

Stem Cell Patent Landscape and Patent Strategy

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The year of 2009 witnesses the roller coaster ride towards finding cures for diseases based on stem cell research. In January, the U.S. Food and Drug Administration (FDA) gave the green light to Geron Corporation's Investigational New Drug (IND) application for the clinical trial of GRNOPC1. GRNOPC1 is a human embryonic stem cell (hESC)-based therapeutic candidate that contains hESC-derived oligodendrocyte progenitor cells, for treatment of patients with acute spinal cord injury. Eight months later in August, FDA put the trial on hold pending the agency's review of new non-clinical animal study data submitted by Geron. The following month FDA cleared the way for Neuralstem to begin the first human trial of a stem cell therapy for Lou Gehrig's disease using spinal cord stem cells.

Nevertheless, both venture capitalists and big pharma pumped millions of dollars into the stem cell business in 2009. In March, Stemgent, a startup that makes consumable materials for stem cell research labs raised \$14 million in venture capital. In May, Pfizer announced the expansion of its regenerative medicine unit in the UK and US with an injection of \$100 million. In July, two stem cell startups, Pieiran and Izumi Bio, merged into IPierian, with additional \$11.5 million of VC funding. In November, Fate Therapeutics has rounded up \$30 million in a Series B to help advance its work on a pipeline of stem cell modulators. This article will spare the introduction to the stem cell technology, which is covered in more detail in the excellent companion reviews in this special issue. Instead, this article will first briefly explain three important concepts (patent landscaping, patentability, and freedom-to-operate), then present an overview of the stem cell patent landscape, and finally discuss stem cell patent strategy.

I. Patent Landscaping, Freedom-to-Operate, and Patentability

There are three types of patent analyses that are inter-related but distinct and serve different purposes: patent landscaping, freedom-to-operate, and patentability.

A. Patent Landscaping

Patent landscaping is a high-level, bird's eye's view analysis of the patent landscape of a given technology field. Patent landscaping generally is conducted before a company has committed to any particular technologies to guide its R&D planning. It identifies the major patent portfolio and players in the field: what are the major patents, what is the scope of those patents, who owns them, and who are the active players. A thorough understanding and appreciation of the technology development history and the current state of research efforts and industry trends is essential in a patent landscaping analysis.

Patent landscaping analysis generally focuses on issued/granted

patents, and often starts with a search of issued patents in the U.S. and moves on to patents granted in other major jurisdictions, such as in Europe. After the major patents are identified, the analysis can be broadened to include the pending applications that are in the same patent family, as well as the published applications by the same inventor/company of the identified major patents.

Patent landscaping usually is carried out before a company enters a field and is used as guidance for devising both a business plan and a patent strategy. For example, if there is a dominant patent portfolio owned by a major player who is actively committing resources in the field, to develop a competing product using the same technology might be ill-advised. However, a significant technology improvement that can be protected by patents can provide a good value proposition for potential investors or business partners. This is true even if the technology improvement does not have freedom-to-operate because of the current dominant patent portfolio. For example, the existing patents may expire before the launch of any products. This is especially true in areas where the product development cycle is rather long, such as drug development. Alternatively, the existing dominant player may be interested in acquiring or licensing the technology improvement to maintain its lead. This can provide partnership opportunities and/or exit strategies for the late comer.

B. Patentability

A patentability analysis is done to evaluate whether one can obtain a patent to protect his or her invention. A patent is country specific and can only be issued or granted if it meets the patentability requirement in that particular country. In the U.S., a patent can be issued only if the claimed invention is patentable subject matter¹, useful, novel (e.g. no one has previously invented the subject matter), and non-obvious (e.g. is it merely an obvious variation of something previously done)². In addition, the specification (the description of the invention) must support the claimed invention. In the US, the specification must also meet the written description requirement (the specification must demonstrate that the inventor was in possession of the full scope of the invention as claimed), the enablement requirement (the specification must teach how to make and use the full scope of the invention as claimed), and the best mode requirement (the specification discloses the best way of making and/or using the invention contemplated by the inventor at the time the application is filed).

A patent confers the patent owner the right to exclude others from practicing the claimed invention; it does not confer the patent owner the right to practice the

invention himself. In the U.S., this means other people cannot make, use, sell, offer to sell, import into the U.S. the claimed invention without the permission from the patent owner. However, the patent owner may also not be able to practice the invention claimed in her patent if practicing such invention infringes someone else's patent that is still in force. Therefore, even if one has obtained a patent to his invention, he still needs to have the freedom-to-operate to be able to practice the invention himself, as discussed below.

A simple analogy is in order. Party A patents a car with 4 wheels, and engine and a steering wheel. Party B patents intermittent windshield wipers. Neither party can sell a car with intermittent windshield wipers, as Party A can exclude Party B from selling a car and Party B can exclude Party A from selling intermittent windshield wipers.

In a patentability analysis, one looks at one's own invention in view of all of the relevant references in the public domain, which could be patents, published patent applications, journal articles, posters, sales, or public presentations or demonstrations that were publicly available as of either the date of invention or the filing date of the invention (collectively called "prior art"). All parts of the prior art are used in the analysis, including the claims of patents and patent applications as well as the disclosures.

Having identified any and all prior art that could be relevant, a patentability analysis is done to see if the invention meets the statutory requirements within the country of interest. In the U.S., this analysis asks, is the invention patentable subject matter, is it useful, is it novel, and is it not obvious over the prior art?

A common mistake in patentability analyses is to focus on what the reference did, not what it describes. For example, a patent application or a research paper may only have done work in primate stem cells; however, if the prior art says it can be done with human stem cells, this needs to be taken into account, even if there is no data to support the statements.

C. Freedom-to-Operate

In contrast to patentability analyses, an FTO analysis is generally conducted when the company has narrowed its interest in one or more particular technologies or has locked in a product prototype. In an FTO analysis, one looks at his own activities or products (existing or proposed) in view of other people's patents and asks: can I practice this technology without infringing other people's valid patents? The focus of an FTO analysis is

the claims of other people's patents because it is the claims of a patent that define the scope of the patent. Non-patent literature is not considered. For example, a company without prior experience in stem cell development is interested in developing a stem cell based therapy to treat diabetes. The company would first carry out a landscaping analysis to understand what are the major platform technologies related to stem cells generation, modification, and production. If the company decides to use one of the platform technologies, it then would carry out an FTO analysis to ensure using the selected platform technology would not infringe any third party's valid patents. If the technology is cleared by this FTO analysis, a separate FTO is generally carried out on any identified target genes (called "target clearance") before the company starts to develop lead antibodies that act on those target genes.

The reason to conduct an FTO analysis is that infringement is a strict liability offense: patent holders need not prove or even allege intent to prevail on a claim of infringement. Moreover, even if one invents a technology independently, not knowing the existence of Third Party patents, practicing the independently invented technology is still an act of infringement if there is an issued patent.

FTO analyses are done for a specific patent based on a specific proposed activity. Of course, there may be more than one Third Party patent to analyze, but these are done separately, as an FTO analysis is completely fact driven. It is important to note that as a result, sometimes "updates" of the FTO analysis may need to be done, for example when the proposed product changes or is improved³. One should also identify where and when the technology will be practiced - where and when the R&D will be conducted and where and when the products will be sold. Then one should search patent databases for patents still in force for each jurisdiction in which there are plans to practice the invention, e.g., U.S., Europe, Japan, China, Canada, and Australia, for patents that cover any aspect of the technology to be practiced. The priority in the analysis is patented technology, covered by an issued patent.

To answer the question of whether a company can practice a technology without infringing another party's valid intellectual property, the company needs to analyze the scope of the claims of the identified patents and do a multi-prong analysis. Does the company actually infringe these patents? Are the patents valid, e.g. is there prior art that would render them not valid under any statutory requirement? Either a finding of non-infringement or of invalidity can be a valid defense to

infringement, and there are many steps to this analysis. Part of this analysis should also include whether a license to the patent is available at a reasonable cost, whether the patent will expire before projected launch, and whether or not there has been any litigation on the patent that would guide the analysis.

If there are problems identified in the analysis, e.g. the patents appear both infringed and valid, then several things can happen. In some cases, business development people, scientists and patent attorneys should work together to determine if there is a suitable alternative to the patented technology that is economically feasible for the company (e.g. is there a "design around"). If a "design around" is identified, is any aspect of the "design around" patented? If a "design around" is created, is the "design around" itself worthy of patent protection? If no suitable alternative is found, is the patent available for assignment/license? In some cases, the work must stop and be redirected in a different way.

Another aspect of an FTO exercise is to analyze the technologies covered by published applications. Published applications can potentially confer some rights, at least in the U.S., though there are very strict guidelines for collecting damages from a published application. However, this analysis can help identify the size of the potential problem, which can be a factor in continuing a research path.

FTO is generally an ongoing process. This is especially true in areas where the technology is new and constantly evolving, such as stem cell research, and patents are continually issuing.

II. The Evolving Stem Cell Patent Landscape

Stem cell research can be traced back to a century ago when Alexander A. Maximow gave a presentation on hematopoiesis at a special meeting of the Berlin Hematological Society on June 1, 1909.⁴ The first U.S. patent with the term "stem cell" in a claim was not issued until 1977 (U.S. Patent No. 4,042,678). However, by October 17, 2009, 1703 U.S. patents have issued with the term "stem cell" in a claim, most of which were issued since 1990. In comparison, there are 6,107 U.S. patent applications published since 2001 by the same date with the term "stem cell" in a claim. Therefore, the patent landscape of stem cell technology is littered with several thousand patents still in force and even more pending applications with claims the scope of which is in flux. This is further complicated by the rapid progress in stem cell research that could easily render a technology obsolete anytime.

A. Adult Stem Cell Patents

Adult (or Somatic) Stem Cells (ASCs) are undifferentiated cells isolated from a specific organ or tissue from an animal that are normally present to maintain and repair injured tissue or organs. ASCs have been found in tissues such as brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis.

Many of the U.S. patents related to ACS are directed to hematopoietic stem cells and bone marrow stromal cells (mesenchymal stem cells) and were issued in the 1990s, and thus have expired or will expire soon. The followings are several exemplary patent families.

U.S. Patent Nos. 4,714,680, 4,965,204, 5,035,994 and 5,130,144 (issued to Johns Hopkins University and licensed to Becton-Dickson claim human pluripotent lympho-hematopoietic stem cells and related monoclonal antibodies.)

U.S. Patent Nos. 5,004,681, 5,192,553, 6,461,645, 6,569,427, 6,605,275 (issued to PharmaStem Therapeutics) claim a method for obtaining human neonatal for fetal hematopoietic stem or progenitor cells and method of using such stem cells for treatment (e.g. leukemia, anemia and immune deficiencies).

U.S. Patent Nos. 5,409,825, 5,744,361, and 6,241,984 (assigned to Indiana University Research and Technology Corporation, all expired) claim methods for growing human hematopoietic stem cells in a liquid culture medium using individual or combinations of cytokines, particularly IL-3, GM-CSF, and c-kit ligand.

U.S. Patent Nos. 5,437,994, 5,399,493, 5,459,069, 5,605,822, 5,635,386, 5,646,043, 5,670,147, 5,670,351, 5,763,266, 5,888,807, 6,326,198, and 6,667,034 (issued to the University of Michigan) relate to human hematopoietic stem cells.

U.S. Patent Nos. 5,968,829, 6,103,530, 6,498,018, 6,777,233 (issued to Cytotherapeutics/StemCell) relate to human CNS neural stem cells.

These patents may expire soon, but some or all of them could be relevant for disclosures related to stem cells during a patentability analysis and/or prior art to affect Third Party patents in an FTO analysis.

B. Embryonic Stem Cell Patents

Embryonic Stem Cells (ESCs) are derived from a pre-

implantation embryo (implantation normally occurs around seven days after fertilization). ESCs must be able to divide for prolonged periods of time in culture without differentiating. ESCs are recognized as theoretically having the ability to give rise to all tissues and organs of a complete organism, i.e., the cells are “totipotent”. However, there seems to be no set academic or industry standard for characterizing a cell as an ESC. There are several ways to characterize a cell as an ESC: (1) culturing the cells in an undifferentiated state for months/years; (2) detecting specific cell markers characteristic of ESCs, such as Oct4, Nanog, Stella (transcription factors); (3) detecting cell surface markers (cell phenotype), e.g. SSEA-4, lectin receptors; and (4) testing pluripotency of the cells, i.e., determine if cells can be induced to produce various tissue types.

The Thomson patents (U.S. Patent Nos. 5,843,780, 6,200,806, 7,029,913, 7,582,479) are generally considered the dominant patents in the ESC field with the first three patents survived re-examination. The Thomson patents also are referred to as WARF patents as they are assigned to Wisconsin Alumni Research Foundation (WARF), and licensed to Geron. These patents claim primate ESCs derived from pre-implanted embryos. However, these patents may become less important as more attention is turned to induced pluripotent stem (iPS) cells.

C. Induced Pluripotent Stem Cell Patents

No patents have been issued that claim iPS cells. All of the patent applications related to iPS cells are filed in the U.S. on or after 2006 and have not been examined yet. Due to the backlog at the U.S. Patent and Trademark Office (USPTO), it generally takes two or more years for any applications to be examined and several more years for the patents to be issued, if ever. In fact, we assume that most applications related to iPS cells have not yet been published as applications do not publish in either the PCT or the U.S. until 18 months from the filing date.

For example, the first Yamanaka patent application was filed in 2005 in Japan and was published early 2007 (WO2007069666A1). This application is based on Shinya Yamanaka’s pioneer work that showed the mouse embryonic fibroblasts (also known as MEFs and are skin-like cells) were “induced” to become stem-cell-like by forced expression using viruses of four genes, Oct-4, Sox-2, Klf-4, and c-Myc, a process is called genetic reprogramming.⁵

In 2007, Yamanaka’s lab reported the generation of iPS stem cells from adult human fibroblasts by defined factors.⁶ This led to two additional patent applications

filed in 2007 that later were combined into a single application published in 2009 (WO2009057831A1).

Also in 2007, the Thomson lab separately reported that human foreskin was genetically reprogrammed using four different genes: Oct-4, Sox-2, Nanog, and Lin-28.⁷ The patent application based on this work was published a year later as WO2008118820A2.

In 2009, two labs separately reported the creation of iPS cells from MEFs⁸ using only proteins and small molecules to create human iPS cells.⁹ We assume patents have been filed on this work, although it is too early for publication.

Therefore, as for any stem cell technology, one needs to monitor the patent applications to monitor the patent landscape of iPS cells from time to time. In addition, because no claims have been issued related to iPS cells, monitoring the prosecution of relevant patent applications will also be important.

D. Other Patents

There are also patents covering technologies that are not tied to any particular types of stem cell or not tied to stem cells at all, but are still important to stem cell research and development. They include patents claiming cell culture media, reagents (e.g. different factors need to maintain stem cells in the culture media), methods of transfection, etc. For example, U.S. Patent No. 5,405,772 (issued to Amgen) claims serum-free or serum-depleted culture media for supporting the proliferation and development of cells, such as hematopoietic progenitor cells.

Therefore, a thorough FTO analysis for a stem cell related product needs to review not only stem cell related patents, but also other patents relating to the manufacturing of the product, such as cell culture media, reagents (vectors, growth factors, etc.), methods of isolating cells, methods of growing the cells, methods of differentiation, etc.

III. Building a Stem Cell Patent Portfolio

Generally, it is desirable to build a patent portfolio around a company's technology and products, to prevent others from copying. A patent portfolio is a collection of patent families that cover any given technologies or products. A patent family is a collection of patents directed to the same subject matter with related priority claims. A patent family can include tens or even hundreds of patents in different jurisdictions

around the world to protect different aspects of a technology, and a company may have a number of different patent families within their portfolio

A patent portfolio is generally more effective than a single patent in defending an IP space because it is much more difficult and expensive for a competitor to analyze and challenge several patents, particularly in the U.S. However, as prosecuting and maintaining patents is generally expensive, the size of a patent portfolio (how many patents, in how many different jurisdictions) depends on the IP budget of a company, which in turn should be decided as any other budgets of a company: to be based on the calculation of cost and return.

For example, an early stage company with limited funding may want to have a few solid patents to cover its core technologies (e.g. a platform technology) with a limited patent budget. However, a well-funded company may want to build a comprehensive patent portfolio not only for the defense purposes (covering their own products) but also for the offensive purposes (e.g. filing patent applications to block a competitor even if such applications do not cover its own core technologies or products).

In building a patent portfolio around new technologies such as stem cells that evolve quickly, the strategy should also be flexible and be revised from time to time to keep up with the pace of, or even foresee, the progress in research. For example, the emerging iPS cell technologies would render many patents focusing on ES cells irrelevant. The possibility of using small molecules to induce iPS cells might also render the patent applications focusing on using protein factors to induce iPS cells irrelevant.

A patent portfolio can be built either by in-licensing patents/applications from other parties (e.g. universities) or by filing applications based on technologies developed in-house, and usually it is a combination of both. No matter which path, a company should understand that not all the patents/applications are equal. The value of a patent/application not only depends on the technologies it intends to protect, but also depends on how the patent/application is drafted. Two major components of a patent are the disclosure (called the specification) and the claims (which is also part of the disclosure).

The protection a patent confers is defined by the claims, and the scope of a claim is a double-edged sword. A broad patent claim covers a bigger IP space; but it also is subject to more prior art as a result and thus can be more difficult to prosecute and defend when being

challenged. On the other hand, a narrow claim is easy to be allowed, but may not have much value, due to easy “design arounds”. Thus, a patent application should be drafted with claims of various scopes to have multiple fallback positions between the broadest claim and the narrowest claim.

There are several different ways to claim an invention related to stem cells:

- (1) Compositions of stem cells. The stem cells can be defined by the source, the function, the source, the phenotype (expressed cell markers), or other characteristics;
- (2) Methods of generating stem cells, such as how to induce pluripotency and various cell culture methods;
- (3) Methods of maintaining undifferentiated states or methods of differentiating cells;
- (4) Compositions of the culture medium;
- (5) An article of the culture container (such as a unique surface);
- (6) Therapeutic methods, including compositions of regenerated tissue; and
- (7) Screening methods.

One difficulty relating to (1) in drafting stem cell patent applications is how to identify the stem cells. A claim defining the stem cells should ensure that it does not include any stem cells in the public domain, which will render the claims not novel. The claim also should define the stem cells in a way that it should not be very onerous to prove someone has used the claimed cells, thus infringing the claims. As there seems no standard way to define a stem cell, an applicant may want to characterize a stem cell in different ways in the specification and/or claim it accordingly.

Another difficulty in drafting a stem cell patent application is how to build in enough flexibility to support the prosecution process which may take years. During the several years an application is prosecuted, new references may be uncovered, new technologies may be developed, and moreover, the patent law itself may change (which is at least true in the U.S.). A well-drafted patent application should not only support the claims presented when the application is first filed, but also provide support for amending claims in the future in light of new references, new research results and the change of law. However, the specification also should not include unnecessary disclosure that is not enough to support claims (e.g. the disclosure does not

enable a claim), but are enough to be considered prior art and thus affect the patentability of one’s later filing application on the improvements.

IV. Conclusion

The recent development in iPS cell research has not only reenergized the whole field of stem cell research, but also opened new frontier for drug development in general. For example, iPS cells make it possible to generate disease models more easily to enable cell-based high throughput drug screening.

The IP landscape of stem cells is complex and constantly changing. Nevertheless, one should recognize that patent is only one of the many tools to enable a company to achieve its business objectives. In addition, other types of IP coverage, such as trade secret protection, may play a role in the IP strategy of a company.

The success of a company is far most dependent on the products it can develop and sell, be it a drug or CRO service, or a technology package wrapped in know-how or patents. Thus, a company should not underestimate the importance of patents, but should in general be technology driven to find successful products and/or services. Have a sound patent strategy, but then focus on developing the technologies and the products that customers want to buy.

Reference

1. For examples WWwaddressed in ways outside the scope of this article.
2. In many other countries such as Europe, Japan and China, the “non-obvious” requirement is stated as a requirement that the invention have “inventive step”, which is legally very similar to “obviousness”.
3. These analyses must also be updated if new patents issue that are relevant.
4. Folio Haematologica, 1909, 8:125-134.
5. Takahashi K. and Yamanaka S. Cell 2006, 126:663-76
6. Takahashi K. et al., Cell 2007, 131:861-72.
7. Yu J., et al., Science 2007, 318:1917-20.
8. Zhou et al., Cell Stem Cell 2009, 4:381-384.
9. Kim et al., Cell Stem Cell 2009, 4:472-476