

*ARTICLE:*

**OWNERSHIP OF INVENTIONS DERIVED FROM  
NATURAL PRODUCTS AND HUMAN TISSUES,  
AND SHARING OF BENEFITS FROM THE  
COMMERCIALIZATION OF SUCH INVENTIONS**

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In the course of collecting biological materials that may be used to develop drugs or other commercial products, what rights does/should the source region, source community or individual donor have to share in benefits from possible future commercialization? The 1992 United Nations Convention on Biological Diversity sets forth the general principle that source countries for non-human biological materials have the right to share in such benefits, as well as the right to share technologies developed to conserve and exploit such materials. However, rather than setting forth specific obligations, it calls on parties to adopt legislation to implement these principles.<sup>1</sup>

The National Cancer Institute (NCI) of the U.S. National Institutes of Health (NIH) has had an active program to collect and screen plants, fungi, microorganisms and marine organisms for anti-cancer properties and to develop drugs from promising candidates. In 1990, the NCI began signing "Letters of Intent" with source countries under which it pledged to make "best efforts" to ensure that corporate licensees of NCI inventions derived from natural products provide some compensation to the source countries. In 1992, the NCI began using a special "Letter of Collection" agreement under which it pledged to make the grant of any such license contingent upon the licensee negotiating a reasonable benefits sharing agreement with the source

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<sup>1</sup> See articles 15, 16 and 18. The convention does not explicitly exclude application to human tissues. However, the dominant view, at least in the U.S., is that the signatories did not intend the Convention to apply to human tissues, and if it did apply, it would give source country governments unacceptable control over individuals [Greely 1993]. At least 167 countries have signed the Convention [Mossinghoff 1998]. President Clinton signed on behalf of the U.S. in 1993, but the Senate has yet to ratify it. However, the current policy of the U.S. Government is to abide by its terms.

country (or source country organization) that provided the materials.<sup>2</sup> According to a 1995 OECD survey, the NCI's policy of ensuring benefits sharing via the LOCs, was the most concrete program any developed country had to give effect to the Biodiversity Convention [OECD 1996].

NCI has signed over 25 LOCs or equivalent "Memoranda of Understanding" with source countries or source country organizations. To date, one benefits sharing agreement has been negotiated, this between the Government of Sarawak, Malaysia, and Medichem, an Illinois biotechnology company. Medichem licensed NCI's patents on calanolides, which NCI showed to have *in vitro* anti-HIV activity after isolation from *Calophyllum* trees collected in Sarawak. Medichem is now pursuing the clinical development of calanolides as anti-HIV/AIDS agents. Calanolide A is in phase 2 trials in the U.S., Malaysia and Singapore.

The above applies to inventions made in the NCI's own (intramural) laboratories. As for inventions made in extramural institutions (such as universities) under NCI grants or contracts, the NCI requires such institutions to obtain proper clearance from source countries and urges such institutions to follow the spirit of the LOC. A Canadian university participating in the NCI National Cooperative Natural Products Drug Discovery Program isolated a promising anti-cancer agent from a sponge found on the coast of \_\_\_\_ [name of country withheld until agreement publicly announced]. Recently, the university signed a license agreement with a major pharmaceutical company under which the university agreed that [\_\_\_\_] would receive a share of the royalties it receives from the pharmaceutical company under this license.

In the event human tissues are involved, the situation can become more complex and politically charged. In 1990, the Centers for Disease Control (CDC) filed a patent on a human T-lymphocyte cell line containing one of the first-identified strains of Human T-Lymphocyte Virus Type 2 (HTLV-2). This cell line was isolated from the blood of a woman of the Guaymi tribe in Panama. In 1990 and 1991, the NIH filed patents on two cell lines each containing a genetically distinct variant of the HTLV-1 virus. One of these cell lines was isolated from a member of the Hagahai tribe in Papua New Guinea and the other from an inhabitant of the Solomon Islands. Various groups representing indigenous peoples attacked these three

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<sup>2</sup> The LOC does not specify the terms of benefit sharing agreements nor does it make NCI the arbitrator of what terms are acceptable. Article 9 recognizes that such terms depend on many factors: "[The requirement to enter into a benefit sharing agreement] shall apply equally to instances where the invention is the actual isolated natural product, or a product structurally based on the isolated natural product..., though the percentage of royalties negotiated as payment might vary depending upon the relationship of the marketed drug to the originally isolated product." [ten Kate 1998].

applications as “biopiracy,” more specifically, as attempts by scientists and corporations in developed countries to profit from the tissues of members of vulnerable indigenous populations, without prospect of benefit to these populations. Some of these groups also charged that the very process of blood collection endangered the donor tribes, and that the tissues might be used to make genocidal weapons.

There are few laws relating to rights of donors in tissues taken for medical research. Regulations for the Protection of Human Research Subjects place a clear obligation on federally supported researchers to inform potential research subjects of the risks and benefits of participating in a study. Potential subjects must also be free of any coercion or undue financial inducements to participate, and the privacy of subjects and confidentiality of data must be ensured. However, these regulations give donors no rights in their tissues once they are removed. [45 CFR 46]. In probably the most significant judicial decision to date on this issue, the California Supreme Court ruled unanimously in the 1990 *Moore* case that medical personnel are under a fiduciary obligation to disclose to patients financial interests they have in their treatment. However in the same case, the judges by a 5-4 split decision ruled that patients do not have a strong enough ownership interest in tissue removed from their bodies to allow them to sue medical personnel for conversion (i.e., illegally appropriating such tissues for their own benefit).<sup>3</sup>

The possibility that the U.S. Government might have been sued for not sufficiently disclosing to the Guaymi, Hagahai and Solomon Island donors that their samples may give rise to economically valuable substances that the U.S. Government would patent, may have been one factor that lead the CDC and NIH to abandon the Guaymi and Solomon Island applications and, in 1996, to disclaim the Hagahai HTLV-1 cell line patent, even after the USPTO had issued it [Greely 1993, but see note 3]. Today, it is increasingly

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<sup>3</sup> In the *Moore* case, a patient with hairy cell leukemia who lived in Seattle was asked to make several trips to UCLA Medical Center. Later he learned that his team of doctors, had isolated and cultured a hairy cell leukemia cell line from his tissues, obtained a patent on this cell line, and entered into collaborative agreements with Genetics Institute and Sandoz under which the two principal researchers received stock and over \$440,000 in salary and research support. The trial court found that the UCLA team had the commercial development of a cell line in mind during the course of Mr. Moore’s treatment. Also, the medical necessity of some his trips to UCLA was questioned. It is unclear what relevance the *Moore* ruling has to commercial projects that are formulated only after treatment ceases. In other words, it is unclear whether patients have to be informed of the potential for commercial benefit as well as actual plans for commercial exploitation. It also is unclear what relevance the decision has to research projects where no (or only incidental) medical benefits are offered to participants and there is no fiduciary relationship between researchers and subjects. The U.S. Supreme Court denied certiorari (i.e., it declined to review the ruling).

common for the informed consent process to include notification to subjects that commercially valuable products may be derived from their tissues. For example, in its next round of DNA sample collections for epidemiologic studies to study the relationship between genes and risks for various diseases, the Medical Research Council of the U.K., is requiring as part of the informed consent procedure that (1) subjects agree that their tissues samples are charitable donations and that they renounce their ownership of them, and (2) subjects be informed that their sample or products derived from it may be used by the commercial sector and that they will not be entitled to share in any profits that might ensue [[http://www.mrc.ac.uk/tissue\\_gde.pdf/](http://www.mrc.ac.uk/tissue_gde.pdf/)].

The issues ownership and benefits sharing reached a high stakes confluence in the case of human tissues collected in the course of collaborative research with Chinese institutions. In 1997, senior Chinese geneticists expressed concern that if foreign laboratories analyze Chinese tissue samples, discoveries related to these samples would likely be patented and commercialized by foreigners, and China would not share in the commercial benefits. This concern, which has reached the highest levels of the Chinese Government [Jiang Zemin 2000], was directed towards transfer of samples to academic as well as for-profit laboratories. For a few months in 1997, the export of most samples was halted [Li 1997].

It appears that most transfers of samples to U.S. universities and federal laboratories had resumed even before the Chinese State Council issued *Interim Measures for the Administration of Human Genetic Resources* in June 1998. The *Interim Measures* call for the Science and Technology Ministry and the Public Health Ministry to jointly establish a Human Genetics Resources Administration of China (HGRAC), to which all human genetic collection and export activities must be reported. The Chinese collaborator in international research projects must obtain project approval from the Science and Technology and the Public Health Ministries as well as the HGRAC. HGRAC permission is needed for the export of samples, publication of information about the samples, and patent applications based upon the samples. The Chinese and foreign collaborators should jointly apply for and co-own patents. Transfers to third parties of IP rights, data, and probably also know-how and trade secrets resulting from the collaboration require the agreement of both parties. Finally, the benefits obtained from the collaboration must be shared in accordance with the parties' respective contributions. The *Interim Measures* require the Chinese and foreign collaborators to enter into a contract that formalizes these obligations and the HGRAC will review such contracts as part of the project approval process.

It is still unclear how the *Interim Measures* are being implemented in practice. However, if strictly implemented, the *Interim Measures* will require U.S. universities and the NIH to adjust their normal technology management practices under the Bayh-Dole amendments to U.S. Patent Law [35 USC 200-212 and 37 CFR 401] and the 1986 Federal Technology Transfer Act [15 USC 3710a-d] governing technology transfer from federal

laboratories. Under U.S. patent law, patent ownership is determined not by who files the patent, but rather than by inventorship and a clear chain of written assignment from the inventors. Ownership originally vests with the inventors and the only way inventors can transfer their ownership rights is by a written assignment agreement [35 USC 1.53; 37 CFR 1.41]. Therefore, if the only inventors are U.S. university researchers, the U.S. university will have full ownership of the invention by virtue of the written assignments that all university employees are usually required to sign as part of their employment contracts, and the Bayh-Dole amendments to U.S. Patent Law, which give universities the right to patent and license federally funded inventions.<sup>4</sup> Unless one of the inventors is a source country scientist, the only way a source country institution can obtain ownership rights is for the U.S. university to assign a portion of its rights to the source country. However, this would require permission from the federal funding agency, assuming federal funding is involved. For this and other reasons, U.S. universities almost always license, rather than assign, rights to their inventions. Similarly in the case of inventions made by employees of federal laboratories, the laboratories obtain ownership rights and almost always transfer such rights by licenses rather than assignments.<sup>5</sup>

Thus, in order to abide by the full letter of the *Measures*, U.S. universities and NIH will have to adopt unusual assignment and contract provisions. In the case of NIH, since future IP rights are involved, all future collaborative research with China may have to be carried out under formal Cooperative Research and Development Agreements (CRADAs) as specified under 15 USC 3710a. If the Chinese *Interim Measures* become the model for future collaborations with other countries involving transfer of natural products or human tissue, the complexity and transaction costs of such collaborations may increase significantly.

Academic biomedical researchers and their institutions will probably have to increasingly frequently negotiate contracts with source countries to address issues of ownership and benefits sharing. Whether the NCI LOC or the Chinese *Interim Measures* become the model for such contracts, it is

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<sup>4</sup> In Japan as in the U.S., ownership derives from inventorship. However, written assignment agreements are not required and assignments are presumed to be valid unless challenged by the inventor before publication of patent applications 18 months after filing [Japanese Patent Law, articles 33, 34]. Under such a system, the key determinant of ownership is who files the patent application. The Chinese *Interim Measures*, may have had a Japanese-style system of patent ownership and assignment in mind, when it specified how Chinese and foreign collaborators should manage IP rights.

<sup>5</sup> However, the 1986 FTTA ( 15 USC 3710a(b)), does permit federal laboratories to assign as well as license their inventions.

important that the key needs/desires of the various parties are addressed: Among these are the need/desire of:

1. the international public for effective new drugs and diagnostics that can be developed quickly and cheaply;
2. scientists and research institutions in developed countries for access to biomaterials, freedom to work with them and publish results, and ability to rapidly develop and commercialize drugs and diagnostics derived from them;
3. scientists and research institutions in source countries for access to data from foreign collaborators, transfer of new R&D technologies, influence over how commercialization occurs (particularly with respect to their home/regional market), and a “fair” share of benefits in the event of successful commercialization; and
4. donor individuals and populations for assurance that sample collection will not harm them, for appropriate informed consent, and for sharing of benefits in the case of successful commercialization.

By insisting on co-ownership of patents and data and on government approval to publish research findings, the Chinese *Interim Measures* seek assure Chinese institutions of the items in (3) above. However, it may be possible to satisfy the legitimate interests of source countries in less intrusive and restrictive ways which make collaborative research and commercialization of discoveries easier, ultimately to the benefit of all parties. One possibility would be to develop an MTA that provides for many of the elements in (3) as well as satisfying (1), (2) and to some extent (4). In other words, the MTA might grant donor institutions some influence over licensing decisions (perhaps, for example, the right to be consulted in advance about license decisions, particularly licenses that cover market rights in the source country) and might require sharing of royalties with the source institution. It could also provide for data sharing and for appropriate opportunities for source country researchers to conduct research and receive training in the foreign collaborating institution. The NCI LOC could be easily modified to meet these needs of the source country. It already provides for sharing of data and training for source country researchers. The NCI LOC even contains language recognizing the possibility that donor communities should share in benefits from commercialization, considerations that are absent from the Chinese *Interim Measures*.

However, in order to take advantage of the flexibility in the NCI LOC model, research institutions in developed countries will have to be proactive in advocating this model as well as sensitive to the desires of source

countries. Getting donor countries to assent to the simpler, more flexible terms of the LOC requires a higher level of mutual trust than the Chinese *Interim Measures*. Currently negotiations are nearing completion between a major U.S. and a major Chinese academic medical center regarding ownership of IP and allocation of benefits that may arise from a collaborative research project that is a follow on to a project that experienced a temporary embargo on sample transfers. It will be interesting to see whether this agreement hues more closely to the strict requirements of the *Interim Measures* or adopts a more flexible LOC-like approach.

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