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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/308,135	12/03/2002	Stuart A. Newman	45010-00601	2222

25243 7590 03/05/2003

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/05/2003

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 _____ .

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) *1-36* 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4a) Of the above claim(s) _____ is/are withdrawn from consideration.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) *1-36* 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).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ 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.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

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) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 1-36 are pending.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: A reference to prior application 08/933,564 must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions , Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Further, the present application was filed as a "divisional" of 08/993,564, but as no restriction/election requirement was made in the parent application, and the claims are

directed to the same subject matter, the present application should be indicated as a continuation.

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 1-36 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-92 of copending Application No. 08/993,564. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *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). Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter found in present claims 1-36 is generic to the subject matter found in claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-92 of '564.

Present claims 1-36 are drawn to a chimeric embryo comprising cells from a first human and one more second nonhuman animals; cell lines developed from the chimeric embryo; animals which develop from the chimeric embryo, and descendants of the animals. Claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-92 of '564 are drawn to chimeric embryos comprising embryonic cells from a first human animal species and a second one or more nonhuman primate animal species, where the embryonic cells are blastomeres, blastocyst cells, undifferentiated immortal cells, pluripotent cells or totipotent cells, wherein the embryonic cells remain attached to one another and cooperate in the formation of a further developing embryo; a cell line isolated from the chimeric embryo; and chimeric animals originating from the chimeric embryo.

The present claims are anticipated by claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-92 of '564 because the present claims are generic to the species set forth in the claims of '564. The term "cells" in the present claims is defined by the specification as the specific embryonic cells specifically claimed in '564. The embryos, cell lines and animals claimed in '564 are defined in the '564 specification as being non-transgenic or transgenic as presently claimed. The present specification defines the embryo as comprising human and nonhuman primate cells as claimed in '564. Thus, some embodiments of the present claims are found in claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-92 of '564, claims 1-36 in the present application are not patentably distinct from the claims of '564.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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 1-36 are 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.

The specification fails to provide an enabling disclosure for how to make and use the claimed invention because the teachings of the specification fail to provide the required teachings and exemplifications that would have permitted the artisan to have prepared the chimeric embryos and animals as instantly claimed and as described in the specification without undue experimentation.

The invention of claims 13-18 is drawn to chimeric animals, where the chimerism is human/animal. However, the specification fails to provide an enabling disclosure for the preparation of any animals that derive from human chimeric embryos because given the state of the art and the nature of the invention, one would not have been able to generate viable progeny of human chimeras without specific guidance that is lacking in the specification as originally filed. In regard to claims 1-12 and 19-36, drawn to human/nonhuman animal chimeric embryos and cell lines developed from such chimeric embryos, rather than to animals *per se*, it is noted that within the specification at page 1, lines 1-4, it is stated that:

> The invention relates to chimeric embryos and chimeric animals created from human embryos or embryonic stem cells and embryos or ES cells from one or more nonhuman animals, which have been aggregated under conditions in which a **viable embryo form** (Emphasis added).

However, as supported below, the specification fails to provide an enabling disclosure for how to prepare embryos that give rise to any human/nonhuman animal chimeras. Since

viable chimeric embryos may be considered to be those that give rise to independent animals and/or human beings, the specification fails to provide an enabling disclosure for how to make the claimed chimeric animals, chimeric embryos and cell lines as claimed without undue experimentation.

In regard to the nature of interspecies chimeras, as are the claimed human/nonhuman animal chimeric embryos, animals developed from the embryos, and cell lines developed from the chimeric embryos, the art at the time of filing indicates several problems with unpredictable outcomes, including the loss of one species contribution over another without *a priori* prediction of which of the parental species are lost, and a lack of fecundity of chimeric animals that may be formed under particular circumstances.

Such unpredictability is evidenced by consideration of the sheep-goat chimeras reported by Fehilly et al. (1984) Nature 307, 634-638 (referenced in the instant specification at page 2, first paragraph). The chimeric animals that were produced "had the general appearance of lambs, but in three of these animals the fleece had transverse bands and patches of hair contrasting sharply with the surrounding densely curled wool" (see page 635, second column, full paragraph therein). Thus the chimeras had contributions from both goat and sheep "parents". However, as noted by Fehilly, there was no prediction as to what percentage of the chimera was from the goat parent or how much was from the sheep parent. In addition, Fehilly et al. (1985) J. Reprod. Fert. 74, 215-221 disclosed that in the production of chimeric goat-sheep, there were biases towards chimeras whose genotype and phenotype was most like that of the recipient, and that the successful production of chimeras resided in the neutralization of incompatibility between the chimeric embryo (see page 221, para. 1). To achieve neutralization in the goat-sheep chimera required particular means of chimeric embryo construction that included means of controlling the formation of and contribution by the donor embryo cells of the chimera (see page 221, para. 1).

However, the present specification, fails to provide any guidance as to the parameters to be used for controlling chimeric embryo chimerism and/or the structure of the chimeric embryos formed such that viable embryos, which give rise to viable human/nonhuman animals can be made with any prediction without undue experimentation. That this issue remains in the development and establishment of chimeric embryos is supported by reference to Ruffing et al. (1993) Biol. Reprod. 48, 889-904, which states on page 889, second column, that

> The results of the descriptive analysis on chimerism in the conceptus were used to evaluate the importance of the relative ages of the blastomeres in the chimeric embryo in the distribution of chimerism in the conceptus and, in addition, to examine the effects of chimerism on pregnancy outcome, including fetal and placental growth.

In these studies, reference to Table 1, on page 893, reveals that the number of term offspring is variable dependent upon the host used to carry the chimeric embryo, and that even so, no animals that were fecund were reported. Thus, while the specification relies upon the results and techniques reported from the generation of sheep-goat chimeras (see, e.g., specification at page 3, last paragraph), no guidance is present in applicant's specification as to how one would extend or adapt the techniques employed for the production of goat-sheep chimeras to those that would include humans and any other animals or nonhuman primates, to obtain a human/nonhuman animal chimera without undue experimentation.

All of these uncertainties and unpredictabilities are further enhanced when one considers the scope of the invention as presently claimed. In claims 1-9, and 13-15, the claimed chimeric embryos are prepared from a human and "one or more" second animals species. In claims 28-36, the claims include chimeras prepared from a human and one or more second species selected from the group "comprising" several primates, pigs, mice, rats, and rabbits (note that the language of the claim is not closed and therefore, includes any animal, although only several species are recited). Two basic points are apropos to the

scope of the claims. First, the claims include chimeras prepared between two **or more** parental cells. However, any problems that would be associated with preparing chimeric embryos and animals from two species would have been expected to have been greater when more than two species were present since the number of cell interactions that would need to be considered would be geometrically multiplied. To illustrate: In a two way chimera, three sets of cellular interactions are present; human/human, human/animal, and animal/animal. In contrast, in a three way chimera, seven sets of cellular interactions are present; human/human, human/animal 1, human/animal 2, animal 1/animal 1, animal 1/animal 2, animal 2/animal 2, and human/animal 1/animal 2. Further, with the exception of the recitation of "one or more" animal donors in the claimed chimeras, the specification is silent as to how such would be made or used.

The second problem with formation of chimeras between diverse animals may be best illustrated by reference to embryonic formation between animals extending across a relatively limited phylogenetic range (sea urchin, amphibian, avian, and mammal). Reference to Figure 2-1 of Ham and Veomet, at page 16, shows the widely diverse pattern of embryonic development among these representative animals (Mechanisms of Development, R.G. Ham and M.J. Veomett, authors, C.V. Mosby Co., St. Lous, 1980). However, the specification is silent in regard to any guidance as to how one would make and use, without undue experimentation, chimeric embryos and animals generated between such a diverse set of animals and indeed how one would have addressed the differences that exist in the fundamental manner in which the embryos develop. In the absence of such guidance, the artisan would not have been able to have prepared and used chimeras between such phylogenetically diverse animals without undue experimentation.

Furthermore, the specification discloses numerous uses for the claimed embryos and animals. Such uses including studying regulation of differentiation, teratology, toxicology,

and in the creations of model systems for clinical testing (see specification at pages 7 and 8). However, as the making of human/nonhuman animals is seen as not enabled, the specification also fails to teach how to make human/nonhuman chimeras, without undue experimentation, for the disclosed uses.

The specification further fails to provide an enabling disclosure for the preparation of chimeric human embryos and animals that require the use of embryonic stem (ES) cells from said humans and/or cognate animals because the specification fails to provide an enabling disclosure in regard to how one would have prepared such cells and the art at the time of filing of the present specification indicates that the preparation of such cells would not have been considered to have been within the level of skill of the artisan.

In order to prepare the claimed chimeric embryos and animals of claims 2-7, 10-18, 20-25 and 29-34 using ES cells, the artisan required guidance regarding the preparation of preblastocyst embryos, the placement of such cells in *in vitro* culture and the fusion of any resultant cell lines with host embryos. At the time of filing, the art regarded as unpredictable the obtaining of ES cells that would contribute to the germ line of the resultant animal. In particular, the unpredictability and variability of establishment of embryonic stem cells is evidenced by data taken from a single species, mouse, as reviewed by Baribault et al. (1989) Mol. Biol. Med. 6, 481-492. In Table 1 of Baribault et al., data is presented in regard to the ability of embryonic stem (ES) cells derived from various strains of mice to contribute to germ line chimerism that is contributions by both parental embryonic cell types. It is noted that dependent upon the strain of mice from which the ES cells were derived, the frequency of germ line chimerism (a hallmark of an ES cell line) ranged from 1% to 19%. Thus, even within a single species, the establishment of ES cells was highly variable and unpredictable. Such variability would have been expected to have been even greater when one considered crossing species boundaries, and the practitioner would not have accepted assertions of establishment of ES cells from species other than mice in the absence of supporting data evidencing not only the establishment of cells in

culture but also demonstrating the ability of such cells to contribute to the germ line of host animals. This requirement of the artisan is evidenced by Bradley et al., which states within the paragraph bridging pages 537 and 538 that

> A number of reports have claimed the isolation of ES cells from farm animals such as pigs and sheep. However, the description of these cell lines is yet to be supported by documentation that they can proliferate and differentiate in an embryo *in vivo*, contributing to somatic tissues or germ cells (Bradley et al. (1992) Bio/Technology 10, 534-539).

Thus, the artisan required such evidence in order to accept the validity of the establishment of ES cells and the instant application lacks such evidence. Further evidence for the lack of correlation between conditions of manipulating at least ES cells to be prepared from different species comes from the reference to Saito et al., which states in the second paragraph of the discussion that

> It is essential for ES cell culture to investigate the optimal medium conditions of early preimplantation embryos. In the bovine, continuous culture of cells from a day-11-embryo was achieved on polystyrene in fetal bovine serum...In sheep, Handyside et al. used a mouse STO fibroblast or sheep fibroblast line as the feeder-layer for culture of the ICM [inner cell mass]. They did not observe colonies with an ES-like morphology. Piedrahita et al. did not obtain ovine cell lines with an ES-like morphology when plated on mouse STO feeder-layers or STO with BRL-conditioned medium. These findings suggest species differences in terms of the conditions required for ES-cell cultures. In addition, LIF-conditioned medium has been shown to enable the formation of murine ES cells in the absence of feeder cells. It is currently not fully understood which role feeder cells and their differentiation inhibitory activity contained in LIF- or BRL-conditioned media play in promoting the continuing proliferation and in inhibiting the differentiation of ES cells (Saito et al. (1992) Roux's Arch. Dev. Biol. 201, 134-141).

The criticality of the teachings required for the preparation of ES cells is further evidenced by the reference to Gardner et al.. In reviewing the extant state of the ES cell art up to that time, the reference to Gardner et al. states in its abstract that:

> Remarkably little is known about mammalian embryonic stem (ES) cells despite their very widespread use in studies on gene disruption and transgenesis. As yet, it is only in the mouse that lines of ES cells which retain the ability to form gametes following reintroduction into the early conceptus have been obtained. Even in this species, most strains have so far proved refractory to the derivation of such cell

> lines. Apart from persisting ignorance as to how the various procedures that have been claimed to improve success actually do so, even the tissue of origin of ES remains uncertain (Gardner et al. (1997) Int. J. Devel. Biol. 41, 235-243).

Thus, these teachings indicate not only that ES cells have not been prepared across species despite significant effort by the artisan, but also indicate that the animals from which ES cells are to be prepared must be considered and represent a factor contributing to the unpredictability of the establishment and use of ES cells. In particular, even in the well-studied mouse system where many inbred strains were available, not all strains were equal when preparing ES cells. This problem is exacerbated when one considers that the instantly claimed invention is drawn to humans and other animal species in which well characterized, genetically uniform, strains are not available and unlikely to be generated given that many animals in general, and primates in particular, have long generation times, and limited abilities to be inbred in the absence of the large numbers of animals that are required to be culled to generate viable strains.

Therefore, given the unpredictable nature of the claimed invention, the artisan would have been required to have exercised undue experimentation in the elaboration of which particular combinations of donor species that would result a human/nonhuman animal chimera for each particular combination. In addition, given the lack of guidance and unpredictability in obtaining ES cells for the breadth of the claims as supported by the teachings of the art at the time of filing that the establishment and culture of ES cells was unpredictable, the production of chimeric human/nonhuman animal chimera from ES cells is also not enabled. In the absence of additional guidance from the specification as to the methodology for the formation of human/nonhuman animal chimeras that would give rise to a viable chimeric animal of any particular degree of chimerism, the skilled artisan would not have been able to practice the claimed invention at the time of filing in the absence of significant, unpredictable experimentation, which is considered to be undue. Consequently,

as the specification fails to provide any particular guidance whatsoever in regard to how one would have prepared any human chimeric animals or embryos, the specification fails to provide an enabling disclosure for any embodiment of what is claimed.

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

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-36 are vague and indefinite in regard to the requirements for what would be considered to be a chimeric embryo within the scope of claims. At page 1, lines 4 and 5, it is indicated that chimeric embryos and animals are required to be "viable embryo forms." However, it is unclear as to what would be considered to be such a form. Further, at pages 19-21, it is acknowledged that not all chimeras within the scope of the claims would be viable (i.e., give rise to any animal). Thus, applicant has not pointed out and distinctly claimed their invention such that the metes and bounds of the subject matter are clear.

Claims 1,5-7, 9, 19,23-25, 27, 28,32-34 and 36 are vague and indefinite because claims 1, 19, and 28 recite one or more second animal species and claims under consideration recite characteristics of the cell from the second animal species. However, since multiple second animal species are recited, it is unclear as to which of these species are referred.

Similarly, claims 1, 9, 10, 12, 13, 15, 19, 27, 28 and 36 are vague and indefinite because it is unclear as to which of said one or more second animal species have the transgene and if the one or more transgenes are required to be in one or several of the cells of the species of second animal cell.

Claims 10, 13, and 28 are vague and indefinite because it is unclear as to the scope of what is being claimed. The claims use a hybrid linking phrase "selected from the group **comprising**...". The phrase used when reciting a Markush group of elements, which is a closed set of alternatives, is "selected from the group **consisting of**...". Therefore, it is unclear as to what is being claimed, or if applicant mistakenly used "comprising" instead of "consisting of" (see MPEP 2173.05(h)(a)). Clarification is requested.

Claims 13-15 are vague and indefinite because the use of the phrase "developed from a chimeric embryo" makes it unclear as to whether the claims are drawn to chimeric animals or to the progeny of chimeric animals.

Similarly, claims 10-12 are vague and indefinite because it is unclear as to what would be required for a cell to be "developed" from a chimeric embryo and how such would be distinguishable from a cell prepared from any other source.

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 1-7, and 13-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Zanjani et al. (1996) Int. J. Hematol. 63, 179-192 or Almeida-Porada et al. (1996) Experimental Hematol. 24, 482-487.

Each of Zanjani et al. and Almeida-Porada et al. discloses the introduction of human hematopoietic cells into sheep *in utero*. Therefore, in so far as the claimed embryo chimeras read on the combination of sheep and human cells, each of these references anticipates what is claimed.

Claims 1-7, and 13-25 and 28-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Pixley et al (1994) Pathobiol. 62, 238-244.

Pixley et al. disclose the introduction of human hematopoietic cells into mice *in utero*. Therefore, in so far as the claimed embryo chimeras read on the combination of mice and human cells, each of these references anticipates what is claimed.

Claims 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al. (1994) Develop. 120, 3145-3153.

The claimed invention is drawn to cells prepared from chimeric embryos wherein the chimeric donors are a human and a nonhuman. Therefore, in so far as the claimed cells, once isolated, read on any nonhuman cells, the claimed cell lines read on the mouse primordial germ cells disclosed by Cheng et al., (see e.g. Abstract). Thus, Cheng anticipates what is claimed.

Note that in regard to the limitation that the one or more of the donor cells harbor transgenes, the animals that are prepared from the chimeras may not harbor any transgene if the germ cell from which the animals derive did not harbor a transgene.

Claims 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Catalog of Cell Lines and Hybridomas, 7th ed., American Type Culture Collection (ATCC), Rockville, MD. 20852-1776, 1992, entry HTB 157, HTB 158, and HTB 160, page 271.

In so far as the claimed cell lines read on those that are prepared from human embryos or fetuses, the indicated ATCC.HTB human fetal and embryo cell lines (Fhs 738Lu, Fhs 173We, and Fhs 738BI) anticipate what is claimed.

Note that in regard to the limitation that the one or more of the donor cells harbor transgenes, the animals that are prepared from the chimeras may not harbor any transgene if the germ cell from which the animals derive did not harbor a transgene.

Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by ATCC entry CRL-2378, designated MA-104.

MA-104 was deposited with the ATCC May 1994. MA-104 is a cell line isolated from the embryonic kidney tissue of a Rhesus monkey. Therefore, the claims are anticipated because cells isolated and used to generate a cell line may include only one species. The breadth of the claims would encompass a cell line isolated from embryonic kidney tissue of a Rhesus monkey, a nonhuman animal species.

Claims 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Bradley et al. (1992) Bio/Technology 10, 534-539.

As noted above, in regard to claims 13-15, it is unclear as to whether the claimed animals are drawn to human/animal chimeras or to animals that are the progeny of such animals. In so far as these claims read on the progeny of chimeric animals and therefore overlap with the descendants defined in claims 16-18, the claims read on the "one or more second animal species" that is recited in claim 13. While the claims recite process language regarding how the claimed animals and descendants were prepared, the products that would result from, for example, a chimera formed between a human and a mouse, could be indistinguishable from a mouse prepared by any other means. Therefore, in so far as the claims read on the second animal, Bradley et al. anticipate the claimed invention, which discloses transgenic mice (see e.g. Figure 1).

Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Starzl et al.

Starzl et al. discusses human in which baboon kidneys or livers were transplanted and the resulting chimerism of the patient (see pages 214m 215 and 219). On page 219, Starzl et al. states that the graft and recipient became genetic composites. It is noted that certain claims recite that the chimeric animal was made or not made in a particular way. However, the process limitations are not given weight in consideration of the product claims

unless they define the product itself. Because the breadth of the claims encompasses the humans disclosed by Starzl et al., there is no change to the product garnered by the method of making. Applicant is referred to MPEP 2113 for a discussion on Product-by-Product type claims.

Claim 16 rejected under 35 U.S.C. 102(b) as being anticipate 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 16 is direct to a descendant of chimeric animal of claim 13. 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 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 animal or a non-primate animal and the same species animal was used as a mate, then, the descendant would be totally a nonhuman animal of that singular species. Therefore, the descendants would not be any different from humans, nonhuman animals or non-primate animals found in nature. Therefore, the descendant would be anticipated by, or made obvious over known humans, nonhuman animals or non-primate animals.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 19-25 and 28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gustafson et al. (1993) J. Reprod. Fert. 99, 267-273.

Gustafson et al. teaches that five sheep-goat chimeras received hybrid embryos and developed pregnancies as determined by ultrasonography (page 269, col. 1, para. 2, lines 1-4). The hybrid embryos were the result of breeding between a goat doe and an ovine ram (page 268, col. 1, para. 1, lines 1-3). Of the five, one chimera, 8810, returned to estrus on day 46, indicating a failure to maintain pregnancy (page 269, col. 1, para. 2, lines 4-6). On day 31, 8809 and 8811 showed irregularities in the uterine wall and by day 40, placentome formation in all four chimeras was evident (page 269, col. 1, para. 2, lines 6-9). Heartbeats were detected in the four fetuses on day 35, and were used to establish fetal viability (page 269, col. 1, para. 2, lines 11-13). In 8702 and 8806, fetal movement was also detected (page 269, col. 1, para. 2, lines 13-16). Chimera 8811, was the first to resorb the hybrid pregnancy, followed by 8809, 8806 and 8702 (page 269, col. 1, para. 3, line 1 to page 270, col. 1, para. 1, line 3). Gustafson et al. provides motivation in stating that the establishment of chimeric goat-sheep pregnancies with chimeric goat-sheep embryos is to analyze the influence on the maternal environment on placental function in the chimeric foster mother (page 273, col. 1, para. 1, lines 7-10). Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to make chimeric human animal embryos given the teachings and motivation of Gustafson et al. Such an analysis would be of obvious benefit in determining factors that lead to placental failure. A reasonable expectation of success is provided as the claims state only chimeric embryos, without stating any size or age limitation, or developmental potential. Thus for achieving an embryo, which can be as small as one cell, Gustafson et al. provides sufficient teachings and motivation

Claims 1, 8, 9, 19, 25-28 and 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al. (1992) Develop. 114, 331-338 in view of Robertson et al. (1986) Nature 323, page 445-448.

Watanabe et al. teach the production of chick-quail chimeric embryos by injecting quail stage XI-XIII blastoderm cells into stage XI-XIII and stage XIV-2 chick blastoderms *in ovo* (page 332, col. 1, para. 1, lines 3-6 and 16-24). The descendants of the donor quail cells were then determined by histological analysis of the chimeric embryos after 9 days of incubation (page 332, col. 1, para. 2, lines 1-4). The analysis shows that the location of injection of the quail cells determined the site of chimerism (page 336, col. 2, para. 3, lines 1-3, para. 3, lines 1-4 and para. 4, lines 1-3). However, Robertson et al. teaches the identification of chimeric mice by the detection of proviral sequences, a transgene, into the genome of suspected chimeric mice (page 446, col. 2, para. 2). Thus, given the teachings of Watanabe et al. in view of Robertson et al., it would have been obvious to the ordinary artisan at the time of filing of the present application to make human animal chimeric embryos to determine the localization of donor cells in recipient embryos by the presence of integrated transgene sequences. Motivation is provided by Robertson et al. which states proviral marker sequences provide a set of markers for chromosome linkage analysis (page 447, col. 2, para. 1). A reasonable expectation of success is provided as the claims state only chimeric human-animal embryos, without stating any size or age limitation, or developmental potential. Thus for achieving such an embryo, which can be as small as one cell, Watanabe et al. in view of Robertson et al. provides sufficient teachings and motivation.

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 therefore, subject to the conditions and requirements of this title.

Claims 1-9 and 13-36 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The broadest reasonable interpretation of the claims when read in view of the specification is that they include a human. The disclosure provides no guidance as to the cellular composition of the claimed chimeric embryos or chimeric animals that would render them "human" or "nonhuman." The specification, also, advises that "[t]he invention comprises, in part, human embryos," and that the human cells and nonhuman cells contained in the chimeric embryo are composed of "any number of cell types," page 16. The usefulness of the invention is said to relate to features described as "human." E.g., "[t]he present invention is an invaluable model in the study [of] the effects of various stimuli on human heart tissue," specification, page 10, and "[o]nly by studying the actual development of human tissues and organs can we understand the disorders that affect human development . . .," page 13. The invention is said to provide a source for "human tissue and ultimately human organs," page 14. Further, claims 1 and 28, drawn to chimeric embryos, and claim 13, drawn to a chimeric animal, while being composed of human and nonhuman cells, are not limited to "human" or "nonhuman" products. The claims include any proportional mixture of human and nonhuman cells, and the art recognized that a human could have a proportion of nonhuman animal cells and still be considered "human." Starzl et al. report that, in humans receiving grafted primate tissues, leukocytes migrated throughout the body and the human patients became "chimeras," made by human intervention, comprising human and nonhuman cells. However, the patients were not converted to nonhuman status by engraftment of the nonhuman cells. Similarly, the claimed embryos and chimeras are not converted to nonhuman status merely because they include some nonhuman cells. A proportion of nonhuman cells do not negate the human's status as a human, nor does alteration by human intervention. Thus, it is clear from a reading of the claims in view of the specification and in view of the art that the breadth of the claimed invention includes "humans."

It needs to be pointed out to applicant that there is statutory authority for the rejection of claims 1-9 and 13-36 under 35 U.S.C. 101. Ordinary canons of statutory construction support the present interpretation of patentable subject matter. Statutory words in the first instance must "be interpreted as taking their ordinary, contemporary, common meaning." *Perrin v. U.S.*, 444 U.S. 37, 42 (1979). As the Supreme Court stated prior to the passage of § 101, "legislation when not expressed in technical terms is addressed to the common run of men and is therefore to be understood according to the sense of the thing, as the ordinary man has a right to rely on ordinary words addressed to him." *Addison, et al. v. Holly Hill Fruit Products, Inc.*, 322 U.S. 607, 617-18 (1944). Despite the breadth of these terms, recognized in *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980), the terms "manufacture" or "composition of matter" would not have been regarded in ordinary parlance when § 101 was passed as possibly reflecting a Congressional intent to encompass human beings. Rather, these terms, in their ordinary common meaning, would have been regarded contemporaneously as referring to items other than humans that can be possessed, introduced into commerce, and made the subject of trade. *Cf. Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 480 (1973) ("The productive effort thereby fostered will have a positive effect on society through the introduction of new products and processes of manufacture into the economy, and the emanations by way of increased employment and better lives for our citizens.") In contrast, humans are the beings for whose sake such new products or methods of manufacture would be introduced.

This construction is not contradicted by the legislative history of the Patent Act. As the Supreme Court noted in Chakrabarty, the Committee Reports accompanying the 1952 Act reflect an intent to mandate a broad scope for patentable subject matter to "include anything under the sun that is made by man." S.Rep.No.1979, 82d Cong., 2d Sess., 5 (1952); H.R.Rep.No.1923, 82d Cong., 2d Sess., 6 (1952). These statements too, however,

do not reach so far as to include human beings within patentable subject matter. Rather, like the terms of the statute itself, they presume a dichotomy between man and those inventions and discoveries that could be made by man.

The American rule that statutes are to be construed to avoid Constitutional issues also applies to this question. It has long been an axiom that "where an otherwise acceptable construction of a statute would raise serious constitutional problems, the court will construe the statute to avoid such problems unless such construction is plainly contrary to the intent of Congress." *Edward J. DeBartolo Corp. v. Florida Gulf Coast Building & Construction Trades Council*, 485 U.S. 568, 575 (1988). In a public policy statement and testimony to Congress made fifteen years ago, the USPTO made it clear that it would not interpret statutory subject matter to encompass humans because the exclusionary rights conveyed by a patent would be difficult at best to apply to humans in view of the constitutional rights of human persons. "Animals – Patentability", 1077 Off. Gaz. 24 (April 21, 1987); "Patents and the Constitution: Transgenic Animals: Hearings Before the Subcommittee on Courts, Civil Liberties, and the Administration of Justice of the Committee on the Judiciary," House of Representatives, 100th Cong. 1st Sess. (June 11, July 22, August 21, and November 5, 1987). The rule directing that ambiguous statutory language be construed not to give rise to Constitutional questions is a direction that certain kinds of questions are a matter for the legislature to address in the first instance.

"The grant to the inventor of the special privilege of a patent monopoly carries out a public policy adopted by the Constitution and laws of the United States, 'to promote the Progress of Science and useful Arts, by securing for limited Times to . . . Inventors the exclusive Right . . .' to their 'new and useful' inventions. *United States Constitution, Art. I, s. 8, cl. 8.*" *Morton Salt Co. v. G.S. Suppiger Co.*, 314 U.S. 488, 492 (1942). Long before the term "useful" was incorporated in current § 101, "useful" as used in the patent context

had been construed to include the connotation that an asserted invention "should not be frivolous, or injurious to the well-being, good policy, or good morals of society." *Tol-O-Matic, Inc. v. Proma Produkt-Und Marketing Gesellschaft m.b.H.*, 945 F.2d 1546, 1552-53 (Fed. Cir. 1991), *citing*, *inter alia*, *Lowell v. Lewis*, 15 F.Cas. 1018 (C.C.Mass. 1817) (Story, J.). Public policy takes into account the common sense of the community, issues that are controversial by nature, and issues that tend to be injurious to the public or contrary to public good. Black's Law Dictionary 1231 (6th ed. 1990). The question of whether humans should be the subject of exclusive patent rights raises grave issues going to the core of what a "useful" invention is.

When Congress included the term "useful" in the statute, the requirement that an invention not be frivolous, or injurious to the well-being, good policy, or good morals of society was incorporated with it because Congress did not disavow any of these limitations. *Cf. Lorillard v. Pons*, 434 U.S. 575, 580-81 (1978) ("where, as here, Congress adopts a new law incorporating sections of a prior law, Congress normally can be presumed to have had knowledge of the interpretation given to the incorporated law, at least insofar as it affects the new statute."). "It is the public interest which is dominant in the patent system." *Mercoid Corp. v. Mid-Continent Inv. Co.*, 320 U.S. 661, 665 (1944). However, both the Office and its reviewing court have recognized that this doctrine must be applied so as not to displace the police powers of the states or other federal agencies. *Ex Parte Murphy*, 200 USPQ 801, 803 (Bd. Pat. App. & Int. 1977); *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 USPQ2d 1700, 1702 (Fed. Cir. 1999).

Concerns for deference to the powers of other institutions of government weigh in favor of considering the patenting of humans as the kind of invention that would not be considered "useful" under the doctrine of *Lowell v. Lewis*. It is essential that the USPTO not, by granting patents before the people's representatives have spoken, usurp the power

of Congress to speak first to these issues. The discretion to consider the well-being and good policy of society implicit in the statutory term "useful" is properly applied when a refusal to grant a patent is necessary to avoid preempting the power of Congress to define essential questions of public policy. This principle is all the more applicable in the current context, since Congress has long understood that the USPTO would decline to issue patents covering such subject matter and thus would have good reason to regard itself as having been preempted if the USPTO were instead to issue such patents. Contrary to applicant's argument, given this history, the USPTO would be acting improperly in the place of Congress to "fill a gap" in the law if it were to grant a patent covering human beings; it acts pursuant to soundly based deference to the constitutionally empowered institutions of government in denying such a patent application.

Moreover, it is well established that judicial deference to such an agency interpretation is "particularly appropriate where, as here, an agency's interpretation involves issues of considerable public controversy, and Congress has not acted to correct any misperception of its statutory objectives." *United States v. Rutherford*, 442 U.S. 544, 554 (1979). Congress amended Title 35 several times since the PTO's pronouncements on these issues in 1987. It could have acted to correct any misperception, but took no steps to do so. Indeed, the Supreme Court in *J.E.M. AG Supply v. Pioneer Hi-Bred Int'l*, 534 U.S. 124 (2001), in declining to exclude plants from patent eligibility, relied on the fact that, in the sixteen years after the USPTO's "highly visible" decision to issue utility patents for plants, Congress "failed to pass legislation indicating that it disagrees with the PTO's interpretation of § 101". Just as Congress's acquiescence in the USPTO's announced views on the patentability of plants weighed in favor of the Court's finding plants eligible for utility patents, Congress's acquiescence in the USPTO's announced views on the non-patentability of humans weighs in favor of finding humans not eligible for patents.

Further, should the issue be raised that other patents have issued on animals comprising human cells and that Applicant's invention should be patented under the same standard, the examiner is of the view that the same standard under 35 U.S.C. 101 is being applied in this case as in others. However, patentability is determined on the totality of the record on a case-by-case basis. Whether similar claims in other applications may have been treated differently is neither controlling nor dispositive on how they are to be treated in any other application. *In re Wertheim*, 541 F.2d 257, 264, 191 USPQ 90, 97 (CCPA 1976).

Claims 1-9 and 13-36 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific, substantial or credible asserted utility or a well-established utility.

Applicant's disclosure asserts several utilities for the claimed compositions. These utilities are summarized on page 14 of the specification and encompass use of the chimeras for: (1) developmental toxicology assays; (2) studies of embryonic developmental disorders; (3) cryopreservation for future use; (4) studies in cardiovascular physiology; (5) sources of bone marrow for transplantation; (6) source of hearts for transplantation; (7) sources of tissue for skin grafts; (8) source of organs for transplantation; (9) model system for use in research; and (10) model system for use in clinical trials.

Applicant's claims can be divided into two general categories of invention. The first category are claims directed to an embryonic stage of development where the claims do not require that the embryonic chimeras have developed to the stage of producing organs or specific tissue. These claims are 1-9, and 19-36. The second category is claims that require that the embryonic chimera has developed to produce a specific tissue, organ, or animal. These claims are 13-18.

Utilities (4)-(10) recited above are only applicable to the second category of claims, while utilities (1)-(3) above are mostly applicable to the first category of claims, but may potentially be applicable to the second category as well.

Utilities (1)-(3) are not specific or substantial utilities. A specific utility is one that is not general to a broad class of the invention. Developmental toxicology assays, studies of embryonic developmental disorders and cryopreservation for future use in research are all general utilities that would be applicable to any embryonic cell or human embryonic cell. Applicant's disclosure fails to provide any specific utility of the claimed invention that would not generally apply to all embryos. Thus, asserted utilities (1)-(3) are not specific.

Utilities (1)-(3) are also not substantial. A substantial utility is one that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" use are not substantial utilities. Utilities (1)-(3) are all directed to utilities that are directed to studying the properties of the claimed embryonic chimera itself or the mechanisms by which the chimera develops. Thus, asserted utilities (1)-(3) are not substantial.

Finally, none of utilities (4)-(10) are credible. Utilities (4)-(10) each require the development of the human/nonhuman primate chimera to a stage that produces a specific tissue, organ, or animal. As of the filing date of the application, and even currently, development of specific tissues, organs or animals from embryonic cells is not credible. Pennisi et al. (Science, Vol. 288, 9 June 2000) and Westhusin et al. (Theriogenology, Vol. 55, 2001) each indicate that there are considerable differences in the success of growing cloned embryos from different species. While the cloning methodology has met success in a variety of different species mammals, the tools, details and "tricks of the trade" have differed for almost all species (see Pennisi et al., page 1722, column 3, page 1726, and page 1727, columns 1 and 2; and Westhusin et al., abstract, paragraph bridging pages 36-

37, last paragraph page 40, and last two paragraphs of page 41.) These references clearly establish that even within more developed techniques for embryo manipulation, such as cloning, the species and methodology are important in gaining success. This invention, however, did not involve a methodology as well developed as cloning, but instead allegedly utilizes chimerism to produce specific tissues, organs and animal chimeras. However, in November of 1998, almost a year after the filing of this application, Gearhart, a well respected embryonic stem cell researcher, is referenced as indicating that the production of human chimera utilizing stem cell research is "an even greater shot in the dark than cloning." Tenenbaum, Dave, http://whyfiles.org/shorties/stem_cell.html. Thus, it is clear from the post-filing art that at the time of filing, the production of a human/nonhuman primate chimera that can produce specific tissue, organs or an animal chimera was not credible.

As is often quoted, "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner v. Manson,* 383 U.S. 519, 536, 148 USPQ 689, 696.

Therefore, for the reasons set forth above, the claimed invention lacks a specific, substantial and credible utility.

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. 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, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
March 5, 2003