Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@cdflaw.com
tgiordano@cdflaw.com
Office Action Summary

Application No. 14/397,080
Applicant(s) VACANTI ET AL.
Examiner STEPHANIE MCNEIL
Art Unit 1653
AIA (First Inventor to File) Status No.

-- 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 MONTHS 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 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 1/6/2017.
   □ A declaration(s)/affidavit(s) under 37 CFR 1.130(b) was/were filed on _____.
2a)☐ This action is FINAL. 2b)□ This action is non-final.
3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
4)☐ 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*

5)☐ Claim(s) 75-94 is/are pending in the application.
   5a) Of the above claim(s) _____ is/are withdrawn from consideration.
6)□ Claim(s) _____ is/are allowed.
7)☐ Claim(s) 75-94 is/are rejected.
8)☐ Claim(s) _____ is/are objected to.
9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the Patent Prosecution Highway program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)□ The specification is objected to by the Examiner.
11)☐ 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).

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).

Certified copies:

   a)☐ All  b)☐ Some**  c)☐ None of the:
   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)  3)☐ Interview Summary (PTO-413)
   Paper No(s)/Mail Date: _____.
2)☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)  4)☐ Other: ______.
   Paper No(s)/Mail Date: ______.
Applicant should note that the examiner on this case has changed.

DETAILED ACTION

This application is being examined under the pre-AIA first-to-invent provisions of the Patent Act.

Response to Amendments

Applicant’s amendments filed 1/6/2017 to claims 75, 80, 82-85, and 87 have been entered.

Claims 75-94 remain pending and are being considered on their merits. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant’s comments.

Priority

Applicant’s claim for the benefit of a prior-filed application under 35 U.S.C. § 119(e) to provisional applications 61/637,631 and 61/779,533 is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119(e). To be entitled to domestic benefit, a later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the provisional applications, in this case). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. 112(a) or the first paragraph of pre-AIA 35 U.S.C. 112, except for the best mode requirement. See Transco Products, Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The '631 and '533 applications contain Examples 1 and 2 from this nonprovisional application, plus various aspects of the broad disclosure. The provisional applications contain nothing that is not also present in the nonprovisional application. This disclosure therefore fails to provide an enabling disclosure for the reasons discussed at length in the rejection under 35 U.S.C. § 112, first paragraph, below. The effective filing date for all claims is 4/24/13, the date PCT US13/037996 was filed with WIPO.

Claim Rejections - 35 USC § 112

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

(a) IN GENERAL.—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 or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 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 75-94 remain rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. The claims contain 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. The specification does not reasonably provide enablement for methods of preparing pluripotent cells from every type of mammalian somatic cell using only the stresses in claim 75. In particular, the specification is completely nonenabling for any method of producing a totipotent cell by any method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a prima facie case.

Claim 75 is broadly drawn to generating a pluripotent cell from any type of isolated mammalian somatic cell comprising subjecting that cell to an environmental stimulus selected from a list; these stimuli include the broadly recited “dissociation” and “strong visible light” and the more specific “UV exposure” and “ultrasonic stimulation.” Claim 76 specifies that the pluripotent cell is generated without introducing genes, proteins, or cell components to the isolated cell. Claims 77-79 describe methods for selecting the pluripotent cell. Claims 80-85 further describe certain stimuli. Claims 86-91, 93, and 94 describe
downstream manipulations of the pluripotent cells; claim 93 requires an administration step and claim 94 requires an in vitro differentiation step. The effective filing date for the claims is 4/24/13, the date PCT US13/037996 was filed with WIPO. Numerous aspects of the claims fail to be supported by an enabling disclosure, and the examiner will address them in turn.

*Generating Pluripotent Cells from Somatic Cells Solely by Environmental Stress*

The scope of the claims includes methods in which the isolated cell used to generate pluripotent cells is a terminally differentiated adult somatic cell and in which the cells are not genetically modified or provided with any protein or mRNA. Several years before the invention, skilled artisans developed protocols for reprogramming somatic cells into pluripotent cells by transducing them with exogenous genes. For example, Yamanaka et al. (2009, US Patent Application Publication 2009/0047263) teach isolating MEFs and transducing them with a retroviral construct containing genes encoding Oct3/4, Sox2, Klf4, and c-myc in selective G418-containing media. (Paragraphs 148-50.) Yamanaka teaches that when MEFs are contacted with this retroviral construct, they express the pluripotency markers Oct3/4 and Nanog. (Paragraphs 151-52.) Yamanaka teaches that his reprogrammed cells (“induced pluripotent stem cells” or “iPS cells”) form teratomas in nude mice and therefore concludes that they are pluripotent. (Paragraph 153.) Bayart and Cohen-Haguenauer (2013, *Current Gene Therapy* 13: 73-92) teach that Yamanaka’s work earned him the 2012 Nobel Prize in Physiology or Medicine. (Page 73, column 1.)

Bayart and Cohen-Haguenauer further teach that by the filing date, skilled artisans had developed protocols beyond Yamanaka’s for reprogramming adult somatic cells to pluripotent stem cells. (Figure 2 at page 75.) For example, delivery of the reprogramming factors Oct3/4, Sox2, Klf4, and c-myc can be accomplished not only by retroviral transduction and integration, but also by nonintegrative viruses (adenovirus and Sendai virus) and by transfection of nonviral nucleic-acid constructs. (Figure 2 at page 75; sections 1.1 through 1.3 at pages 75-80.) Furthermore, skilled artisans had developed protocols that do not require insertion of any transgenes, for example delivery of mRNAs encoding Oct3/4, Sox2, Klf4, and c-myc and delivery of these proteins themselves. (Section 1.4 at pages 80-81.) Bayart and Cohen-Haguenauer note that before iPS cells can be considered safe enough for the clinic, the art must identify conversion methods that “do not leave genetic traces beyond the cell conversion phase,” i.e. methods
that do not permanently alter the genetic state of the cell. (Page 87, column 2.) But Bayart and Cohen-Haguenauer identify no such protocols as being available as of the application's filing date. Therefore as of the filing date, the state of the art was that either insertion of an exogenous gen, transcript, or protein was required to make iPS cells.

**Claims 90-92: Totipotent Cells**

Claims 90-92 include embodiments in which the isolated cell used in the method is a terminally differentiated adult somatic cell and in which the resulting cell is not only pluripotent (capable of forming cells from all three embryonic germ layers), it is totipotent (capable of forming placental structures in addition to embryonic ones). A diligent search of the art revealed no prior-art reference suggesting that such a method is possible.

**Relationship Between Unpredictability and Guidance Required from Applicants**

M.P.E.P. § 2164.03 reads, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required.")."

As the above discussion illustrates, methods producing pluripotent (or totipotent) cells from adult somatic cells without genetically modifying the cells or providing them with mRNA or protein were unpredictable at the time of the invention, so those methods must be considered "nascent," and the amount of guidance required is relatively high.
**Guidance by Applicants**

Applicants provide detailed working examples,¹ including one in which Stimulus-Triggered Acquired Pluripotent (STAP) cells are prepared by subjecting CD45+ cells isolated from mouse spleen tissue to acidic culture media (pH 4.5-6.0) for several days; the working examples show that CD45+ cells treated in this way begin to express the pluripotency marker Oct4 and form teratomas in nude mice. (Example 2, paragraphs 212-61 at pages 62-76.) Applicants also provide a working example showing that STAP cells contribute to the formation of the placenta when they are injected into blastocysts. (Example 4, paragraphs 264-94 at pages 77-88.) All of the material in these working examples has been published in a peer-reviewed journal. Example 2 was published as Obokata et al. (2014, *Nature* 505: 641-47; on 5/24/16 IDS; “Obokata 1”), while Example 4 was published as Obokata et al. (2014, *Nature* 505: 676-80; on 6/1/16 IDS; “Obokata 2”). These non-patent references have since been retracted by the journal (see “This Week: STAP Retracted,” 2014, *Nature* 511: 5-6), and work carried out by independent investigators has led the iPS-cell field to conclude that Obokata 1 and Obokata 2 contained data that was, at best, unverifiable.

Less than a year after the publication of Obokata 1 and Obokata 2, *Nature* retracted both papers because “errors were found in the figures, parts of the methods descriptions were found to be plagiarized and early attempts to replicate the work failed.” (“This Week: STAP Retracted,” 2014, *Nature* 511: 5-6, page 6, column 1.) *Nature* reported that an investigation by the RIKEN research center, one of the co-sponsors of the work, revealed that “data that were an essential part of the authors’ claims had been misrepresented [and that] figures that were described as representing different cells and different embryos were in fact describing the same cells and the same embryos,” and *Nature* further noted that all of the co-authors of the papers “finally concluded that they cannot stand behind the papers” and agreed to the retraction. (*Id.;* the seven inventors listed on this application were all listed as authors on both Obokata 1 and Obokata 2.)

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¹ None of the working examples employ any type of cell other than a mammalian cell, so the working examples cannot provide guidance for employing any given “isolated cell” as the claims embrace.
At least three independent research groups have provided strong evidence that the protocols of Obokata 1 and Obokata 2 (i.e., examples 2 and 4 in this application) are inoperable. The RIKEN center’s own work concurs with the work of these three groups. (See “Report on STAP Cell Research Paper Investigation,” 2014, on 5/24/16 IDS; available online at http://www3.riken.jp/stap/e/f1document1.pdf.)

Tang et al. (2014, F1000Research 3:102; on 5/24/16 IDS) attempted but failed to reproduce the protocol in which STAP cells are produced from CD45+ neonatal splenocytes or lung fibroblasts by culturing them at pH 5.7 for several days, finding that cells treated in this way did not express the pluripotency markers Oct4, Sox2, and Nanog. (Pages 2-4.) Tang carefully controlled the pH of his media and therefore concluded that his “inability to produce STAP cells could not be attributed to changes in the pH during the cell stimulus procedures.” (Pages 5-6.) Tang speculates that strain-specific properties of the EGFP construct in Obokata’s C57BL 6J mice could have contributed to the Oct4 fluorescence observed in Obokata 1 and Obokata 2. (Page 6, column 1.)

Konno et al. (2015, Nature 525: E4-E5; on 5/24/16 IDS) also investigated the STAP cells produced in Obokata 1 and Obokata 2 and found reproducible genetic evidence that the STAP cells are actually derived from ES cells, not from the CD45+ spleen cells. (E4, column 2, through E5, column 1.) Konno prepared paraffin-block slides from the same animal reported in Obokata 1 as containing STAP cells in its intestinal epithelium and pancreas but failed to identify any cells in those tissues other than the host mouse’s. (E5, column 1.) Konno concluded that “all of these materials [STAP cells] are derived from previously established ES cell lines and refute the evidence shown in [Obokata 1 and Obokata 2] that cellular stress can reprogram differentiated cells into pluripotent cells.” (E5, column 2.)

Finally, de los Angeles et al. (2015, Nature 525: E6-E9; on 5/24/16 IDS) also attempted to replicate the STAP protocols detailed in Obokata 1 and Obokata 2, working in inventor C. Vacanti’s laboratory (where the original studies were performed), but found that these “existing STAP protocols are neither robust nor reproducible.” (E8, column 1.) First, de los Angeles concluded that the Oct4 signal Obokata 1 and Obokata 2 observed was an autofluorescent artifact. (E6, column 1.) De los Angeles further noted that STAP cells did not form teratomas in nude mice and did not contribute to the formation of embryos upon injection into blastocysts. (E6.) De los Angeles discovered that although the CD45+ cells
used to initiate STAP formation were from female mice, all of the STAP cells reported in Obokata 1 and Obokata 2 were male. (E6, column 2.) Finally, de los Angeles determined that the STAP cells’ apparent ability to contribute to the formation of placental structures was due to contamination by trophoblast stem cells (TSCs), progenitors of placental cells. (E7-E8.)

Since Obokata 1 and Obokata 2 were published, the vast majority of skilled artisans in this field have concluded, based on the work of the RIKEN center and the results of Tang, Konno, and de los Angeles, that treating adult somatic stem cells with low-pH media for a few days without transducing them with any pluripotency genes does not actually yield pluripotent cells. (See Vogel (2015, “Sleuthing sheds light on STAP cell fiasco,” available online at http://www.sciencemag.org/news/2015/09/ sleuthing-sheds-light-stap-cell-fiasco; reference W (reporting on the publication of de los Angeles in Nature)); Cyranoski (2014, Nature 511: 140-43 (detailing irregularities in publications and lack of independent verification prior to publication)); Cyranoski (2015, Nature 520: 600-03 (characterizing Obokata 1 and Obokata 2’s data as “false”)).

The examiner was unable to locate any studies—other than the discredited Obokata 1 and Obokata 2 papers—suggesting that the skilled artisan would reasonably conclude that treating any type of adult somatic cell with the stresses recited in claim 75 results in pluripotency in the absence of transducing at least some of Oct3/4, Sox2, KIf4, and c-myc into those cells and no evidence that totipotent cells can be made in this way.

The experimental results in the working examples are the same as those from Obokata 1 and Obokata 2 (Examples 2 and 4), are derived from those discredited protocols (Example 1), or are speculation based on those protocols (Example 3), and they must be considered against the backdrop of skilled artisans’ evaluation of the claims in Obokata 1 and Obokata 2. The Office cannot overlook the fact

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2 The Office notes that inventors C. Vacanti and Kojima published a “Revised STAP Cell Protocol” on the website of the Brigham & Women’s Hospital Department of Anesthesiology, Perioperative & Pain Medicine on Sept. 3, 2014. (https://research.bwhanesthesia.org/site_assets/51520d191eea6679ce000001/cterm/Revised_STAP_protocol-28bcd7e61d02a23624eb590717e241fe.pdf; see reference V2 (archived PDF).) The BWH website no longer hosts this document, however, and a diligent search revealed no evidence that the Vacanti/Kojima revised STAP protocol overcomes the numerous difficulties identified by de los Angeles (who did his work in inventor Vacanti’s laboratory), Konno, and Tang. See Cyranoski (2014) at page 143, column 1 (discussing the revised protocol and noting that inventor Vacanti “has produced no additional evidence that he has derived STAP cells in his laboratory”).
that Obokata 1 and Obokata 2 are generally considered by skilled artisan to contain inaccurate or even falsified data. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention across its entire scope, particularly the embodiments in which pluripotent (or totipotent) cells are derived from adult somatic cells solely by exposing them to one of the stresses listed in claim 75.

**Response to Arguments**

Applicant's arguments filed 1/6/2017 have been fully considered but they are not persuasive.

Applicant alleges that the fact that other use method that include genetic modification and/or proteins or mRNA to reprogram somatic cells to stem cells is not a proper basis for rejection. These teachings of methods used in the art to reprogram cells is not the sole basis for the rejection, but rather it is part of the analysis to determine if the instant claims are enabled. As discussed above, the analysis for enablement is several fold, including considering state of the art at the time of invention.

Applicant alleges that they have demonstrated the ability to reprogram cells by subjecting them to environmental stress as laid out in the examples in the specification. However, as the examiner has addressed the examples in the specification in detail, generalized statements alleging enablement are not persuasive. If the applicant feels that there are specific flaws in the examiner's analysis, the applicant should point to those specific sections. Applicant does state that the retraction of the papers showing the results of the claimed method, and the statements for the retraction, "merely represent on opinion from certain of the inventors". However, the published statements are from all of the inventors, not some of them as the applicant alleges. Furthermore, as discussed above, several other groups have shown that the state of the art considers the methods published by the applicant, and retracted by the authors, to be inoperable.

Applicant points to a declaration by inventor Vacanti, and alleges this declaration demonstrates that the method of the present disclosure can, indeed, produce the recited pluripotent cells. In the declaration, Vacanti alleges that the retraction does not mean the data are inaccurate. As Vacanti is a listed inventor on the instant application, Vacanti's interest in the application is high. Therefore the examiner is also taking into account the statements made by others. As discussed above, the published
record demonstrates that the date presented in the retracted papers was found to be inaccurate. Independent groups have drawn this same conclusion, that the methods published in the retracted papers could not be replicated. In line with this, Vacanti states at the end of paragraph 7 of the declaration that "it is not easy to replicate many of the techniques". Therefore even Vacanti appears to acknowledge that more than ordinary skill in the art is required to use the claimed method.

Vacanti provides examples in the declaration to attempt to show that one type of cell, human foreskin fibroblasts (HFF), can be reprogramed in response to trituration stress, hypoxia, and exposure to an acidic solution composed of ATP at a pH of 5-6. While applicant stated passively that hypoxia was used to reprogram cells, the applicant does not provide any methods or results for this condition. For the trituration example in the declaration, applicant uses pipettes with diameters of 500-600 microns. This is stark contrast to the methods in the specification which states pipettes with diameters of 50 microns should be used (see paragraph [0088] of the specification). Therefore the example using trituration is very different from the example presented in the instant application. For the example using exposure to an acidic solution in the declaration, applicant uses one narrow example wherein the cells are exposed to 0.2mM ATP for 30 minutes. The claims broadly state the stimulus may be an "unphysiologically acidic environment" (independent claim 75), and that said unphysiologically acidic environment may "be a pH of from about 3.0 to about 6.8" (claim 80). None of the claims state that the acid is APT. Therefore this example in the declaration is at best one every narrow embodiment of the claims. Vacanti also provides an example wherein the treatments of trituration stress and exposure to the ATP solution are combined. However, independent claim 75 is drawn to a method wherein "a stress" from the list is applied, not to a method of combining the stresses. Applicant only provides the actual data for the cells that were treated with the combination of the two stresses (which is outside the scope of the claimed method), in Figures 1 and 2. While applicant generally states in the declaration that cells treated with each of the stimuli expressed specific cell markers, no actual data is provided. Even so, expression of a few cellular markers does not establish that the cell have in fact been reprogramed into a "pluripotent cell" or a "totipotent cell" as required by the claimed method. While Figures 1 and 2 show that the cells receiving the combination treatment formed spheres, and later neurites when placed in an induction media, this too does not
establish that the cells are pluripotent (capable of forming cells from all three embryonic germ layers), or totipotent (capable of forming placental structures in addition to embryonic ones). Therefore these arguments and evidences are not persuasive.

Claims 75-94 remain rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claims contain 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 or a joint inventor, or for pre-AIA the inventors, at the time the application was filed, had possession of the claimed invention.

The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). See M.P.E.P. § 2163.02. In this case, the skilled artisan would not have reasonably concluded at the time of the invention that applicant was in possession of the entire invention as claimed.
The relationship between the allegations and experimental showing in this application, the publications of these same experiments in Obokata 1 and Obokata 2, and the retractions of Obokata 1 and Obokata 2 has been thoroughly discussed in the above enablement rejection, and that discussion is incorporated in its entirety into this rejection. Given the widespread criticism of Obokata 1 and Obokata 2, the fact that these papers present the same data contained in this specification, and the fact that this data is the only grounds for concluding that Applicants’ claims about their technology is true, the skilled artisan would not conclude that Applicants actually possessed the method instantly claimed.

Response to Arguments

Applicant’s arguments filed 1/6/2017 have been fully considered but they are not persuasive. Applicant has not provided any arguments specific to this rejection.

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 75-94 remain rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. This rejection addresses the embodiments of the claims in which the “isolated cell” is either a non-mammalian cell or an adult somatic mammalian cell and in which the method subjects the cell to the recited stresses without providing at least some of Oct3/4, Sox2, Klf4, and c-myc either by genetic means or by contact with the proteins themselves, wherein the method produces pluripotent or totipotent cells.

“An invention that is ‘inoperative’ (i.e., it does not operate to produce the results claimed by the patent applicant) is not a ‘useful’ invention in the meaning of the patent law.” M.P.E.P. § 2107, part II. “Situations where an invention is found to be ‘inoperative’ and therefore lacking in utility” arise when the factual record of the case demonstrates that “the invention could not and did not work as the inventor claimed it did.” Id.
The relationship between the allegations and experimental showing in this application, the publications of these same experiments in Obokata 1 and Obokata 2, and the retractions of Obokata 1 and Obokata 2 has been thoroughly discussed in the above enablement rejection, and that discussion is incorporated in its entirety into this rejection. Given the widespread criticism of Obokata 1 and Obokata 2, the fact that these papers present the same data contained in this specification, and the fact that this data is the only grounds for concluding that Applicants’ claims about their technology is true, it is reasonable to conclude that the claimed invention does not, and cannot, work as Applicants suggest it does.

"An assertion [of utility] is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. . . . One situation where an assertion of utility would not be considered credible is where a person of ordinary skill would consider the assertion to be ‘incredible in view of contemporary knowledge’ and where nothing offered by the applicant would counter what contemporary knowledge might otherwise suggest. . . . Rejections under 35 U.S.C. § 101 based on a lack of credible utility have been sustained by federal courts when, for example, the applicant . . . asserted a utility that . . . was wholly inconsistent with contemporary knowledge in the art.” M.P.E.P. § 2107.02, part III. B. In this case, the record contains nothing to counter the art’s contemporary knowledge about the findings in Obokata 1 and Obokata 2 (i.e., working examples 2 and 4 in this application). Applicants can rebut this rejection using any combination of the following: amendments to the claims, arguments or reasoning, or new evidence submitted in an affidavit or declaration under 37 CFR § 1.132, or in a printed publication. New evidence provided by an applicant must be relevant to the issues raised in the rejection. See id., part VI. Evidence of credible utility will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. Id., part VII.

Response to Arguments

Applicant's arguments filed 1/6/2017 have been fully considered but they are not persuasive. Applicant relies on the arguments above, but those arguments were not persuasive.
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 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 75, 77, 78, and 86 remain rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Yamanaka et al. (2009, US Patent Application Publication 2009/0047263). This rejection addresses the embodiment in which a pluripotent cell is generated by subjecting an isolated mouse embryo fibroblast (MEF) exposure to a “toxin”, wherein the toxin is the antibiotic drug G418. Claim 75 is drawn to a method comprising subjecting an isolated cell to one of the stresses, meaning that it does not exclude unrecited steps. See M.P.E.P. § 2111.03.

Yamanaka teaches isolating MEFs and transducing them with a retroviral construct containing genes encoding Oct3/4, Sox2, Klf4, and c-myc in medium containing selective G418-containing media. (Paragraphs 148-50; the G418 is a “toxin” in the broadest reasonable sense of the term.) Yamanaka teaches that when MEFs are contacted with this retroviral construct, they express the pluripotency markers Oct 3/4 and Nanog. (Paragraphs 151-52.) Yamanaka teaches that his reprogrammed cells ("induced pluripotent stem cells" or "iPS cells") form teratomas in nude mice and concludes that they are pluripotent. (Paragraph 153.) Yamanaka teaches culturing his iPS cells in vitro (Paragraph 158.)

Response to Arguments

Applicant’s arguments filed 1/6/2017 have been fully considered but they are not persuasive. Applicant that Yamanaka does not teach exposing the cells to one of the environmental stimuli in independent claim 75. However, as stated above, the antibiotic G418 is a “toxin” in the broadest reasonable sense of the term. Therefore Yamanaka’s method read on the option wherein a toxin in part of the method.
Conclusion

No claims are allowed.

Applicant’s amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). 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 date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE MCNEIL whose telephone number is (571)270-5250. The examiner can normally be reached on Monday - Thursday, 8:00 AM - 5:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571) 272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. M./
Examiner, Art Unit 1653

/SHARMILA G. LANDAU/
Supervisory Patent Examiner, Art Unit 1653