5. INTELLECTUAL PROPERTY OF HUMAN PLURIPOTENT STEM CELLS

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This report will provide an update in the area of intellectual property issues related to human pluripotent stem cells, and specifically, to human embryonic stem cells (hESCs). As anticipated, the patent landscape with respect to stem cells continues to become more complex in the United States, with new patents issued in various areas involving differentiated or modified cells and methods to differentiate cells. In Europe, some patent claims that involve unmodified hESCs currently stand rejected, although their ultimate outcomes are undetermined, as several parties have appealed the rejections they have received.

THE UNITED STATES PATENT LANDSCAPE

Since Thomson and colleagues were issued a patent on March 13, 2001 that specifically claimed hESCs,[1] a number of patents have issued in the U.S. involving claims to methods of using, maintaining, or inducing differentiation of hESCs or to the modified or differentiated cells themselves. According to data provided by the United States Patent and Trademark Office (USPTO) on October 22, 2004, nearly 300 patents had been issued with claims to embryonic stem (ES) cells or processes, of which approximately 38 encompass human products or processes. Approximately 700 pending patent applications had been published with claims to ES cells or processes, of which approximately 200 encompass human products or processes. Approximately 150 published patient applications encompass "totipotent" ES cells or processes. These patents claim various cell types that would be used in regenerative medicine (as described below) or auxiliary technologies, such as conditioned medium for cell growth, that support the use of hESCs.[2]

Among the patents issued more recently, one stands out in particular — a patent issued to Geron with broad claims to cells grown feeder-free.[3] One broad claim from this patent states, "A cellular composition comprising undifferentiated primate primordial stem (pPS) cells proliferating on an extracellular matrix, wherein the composition is free of feeder cells." Another recites, "A cell population consisting essentially of primate embryonic stem (ES) cells proliferating in culture on an extracellular matrix in a manner such that at least 50% of the proliferating ES cells are undifferentiated." The term "primordial" as used in the application refers to pluripotent or totipotent cells such as embryonic germ cells and ES cells. The claims cover cells that have been weaned from feeder cells as well as those that were derived *de novo* in feeder-free cultures. This patented technology, along with the original Thomson hESC technology, will likely be necessary in the use of many anticipated therapeutic applications of hESCs.

Other patents have issued to methods of inducing differentiation and to partially or fully differentiated cells. Such patents include the University of Utah's patent claiming neuroepithelial stem cells and Geron's patent claiming "directed differentiation of human pluripotent stem cells to cells of the hepatocyte lineage."[4] The Thomson patent will dominate such technologies to the extent that they utilize hESCs as starting or intermediate materials. However, technologies exist that do not require the use of the Thomson patent claims because they rely on lineage-specific stem cells obtained from sources other than hESCs. One such technology patented by Snyder *et al.* is a "pluripotent and self-renewing neural stem cell of human origin" isolated from embryonic neural tissue.[5] Another patent claim is directed to a method of obtaining a "substantially homogeneous population of pluripotent brain stem cells" from brain tissue rather than from hESCs.[6]

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Scientists and physicians envision therapeutic uses of stem cells that are genetically modified in some manner to enhance their utility. For example, a pluripotent stem cell could be modified with a gene construct that enhances the ability to remove trace undifferentiated hESCs from an otherwise differentiated population of cells. This construct might include a gene encoding an enzyme that converts a pro-drug to a toxic drug linked to a promoter that is active only in undifferentiated hESCs. After isolating a differentiated population of cells modified in this manner, the pro-drug could be added to the culture, where it would be converted to a toxin in any residual undifferentiated cells.[7] The depletion of undifferentiated cells from a population of differentiated cells prior to implantation into patients reduces the risk that "contaminating" undifferentiated cells would form tumors.

THE EUROPEAN PATENT LANDSCAPE

In Europe, the first patents claiming unmodified stem cells have been denied based on a European Patent Convention (EPC) rule that excludes inventions involving the use of human embryos for industrial or commercial purposes. These denials include that of James Thomson of the Wisconsin Alumni Research Foundation (WARF).[8–10] While it does not appear that unmodified human embryonic stem cell patents will issue in Europe, the door has not yet been closed, as these decisions are currently being appealed.[11]

In arriving at the decision to deny the WARF application, the Examining Division maintained that the EPC rule against patenting embryos did not apply to downstream products from embryos as long as those products did not necessitate the use of a human embryo. Because the WARF technology necessitates use of a human embryo, it could not be patented. Commentators opposed to this decision view the rule more narrowly, arguing that the limits of ethical acceptability as defined by the rule should not be so broad as to include claims that involve starting materials that are already embryonic cells or cell mixtures. Such reasoning would limit the exclusion to claims that include a preliminary step of producing freshly disaggregated cells by destroying a human embryo, but not necessarily to isolated human embryonic stem cells *per se,* which are available through legal importation in many European countries.[10]

FACILITATING ACCESS TO STEM CELLS

Several new model agreements have been approved by NIH for use in distributing hESCs under Infrastructure Grants. These include model material transfer agreements (MTAs) from MizMedi Hospital, Seoul, Korea; Technion-Israel Institute of Technology, Haifa, Israel; and Cellartis, AB, Göteborg, Sweden (for details, see http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp). The terms are similar to the previous model agreements that the NIH has entered into or approved for use with NIH-funded hESC distribution.

CONCLUSIONS

To date, two patents, one from WARF and one from Geron, dominate most of the anticipated commercial uses of hESCs in the U.S. Europe has taken a different course by not currently permitting the patenting of unmodified hESCs. In both North America and Europe, it is likely that more patents will continue to issue on other types of pluripotent stem cells, tissue-specific stem cells, methods that use these cells, and materials and methods associated with their propagation. More stem cells are now available for broad distribution with U.S. Federal funding under terms that permit reasonably unrestricted use in non-profit research.

While many scientists have received hESCs for non-profit research, fewer have been able to reach agreements with providers for collaborative research that directly benefits the commercial sector. In these instances, the research is high-risk and often does not result in new intellectual property, yet the industrial collaborator seeks an agreement in advance that includes the right to license new inventions, particularly new uses of the materials, should they occur. The industrial collaborator usually must negotiate an agreement and pay a fee in advance to patent holders and owners of the cell lines. This can be a high hurdle for small companies that have limited funds and for large companies that do not have a strong interest in the field but want to protect their investment in proprietary materials while providing them to non-profit researchers. Finally, WiCell, recipient of the NIH contract for the National Stem Cell Bank, must reach agreements with owners of patents and proprietary cell lines to facilitate the distribution of the cells through the Bank while protecting the interests of all parties.

The NIH experience with agreements to transfer proprietary materials from companies to government researchers suggests that only a small fraction of these collaborations lead to new inventions, yet they result in important scientific publications that advance biomedical research. Hopefully, patent owners, cell providers, and researchers will work together to facilitate these public-private partnerships.

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