

The Intellectual Property Landscape for iPS Cells

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I. Introduction	17
II. The Science of Induced Pluripotent Stem Cells.....	18
A. The Origins of iPS Cells	18
B. Historical Overview and the Potential Future of iPS Cells.....	19
C. The iPS Cell Reprogramming Process.....	20
1. The Choice of Factors for Reprogramming.....	21
2. The Methods Used to Deliver Reprogramming Factors.....	21
3. Choice of Adult Somatic Cell Type.....	22
4. Culture Conditions Used to Derive iPS Cells.....	23
5. Identifying and Characterizing Reprogramming iPS Cells	23
C. Additional Problems with iPS Programming.....	24
III. Shifting Sands in Modern Patent Law	24
A. The Disclosure Doctrines.....	25
B. Patent-Eligible Subject Matter	28
C. Obviousness	31
IV. Conclusion.....	34

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I. INTRODUCTION

It is an honor to participate in this conversation among such a distinguished group of scientists and policy makers about the future of stem cell research. As you know, for many years, stem cell research has been embroiled in ethical and political controversy. Moral objections to the destruction of human embryos in the process of embryonic stem cell research has created a political firestorm, resulting in limitations on research funding in the United States and limitations on patent rights abroad.

Beginning in 2006, however, induced pluripotent stem cells have raised the tantalizing possibility that stem cell research could move forward without the significant moral and ethical dilemmas that have paralyzed the field. These cells, known as iPS cells, originate from adult somatic cells, but function in a manner that is almost equivalent to embryonic stem cells. Somatic cells are human cells other than sperm, ova, or the cells from which sperm and ova are made. Examples include, cells from skin, bones, blood, and connective tissue.¹ Thus, if iPS cell research lives up to its promise, stem cell research, diagnostics, and treatment could be performed by inducing skin cells, for example, to return to a state similar to the state in which they existed in the embryo. This could be accomplished without destroying or in any way interfering with human embryos or their development.

Although much scientific research lies ahead before iPS cell technology can produce reliable and sustainable results, the emergence of iPS cell technology is indeed a historic event. As the research involving iPS cells continues to emerge, it is worth taking a moment to think about the rights that are available for protection under the American patent law system, and the obstacles that lie ahead in obtaining those rights.

While we may be entering a historic moment in stem cell research, we are also facing a historic period in American patent law. Of the five key principles of patentability, three are currently in flux, creating challenges for those who would navigate the system. In the brief space allotted here, we will survey the shifting landscape in American patent law, as it may affect the rights available to iPS cell inventors. This brief overview may serve not only as an alert for scientists in the field, but also as a reminder to those of us in the patent world that our failure to resolve doctrinal uncertainties can have a tangible effect on scientific research.

For the purposes of this symposium, this piece is intended to provide a basic understanding of the legal landscape for those in the science field and a basic understanding of the scientific landscape for those in the legal field. Part II describes the science involved in current iPS cell research. The section includes historic background on stem cell research, an overview of the reprogramming process, a description of five factors that are affecting development in the iPS stem cell research arena, and an explanation of additional scientific challenges in the field.

Part III of the piece describes the legal landscape. It explains why stem cell lines are patentable in the first place, and describes the types of innovations that are potentially patentable in iPS cell technology. This part then identifies three elements of patent law that are currently in flux. It explains the implications of these uncertainties for the types of patent claims that are likely to arise from iPS cell innovation.

¹ See BRUCE ALBERTS ET. AL., *MOLECULAR BIOLOGY OF THE CELL* 1270-71 (2008).

II. THE SCIENCE OF INDUCED PLURIPOTENT STEM CELLS

The following is a brief overview of induced pluripotent stem (iPS) cells, intended for those who have little scientific background and are unfamiliar with the field. The section provides a basic scientific framework, highlighting some of the current issues, problems, and aspirations of those working in various areas of iPS cell research.²

A. *The Origins of iPS Cells*

Understanding the process by which embryos are formed in mammals is critical to understanding the origins of cells and the uniqueness of iPS cells. In early embryo formation, the fertilized egg, which is made up of a single cell, undergoes cell division. This gives rise to hundreds of different cell types, including muscle, neuron, blood, fat, and epidermal cells.³ The generation of cellular diversity is called cellular differentiation.⁴ Specifically, before implantation in the uterus, the embryo has two sets of cells, including an inner cell mass.⁵ Embryonic stem cells are cell lines derived from the inner cell mass.⁶

Given that these lines are derived from embryonic cells removed before uterine implantation, the process has created ethical and moral controversy in light of the destruction of cells that have the potential for life. As a result, scientists have searched for a way to create cells that function similarly to embryonic stem cells, but do not originate from the inner cell mass and would not require the destruction of embryos.

In 2006 in Japan, scientists first created and published about iPS cells, which have functional similarity to embryonic stem cells, but are generated not from the inner cell mass, but from adult somatic cells.⁷ As described above, somatic cells are human cells other than sperm, ova, or the cells from which sperm and ova are made. Examples include the cells of skin, bones, blood, or connective tissue. The Japanese scientists took adult somatic cells, and through various signaling mechanisms were able to trigger the cells to re-program themselves to re-start their embryonic programming. The cells thereby became pluripotent, that is, they had the ability to differentiate into any cell type, just like embryonic stem cells.

The iPS cells were highly similar to embryonic stem cells in molecular and functional terms.⁸ The iPS cells, however, were created by reprogramming cells that are unrelated to cells within the gestational process, for example cells taken from the connective tissue or skin of adult patients with specific diseases. Such research avoids the ethical concerns that have plagued the embryonic stem cell field. In addition, given that iPS cells are derived from an adult cell, if they are transplanted back into the adult donor's body, they are patient-specific and therefore less

² This section of the piece is not intended to be comprehensive, and the authors urge interested readers to look at the references cited and to further scientific literature. In particular, for more thorough and detailed scientific discussions of iPS cells, please see Konrad Hochedlinger & Kathrin Plath, *Epigenetic Reprogramming and Induced Pluripotency*, 136 DEVELOPMENT 509 (2009); Alexandra Rolletschek & Anna M. Wobus, *Induced Human Pluripotent Stem Cells: Promises and Open Questions*, 390 BIOLOGICAL CHEMISTRY 845 (2009); Shinya Yamanaka, *A Fresh Look at iPS Cells*, 137 CELL 13 (2009); Shinya Yamanaka, *Pluripotency and Nuclear Reprogramming*, 363 PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B 2079 (2008).

³ SCOTT F. GILBERT, DEVELOPMENTAL BIOLOGY 4 (7th ed. 2003).

⁴ *Id.*

⁵ See *id.* at 5, 366-367; Hochedlinger, *supra* note 2.

⁶ Hochedlinger, *supra* note 2, at 509.

⁷ *Id.* at 511.

⁸ *Id.* at 509.

likely to be rejected. This has the potential to remove one of the major hurdles facing therapeutic uses of human embryonic stem cell lines.⁹

B. Historical Overview and the Potential Future of iPS Cells

The first generation of iPS cells were created by the Yamanaka Lab in Japan in 2006 using mouse cells, and in 2007 the Thomson Lab in Wisconsin created human iPS cells.¹⁰ Since this first major iPS milestones, reprogrammed skin cells using the Yamanaka Lab's procedure have been shown to alleviate the symptoms of Parkinson's disease and sickle cell anemia in mouse models.¹¹ Additionally, patient-specific iPS cell lines have been derived from individual human patients with a variety of diseases, including Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease, and diabetes.¹² Moreover, scientists are continuing to take significant strides in improving the efficiency of iPS cell technology. For example, fibroblasts are cells that create the structural framework for connective tissue. It has generally taken one to two weeks to generate iPS cells from mouse fibroblasts. Recently, however, a procedure using three drug-like chemicals has made inroads in the lengthy process, potentially shortening the time by half, and making the procedure two hundred times more efficient.¹³

In the short term, iPS cell technology may be available for drug and toxicology screening and for creating disease models in the lab.¹⁴ Drug screening could potentially be used to predict the toxicity of new pharmaceuticals or study new candidate drugs in the lab in cell lines of individuals with various medical problems.¹⁵

Laboratory disease models, which are already underway, hold great promise for helping to clarify disease mechanisms. Reaching that point, however, poses significant challenges for scientists.¹⁶ First, scientists must be able to replicate the disease in cells derived from patient-specific iPS cells.¹⁷ In addition, scientists must work to mimic cellular stress conditions, such as oxidative stress, aging, and other environmental stressors that may have an effect on the development of the disease.¹⁸

In genetically inherited diseases, iPS cells derived from two genetically linked patients may aid scientists in studying the mechanisms of the diseases.¹⁹ Diseases attributed to more than one cell type, may be harder to study given that iPS cells will need to be generated from patient-

⁹ Shinya Yamanaka, *A Fresh Look at iPS Cells*, 137 CELL 13, 13 (2009).

¹⁰ These cells were similar to embryonic stem cells in morphology, proliferation, the expression of some ES cell marker genes, and the formation of teratomas. *Id.* See also Kazutoshi Takahashi & Shinya Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663 (2006); Junying Yu, et. al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCIENCE 1917 (2007).

¹¹ Hochedlinger, *supra* note 2, at 510. See also Jacob Hanna et. al., *Treatment of Sickle Cell Anemia Mouse Model with iPS Cells Generated from Autologous Skin*, 318 SCIENCE 1920 (2007); Marius Wernig et. al., *Neurons Derived from Reprogrammed Fibroblasts Functionally Integrate into the Fetal Brain and Improve Systems of Rats with Parkinson's Disease*, 105 PNAS 5856 (2008).

¹² Hochedlinger, *supra* note 2, at 510.

¹³ 'Ethical' Stem Cell Crop Boosted, BBC NEWS, <http://news.bbc.co.uk/2/hi/8311055.stm> (last updated Oct. 18, 2009).

¹⁴ Yamanaka, *supra* note 9, at 14.

¹⁵ *Id.*

¹⁶ *Id.*

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Id.*

specific cells of multiple types.²⁰ In addition, some human iPS cells, such as motor neurons for studying ALS, may need to be transplanted into a mouse, to generate an effective disease model.²¹

If successful, scientists may be able to produce patient-specific iPS cells as a cell replacement and/or for tissue substitution as a means to fight disease.²² In 2008, for example, iPS cells derived from skin fibroblasts showed potential to differentiate into islet-like clusters and release insulin in response to glucose, an approach that could potentially provide a strategy for treating diabetes.²³

C. The iPS Cell Reprogramming Process

Reprogramming adult somatic cells to iPS cells follows a defined sequence of molecular steps. Ordinarily, after embryos are formed in normal cells, multiple repressive mechanisms function to silence the embryonic program, in essence moving the cell to an “adult” state.²⁴ During the reprogramming of iPS cells, the adult cell first has to be signaled to turn off its “adult” programming, and then again signaled to turn back on its embryonic programming. These signals have to be given to the cell in the correct sequence in order to change the cell from an adult somatic cell to an iPS cell.

The overall success of re-programming adult cells to iPS cells is generally inefficient, 0.01% to 0.1%, and thus is the focus of much of the current iPS research.²⁵ In order for iPS cells to become a viable clinical tool, the efficiency rate of reprogramming must dramatically increase.

Scientists are concerned about other issues at the end point of the reprogramming process. In considering therapeutic applications of iPS cells, the cell graft, or group of cells created, will have to fulfill disease-specific requirements, including correct cell integration, migration, and survival within the surrounding tissue of the recipient.²⁶ One of the major issues concerns whether scientists will be able to generate a sufficient quantity of functional cells through the iPS reprogramming model. It is also unknown whether the “genetic memory” of the adult cells will carry through to the reprogrammed cells, or what the role of cellular aging, which can cause increased recessive mutations due to cellular stress, might be in patient-specific iPS cells from older-age donors.²⁷

In addition, there are many factors that must be considered when reprogramming cells from adult cells to iPS cells, including: (1) the choice of factors used to reprogram cells; (2) the methods used to deliver these factors; (3) the choice of target cell type; (4) the culture conditions used to derive iPS cells; and (5) the methods of characterizing and identifying reprogrammed cells.²⁸ Considerations of these factors are critical when determining whether creation and maintenance of iPS cell lines will be successful, and exploration of these areas may yield

²⁰ *Id.*

²¹ *Id.*

²² Rolletschek, *supra* note 2, at 845.

²³ *Id.* (citing Tateishi et al., *Generation of Insulin-Secreting Islet-Like Clusters from Human Skin Fibroblasts*, 283 J. BIOLOGICAL CHEMISTRY 31601 (2008)).

²⁴ *See generally* Hochedlinger, *supra* note 2, at 518.

²⁵ *Id.* at 513.

²⁶ Rolletschek, *supra* note 2, at 847 (2009).

²⁷ *Id.*

²⁸ Nimet Maherali & Konrad Hochedlinger, *Guidelines and Techniques for the Generation of Induced Pluripotent Stem Cells*, 3 CELL STEM CELL 595, 595 (2008).

numerous patentable inventions. The paragraphs below consider the issues arising in these five areas.

1. The Choice of Factors for Reprogramming

In 2006, when the Yamanaka Lab in Japan first reprogrammed mouse fibroblasts from connective tissue to obtain iPS cells, twenty-four candidate genes were implicated in the establishment and maintenance of the pluripotent state.²⁹ The first human iPS cell lines were generated by transducing adult fibroblasts with retroviral vectors expressing certain transcription factors.³⁰ While these transcription factors are required for reprogramming, they are not sufficient for adult cells to reprogram to iPS cells. Most likely, other random events contribute to reprogramming.³¹ Thus, much about the process remains unknown, and authorities may wish to be cautious about granting patents too broadly to avoid sweeping in control of additional innovation.³²

For example, consider the transcription factor Nanog. Nanog is known to lie at the heart of a mechanism for attaining the pluripotency both in embryonic development and in the final phase of somatic cell reprogramming. Further studies are needed to determine Nanog's interaction with other transcription factors, if any, and its other potential roles.³³

A handful of other small molecules and additional factors have also been reported to enhance the reprogramming process and/or functionally replace some of the transcription factors, perhaps leading to the future use of small molecules in iPS cell lines.³⁴ These small molecules and factors are appealing for their ease of use and lack of permanent genomic modification. Nevertheless, they may have broad, off-target effects during reprogramming, and more must be learned before they can be utilized in iPS cell lines.³⁵

2. The Methods Used to Deliver Reprogramming Factors

The production methods used to deliver the reprogramming factors has so far limited the potential therapeutic uses of iPS cells. The reprogramming factors generally have been introduced, or transfected, into the cells by using viruses as delivery methods.³⁶ Given that these approaches use uncontrolled insertions into the genome, such viruses could potentially activate tumor forming genes when the iPS cells are transplanted.³⁷ In addition, other gene functions

²⁹ *Id.* (citing Takahashi, *supra* note 10).

³⁰ These transcription factors are either the reprogramming transcription factors Oct4, Klf4, Sox2, and c-Myc, or Oct4, Sox2, Nanog, and Lin28. See Rolletschek, *supra* note 2, at 845-46 (2009). For a more detailed discussion of the transcription factors, please see, Shinya Yamanaka, *Pluripotency and nuclear reprogramming*, 363 PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOC'Y B 2079 (2008). In general, Oct3/4 is considered the most important, as its expression is highly specific for pluripotent stem cells, whereas the other factors are also expressed in other cells, and Oct3/4 is absolutely required for the maintenance of pluripotency, whereas the other factors can be replaced by homologous factors. See Yamanaka, *supra* note 9, at 14-15 (2009).

³¹ Hochedlinger, *supra* note 2, at 514.

³² See Robin Feldman, *Rethinking Rights in Biospace*, 79 S. CAL. L. REV. 1 (2005) (arguing that patent rights should not be allowed to reach beyond the state of the art at the time of the invention); see also Robin C. Feldman, *The Inventor's Contribution*, 2005 UCLA J.L. & TECH. 6 (2005) (suggesting that appropriate limitation of claims can be accomplished by proper interpretation of the enablement requirement without a separate written description requirement).

³³ Jose Silva, et al., *Nanog Is the Gateway to the Pluripotent Ground State*, 138 CELL 722, 733 (2009).

³⁴ Maherali, *supra* note 28, at 595-596.

³⁵ *Id.* at 596.

³⁶ *Id.*

³⁷ See *id.* at 597.

may be altered.³⁸ Retroviral delivery systems also have been criticized because they can only infect dividing cells, thus restricting the range of cell types that can be reprogrammed; moreover, there is a lower efficiency of conversion due to a gradual silencing of the vectors over the course of the induction.³⁹ In contrast, lentiviruses can infect non-dividing cell types with high expression levels, but they are poorly silenced in the pluripotent state, making them less suitable for reprogramming attempts. In addition, it is unclear if using lentiviruses in the process will interfere with differentiation.⁴⁰

Thus, non-viral delivery methods, which do not integrate with the host genome, would be preferable. So far, a few approaches, including adenoviral delivery, transient transfection, and small molecule/chemicals, have shown potential.⁴¹ Inducing reprogramming directly by chemical, or “small molecule” factors, which specifically modulate the status of the cells, would provide an optimal solution. Most recently, U.S. researchers have utilized thiazovivin, a small molecule involved in cell survival, to boost the number of iPS cells created in the reprogramming process of human cells by two hundred fold, also reducing the time necessary for the generation of the iPS cells nearly in half.⁴² Other small molecule attempts also have demonstrated success.⁴³ Other approaches, such as delivery by a single virus, removal of the viral vectors after transfer, using Cre-recombinase excisable viruses, and, most recently, a protein-induced reprogramming, which requires no genetic modification, also have been utilized and reviewed.⁴⁴

Some of the key issues that remain include increasing efficiency of the reprogramming methodology, and creating a detailed molecular analysis to show that the cells have the genetic “memory” of the adult cell even after reprogramming into the pluripotent state.⁴⁵ In addition, quality control, regulatory mechanism, and standardization remain concerns.

3. Choice of Adult Somatic Cell Type

The type of adult cell strongly influences the success of reprogramming.⁴⁶ Cell type affects the efficiency of the reprogramming process as well as the ease of delivery of the reprogramming factors to the cell.⁴⁷ For example, mouse stomach and liver cells show reactivation of reprogramming factors much faster than fibroblasts and contain fewer viral integrations. Similarly, human keratinocytes, derived from skin cells, reprogram faster and more efficiently than human fibroblasts.⁴⁸ Lastly, older or damaged cells are less likely to be suitable for clinical applications because they are less likely to successfully reprogram into pluripotent iPS cells.⁴⁹ Thus, for therapeutic success, donor cells will need to be easily and safely attainable, less likely to contain genetic aberrations, and easy to reprogram with transient approaches.⁵⁰

³⁸ Rolletschek, *supra* note 2, at 846.

³⁹ Maherali, *supra* note 28, at 596.

⁴⁰ *Id.*

⁴¹ *Id.*; Yamanaka, *supra* note 9, at 15.

⁴² BBC News, *supra* note 13.

⁴³ See Yan Shi, et al. *Induction of Pluripotent Stem Cells from Mouse Embryonic Fibroblasts by Oct4 and Klf4 with Small Molecule Compounds*, 3 CELL STEM CELL 568 (2008).

⁴⁴ See Rolletschek, *supra* note 2, at 846 (2009) for a further review of methodologies.

⁴⁵ *Id.*

⁴⁶ Maherali, *supra* note 28, at 599.

⁴⁷ *Id.*

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ *Id.*

4. Culture Conditions Used to Derive iPS Cells

Human and mouse iPS cell derivation currently use the same cell culture conditions that are used for ES cell maintenance.⁵¹ In the future, there will most likely be a push towards creating cell culture conditions that will allow iPS cells to be more suitable for clinical applications.⁵² The appropriate conditions for culturing must be tailored to satisfy the needs of the donor cell and the arising iPS cell. For example, human iPS cells are more sensitive than their mouse counterparts to the conditions under which they are grown.⁵³

5. Identifying and Characterizing Reprogramming iPS Cells

Once a single iPS cell has been created, it must be positively identified as an iPS cell. Although iPS cells can be identified based on a series of criteria related to form and shape, such identification takes a considerable degree of embryonic stem cell expertise, because colonies that appear similar to iPS cell colonies will arise during the course of reprogramming.⁵⁴ Generally, mouse colonies of iPS cells can be distinguished by their shiny appearance and tight, well-defined borders. Human colonies of iPS cells display a cobblestone appearance with prominent nucleoli and pronounced individual cell borders.⁵⁵ Other techniques have been used when basic form and shape identification is not possible.⁵⁶

Once an iPS cell has been identified, the cell is ready for passage, which is the process of creating a cell line. Passage is a complex procedure and differs in human and mouse iPS cells. Mouse iPS cells can survive as single cells alone.⁵⁷ Human iPS cells, however, survive poorly as single cells, and initial passaging of new colonies is a slow, mechanical procedure requiring five to ten passages before the cells can be separated by enzymes.⁵⁸ In addition, human iPS cells have a tendency to differentiate during the passages, which can undermine the entire procedure.⁵⁹ Finally, once the iPS cell line has been created, it must be tested to determine whether a fully reprogrammed state has been achieved.

Even within each set of cloned cells, iPS cells are not uniform.⁶⁰ After retroviral integration, for example, it takes at least ten days before reprogramming is achieved. This means that a single cell has undergone multiple divisions during this period. Thus, progeny cells may be different in their reprogramming status, even though they originated from the same origin cell.⁶¹ Screening for aberrant reprogramming is essential, therefore, to prevent formation of tumors after transplantation into patients.⁶² Towards that end, the cells must exhibit an array of unique features associated with pluripotency, encompassing morphological, molecular, and functional attributes.⁶³

⁵¹ *Id.* at 600.

⁵² *Id.*

⁵³ *Id.*

⁵⁴ *Id.* at 601.

⁵⁵ *Id.*

⁵⁶ Such techniques include embryonic stem cell-specific surface antigen expression, and loss of transgene dependence. *Id.*

⁵⁷ *Id.*

⁵⁸ *Id.*

⁵⁹ *Id.*

⁶⁰ Yamanaka, *supra* note 9, at 16.

⁶¹ *Id.*

⁶² *Id.*

⁶³ Maherali, *supra* note 28, at 602 (current standards for morphological, molecular, and functional attributes of iPS cell lines).

C. Additional Problems with iPS Programming

There are many potential and known pitfalls in the reprogramming process, including teratoma formation, which is the formation of a germ cell tumor comprising several cell types that is formed from a small number of undifferentiated cells.⁶⁴ When many iPS cells remain undifferentiated together in one cell culture, they have the potential to “clump,” creating teratomas. In order to use iPS cell lines in a clinical setting, scientists must find ways to reduce this risk.⁶⁵

In addition, no known technique exists to determine whether an individual iPS cell has completely reprogrammed.⁶⁶ Aberrant reprogramming can result in impaired differentiation, creating an increased risk of immature teratoma formation or retarded pluripotency of the cell.⁶⁷ Several positive and negative selection techniques have been proposed to eliminate any contamination by undifferentiated cells.⁶⁸ However, these selection techniques are not routinely available yet, and they would need to be more fully developed before the risk of tumor generation could be substantially reduced.⁶⁹

A final issue concerns the presence and activation of transgenes within differentiated iPS cells. Most iPS cells are currently generated by transducing somatic cells with viruses carrying transgenes. The transgenes are integrated into the host cell genome during reprogramming, and are then largely silenced in pluripotent iPS cells.⁷⁰ However, re-activation of these transgenes could lead to tumor formation. In addition, the genes could be faulty either in terms of activating or deactivating incompletely or improperly.⁷¹

As the discussion above illustrates, the field of iPS cells remains in its infancy, full of exciting potential with much left to develop and to understand. Each of the many approaches to iPS cell technology can yield a variety of patent claims. Moreover, each variation on a process may yield additional improvement patents. Inventors who claims any of these rights will have to navigate the considerable uncertainties in the modern patent system. The sections below describe these shifting sands and suggest ways in which the uncertainty may implicate patent rights in iPS cell lines and technology.

III. SHIFTING SANDS IN MODERN PATENT LAW

One might begin by asking how iPS cells could be patentable in the first place. After all, patents are supposed to be granted on the inventions of man, rather than the products of nature, and one could argue that iPS cells are living, natural products. The logic that allows patenting of iPS cells can be traced to two lines of case law, one of which dates back to 1911. In the case of *Parke-Davis v. Mulford*,⁷² the legendary judge Learned Hand ruled that an inventor can patent something found in nature, if the inventor has isolated and purified it from its natural state in a way that allows one to do something new with it. In addition, in the 1980 case of *Diamond v. Chakrabarty*, the Supreme Court ruled that if an inventor alters something found in nature, the

⁶⁴ Yamanaka, *supra* note 9, at 13.

⁶⁵ *See Id.*

⁶⁶ *Id.* at 14.

⁶⁷ *Id.*

⁶⁸ Rolletschek, *supra* note 2, at 846.

⁶⁹ *Id.* at 846-47.

⁷⁰ Yamanaka, *supra* note 9, at 14.

⁷¹ *See id.*

⁷² *Parke-Davis & Co. v. H. K. Mulford Co.*, 189 F. 95, 103 (C.C.S.D.N.Y. 1911).

resulting invention may be the handiwork of man rather than the handiwork of nature, even if the invention is living.⁷³ These two lines of authority allow iPS cell researchers to patent their cells as isolated and purified from nature as well as altered from the state in which they naturally exist.

This underlying logic for allowing patentability of isolated and purified natural substances, particularly where those substances have been altered, has formed the underpinnings of patentability for genes and genetic inventions for thirty years. In March of 2010, however, a federal district court judge in New York ruled that patents on the genetic mutations associated with certain forms of breast cancer were unpatentable on the grounds that they fell within the “products of nature” exception to patentable subject matter.⁷⁴ The case, which is currently on appeal, threatens to disrupt thirty years of precedents that apply broadly throughout the field of biotechnology, implicating patents on isolated and purified genes, antibodies, and other substances. Although iPS cell inventors might be able to argue that their inventions are sufficiently distinct from nature to satisfy any understanding of the term “products of nature,” the decision does create turmoil and uncertainty for inventors in this area.

A number of other types of patents may be available in addition to the patents on the cells themselves. Inventors could apply for a patent on the method of producing that type of cell. If there is a testing application, one could apply for a diagnostic patent on the method of using the cells to reach a diagnostic conclusion. Finally, once there are therapeutic applications, one could apply for a patent on the method of using the cells in a particular therapeutic manner. Each of these, of course, would be broken down into multiple patents with numerous claims.⁷⁵

For any given patent, there are five basic elements that must be satisfied for patentability.⁷⁶ These are proper subject matter, novelty, nonobviousness, utility, and proper disclosure. Three of these elements, disclosure, nonobviousness, and subject matter are currently in flux in the courts. The resolution of those issues may affect the rights that inventors may claim and may shape research choices along the way.

A. *The Disclosure Doctrines*

The disclosure doctrines, typically identified as written description and enablement, relate to an inventor’s contribution to society and to the question of whether the inventor has given society enough to receive the rights requested.⁷⁷ In exchange for the powerful patent right, an inventor must provide sufficient disclosure that one skilled in the art could make and use the invention. The disclosure doctrines serve many purposes, including determining whether an inventor actually has possession of what is being claimed, whether the inventor told the public enough of the information the inventor knows, and whether the inventor truly has made it possible for others to do what the inventor is claiming.

⁷³ *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). Eight years later, the Board of Patent Appeals held that § 101 should be extended to include multi-cellular animals. See *Ex parte Allen*, 2 U.S.P.Q.2d (BNA) 1425 (B.P.A.I. Apr. 3, 1987).

⁷⁴ See *Assoc. for Molecular Pathology v. U.S. Patent & Trademark Office*, 702 F.Supp.2d 181 (S.D.N.Y. 2010).

⁷⁵ For an interesting recent discussion of the details of the claims within those few patents that have been granted in the iPS cell space and an analysis of that language under various patent doctrines, see Brenda M. Simon, Charles E. Murdoch, & Christopher T. Scott, *Pluripotent Patents Make Prime Time: An Analysis of the Emerging Landscape*, 28 NATURE BIOTECHNOLOGY 557 (2010).

⁷⁶ See 35 U.S.C. §§ 101-112.

⁷⁷ For more information on the disclosure doctrines and the surrounding controversies in modern law, see Robin C. Feldman, *The Inventor’s Contribution*, 2005 UCLA J.L. & TECH. 6 (2005).

In recent decades, the Federal Circuit has been struggling with the question of whether the language of the Patent Act contains a written description requirement that is separate from and in addition to an enablement doctrine. The Federal Circuit identified a separate written description requirement for original claims in the 1997 case of *Regents of the Univ. of Cal. v. Eli Lilly & Co.*⁷⁸ Since that time, the Federal Circuit has been unable to clearly explain what the written description doctrine requires, how it differs from the enablement doctrine, and how the two doctrines might relate to each other. The confusion has resulted in continued calls for a re-examination of the written description doctrine, as well as some outright demands to eliminate the doctrine altogether.⁷⁹

As tensions surrounding the disclosure doctrines have increased, practitioners report that the PTO has continued to narrow the scope of the claims that biotechnology applicants can receive. In particular, the PTO appears to be rejecting broad disclosures that attempt to claim a broad genus by enabling only one species of the genus. In other words, the PTO wants to see inventors demonstrating mastery over more than one or two members of a group in order to claim the entire group.

The Federal Circuit again tried to tackle the question of a separate written description in 2010.⁸⁰ In an en banc decision in the *Ariad Pharm. Inc. v. Eli Lilly & Co.*, case, the Federal Circuit, addressed the question of whether a separate written description doctrine should exist and, if so, what the scope and purpose of the doctrine should be. Although the Federal Circuit reaffirmed the existence of a separate written description, the decision leaves much uncertainty in its wake.

In *Ariad*, the patent holder claimed methods compromising the single step of reducing activity in the NF-KB biochemical pathway.⁸¹ Thus, the claim covers the broad category of all methods that can reduce the pathway's activity. In support of the claim, the patent hypothesized three classes of molecules potentially capable of reducing NF-KB activity.

The accused infringers argued that the disclosure in the patent was no more than a research plan and that the claim reached far beyond what had been disclosed.⁸² The three-judge panel of the Federal Circuit agreed. The court held that the patent holder had to sufficiently disclose molecules capable of reducing NF-KB activity, so as to satisfy the inventor's obligation to disclose the technology on which the patent is based and demonstrate that the inventor was in possession of the claimed invention.⁸³

The case implicates a number of broader questions wrapped up in the issue of what is required by a separate written description. In particular, what must one know about a group or individual members of a group in order to claim that group? Is it enough to demonstrate success

⁷⁸ *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997).

⁷⁹ In 2004, the Federal Circuit declined to reconsider en banc the written description requirement. The denial itself was controversial, producing five separate concurring and dissenting opinions. See *Univ. of Rochester v. G. D. Searle & Co., Inc.*, 358 F.3d 916, 920 (Fed. Cir. 2004), *reh'g en banc denied*, 375 F.3d 1303 (Fed. Cir. 2004).

⁸⁰ See *Ariad Pharm. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc).

⁸¹ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 560 F.3d 1366, 1372 (Fed. Cir. 2009).

⁸² *Ariad*, 560 F.3d at 1373.

⁸³ *Id.* The court cited the *Rochester* case as invalidating a similar method for lack of written description. See *Rochester*, 358 F.3d at 918. (The method claims recited a broad type of compound that was inadequately described in the specification: "1. A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a *non-steroidal compound* at selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment) (emphasis added).

with a few members of the group and a functional relationship among the members? How many members of the group, how much of a relationship, and how much knowledge must be required?

Despite an opinion that ran to almost forty pages, the *Ariad* case left many of these issues unresolved. For example, the Court noted generally that “the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.”⁸⁴ It does not, however, provide much enlightenment on the topic of what constitutes “sufficient.”⁸⁵ In the case at hand, the court simply needed to note the lack of any species disclosed when claiming the full genus. The tougher questions remain to be resolved.

Inventors in the iPS cell space must file patent applications in this uncertain environment. What can one claim with a particular invention, and how much supporting research should be done in order to make that claim? These issues will arise for iPS cell inventions in a number of areas.

Questions related to pathways may be particularly relevant to iPS cell research. For example, the p53 pathway has shown promise as a research tool with iPS cells. Can researchers craft a disclosure that is narrow enough to survive PTO examination, but not so narrow as to limit the patent’s usefulness once it is issued? Analogous to *Ariad*, if they wish to claim methods comprising the single step of reducing activity in the p53 pathway, would that be too broad, if their work consisted only of iPS cells? Although uncertainty abounds, signals from both the PTO, in its current preference for narrowing claims, and the courts suggest a more restrained approach. The researcher, however, may be able to patent a cell line utilizing the p53 pathway. Claim language for that patent might have the potential to reach downstream, depending on what breadth the PTO is willing to allow.

Similar dilemmas will arise in developing claims to the cell lines themselves. Patent language that is inclusive of any potential factor that may be utilized for de-differentiation from the adult somatic cell to the pluripotent cell, but provides examples of only a few factors, for example, may appear overly broad. Such a claim could be particularly problematic in light of scientific literature showing unpredictability of the field or negative results for some factors. A disclosure for a certain set of factors, or for a certain group of factors with examples, however, may be sufficient for disclosure if it is narrow enough in scope so that the applicant has enabled a person of ordinary skill in the art to make or use the cell line.

Questions related to the proper scope for genus and species may also arise for iPS cell inventors. A disclosure for iPS cells in “all animals including human” would probably be too broad, unless the applicant has shown that the iPS cells work in multiple animals, such as mice, rats, non-mammalian species, and in humans. In the early stages of this emerging science, the technology is too unpredictable, and the PTO may be hesitant to allow a broad claim encompassing different species without an adequate disclosure and examples. In addition, given that iPS cell science is a rapidly emerging field, the standard of a person of ordinary skill in the art is likely to change over time, which could affect both the way in which the claims are viewed and the tests that are applied.

All of this must be understood in the context of the considerable doctrinal uncertainty that continues to plague this area. The Federal Circuit is trying to develop a consistent and coherent approach, despite more than a decade of disarray. Most importantly, the Supreme Court has yet to weigh in and could adopt an entirely different approach, if it chose to enter the fray.

⁸⁴ *Ariad*, 598 F.3d at 1349.

⁸⁵ *See id.* at 1350 (noting that “the specification does not disclose a variety of species that accomplish the result”).

B. Patent-Eligible Subject Matter

The second area of patentability law that is embroiled in uncertainty relates to patent-eligible subject matter. We should be clear at the outset that we are not talking about moral objections to particular inventions. American patent doctrines largely ignore issues of morality and ethics, adopting a purely utilitarian approach and leaving morality to Congress. Historically, the utility doctrine occasionally has been used to block patents related to items such as gambling machines or flag-decorated condoms on the grounds that such inventions lacked any morally appropriate use. These precedents have fallen out of favor, however, and are generally ignored in modern American patent law.

Section 101 of the Patent Code states that a patent may be obtained on “any new and useful process, machine, manufacture, or composition of matter.”⁸⁶ This section thus creates a utility requirement and identifies patent-eligible subject matter. Proper subject matter under patent law has been interpreted quite broadly, particularly in the biotechnology field. In the seminal case of *Chakrabarty*, for example, the Supreme Court upheld the patentability of a genetically engineered living bacterium noting that, “Congress intended statutory subject matter to ‘include anything under the sun that is made by man.’”

This is not to suggest that § 101 has no limits or that the patent law embraces every discovery. Laws of nature, physical phenomena, and abstract ideas have been held not to be patentable.⁸⁷ These lines have proven particularly difficult to draw as they relate to modern inventions. Inventions related to software, medicine, and methods of doing business press on the questions of what constitutes a proper invention and what is no more than an abstract idea or the recognition of a natural phenomena.

The Supreme Court came close to addressing the issue in a biotechnology case in 2006. In *LabCorp v. Metabolite Laboratories, Inc.*, the patent at issue was a process patent to help diagnose two vitamin deficiencies utilizing an assay test that measured the level of a certain amino acid in bodily fluid.⁸⁸ The claim language was quite broad, including a claim with no more than the following language:

A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of: assaying a body fluid for an elevated level of total homocysteine; and correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.⁸⁹

In other words, the claim covered any method of testing for a level of a certain fluid and correlating the result with a particular vitamin deficiency.

The Supreme Court granted cert., raising questions not fully raised in the lower courts, heard oral argument, and then ducked the case, dismissing it as improvidently granted. Three Justices joined in a dissent to the dismissal expressing concern about patents that block or tie up natural processes. The dissent noted that phenomena of nature are the basic tools of scientific and technological work, part of the storehouse of knowledge that is free to all men and reserved

⁸⁶ See 35 U.S.C. § 101.

⁸⁷ *Chakrabarty*, 447 U.S. at 309.

⁸⁸ *LabCorp v. Metabolite Laboratories, Inc.*, 548 U.S. 124, 125 (2006).

⁸⁹ See *id.* at 129.

exclusively to none.⁹⁰ The case foreshadowed struggles on the limits of patentable subject matter that continue to plague the courts.

A number of recent cases press at the boundaries of patentable subject matter in a way that may affect patentability of inventions related to stem cells. One of the most closely watched cases in this area is the *Bilski* case, which concerns commodities trading.⁹¹ Why should the biotech industry care deeply about commodities trading? The answer is simply that the case lies at the intersection of subject matter patentability issues that affect many types of method patents, from software to medical diagnostics and therapeutics.

In an en banc decision, the Federal Circuit held the claims unpatentable. The Court ruled that the proper way to determine whether an invention falls within the proper subject matter area for process or method patents is to ask whether the invention “(1) is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing.”⁹² The Federal Circuit held that the so-called “machine or transformation test” should be the sole test for determining subject matter patentability for process claims.

The Federal Circuit decision brought a howl of protest from the life sciences sector. Many life science patents relate to diagnostic or treatment methods that are unrelated to any machine, and one would have to strain to fit within the notion of a transformative process. Of the numerous amicus briefs to the Supreme Court, some argued in opposition to the test on those grounds.

Reacting to these concerns, as well as to the Supreme Court’s penchant for overturning the Federal Circuit in recent years, the Federal Circuit tried to send a message that “all is well.” While *Bilski* was pending at the Supreme Court, the Federal Circuit decided *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*.⁹³ The case applied the machine or transformation test to a medical diagnostic patent, applying the text in an extremely flexible manner, and signaling that the life sciences field has nothing to fear.

The patent at issue in *Prometheus* concerned methods for calibrating the proper dosage of drugs by administering the drug to a subject, determining the level of the drug’s metabolites in the subject’s system, and then correlating that with pre-existing information to decide whether the drug needed to be increased or decreased. In upholding the patent, the Federal Circuit signaled that its “machine or transformation” test could be interpreted quite loosely in the life sciences field. In particular, the Federal Circuit took pains to distinguish its decision in *Prometheus* from an earlier Federal Circuit decision in which claims directed to a mathematical algorithm with a data gathering step that included performing clinical test was found to be unpatentable.⁹⁴ Thus, *Prometheus* appeared to be a plea to the Supreme Court to uphold the machine or transformation test for method patents in all areas in its *Bilski* opinion, with the understanding that the Federal Circuit will spare the life sciences. The *Prometheus* opinion, however, lacked the firm logic that would clearly differentiate between patentable and nonpatentable subject matter in these arenas.

⁹⁰ See *id.* at 127.

⁹¹ *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008) (en banc), *aff’d*, 130 S. Ct. 3218 (2010)

⁹² *Id.* at 954. The test has two further aspects. The use of a specific machine or the transformation of an article must impose meaningful limits on the claim’s scope, and that the involvement of the machine or transformation in the claimed process has to be central to the purpose of the claimed process. See *id.* at 961-62.

⁹³ *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, 581 F.3d 1336 (Fed. Cir. 2009), *vacated, remanded by*, 130 S. Ct. 3543 (2010).

⁹⁴ See *id.* at 1348; see also *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989).

At the last moment of the term that ended in July of 2010, the Supreme Court issued an opinion in *Bilski* agreeing with the Federal Circuit's conclusion that the patent failed to satisfy the test for subject matter patentability, but overturning the Federal Circuit's logic.⁹⁵ In particular, the opinion of the Court held that the Federal Circuit had erred in suggesting that the "machine or transformation" test is the sole method of determining patentable subject matter for method patents.⁹⁶ The opinion left it up to the Federal Circuit to further develop tests in this area, and it noted cryptically that "nothing in today's opinion should be read as endorsing interpretations of §101 [patentable subject matter] that the Court of Appeals for the Federal Circuit has used in the past."⁹⁷ In other words, we won't tell you exactly what is right, but we will tell you that the Federal Circuit is wrong.

The *Bilski* Supreme Court opinion not only left many issues unresolved, it is also a muddle. The opinion of the Court drew only four votes for the opinion in full, receiving the deciding fifth vote as to only certain portions. The decision also drew two concurring opinions, one of which again drew agreement from another member of the Court as to only particular sections. In short, the Supreme Court's tea leaves are particularly difficult to read in this case, and much remains to be clarified and decided. Finally, additional controversies exist that could spill over into questions related to patentability of biotech products themselves.⁹⁸

Uncertainty in the area of subject matter patentability could affect a variety of inventions related to iPS cells. iPS cell lines themselves are likely to be unaffected, unless genes and related inventions are ruled entirely unpatentable, as discussed earlier in this piece.⁹⁹ Those cell lines will be claimed as product patents, patentable under the lines of authority described at the outset of the piece. The current uncertainty surrounding patentable subject matter, however, relates to patents that claim particular methods, rather than those that claim particular products.

Method patent issues could arise for iPS cell inventors, however, in the creation of the cell lines. Patents that claim methods of creating the cell lines could possibly collide with the current controversies. Consider the *Ariad* case described above, in which the patent holder claimed the method of reducing activity in the NF-KB biochemical pathway. The appellate court rejected the claim on disclosure grounds. In earlier rounds of the litigation, however, challengers also argued that the pathway is a naturally occurring phenomenon and that the patent had the effect of tying up the phenomenon. The district court in *Ariad* rejected the argument, but that decision is only at the district court level and it can be contrasted to another case, *Classen Immunotherapies, Inc. v. Biogen IDEC*.¹⁰⁰

In *Classen*, the Federal Circuit in an unreported decision rejected a patent that was based on the inventor's purported discovery of a relationship between the timing spread of vaccinations

⁹⁵ See *Bilski v. Kappos*, 130 S. Ct. 3218 (2010).

⁹⁶ See *id.* at 3226.

⁹⁷ See *id.* at 3231.

⁹⁸ See *supra* text accompanying note 74 (describing the trial court holding in *Assoc. for Molecular Pathology*, that denied patentability for a series of inventions related to a particular genetic mutation). Similarly, Congressman Becerra introduced a bill on Feb. 9, 2007 that would have forbidden the patenting of genes and related products. See Genomic Research & Accessibility Act, H.R. 977, 110th Cong. (1st Sess. 2007).

⁹⁹ See *supra* text accompanying note 74 (describing the case, *Assoc. for Molecular Pathology*).

¹⁰⁰ See *Classen Immunotherapies, Inc. v. Biogen IDEC*, Nos. 2006-1634, 2006-1649, 2008 WL 5273107 (Fed. Cir. Dec. 19, 2008) (citing *In re Bilski*, 545 F.3d vacated, remanded by, 130 S. Ct. 3541 (2010)); see also Chris Holman, *Courts Grapple with the Question of Whether Biological Phenomena Constitute Unpatentable "Natural Phenomena,"* CHRIS HOLMAN'S BIOTECH IP BLOG (Aug. 27, 2008, 1:34 PM), <http://holmansbiotechblog.blogspot.com/2008/08/courts-grapple-with-question-of-whether.html> (comparing the *Ariad* and *Classen* cases).

and certain disorders. The patent broadly claimed methods of comparing vaccine schedules to determine the safest schedule. The Federal Circuit panel summarily affirmed the district court's decision that the claims were invalid, citing the Federal Circuit's machine or transformation test as described in *Bilski*. The logic of the *Bilski* decision has been rejected by the Supreme Court, however, leaving the decision in the case in doubt.¹⁰¹

Thus, methods of creating the cell lines, particularly those that involve pathways, may face challenges from the notion that the patent holder is trying to patent a natural phenomenon or that the claim impermissibly embodies that phenomenon. In addition, cases like *Ariad*, *Classen*, and *Labcorp* suggest that the courts are far from being able to draw a line between patentable methods and unpatentable phenomena of nature.

In addition, as iPS cell technology advances to the point of diagnostic and therapeutic methods, the technology will face uncertainties reflected in the *Bilski* debates, not to mention the application of any subsequent test. All of these issues reflect that the American courts have yet to delineate the boundaries of method patents in the life sciences arena. iPS Cell scientists will have to draft patents in the fog of this uncertainty.

C. Obviousness

The third and final patent area currently in flux is obviousness.¹⁰² For an invention to be patentable, the invention must not only be new, it also cannot be obvious to one of ordinary skill in the art based on the information available in the art. The courts have ruled that obviousness is a legal question based on factual determinations including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, and evidence of secondary factors.¹⁰³ The teachings of a prior art reference are underlying factual questions in the obviousness inquiry.¹⁰⁴

In the years leading up to 2007, the Federal Circuit had been applying the so-called TSM test for determining obviousness. According to the test, an invention would not be ruled patentable as a combination of information available in the prior art unless that art contained a specific teaching, suggestion, or motivation to combine the prior art.

In the 2007 case of *KSR Int'l Co. v. Teleflex Inc.*, the U.S. Supreme Court rejected the Federal Circuit's application of the TSM test in a case concerning automobile gas pedals.¹⁰⁵ The Supreme Court ruled that the test had been applied too rigidly. The Court also held that the Federal Circuit also erred in concluding that application of the TSM test was mandatory.

Rather than identifying or rejecting a particular test, however, the Supreme Court noted that TSM was one possible test that could be used, as long as it was not used in too rigid a fashion. The opinion left to the lower courts the task of determining what tests might be proper in what circumstances, and what a less rigid application of TSM might look like.

The message of *KSR* was clear. Patent holders should be warned that it will be much tougher to show that one's invention is not obvious. The PTO has taken the message to heart,

¹⁰¹ See *supra* text accompanying notes 95 to 97.

¹⁰² "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 negated by the manner in which the invention was made." 35 U.S.C. § 103(a).

¹⁰³ *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

¹⁰⁴ *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009).

¹⁰⁵ See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

and practitioners report that the agency has been much tougher on obviousness in the wake of the *KSR* decision. Nevertheless, the boundaries of that decision as it will be applied in various contexts remains in flux, as the lower courts grapple with the Supreme Court's uncertain mandate.

The Supreme Court in *KSR* and the Federal Circuit in a case following in the wake of *KSR* offered some clues, but those clues tend to be at the level of generalizations at this point. For example, the Supreme Court explained that when there is a design need or market pressure to solve a problem and there are a "finite number of identified, predictable solutions," a person of ordinary skill has good reason to pursue the known options within their technical grasp, and if successful, the fact that a combination was obvious to try might show it was obvious.¹⁰⁶ "In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness."¹⁰⁷

On the contrary, when prior art teaches away from combining certain elements together, the discovery of a successful combination of such elements is likely to be nonobvious.¹⁰⁸ If a work or a technique is available in one field of endeavor, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is most likely obvious unless the application of such a technique is beyond the person's skill.¹⁰⁹

The *KSR* decision has already had an impact in the biotechnology field. Prior to *KSR*, the Federal Circuit had held for years that providing the sequence of a gene would be sufficient to overcome obviousness, as long as the prior art did not provide or suggest the sequence.¹¹⁰ The decision had been highly criticized as setting too low a bar for patentability. Following *KSR*, the Federal Circuit held in *Kubin* that a claim for a gene sequence encoding a particular protein was obvious because the prior art contained the protein of interest, a motivation to isolate the gene coding for that protein, and illustrative instructions to use a monoclonal antibody specific for the protein for cloning the gene.¹¹¹ The court concluded that the invention was not the product of innovation, but rather a product of ordinary skill and common sense, one that "a skilled artisan would have had a resoundingly 'reasonable expectation of success' in deriving the claimed invention in light of the teachings of the prior art."¹¹²

The Federal Circuit in *Kubin* also declined the invitation to limit *KSR* and its dicta to non-biotechnology cases, stating, "[t]his court cannot, in the face of *KSR*, cling to formalistic rules for obviousness, customize its legal test for specific scientific fields in ways that deem entire classes of prior art teachings irrelevant, or discount the significant abilities of artisans of ordinary skill in an advanced area of art."¹¹³

The obviousness inquiry could potentially create roadblocks for iPS cell inventions, depending on the application of *KSR* and its progeny to the iPS cell research field. Three types of questions could arise: 1) the obviousness of the creation of iPS cells; 2) the obviousness of the transition from murine models to human models for clinical and therapeutic uses, and 3) the obviousness of different cell types.

¹⁰⁶ *Id.* at 421.

¹⁰⁷ *Kubin*, 561 F.3d at 1359.

¹⁰⁸ *KSR*, 550 U.S. at 416.

¹⁰⁹ *Id.* at 417.

¹¹⁰ *See In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).

¹¹¹ *Kubin*, 561 F.3d at 1360.

¹¹² *Id.*

¹¹³ *Id.* (citation omitted)

The question of whether the genre of iPS cells is obvious relates to their role as stem cells. The prior art within stem cells almost exclusively concerns embryonic stem cells. Embryonic stem cells are functionally similar to iPS cells but are created with different methods, techniques, and originator cells. In theory, one could ask whether it would be obvious to try to create iPS cells, knowing only that embryonic cells exist. The answer could lie in a potential misperception of the notion of “obvious to try.” In layman’s terms, the notion of “obvious to try” could mean that it would be obvious for us to try to find a way to do this. In legal terms, however, the notion of “obvious to try” relates to the question of whether the solution you find would be obviously suggested by the prior art in that or another area.¹¹⁴

From this perspective, courts are unlikely to find that iPS cells were obvious to try. iPS cells were first created utilizing a combination of transcription factors that were retrovirally activated in somatic cells to shut off adult programming processes and initiate embryonic processes, which in turn, through a series of complex biochemical steps, transformed the adult cell into a pluripotent cell, or iPS cell. At that point, the pluripotent cell was given signals to begin differentiation, introduced into the system the clinician wanted to treat, and then allowed to fully differentiate as a cell in the proper system. Although any adult somatic cell could hypothetically be used for the process, generally skin or epithelial cells are used, because they are easily obtained and are plentiful. There are also several known techniques for the initial de-differentiation of the adult somatic cell to the pluripotent state, but the most common utilizes a series of four transcription factors. In comparison, embryonic stem cells originate from blastocyst, before implantation into the uterus, and cannot reverse engineer into embryonic stem cells once they have differentiated into a specific cell type.

The techniques involved with iPS cells were quite different from those in embryonic stem cells, nor were they suggested by any other areas prior art. In particular, one cannot argue that there were a finite number of known solutions to the question of how to create an alternative to embryonic stem cells. In fact, there were *no* known solutions. The creation of iPS cells was not a matter of “ordinary skill and common sense.” It represents an extraordinary leap in scientific knowledge, utilizing a maverick style that led to the discovery of an entirely new stem cell field.

One could also ask whether the transition from murine to human models is obvious. Similar issues arise in many life science inventions. The question will turn on many issues including the difficulty involved in adapting this particular murine invention to human models at the time of the invention, the predictability of the area, the similarity of the methods used, and the expectation for success, as well as the details of the obviousness tests that the courts develop.¹¹⁵

At the initial stages of translating murine iPS cell inventions to human models, obviousness will be a much easier hurdle to overcome. At least in terms of the immediate field, there will be no analogous transfers to try to emulate. One could argue that the murine to human translations in the embryonic stem cell field provide analogous prior art. The technology may be sufficiently different, however, that the successful modes of translation will not be obvious.

Over time, however, obviousness will become a patentability issue as researchers increasingly enter the field. Laboratories will be forced to prove that their inventions are not obvious over the patented inventions of the laboratories that came before them. In this context,

¹¹⁴ See, e.g., *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008), *cert. denied*, 130 S. Ct. 493 (2009).

¹¹⁵ See Simon et. al., *supra* note 75, at 558 (discussing this issue in relation to a particular iPS cell claim in which a murine-based product is claimed in a way that it might be extended to any somatic cell line, including mammalian cells).

uncertainty about the boundaries of the test will make it difficult for the inventors to successfully navigate the patent process.

The final area in which obviousness may play a role concerns iPS cell technology that moves from one cell type to another. For example, an inventor may have claims related to iPS cell technology in blood cells when the prior art relates to skin cells. After all, there are a limited number of types of somatic cells. Inventors will have to show that what they have done is beyond simply what would have been obvious given that there are a limited number of cell types, we know what works in one type, and we know various other information about how the cell types relate to each other.

Coming full circle, those who translate iPS cell inventions from one cell type to another, potentially might have to contend with disclosure battles. For example, some early iPS cell patent applications are claiming their invention for all “adult somatic cells” on the basis of work in one cell type. Assume that the work underlying the original patent was performed in skin cells, for example, those who translate that work into blood cells could, in theory, find themselves fighting on two fronts. The later, blood cell inventors would have to demonstrate both that the skin cell inventor’s claim was too broad, and that the blood cell work was so difficult, distinct, and not predicted by the prior art that it should be considered not obvious.

The mechanics for the appearance of such a dual argument would be tricky. The PTO would most likely reject the patent application by the later blood cell inventor on novelty grounds, given that the claims from the earlier skin cell patent cover blood cells as well. The later blood cell inventor, in the context of infringement litigation, would then argue that the claims of the first patent reach too broadly and are invalid for lack of written description or enablement. If successful, the later blood cell inventor might be able to overcome the PTO’s novelty objection. After all, a court would have held that the earlier invention did not cover blood cells, so the blood cell invention would be novel. Nevertheless, the later inventor would still have to show that the blood cell invention was not obvious in light of the work performed with skin cells.

For all of this to occur, the blood cell inventor would have to be sued for infringement by the skin cell inventor and prevail in that litigation before all avenues for appeal on the rejection of the blood cell patent had been exhausted. Those sued for infringement can raise lack of enablement or written description as a defense, but one generally does not have standing to challenge a patent unless there is a threat of infringement litigation. Companies, however, can be remarkably creative in maneuvering each other into court.

In addition to uncertainties about the tests for proper disclosure and obviousness, the relationship between the two is unclear as well. If one is comparing invention A to a future invention for the purposes of infringement, should the reach be the same as if one were comparing invention A to prior art? Scholars have disagreed on this point.¹¹⁶

IV. CONCLUSION

We are at historic crossroads today, both in terms of scientific possibilities in the stem cell field and in terms of patent law. Three of the five major areas of patentability remain in flux, with both the tests and the application of those tests shrouded in uncertainty. We may

¹¹⁶ Compare Robin Feldman, *Rethinking Rights in Biospace*, 79 S. CAL. L. REV. 1, 34-36 (2005) (arguing for parallel treatment), with Dan L. Burk & Mark A. Lemley, *Inherency*, 47 WM. & MARY L. REV. 371 (2005) (arguing for disparate treatment).

emerge from this period with a sense of clarity for inventors or we may continue in our current haze, just rigid enough to ensnare patentees, just flexible enough to confuse them. Even if we are to achieve some degree of clarity, it is likely to take some time to develop. What we can say with certainty is that iPS cell inventors who wish to patent their inventions will have to navigate a challenging and uncertain landscape. The emerging and rapidly evolving field of iPS cell research should serve as a reminder to the patent field of the effect that unresolved conflicts in patent law can have on the scientific endeavor.