

The Challenge of Licensing Human Cells in the Genetics Age

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Sophisticated molecular genetics technology coupled with the sequencing of the human genome provide the means ultimately for understanding most diseases at the genetic level. However, these technologies and related events have heightened public awareness and created an environment mixed with excitement, caution and skepticism. Thus, not only does continuing research into the unknowns of the human genome but the licensing of human cells as research tools requires diligent and thoughtful planning, patient consent and frequent review. Licensing human tissue for research demands a carefully worded license agreement that prioritizes the patients' rights and desires ahead of individual investigator, institutional and company interests. Given the recent experience at our institution, this paper presents our attempt proactively to protect the specific interests and rights of our patient while providing the opportunity for research by other investigators as applied to the licensing of human cells.

BACKGROUND

Scientists in academic research institutes worldwide have traditionally engaged in the free exchange of what are frequently referred to as "research tools". These research tools can take many different forms and have as their common definition; a device (bio-

logical, chemical or otherwise) created through the use of scientific methodology that facilitates the conduct of further scientific experimentation. Examples of such tools include reagents such as monoclonal and polyclonal antibodies, molecular probes, chemical or radioactive markers and more recently gene promoters, novel gene constructs, reporter genes and transgenic mice to name a few.

Of major utility as biomedical research tools, particularly in this era of animal rights, are cultured cells. These cells may be particularly informative if either naturally or experimentally they have been altered to possess a very selective genetic change. Through careful biopsy and cell culture procedures, cells can be isolated from essentially any organ or tissue and become a valuable research tool, particularly if immortalized in such a way as to retain their differentiated properties over successive generations, thus providing an essentially unlimited source of cells.

If the immortalized cells retain features of the original cells before biopsy, they become informative tools for studying important functions and testing the effects of potentially new therapeutics. These studies can lead to novel insights and new therapies. In one such case, a critical hormone for regulating the growth of blood cells was discovered (1). However, the potential for commercial gain raises questions regarding the ownership and control of the cells. It is largely this potential for profit that has heightened concerns of

patients who have contributed or who are being asked to contribute their biopsied tissue to biomedical science. In the case to be described in this report, of greater concern to our patient was the potential for genetic engineering of cloned humans with similar defects.

The utility of immortalized cells in biomedical research is obvious and in many cases, depending on the specific genetic modification contained within, can be of enormous value to society, in particular when used for the development of novel treatments for disease. Care and precaution should be taken when licensing these materials to other academic laboratories and, in particular, to for-profit companies. This report presents a description of one such research tool derived from a one-of-a-kind spontaneous human genetic mutation. The circumstances surrounding the acquisition of these cells, their transfer to other academic investigators and licensing to the corporate for-profit community provide a format to assure protection of future donor patients. Thus, the major objective of this report is to present guidelines that protect patients' rights and desires as applied to the transfer of these and similar human materials for research.

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OBTAINING THE CELLS

The cells of interest were obtained from an otherwise normal 28-year-old white male who presented to his orthopedic surgeon with a history of tall stature and worsening genu valgum, a condition commonly referred to as "knock-knee" (2). While childhood and adolescent development was normal, radiographic studies revealed a remarkably immature skeleton similar to a boy of 15, suggesting a pubertal hormone deficiency despite ostensibly normal pubertal history and physical examination. Other details of the medical history are presented elsewhere (2).

Extensive medical evaluation revealed that the cause of the defect was a mutated, and therefore non-functional, estrogen receptor. This mutation, previously unreported in the medical literature, rendered this patient apparently unresponsive to the natural hormone estrogen. The conditions observed in this patient as a result of this mutation revealed that estrogen is important in both males and females for cessation of linear growth and normal bone mineralization (3).

At age 29, the patient underwent surgery to correct the severe genu valgum. Recognizing the potential value of an established cell line from such a unique disease and with full informed consent of the patient, a biopsy of the femur was performed from which bone marrow cells were harvested (3). The cells were dubbed human estrogen receptor knock out (or HERKO) cells to emphasize their unique feature. These cells were sent to an unnamed institution at which the immortalization process was performed (3) and for which patient consent was likewise obtained.

PATIENT CONSENT FOR TRANSFER AND LICENSING OF THE CELLS

Prior to any consideration of the transfer or licensing of the HERKO cells, the patient was consulted on several occasions to discuss his concerns regarding the use of these cells. The patient was made aware of the importance of studying the functions of estrogen in human health and disease (4). In particular, research with these cells could further elucidate the role of estrogen in bone growth, maturation and metabolism. Furthermore, these studies could provide valuable clues to the etiology and treatment of common bone disorders such as osteoporosis, as well as other bone-related conditions such as short stature. The patient was informed that, subsequent to the publication of the case (2) and other research with the HERKO cells (3), several requests for the cells had been received from investigators at other academic centers. The patient consented to allowing other academic investigators to use the cells specifically for research purposes only but with several caveats: a) no one was to derive financial benefit from the cells, b) no other institution was permitted to distribute the cells, other than the one chosen for this purpose, and c) no one would be permitted to conduct genetic cloning of whole organisms with these cells. Specific to this last point, our patient was acutely aware, based on popular press accounts, of the capability of some laboratories to clone whole organisms from cells. Specifically, the patient did not want humans with his skeletal defects recreated by cloning for subsequent experimentation. Though the patient was reassured that this would be a very unlikely objective of any research, this remained a primary concern. The patient was assured that his concerns would be addressed with

every investigator who requested the cells and his wishes agreed to in writing by the requestor in all cases prior to shipment of the cells.

Academic Material Transfer. To accommodate both the requests from other academic investigators for the HERKO cells and the wishes of the patient, a specific material transfer agreement (MTA) and procedure has been developed. The procedure is as follows:

1. All requests are received by the organization serving as the repository for the cells. Requests must contain a statement of use or they are returned to the requestor for further detailed information.

2. Each request is reviewed and approved by both the technology transfer officer (this author) and his faculty consultants of the original institution. At this point, it is determined whether cloning or similar experiments prohibited by the patient are contemplated. Such review may require a conversation with the requesting scientist to inquire about cloning experiments and to restate the prohibiting of such studies as requested by the patient.

3. With execution of the MTA, an approval to ship the cells is sent to the repository agency along with a letter from our institution that clearly restates and emphasizes the patient's wishes for the use and distribution of the cells.

4. The repository agency then sends the cells to the requestor with a copy of the signed MTA and our letter mentioned above.

The MTA contains the following language:

Article 2. "This Research Material may not be used in human subjects. The Research Material will only be used for research purposes by Recipient's investigator in his/her

laboratory, for the research project described below, under suitable containment conditions. This Research Material will not be used for commercial purposes such as screening, production or sale, for which a commercialization license may be required. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and to the handling of the Research Material."

Article 5. "This Research Material represents a significant investment on the part of Provider and is considered proprietary to Provider. Recipient's investigator therefore agrees to retain control over this Research Material and further agrees not to transfer the Research Material to other people not under her or his direct supervision without advance written approval of Provider. Provider reserves the right to distribute the Research Material to others and to use it for its own proposes. When the Research Project is completed or three (3) years have elapsed, whichever occurs first, the Research Material will be disposed of as directed by Provider."

The letter that accompanies the shipment of the cells to the requestor contains the following language:

"While the patient has given approval for us to disseminate these cells, we are obligated to reaffirm the wishes of the patient regarding the use of the cells. Namely, the HERKO cells are to be used for research purposes only and no commercial benefit should be derived by anyone from their use. Though we realize this is an unlikely objective of any investigation, the patient specifically does not want his cells used for any human cloning studies. Also, the (named repository) should remain the only source of the cells and thus you are not permitted to distribute these cells to other investigators. Any request to do so will respect-

fully be denied."

Licensing. A natural outcome of academic research is the identification of new opportunities for the development of novel therapeutic approaches. In the current age, one looks to academia to provide cutting-edge scientific discoveries that will make new therapies a reality. It is the for-profit sector that takes these results and in a more pragmatic fashion, applies them to the development of new therapies, whether the traditional "pill" or the more novel gene therapy.

With publication of the first two studies characterizing the HERKO cells (2, 3), interest from the corporate community surfaced rapidly. In particular, pharmaceutical companies with major franchises in musculo-skeletal disorders began to inquire relative to obtaining these unique cells for research and drug discovery. Mindful of our primary responsibility, we met again with the patient to address this new challenge. The questions were raised: a) Do we want to provide these cells to the corporate sector? b) What needs to be put in place to insure that the wishes of the patient are fulfilled by any and all licensees? and c) What needs to be decided with respect to any financial issues?

As discussed earlier, current technologies allow a multitude of possibilities in the field of genetic research. Thus, as we approached the topic of licensing the HERKO cells to companies, newer elements would be expected to come into play relative to our patient's wishes for their utility. Therefore, it was decided, with each new company request, a meeting with the patient would take place and the company would be discussed along with the proposed use of the HERKO cells. The patient has suggested that a fee for the cells be assessed and those fees be deposited into the research endowment of our Center. Following receipt of consent of the

patient and approval of the stated research propose (as described above), the licensing process is initiated by forwarding to the requesting company a draft of our nonexclusive license agreement.

Again, it was decided that a carefully worded document is required; one that clearly states which studies are prohibited within the company's research laboratories. For the preparation of the initial draft of the agreement, we sought the assistance of several in-house genetics researchers and an attorney holding an advanced degree in molecular biology to review, suggest and comment on the language of the agreement. The following is now included in our nonexclusive license agreement for these cells ("Licensed Technology" is defined as the HERKO cells and "Licensed Field" is the clearly and specifically defined use):

Article IV: Obligations of the Licensee

4.1 In consideration of the rights to use the Licensed Technology granted herein, Licensee agrees to use the Licensed Technology only within the Licensed Field as described in paragraph 1.1 of this Agreement. To support this utility, Licensee is permitted to culture the Licensed Technology for the sole purpose of maintaining a viable and useful cell line as further described in Exhibit A attached hereto. Licensee may not use the Licensed Technology for any other research or for any other purpose including but not limited to: a) cloning, attempts at cloning or in any cloning experiments beyond the lever of the cell; b) utilizing the genome or any portion of the genetic code, material or information contained within the Licensed Technology to transfect or to otherwise implant such genetic material into any other cell(s), cell line(s), tissue(s), or animal

species: c) selling, have sold or otherwise providing the Licensed Technology or any portion of same to any third party for any purpose.

4.2 Licensee further agrees that the (repository agency) shall remain the only distributor of the Licensed Technology and shall not distribute Licensed Technology to any one or any entity either within or outside of the Licensee's company unless otherwise approved in writing by the Licensor.

4.3 Should Licensee undertake, conduct or otherwise perform any of the activities barred in 4.1 or 4.2 above or somehow commercialize the Licensed Technology, this Agreement shall immediately terminate, and Licensee shall be liable for all consequential damages.

4.4 The conditions set forth in this Article IV shall survive the termination of this agreement and shall remain in force for as long as Licensee is in possession of the Licensed Technology.

CONCLUSIONS

Human genetic research has enormous potential to provide for the development of novel therapies to treat and cure disease. The global scientific community has moved rapidly into this new age of biomedical genomics research and new information in this field is generated daily. While the prize(s)

remain great however, research focus must be balanced by appropriate considerations of the concerns and rights of the patients who contribute to this research by providing the most significant element, the valuable biological research tools. On the contrary, perhaps now more than at any other time, all those involved in any aspect of this research or the licensing of these types of materials should remain committed to preserving the rights of patients and other volunteers who make this contribution. Scientific research flourishes where there is a fair and open exchange of ideas, material and outcomes. This article hopefully provides a guide to the process of exchange of genetic research tools while protecting the consent, rights, wishes and concerns of the contributors of such important material.

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