one mouse strain into a blastocyst of a second mouse strain. Bradley's experiments were to animals of the same genus-species; the only differences were strain differences. Nothing in Bradley offers guidance on producing chimeric embryos of separate genus, which lead to the production of chimeric animals.

Applicant asserts that at least one credible utility has been identified in the specification by describing how the present chimeric animals can be used in toxicology assays. Applicant argues that the specification states that the invention would be useful to determine the teratogenic and developmental toxicity of various chemicals. Applicant argues that Naruse et al and Prati et al describe methodology for using chimeric embryos for teratologic screening. These arguments are not persuasive.

Naruse is directed to toxicology assays using mammalian embryos, such as the exemplified mice, of a single species and not chimeric embryos (Naruse, page 196). Prati is not of record and cannot, therefore, be considered. The present claims are to the chimeric animals. Thus, applicant is arguing subject matter not claimed in this application. With

regard to applicant's statement that chimeric animals can be used in toxicology assays, applicant has not provided any evidence or reasoning as to how results obtained from such studies would be useful. Applicant has stated that the chimera of their invention would be comprised of organs and tissues, which contain cells of both parent cells. However, the results from such an animal would not have any enabled use, as the results would not be applicable to any particular animal. Applicant has not taught what could be gleaned from toxicology experiments on chimeric animals that would be useful to animals in general, or either parent animal in specific. Obtaining toxicological results is one thing but using them is another, and that is not enabled by the specification. Without guidance as to the use of the human/nonhuman primate chimeric animal as toxicology assay, the animal has no enabled use.

Claims 37-50 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record.

Claims 37-50 are drawn to chimeric animals which have developed from chimeric embryos and whose cells are immunologically tolerated by human and a nonhuman primate species, where the embryo is composed of human and nonhuman primate embryonic cells.

As stated previously, the chimeric human/nonhuman primate animals are not disclosed, nor claimed, as having any specific degree of chimerism. There is no description of chimera that conveys to the skilled artisan exactly what type of chimerism applicant envisions as the invention. Furthermore, the specification fails to demonstrate possession of the invention by actual reduction to practice, clear depiction of the invention in a detailed drawing, or description with sufficient relevant identifying characteristics of the invention as

a whole such that a person skilled in the art would recognize that the inventor had possession of the claimed chimeric animals.

Applicant argues that the specification describes the claimed chimeric animal using terms in the same manner as they are well known and regularly used in the art. Applicant argues that by describing and referring to the present invention as a chimera or chimeric animal, which has developed from a chimeric embryo, possession of the invention at the time of filing has been demonstrated. Applicant argues that several scientific articles describe chimeric animals developed from chimeric embryos. Applicant argues that Fehilly demonstrates sheep x goat chimeras produced by combining sheep and goat embryonic cells, and that these sheep x goat chimeric embryos develop into chimeric animals. Applicant argues that the term "chimera" as used in the art and present specification refers to an animal, which develops from an embryo made from two genetically distinct species or two different species. Applicant argues that Meinecke-Tillman describes the production of interspecific chimeric embryos by combining blastomeres from a 4 or 8-cell sheep embryo with an 8-cell goat embryo. (Blastomeres are the cells that compose an early stage embryo.) Meinecke-Tillman, applicant argues, then produced sheep-goat and goat-sheep chimeras from these embryos comprising cells of both sheep and goats. Applicant argues that chimeric animal refers to an animal made from cells of two distinct species. Applicant argues that Rossant demonstrates somatic and germ line mosiacism in interspecific chimeras between *Mus musculus* and *Mus caroli*, and that cells from the two species coexist and interact normally in all tissues studied. Applicant argues that Prather supports their assertion that a chimeric animal contains contributions from both species throughout all its organs and tissues. These arguments are not persuasive.

Applicant also states "... interspecific chimeric animal, like the sheep-goat chimeras disclosed in the cited references, would contain cell contributions from both species

throughout all of its organs and tissues" (response, page 4, parag. 1, lines 2-8). As stated above in the enablement rejection, it is noteworthy that the art at the time of filing defined chimeric animal as "consisting of a mixture of cells derived from more than one animal; and "produced by a mixing of cells from the early stages of development of two different embryos" without any commentary as to the contribution of the parent cells to individual tissues or organs (Rossant (1982), page 1241, col. 2, parag. 1, lines 5-12). Further, Prather never provides a definition of chimeric animal in terms of cellular contribution. Applicant is requested to point to page and line number for such support in Prather. Given either of these references or applicant's definition of the term "chimera," the specification does not show possession by applicant at the time of filing for chimeric human/nonhuman primate because there is no description of parental cell contribution. If one reviews the art of chimeric animal production the lack of written description becomes apparent.

Fehilly teaches that 3 out of 7 (experiment 1a) animals were overt sheep x goat chimeras based upon coat characteristics. These animals had the general appearance of lambs but the fleece had transverse bands and patching of hair contrasting sharply with the surrounding densely cultured wool. The hairy bands were thought to represent goat tissue. In another experiment (2b), the animals had the same general appearance as kids, but along the neck, shoulders and backs of the animals, curly sheep's wool was seen instead of normal straight goat hair. Fehilly teaches that of all the live born sheep x goat chimera, each identified by coat composition, chimerism was demonstrated in blood proteins by only one of the chimeric animals (Fehilly, page 636, col. 2, parag. 1). The goat-lamb described in Meinecke-Tillman exhibited no chimerism by cytogenetic analysis, hemoglobin and transferring typing, blood group serology, polyacrylamide gel electrophoretic analysis of blood and muscle proteins and breeding experiments (Meinecke-Tillman, page 638, col. 1, parag. 1). Meinecke-Tillman clearly states that the goat - lamb is actually a kid born to an

ewe (abstract, last line). Since all the tissues and organs of the chimeric animals of Fehilly and Meinecke-Tillman did not contain cells from both parental complements as stated by applicant, Fehilly and Meinecke-Tillman fail to support applicant's arguments. Further, this prior art is inconsistent with applicant's definition of chimeric animal as having both parental cell types in all of its tissues and organs as argued in their response of February 9, 2004. Rather this art supports the broader definition of the art, that the animal is composed of two parental cell types, without regard to specific tissue composition.

The degree of chimerism or mosiacism in adult chimera, as demonstrated by Rossant (1983), varies widely among the animals analyzed (Rossant, page 196, Table 2). Chimera 2 has only mosiacism in leg muscle, chimera 3 demonstrated blood, brain and leg muscle mosiacism, and other chimera demonstrated mosiacism in all tissues analyzed but the degree of mosiacism varied. Also, the chimeras produced by Rossant are materially different from those claimed; the chimera disclosed in Rossant are of the same genus but of different species. One would expect, perhaps, a better rate of chimera formation when the parental cells are from different species of the same genus, rather than as presently claimed where the parents are of different genus. Rossant, therefore, also fails to support applicant's assertion that all the tissues and organs would contain cells from both parents.

The composition of the claimed human/nonhuman primate animals could not be envisioned at the time of filing given knowledge in the art that chimerism varied greatly between species. None of Fehilly et al, Meinecke-Tillman et al or Rossant et al convey that the art, at the time of filing, described chimeric animals such that the skilled artisan could have envisioned applicant's claimed animals sufficiently to deem that applicant had possession of the animals. Thus, the particular make up of the claimed chimeric human/nonhuman primate animals could not be visualized until a reduction to practice had occurred. The specification does not describe the degree of mosiacism in the various tissues

and/or organs by words or example. As exemplified in Fehilly et al., Meinecke-Tillman et al. and Rossant et al., mosiacism is taught by the art to variable. Thus, the skilled artisan, reading the specification and with the knowledge of Fehilly et al, Meinecke-Tillman et al or Rossant et al, could not have envisioned the claimed chimeric human/nonhuman primate animal because the particular cellular composition of the animal could not be envisioned. Further, none of the descriptions of the prior art experiments are reported to suggest the composition of a human/nonhuman primate chimera animal. The specification does not provide evidence that those of skill in the art would have interpreted these prior art experiments as representative of a human/nonhuman primate chimeric animal. Thus the specification would not have conveyed possession by applicant of the claimed chimeric human/nonhuman chimeric animal at the time of filing. The claims therefore fail to meet the criteria for written description at the time of filing.

Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record.

Claim 40, in summary, is to a human/nonhuman primate animal having two or more organs comprising both human and nonhuman primate cells. Applicant has pointed to page 20, lines 8-11. A review of this citation reveals that there is no disclosure that the chimeric animal specifically has two or more organs comprising both human and nonhuman primate cells. There is extensive discussion of a "heart" comprising both cell types, but nothing regarding two or more organs comprising both cell types. Applicant is requested to specifically point to the line where this disclosure can be found.

Applicant argues that interspecific chimeras developed from chimeric embryos according the references cited above have cells of both originating species in all organs. Applicant argues that, because of the early embryonic stages employed in the production of the chimeric embryos, all of the organs of the resulting chimeric animal would contain contributions from both species. Applicant states that the analysis of the heart was merely one example of an organ expected to contain cells of both species in the claimed chimeric animal. This argument is not persuasive.

The specification does not contain a description of the claimed chimeric animal having two or more organs comprising cells derived from both human and nonhuman primates. No words are used to convey this limitation, nor any drawing, example or reduction to practice that suggests "at least two organs" containing cells from both parents. While the artisan may expect that, since the animal is a chimera of human/nonhuman primate cells, the chimera might contain some number of organs comprising cells from each source, there is no disclosure of at least two, or any other number of organs that would be chimeric. "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention" Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). While applicant cited Lockwood, applicant failed to show "words" that "that fully set forth the claimed invention." Again, applicant is invited to provide specification cite that provides support for "at least two or more organs." Further, for the reasons outlined above, applicant's art Fehilly et al, Meinecke-Tillman et al, Rossant et al and Prather et al do not describe the organs of chimeric animals as each being chimeric.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 37, 41, 42, 44 and 45 remain rejected under 35 U.S.C. 102(b) as being anticipated by Starzl et al for reasons of record.

Starzl et al. discusses a human in which baboon kidneys or livers were transplanted and the resulting chimerism of the patient (see pages 214, 215 and 219). On page 219, Starzl et al. states that the graft and recipient became genetic composites.

Claim 50 is rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a) as being obvious over humans, nonhuman primates or nonhuman animals found in nature.

Claim 50 is directed to a descendant of chimeric animal of claim 37. The descendant of the chimeric animal is not necessarily any different from one of the source species. There is no limitation that the descendant is chimeric. Individual germ cells would represent only one species. Therefore, if the germ cell subsequently used in reproduction was human, and a human was used as a mate, then, the descendant would be totally human. If the germ cell, which subsequently was used in reproduction was a nonhuman primate and the same species animal was used as a mate, then, the descendant would be totally a nonhuman primate. Therefore, the descendants would not be any different from humans, or nonhuman primates found in nature. Therefore, the descendant would be anticipated by, or made obvious over known humans and nonhuman primates.

Applicant states that their arguments in response to the rejection of claims 37, 41, 42, 44 and 45 over Starzl, regarding the limitation, "immunologically tolerated," applies to the rejection of claim 50. Applicant argues that the descendents referred to in claim 50 are those descendants that are immunologically tolerated by both human and nonhuman primates without the influence of immunosuppressive drugs. These arguments are not persuasive.

Applicant argues that the limitation "has developed from a chimeric embryo," whose cells are immunologically tolerated by a human and a nonhuman primate, defines the make up of the product and gives it a feature not anticipated by Starzl. Applicant argues that the chimeric animal claimed developed from the embryonic cells of two different species, human and nonhuman primate that did not exist until the embryonic cells were mixed. Applicant argues that the resulting interspecific animal contains cell contributions from both species through out all of its organs and tissues distinguishing it from the transplanted animal of Starzl. Applicant argues that Starzl teaches a transplanted human that was a fully developed human being originating from a single species. Applicant argues that the transplanting of baboon cells did not change the human's origin or contribute cells from a different species to all of the human's organs. These arguments are not persuasive.

Applicant states in the response "... interspecific chimeric animal, like the sheep-goat chimeras disclosed in the cited references, would contain cell contributions from both species throughout all of its organs and tissues" (response, page 4, lines 2-8). However, there is no support for this definition of applicant's chimeric animal in the specification, and as argued above, in the art at the time of filing. The specification never defines the cellular contribution of the human and nonhuman primate parental species to the various organs of the chimeric animal claimed. The specification, for example, never states that all the organs or tissues of the chimeric animal have to be composed of both human and nonhuman

primate cells. In fact the specification is silent on the issue of cellular composition of the claimed human/nonhuman chimeric animals. Thus, given the broadest reasonable interpretation of human/nonhuman chimeric animal, an animal with one cell from the other animal species can be considered a chimeric. The patient of Starzl is encompassed by the claims because the patient contains a baboon kidney or liver. There is no evidence on this record to dispute that the patient would fall within the definition chimera provided by Rossant (1982), above. Further, the art at the time of filing and cited by applicant, Fehilly, Meinecke-Tillman and Rossant, discussed in detail above, clearly do not teach that each organ or tissue in a chimeric sheep-goat has contributions from both donor species as required by applicant's definition. The goat-sheep chimeras of Fehilly clearly have several sheep whose blood proteins are all of one species (Fehilly, page 636, col. 2, parag. 1). Meinecke-Tillman teaches that a chimeric embryo implanted into a doe developed into a lamb, not a kid (abstract, last line). Further, Rossant taught that in chimeric mice, several chimera contained organs where the cellular contributions were only of one species (Rossant, page 196, Table 2). Thus, applicant's argument that a chimera would have cellular contributions from both donors is simply not supported by the art. The human transplant patient in Starzl clearly represents a possible result in the creation of a human/nonhuman chimera.

Applicant argues that the phrase "immunologically tolerated" was defined in the art at the time of filing, and it was in this context that the phrase has been used. Applicant argues that Gustafson discloses that the sheep-goat chimera tolerated skin grafts from their chimeric siblings and exhibited immune tolerance as measured by the mix lymphocyte response. Applicant argues that the sheep-goat chimera developed an immune tolerance during embryonic development to both species of cells, and this tolerance is in the absence of immunosuppressive drugs. Applicant argues that both Fehilly and Meinecke-Tillman teach

that the single species mother does not reject chimeras in the absence of immunosuppressive drugs. In the same fashion, applicant argues, the human/nonhuman chimeric animal claimed would immunologically tolerate cells from both species without the influence of immunosuppressive drugs. Applicant argues that it was well known in the art at the time of filing that tolerance of foreign cells without the need for immunosuppressive drugs is the commonly accepted criterion to be considered immunologically tolerant. Applicant argues that this definition of the term "immunologically tolerant" is being used as a defining characteristic of the presently claimed chimeric animal. Applicant argues that primates typically do not tolerate one another's cells and tissues without immune suppression and the usual response is rejection. Applicant cites Bartholomew et al in support of this assertion. Applicant argues that there would not be a reasonable expectation of success for the human or baboon cells to be tolerated by one another in the absence of immunosuppressive drugs. These arguments are not persuasive.

Again, the specification fails to define the term "immunologically tolerated." Given this lack of definition, the broadest reasonable meaning of the terms is being used in the present examination. Thus, "immunologically tolerated" or "immunologically tolerant" is defined as the acceptance of a cell, tissue or organ for some period of time prior to rejection, and the cell not undergoing hyperacute rejection as is observed with xenografts. The specification mentions immune tolerance, which is known in the art of immunology to be the situation where an individual's immune system does not recognize the individual's own cells, tissues and organs as foreign (specification, page 11). This concept is sometime referred as "self recognition." It is the mechanism of "self" that permits success in autologous, within the same person, transplantation. However, there is no evidence in the specification or in the art at the time of filing that this process of self-recognition would have taken place during the development of the claimed human/nonhuman primate animals. Gustafson, cited by

applicant, clearly discloses that skin grafts between chimeric and nonchimeric siblings of the chimeric animals were accepted for a period of time and subsequently underwent rejection (Gustafson, page 162, Table 4). Disclosed in Gustafson is the initial acceptance, followed by rejection, of grafts from 87-C to 88-G (chimera no. 87 to goat no. 88), 79-C to 80-G and 82-C to 83-G (page 163, parag. 4, lines 1-2, parag. 6, lines 4-6; and page 164, parag. 1, lines 4-6). Thus, the chimeras disclosed in Gustafson, regardless of mixed lymphocyte response, provide cells that are "immunologically tolerated" by the first and second species of the chimera for a period of time, followed by rejection. That is the grafts were initially "immunologically tolerated" or the animals initially "immunologically tolerated" the grafts. This teaching supports the examiner's definition, above, of "immunologically tolerated" or "immunologically tolerant." Gustafson's results, also, demonstrate that "self recognition" does not occur in the chimeric goat x sheep animals. If "self" had been recognized, there would not have been any rejection of grafted tissues. Furthermore, the specification at page 11, states that Gustafson "found that *some* normal sheep and goat siblings of sheep-goat chimeras were able to tolerate skin grafts from their chimeric siblings and exhibited immune tolerance to their chimeric siblings as measured by the mixed lymphocyte response (MLR)" (specification, page 11, lines 15-18). Additionally, there is no evidence on the record that tolerance induced by immunosuppressive drugs would not be considered by the artisan as causing a cell to be immunologically tolerated. Bartholomew discusses induced tolerance using the mixed chimerism approach (Bartholomew, page 1708, col. 2, parag. 2, lines 1-4), which would indicate that tolerance induced by outside factors is still regarded as making the tissues transplanted immunologically tolerated.

Further, Bartholomew teaches methods to overcome host versus graft disease for replacement transplantation of organs between primates. This does not teach that left untreated, the transplanted organs would not be tolerated for some length of time in a non-

immunosuppressed individual. Given Gustafson, and applicant's reliance on the reference, demonstrating that skin grafts from chimeric animals to its single species siblings are rejected, immunologically tolerated would mean tolerated for some period of time before rejection. Applicant's arguments hinge on a term, immunologically tolerated, that is not defined in the specification and is not defined in the art.

Claim Rejections- 35 USC 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 37-50 remain rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter for the reasons of record.

Applicant argues that the rejection is improper for two reasons: (1) the claims are not directed to a human being, or human embryo, but rather a man-made chimeric animal developed from a chimeric embryo, and (2) even if the claims cover human beings, the statute does not restrict patentability based on whether claims embrace a human being. The arguments have been considered but are not persuasive.

Applicant argues that the claims are directed to a chimeric animal developed from a chimeric embryo that is interspecific. Applicant draws an analogy to the previously known sheep-goat chimera, which Applicant says was neither sheep nor goat.

The last Office action cited Starzl et al.'s report of a human patient treated with cells transplanted from a non-human primate, a baboon. The chimeric human patient did not become non-human merely by possessing some proportion of non-human primate cells. Applicant argues that Starzl's chimeric patient and the chimeric animal of the claims can be distinguished. Applicant concedes, "the transplanting of cells to a human being would not convert the human into a non-human and change its origin," but Applicant focuses on

"origin." According to Applicant, the human/non-human primate chimeric embryo, from which the claimed animal develops, was never exclusively human in origin since it originated as a combination of cells from two different species. That is, the claimed chimeric embryo was never solely a human embryo or a non-human primate embryo, but instead was a combination of two distinct species from the beginning of its existence.

The argument, based on origin, is not persuasive for two reasons. First, the focus is on what is claimed, not its origin. Starzl's treated patient is chimeric because the patient comprises cells of two different species, just as the claimed animal is chimeric because it comprises cells of two different species. The presence of some non-human cells does not make Starzl's patient non-human, and the presence of some non-human primate cells does not make a human embryo non-human. Second, even if origin were relevant, Applicant's new explanation is inconsistent with the specification. Contrary to the argument that the claimed animal was never exclusively human in origin, *i.e.*, that the chimeric embryo never existed as a human embryo, the specification states: "the invention relates to chimeric embryos and chimeric animals created from human embryos . . . ." See specification at page 1, lines 2-5.

Applicant argues that an interspecific animal maturing from the chimeric embryo contains cell contributions from both species throughout all its organs, regardless of whether the chimeric embryo consisted of 100 human cells and one non-human cell or vice versa. There does not appear to be a factual basis in the specification for this argument. Instead, the specification discloses that an animal developing from the chimeric embryo would be a source of human organs. See specification, sentence bridging pages 13-14. Further, as presented previously in this office action, both Fehilly et al and Meinecke-Tillman et al teach that chimeric embryos can develop into animals of chimerism limited to one organ or no chimerism (Fehilly, page 636, col. 2, parag. 1 and Meinecke-Tillman, page 638,

col. 1, parag. 1). Thus based on these results, an embryo of the present claims could certainly produce an animal of only one cell type or an animal predominantly of one cell type. Further, there is no basis for excluding a human that has no non-human cells from the scope of claim 50, which claims a descendant of the chimeric animal. The germ cells of the claimed chimeric animal would be either human or non-human, but not interspecific. Descendant progeny would not be interspecific.

Applicant argues that the statute does not restrict patentability based on whether the claims cover a human being, and that the Director lacks authority to impose a limitation on patenting a human. For reasons already stated on the record, the Office does not agree that humans are patentable subject matter.

Claims 37-50 are rejected under 35 USC 101 because the claimed invention is not supported by either a specific, substantial, or credible asserted utility or a well-established utility for reasons of record.

Applicant argues that the utilities proposed in the specification are specific and substantial. Rather than discuss all the proposals in the specification, Applicant limits the response to a discussion of two utilities: toxicology assays and development studies. According to Applicant, the proposed toxicology assays and studies of embryonic development disorders are real world uses that meet the requirement for a specific and substantial utility.

The arguments are not persuasive. Even assuming toxicology studies are a critical step in the development of new drugs, there is no specific explanation showing that observing developmental disorders in chimeras would have any practical utility. For example, if the chimeras are interspecific and neither human nor non-human, as argued, it is not evident that there is any practical application for toxicology information that does not apply to humans or to non-humans. If a chimeric animal were neither human nor non-

human, as argued, toxicology data collected would lack practical value for the human or the non-human species. The proposed utilities appear to be the kind of "use testing" that does not meet the statutory requirement. That is, the claimed invention has not been brought to the point where specific benefit exists in a currently available form.

Conclusion

Further, with regards to the allowance of claims encompassing humans, Applicant is advised that the "Consolidated Appropriations Act, 2004," contains the following provision: "Sec. 634. None of the funds appropriated or otherwise made available under this Act may be used to issue patents on claims directed to or encompassing a human organism." Pub.L. 108-199, 118 Stat. 3, 101 (January 23, 2004).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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