Putting Intellectual Property to Work: Experiences from around the World

"***By far the best proof is experience,***" wrote Francis Bacon. Given the experience of countries—both developing and developed—that have used intellectual property, IP (intellectual property) protection, and IP management to stimulate innovation, there is ample proof that good IP management has benefited multitudes of people around the world with new technologies, products, and services. Innovations in health and agriculture have greatly enriched lives. But does this experience apply to all countries? If the best proof is experience, then what can be said authoritatively about the effects of using IP systems wisely in developing countries?

The 28 case studies in this section of the *Handbook* (and the 21 case studies in the insert of this *Executive Guide* and more online) demonstrate that a great deal can be said. Developing countries already have a vast amount of experience with IP protection, and this experience proves that they can use intellectual property to their advantage. With more chapters than any other section, this portion of the *Handbook* amply reveals how developed and developing countries alike are deploying and adapting IP management to meet their needs. Tapping into the dynamism of product development partnerships (PDPs) and utilizing the potential of their universities, public sector institutions, and private companies, many **developing countries are quickly and creatively building on the experience of their own institutions, of neighboring countries, and of countries around the globe**.

EXPERIENCES FROM AROUND THE WORLD

Satyanarayana describes India's experience in the pharmaceutical sector. According to Satyanarayana,[1] during the past 50 years, **India** has made great strides in science through a series of policy initiatives promoting high-quality research. But especially since 2005, when India became fully compliant with the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), big changes have occurred. India's rigorous IP rights regime and professional IP management in both private sector companies and public sector research institutions are driving success. But this is only part of a larger coordinated attempt that includes increased public and private R&D expenditures, new policies governing traditional medicines, overhauled regulatory regimes for new drugs and biotechnologies, initiatives to emphasize and build on already competitive regions or technologies, and newly created governmental, research, and educational institutions.

In the pharmaceutical sector, the effects of these policies can be seen in:

- a shift in the Indian pharmaceutical industry from an approach based solely on the low-cost manufacture of generic drugs to

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research-driven innovation of novel drugs for the global market
- the emergence of an entrepreneurial biotechnology sector in India
- the consideration by multinational pharmaceutical companies of investing in R&D and manufacturing operations in India

In agriculture, these effects are apparent in a rich pipeline of new innovations that promise to make India's agricultural sector more competitive and profitable. Besides a substantial allocation of funds for R&D by the government, two new initiatives were started in 2005: the National Agricultural Innovation Project (NAIP) and the Indo-U.S. Agricultural Knowledge Initiative (AKI).

India's transition from a protected economy to an open, global economic power has prompted the government to take a series of steps to address the new challenges of globalization, and the lessons it has learned apply broadly to many developing countries. Strengthening R&D, establishing policies to create and manage intellectual property, and fostering PDPs are all important steps for making important health products available for public distribution available in all countries.

According to Wolson,[2] technology transfer offices (TTOs) are a crucial part of IP management in **South Africa**. But a number of problems challenge nascent TTOs there: a weak flow of invention disclosures, skepticism or a lack of awareness among faculty about the TTO's role, low levels of research funding, high patenting costs, few experienced technology transfer practitioners, and unrealistic expectations about financial returns. Indeed, many there believe that the main motivation for undertaking technology transfer activities at a university is to generate income.

Solutions to these problems are being addressed organizationally by the Southern African Research & Innovation Management Association (SARIMA), legislatively by the Framework for Intellectual Property Rights from Publicly Financed Research (the Framework), and financially through the Innovation Fund. Established in 2002, SARIMA is a stakeholder organization providing a platform for those from government, academia, and industry with an interest in using research and innovation management to foster networking and promote common interests. The Framework is intended to bridge the "innovation chasm": the gap in South Africa between knowledge generators (in particular, universities and research institutions) and the market. It calls for a consistent approach to protecting intellectual property developed with public financing and draws heavily on the U.S. Bayh-Dole Act. Of course, as other countries have discovered, the Bayh-Dole Act cannot simply be imported. Its principles must be adapted to local frameworks and needs. In South Africa, for example, research funding comes mostly from external sources and requires a different structure for determining the use and ownership of project intellectual property.

TTOs in South Africa have already met with success. Some have been operating for several years and more are being launched. A vibrant stakeholder organization provides a platform for networking and professional development in the field, and links have been forged that strengthen international research collaborations and technology transfer partnerships. All of this has government support.

Other chapters in this section describe the experiences of **Brazil**,[3] **Chile**,[4] **China**,[5] the **European Union**,[6] and **Japan**.[7]

PUBLIC SECTOR INSTITUTIONS AND UNIVERSITIES

Salicrup and Rohrbaugh[8] provide more evidence of the ability of for-profit and nonprofit institutions in developing countries to bring new products to market that meet critical regional public health needs. The authors discuss the technology transfer and licensing approach of the U.S. **National Institutes of Health** (**NIH**). The institution's technology transfer experience has shown that many combinations of licensing strategies can be used to segment the world market to meet each region's needs. Even when patent protection is unavailable, unique biological materials (for example, an essential component of a vaccine) can be licensed for commercial use.

Institutions in developing countries have been found to be dependable licensees and partners. With careful review, a capable institution with commercialization capabilities may be found, and one should keep an open mind because, depending on the country, it may be a for-profit company, a nonprofit or government entity, or a semi-privatized company. NIH has several examples of different strategies involving various types of institutions that have reached the early stages of the commercialization process.

While discussions continue about IP capacity building in developing countries, some leading institutions are simply forging ahead and building their own capacity. The **State University of Campinas, or Unicamp**, one of the leading research universities in Brazil, is an example described by Ceron Di Giorgio.[9] A large university with a diversity of affiliated research institutes, Unicamp has moved up the patenting league tables in recent years to become the single largest patentor in Brazil. The university's current portfolio includes almost 50 granted, and 400 filed patents. Unicamp emphasizes chemistry, which accounts for close to half of its portfolio, and engineering, which accounts for a third. In addition, Unicamp conducts significant research in the life sciences (for example, a soy-based phytoestrogen for hormonal therapy licensed to a Brazilian pharmaceutical company).

These major advances in technology transfer at Unicamp are largely due to the efforts of its new technology transfer office, *Inova Unicamp*, founded in 2003. *Inova* began its operations by assessing all of the technologies being researched in Unicamp's many laboratories and institutes. It then aggressively pursued new patent applications and licensing deals for the most promising technologies. In the short space of two and a half years, the office signed 128 technology transfer agreements with both private industry and government agencies. It also saw ten start-up companies in the university's business incubator become self-sustaining.

What lies behind these successes in Brazil? New public policy. In particular, the work of *Inova* is directly informed by two pieces of legislation. A 1996 law gave the university ownership rights to employee inventions. A 2004 law on innovation, however, gives the university the option to either hand over title to the employee inventors, or share 5%–33% of any royalties with them. In addition, the government has instituted a number of sector-specific incentives to support innovation in Brazil, including tax deductions on royalty payments, R&D investments, and foreign IP filing fees, as well as subsidies to firms to help pay scientists' salaries.

The 2004 innovation law requires all government universities and R&D institutions to open an IP management or a technology transfer office. One major consequence of these policies will likely be increased patenting and licensing activities at universities throughout Brazil. Currently, Unicamp's rapid establishment of a functioning technology transfer office stands as a sterling example for other institutions in Brazil to emulate.

Other case studies in this section of the experiences and approaches of a range of institutions include: **Arizona State University**[10] in the United States, **Chinese Universities**,[11] the **Donald Danforth Plant Science Center**[12] in the United States, the **National Health Service** in England,[13] **Stanford University**'s Office of Technology Licensing,[14] the **University of California System**,[15] and the **University of California Agricultural Experiment Station**.[16]

PRODUCT DEVELOPMENT PARTNERSHIPS (PDPS)

Banerji and Pecoul[17] describe the **Drugs for Neglected Diseases Initiative** (**DND*i***) that seeks to give patients in developing countries the opportunity to directly benefit from new products of drug R&D for diseases that lack a viable market. Only a tiny fraction (1.3%) of the drugs that came to market from 1975 to 2004 targeted tropical diseases (such as human African trypanosomiasis, Chagas' disease, leishmaniasis, helminthic infections, schistosomiasis, onchocerciasis, malaria, and tuberculosis) that all together make up 12% of the global disease burden and kill more than 35,000 people a day. The drugs that do exist are either inaccessible to patients or unbearably costly. DND*i* believes that drug research can exist

in the public domain, and that patented products do not always benefit those who need them most.

As clearly articulated in its IP Policy statement, DND*i* is committed to managing intellectual property to pragmatically and effectively advance its mission of providing the most vulnerable populations in developing countries with equitable access to critically needed medicines. As the preamble of DND*i*'s IP policy states:

The DNDi IP approach will be pragmatic, and decisions regarding the possible acquisition of patents, ownership, and licensing terms will be made on a case-by-case basis. DNDi will put the needs of neglected patients first and will negotiate to obtain the best possible conditions for them. The DNDi's decisions regarding IP will contribute to ensuring access and encouraging further innovations.

DND*i* has led two successful campaigns to negotiate terms that allowed them to get important drugs to the world's neediest people at minimal cost. In the first case, DND*i* approached French pharmaceutical giant sanofi-aventis in 2003 to develop artesunate-amodiaquine, a fixed-dose combination therapy for chloroquine-resistant malaria. The negotiation process eventually led to a contract with very favorable terms for DND*i*; the drug was made available for production by generic manufacturers with no payment owed to either sanofi-aventis or DND*i*, and sanofi-aventis agreed to supply the drug at cost to the public sector, NGOs, and international organizations. In the second case, DND*i* successfully collaborated with the University of California, San Francisco's (UCSF) business development office to support research leading to treatments for the lethal human African sleeping sickness. While conventional wisdom holds that a university should always seek the largest possible return on research investment, DND*i* was able to convince university officials of the seriousness of its mission, and a compromise was reached that advances the effort to bring new treatments to persons suffering from this deadly and largely neglected disease.

In pursuing its humanitarian mission, DND*i* has learned that it is crucial to thoroughly familiarize all parties with the organization's aims and guiding principles. By the end of contract negotiations with UCSF, for example, decision makers expressed great personal satisfaction at helping to advance DND*i*'s work. Through similar efforts DND*i* hopes to have developed and made available, by 2014, six to eight field-relevant treatments.

Boadi and Bokanga[18] describe the building of public-private partnerships in Africa by the **African Agricultural Technology Foundation** (**AATF**). AATF emerged from a Rockefeller Foundation initiative in the early 2000s following a wide-ranging and unprecedented consultation among African, European, and North American stakeholders who were, and are, actively seeking to improve food security and reduce poverty in sub-Saharan Africa. AATF recognizes that new and unique public-private partnerships (PDPs) are needed to remove many of the barriers that have prevented smallholder farmers in sub-Saharan Africa from gaining access to existing agricultural technologies. Focusing on the creation of these PDPs, it promotes efforts to create sustainable markets and seeks to dramatically improve access to agricultural technologies, materials, and know-how.

AATF has two unique characteristics: first, it is prepared to in-license technologies from the private sector, which it then sublicenses to its partners. This is no small issue and requires careful considerations of a range of issues, including liability. Second, AATF strongly focuses on downstream activities or, to put it more broadly, on technology stewardship. This includes facilitating access to local, national, and regional markets for products based on transferred technologies. The goals are to create more sustainable technology transfer mechanisms and to allow national institutions to more effectively absorb new technological concepts and adopt them for productive use.

But the fundamental raison d'être of AATF goes much deeper than "merely" IP management. As Gordon Conway, then president of the Rockefeller Foundation, put it in the AATF annual report of 2005:

We should examine the current system and ask ourselves, 'How can those who care about the fate of the small-scale farmer make technological options more available?' The rise of a sophisticated global

IP system covering many building block technologies has meant public researchers [in Africa] have little access to new ideas and tools in their field. Left to its own devices, the gap is likely to grow—with wealthy nations' farmers using techniques that are ever more sophisticated and poor farmers left with the same tools they have used for centuries.

Other case studies sharing PDP experiences describe **PATH,**[19] and **ICIPE**,[20] a nonprofit that partnered with **Africert Ltd** in transferring standards certification know-how, critical for the introduction of new products.

FOCUS ON SOLUTIONS: ACCELERATING PRODUCT DEVELOPMENT AND DELIVERY

Numerous partnership efforts are underway to accelerate access and delivery for agricultural and health products in developing countries. For example, in the tropics, where just about everyone eats eggplant, it is commonly infested by **eggplant fruit and shoot borer (EFSB)**, which inflicts a 70% crop loss. Conventional efforts to breed for resistance have been unsuccessful, so farmers rely heavily on pesticides. These chemicals, however, are expensive, and the pest is becoming more and more resistant to them. Moreover, some pesticides damage the environment and/or are illegal.

Recently, a new solution to the problem of EFSB was developed in partnership with many organizations, writes Medakker and Vijayaraghavan,[21] including by MAHYCO, a private Indian company. It was the first company in India to develop a transgenic hybrid eggplant genetically engineered with a gene that provides resistance to EFSB. The gene (cry1Ac) is obtained from the bacterium *Bacillus thuringiensis* (Bt). A spore-forming bacterium, Bt produces crystal proteins (called Cry proteins) that are toxic to many species of insects, including EFSB. Cultivation of the hybrid eggplant reduces the need for pesticide applications.

This breakthrough was made possible when MAHYCO obtained the rights under license for the use of the Bt cry1Ac gene technology for insect pest management from the Monsanto Company. The license also allows for sublicensing of the technology on a royalty-free basis to a partnership of public institutes and agricultural universities in India, Bangladesh, and the Philippines. This consortium is developing a nonhybrid form of Bt eggplant for use by farmers in developing countries. The nonhybrid form will be less expensive, but the yield is higher for the hybrid technology. Therefore, more farmers might choose the hybrid technology.

Commericial release of the first transgenic Bt hybrids developed by MAHYCO is planned for India by the end of 2007, after the fulfillment of all regulatory requirements. The transgenic Bt open-pollinated varieties under development by the public-private partnership are expected to be commercialized about six months later. This approach to EFSB is an excellent example of how biotechnology applications can be concurrently commercialized for the market and subsidized for poorer market segments.

In health, a prominent example of improvement regarding access to innovations in health is the PATH Malaria Vaccine Initiative (MVI), a program funded by the Rockefeller Foundation that analyzed whether consolidating patents in the malaria vaccine field could streamline access by advancing and accelerating the development of vaccines. The project was designed to ensure **market access for the malaria vaccine candidates** that are most likely to receive regulatory approval and be developed as products. The study, described by Shotwell,[22] assessed the status of the relevant patents, determined their availability for licensing, and explored the potential of patent consolidation or technology trust to enhance access to the vaccine. Developing a broad-based technology trust for existing malaria antigen patents was not recommended. Instead, several other steps were recommended for consolidating available rights and improving access with regard to future patent families.

Before this study, MVI had identified some potentially obstructive IP issues for a malaria vaccine for developing-country markets. Public and academic institutions—institutions with missions that in many cases include some form of public benefit—hold many of the patents related to malaria antigenss. As the study's findings reveal, with few exceptions the patents held by

public and academic institutions have been assigned or exclusively licensed to private companies and, therefore, are currently unavailable for licensing from the original public institution patent holders.

While it may be possible to sublicense these malarial antigen patents from the current private holders of the technology, it is likely to be more difficult and costly; engaging the patent holders to contribute to a patent pool or clearinghouse also might be challenging. Moreover, a patent pool for a malaria vaccine might generate further obstacles: potential antitrust issues, real or perceived, might trigger scrutiny by the U.S. Department of Justice and the Federal Trade Commission. And while the concept of a technology trust or patent pool may be useful for patents filed in the future, even some of those would be under option for license by the private companies holding the current patents. Finally, the number of high-priority cases for any malaria antigen is small, as is the number of entities likely to seek access to any given patent family. This makes the expense of a patent pool even less justifiable. Taking all of these things into consideration means fewer missteps and faster progress towards a vaccine for malaria.

Other chapters in this section provide case studies of licensing experience related to the **Cohen-Boyer patents at Stanford University**,[23] IP issues related to **molecular pharming, specifically for plant-derived vaccines**,[24] **corn/maize breeding and the impact of biotechnology on the breeding and commercialization process**,[25] the **University of California's Strawberry Licensing Program**[26] (the most successful program in terms of the generation of licensing revenues of any U.S. university), the successful resolution of IP constraints that led to the introduction of **virus-resistant papayas**,[27] and a project on the **somatic embryogenesis of grapes in Chile**.[28]

CONCLUSIONS

If indeed the best proof is experience, then the case studies described here, in the *Handbook,* and in the insert of this *Executive Guide* do indeed speak for themselves. The experiences represented by these case studies provide all the evidence needed to spur further efforts to build upon the IP strengths of developing countries. Many forward-thinking people have seen the possibilities, and this section broadly maps out work that is already underway around the globe to make these possibilities into realities. Such experiences offer the most powerful proof of the benefits that can be obtained through creative IP management in developing countries and indeed around the world. ■

All chapters refer to: *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices*. 2007. A Krattiger, RT Mahoney, L Nelsen, JA Thomson, AB Bennett, K Satyanarayana, GD Graff, C Fernandez, and SP Kowalski (eds.). MIHR: Oxford, U.K., and PIPRA: Davis, U.S.A. Available online at www.ipHandbook.org. The online version contains for each chapter a detailed Editor's Summary, Implications, and Best Practices.

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22 Chapter 17.21 by SL Shotwell titled Patent Consolidation and Equitable Access: PATH's Malaria Vaccines, p. 1789.

23 Chapter 17.22 by MP Feldman, A Colaianni and C Kang Liu titled Lessons from the Commercialization of the Cohen-Boyer Patents: The Stanford University Licensing Program, p. 1797. The online version of the *Handbook* also lists one of the Cohen-Boyer licenses.

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Case Studies

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Somatic Embryogenesis of Grapes: Fundación Chile

Fundación Chile is a private nonprofit organization. Its mission is to add economic value to Chile's products and services by promoting innovation and technology transfer for Chile's natural resource, agricultural, and manufacturing sectors. Fundación Chile's primary strategy is to develop new technology-based companies in Chile that can have a significant economic and social impact. These new companies are generally joint ventures with strategic partners, although other models, such as licensing, are used. The main activities are focused in the area of agribusiness, marine resources, forestry and forest products, environment, information technology, education and human resources, and tourism.

Fundación Chile is unusual as a nonprofit institution that participates in the creation of innovative private companies. In fact the foundation is involved in a wide range of activities relevant to different stages of development of new businesses, including technology services, R&D, incubation, scale-up, seed capital, and financial innovation. Fundación Chile's activities are focused on Chilean production of goods that can be exported or that can replace imports, but possibilities for production in additional territories that can increase the volume and value derived from Chilean production are also considered.

Since 1997, Fundación Chile has been active in developing applications of biotechnology that can improve productivity, add value to existing products, and promote introduction of new products.[1] Biotechnology activities are mainly focused in forestry, horticulture, and aquaculture, with increasing emphasis on quality enhancement. Biotechnologies used include recombinant proteins, tissue culture, molecular genetics, functional genomics, and genetic engineering. Strategic alliances in biotechnology in the private sector include a licensing agreement for a salmon vaccine with Syngenta, a strategic alliance in forestry biotechnology with CellFor Inc. (Vancouver, BC, Canada), a collaboration in stone fruit biotechnology with Okanagan Biotechnology Inc. (Summerland, BC, Canada), and a joint venture in grape biotechnology with Interlink Associates LLC (Princeton, NJ, U.S.A.). Fundación Chile seeks to establish strong IP positions through the licensing of key existing IP and the development of new intellectual property in areas of specific strategic importance in Chile.

Fundación Chile's biotechnology activities involve an extensive network of Chilean and foreign research centers and universities, as well as participation in key international consortia. Collaborators within Chile include Fundación Ciencias para la Vida, the Chilean National Institute for Agricultural Research, the University of Chile, the University of Concepción, the University of Santiago, the University of Talca, University Federico Santa Maria, Andres Bello University, and Austral University. Alliances with foreign research centers and universities include the University of California, Cornell University, the University of Florida, the U.S. Department of Agriculture (USDA), New Zealand HortResearch, and New Zealand Forest Research. Fundación Chile is a member of PIPRA (the Public Intellectual Property Resource for Agriculture) and the California Institute of Food and Agricultural Research and is a participant in the ALCUE-Food Specific Support Action funded by the 6th European Framework.

As a result of this networking, Fundación Chile has been able to participate in the development of products within a relatively short time frame. A recombinant protein vaccine for salmon, developed in a collaboration of Fundación Chile and Fundación Ciencias para la Vida, has been licensed to Syngenta and is being

Fernandez C. 2007. Somatic Embryogenesis of Grapes: Fundación Chile. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

introduced into the market. Elite clones of radiata pine developed through somatic embryogenesis in collaboration with CellFor are in advanced stages of testing and are being scaled up for market introduction by the Fundación Chile company GenFor. Other biotechnology programs of Fundación Chile, including genetic engineering of varieties of pine trees, peaches, and grapes, are in earlier stages of development.

THE TECHNOLOGY

Importance of institutional support for a long-term R&D program

Agricultural biotechnology R&D programs are long term, expensive and controversial; an institution undertaking such a program must be committed to the process for the long term. In the late 1990s Fundación Chile made a strategic decision to invest in development of biotechnology applications for strategic sectors of the Chilean economy, particularly forestry, agriculture, and aquaculture. Genetic engineering was clearly a key technology with large potential impact, as demonstrated by the rapid adoption of genetically engineered varieties of maize, soybeans, and cotton in some parts of the world. However, these major crops play a relatively minor role in Chile. Little effort was being expended to make improvements in perennial crop species, such table grapes, in which Chile is a major player.

Building a foundation for the program

Typically, three different types of technological components are needed for development of a genetically engineered plant product:

- germplasm that provides a competitive genetic background
- specific genes that confer new traits of interest
- enabling tools, such as genetic markers, promoters, tissue culture and regeneration systems, and transformation methods

In addition, human resources, laboratory infrastructure, and financing are needed to carry out the R&D required to adapt and combine these components to produce a product. Laboratory infrastructure existed in Chile, but improvements were needed. There were capable researchers in Chile, but they were limited in number. Research efforts were spread across many different objectives, and sustained support for any one specific program was rare.

In the case of grapes, the foundation technologies were not available in the local R&D institutions at the start of the program, except, to a limited degree, germplasm. A global search led to the identification of sources of technologies and expertise. The availability and priority of different components were assessed, and efforts were initiated to access, license, and transfer the key components.

IP and freedom to operate

The IP and freedom-to-operate issues confronted were complex, largely due to the need to address the situation in Chile and the situations in Chile's major export markets, the long and uncertain time frames for development and commercialization of genetically engineered perennial fruit crops, and the concentration of rights to core technologies in the hands of companies with little or no interest in the development of minor crops. A complete solution was not possible in the short term with the resources available. However, it was possible to establish a position in key technologies that maximized the likelihood of being competitive within a specific niche.

A critical aspect was the active involvement of personnel with professional experience in commercial R&D programs and major agri-biotech research centers in other countries, as well as experience in the licensing of agricultural biotechnologies. Practices vary from country to country and from institution to institution within a country. At the initiation of the program there was little experience in Chile with patenting and licensing technologies developed in public research institutions. The involvement of personnel with international experience, providing appropriate examples drawn from a number of sources, played an important part in bridging gaps in experience and expectations.

Establishment of a grape biotechnology platform

At the time the program was initiated there were only a few published reports of transformation of *Vitis vinifera*. In order to be able to obtain R&D funding from public and private sources, and to be considered seriously as a potential licensee by technology providers, it was considered critical to demonstrate the ability to reproducibly transform the target species. For many transformation systems, an important factor is the availability of a robust tissue culture system that makes it possible to regenerate plants efficiently. In our experience, tissue culture systems involve considerable art and are often difficult to reproduce in other laboratories. Thus, establishment of a strong position in grape tissue culture was given the highest initial priority. The process and progress in this area are discussed below. The second priority was access to specific gene candidates for engineering a trait of commercial interest in the Chilean market. This was carried out in parallel in order to ensure that the tissue culture and transformation platform developed could be applied to the production of prototypes with traits of interest with a minimum lag.

Identification of suitable laboratories

The search used different and complementary channels, including reviews of research publications, project databases, conference proceedings, patent documents,

news items, and personal contacts. All of them are relevant, and each provides unique and useful kinds of information.

Access to many of these sources has been facilitated by the rapid improvement of the Internet, both in terms of content and ease of access. Even for people without good Internet access, the availability of high-quality documents in electronic form has greatly reduced the cost of access.

Open sites such as PubMed (www.ncbi.nlm.nih.gov) and HighWire (highwire.stanford.edu) provide convenient access, not only to bibliographic information, but to many full papers. More and more, full papers are available at no charge, some can be downloaded for a fee from sites of journal publishers or specialized clearinghouses. Even for people without good Internet access, the availability of high-quality documents in electronic form has greatly reduced the cost of access.

Online databases such as those at the World Intellectual Property Office (www.wipo.int/ipdl), the European Patent Office (www.espacenet.com), the U.S. Patent and Trademark Office (www.uspto.gov), and many other national patent offices provide increasingly convenient access to issued patents and published applications.

Less widely appreciated, but valuable due to their more specialized content, are online databases of research projects. These often include information that is otherwise difficult or impossible to find. Examples include the European Union Community Research & Development Information Service (cordis.europa.eu), the Current Research Information System of the USDA (cris.csrees.usda.gov), the FAO-BioDeC database of biotechnology projects in developing countries (www.fao.org/biotech/inventory_admin/dep/default.asp), and a database of biotechnology activities, by country, of the Red de Cooperación Técnica en Biotecnología Vegetal para America Latina y el Caribe (www.redbio.org). In Chile, the Web sites of the major funding agencies for R&D, CONICYT (www.conicyt.cl), CORFO (www.corfo.cl), and FIA (www.fia.cl), include databases of projects. Many research institutions provide databases of internal research activities and funded projects, which may be useful once specific institutions of interest have been identified.

Negotiation of a research and option agreement

Once the identification of the laboratory or institution has been made, documents are typically exchanged via e-mail. Most large private companies and universities have standard forms that are adapted to the specific needs of a project. Typically, research agreements will include the following information:

- date
- parties
- definitions of terms such as project, project proposal, sponsor, and joint and recipient intellectual property
- reports and conferences for proper follow up of activities
- costs, payments, and other support
- publications
- intellectual property
- grant of rights
- confidentiality and publicity
- term and termination
- insurance and indemnification
- governing law
- assignment
- agreement modification
- notices
- counterparts and headings

It is important to emphasize that this standard form was designed for use in the United States. Intellectual property laws vary among countries, so, it is important that the content of any agreement is reviewed by a local lawyer knowledgeable in IP matters.

Most universities in the United States, and many other public research institutions, will require that the public institution be able to continue to use the technology for research and education purposes even if exclusive rights for commercial use are granted.

Our general approach has been to negotiate agreements that provide rights to use technologies for R&D, along with an option for a future commercial license. We want to avoid situations where resources are invested in research if the results cannot be commercialized. Due to the high degree of uncertainty in the development and commercialization of agri-biotechnology products, we also want to avoid paying at the outset for full commercial rights, if in the end they will not be used. In technology access agreements we have generally tried to structure compensation in ways that reduce the up-front costs in favor of sharing any benefits eventually realized after commercialization. This is important for making effective use of the resources currently available, but, more importantly, it helps to align the interests of the technology provider with our interests. The agreements typically contain modest up-front payments, milestone payments based on successful transfer of the technology, additional milestone payments if a commercial license is entered into and a product is introduced to market, and royalties based on revenue derived from commercialization of products produced using the technology.

In the case of grape tissue culture technology sought by Fundación Chile, the university at which the technology had been developed already had agreements in place with a private company. Thus, initially we had to negotiate a sublicense agreement with that company. Later, changes in the scope of that company's activities led to a return of the IP rights to the university. We then entered into additional negotiations with the university. Similar events affected other agreements related to the project. It is important

to recognize that management of such agreements is a dynamic process.

Material transfer agreements (MTAs)

In addition to intellectual property, the transfer of agricultural biotechnologies often requires, or is at least facilitated by, the transfer of actual biological materials such as plant tissue cultures, plasmids, vectors, or reagents. The physical transfer and use of the materials are generally covered by an MTA.

In countries with limited international innovation programs, lawyers have not been exposed to or do not have enough experience on matters related to MTAs. In Fundación Chile's case, the most practical approach was to use, as a reference, MTA forms prepared by the technology transfer offices of universities in the United States and other countries with experience in these matters. Some of these offices have sample forms posted on their Web sites.[2]

An MTA should be carefully reviewed. In the past, investigators have sometimes carelessly accepted terms that could have critical affects on the value of the R&D being conducted, terms such as reporting requirements and rights given to the provider of the material to use information generated by the recipient. It is also critical to consider whether the material provided incorporates materials or technologies already owned by third parties. If so, it is advisable to request clarification of any restrictions that my be "inherited" with those materials.

Importation of materials

Each country has its own regulations regarding the importation of biological materials. In Chile, there are forms and procedures that must be followed. Samples of grape tissue culture were imported following these procedures without major obstacles, although significant time and resources were required.

Exchange of professionals between laboratories

Good communication between parties is essential for a successful outcome. For transfer of some technologies, the exchange of written information and materials supplemented by phone calls and e-mails may be sufficient. However, in many cases, successful transfer is greatly facilitated by the active participation of investigators from the provider and recipient laboratories in activities in both laboratories.

In the case of the grape tissue culture system, a Chilean investigator first spent time in the laboratory of the inventor, to get hands-on experience with the procedures, and then returned to set up the system locally. Several months later, the inventor spent a full week working side by side with local investigators, reinforcing the training and providing an opportunity to resolve issues that had arisen during initial implementation. Some time later, the project leader visited the inventor's laboratory to observe the procedures there, with experience accumulated in Chile providing a foundation for increased "receptivity." At the end of each exchange, written reports were prepared, disseminated, and discussed.

CONCLUSIONS

Currently the lab in Chile has been able to master grape embryogenic tissue culture and regeneration techniques and apply them to genetic engineering. The genetic transformation of grape tissue cultures has allowed the production of thousands of transformed grape lines, from which several promising lines have been advanced to the field for additional testing. ■

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2 The online version of *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* provides many sample forms from a host of different organizations around the world (see www.ipHandbook.org).

The Groundnut Story: A Public-Private Initiative Focused on India

Groundnut, or peanut (*Arachis hypogaea*) is a staple oilseed crop grown for food and for forage in India. It is cultivated on 7.5 million hectares with annual production of about eight million tons. More than five million small and marginal farms depend on this crop for their viability.

During the monsoon season of 2000, a new groundnut disease emerged in India. The spread of the disease grew to epidemic proportions causing crop loss corresponding to more than US$65 million. The causal agent of this devastating disease was found to be tobacco streak virus (TSV), which causes stem necrosis in the groundnut plant resulting in complete destruction of the crop. In addition, TSV infects several other economically important crop plants, such as sunflower and marigold, and lives in many weed hosts. Parthenium, a prevalent weed, is a symptomless carrier of TSV and plays a major role in the perpetuation and spread of the disease. The constant threat of TSV outbreak has caused food shortages and financial insecurity for groundnut farmers.

By nature, groundnut plants show little resistance to TSV. Moreover, all currently grown cultivars are susceptible to TSV infection. Therefore, a nonconventional method of incorporating disease resistance in the cultivars was needed to control the disease. Transgenic crop plants that express the coat protein (CP) gene of the target virus pathogen have been shown to provide a high degree of resistance to many plant viruses. The Agricultural Biotechnology Support Project II (ABSPII), which focuses on safe and effective development and commercialization of bioengineered crops in order to benefit resource-poor farmers in developing countries, decided to fund the bioengineering of groundnut genotypes to incorporate the CP gene for conferring TSV resistance.[1]

LICENSING ARRANGEMENTS

Sathguru Management Consultants, the regional coordinator of the ABSPII project in South Asia, approached the Donald Danforth Plant Science Center (the Danforth Center) for the development of a vector construct containing the TSV-resistance gene for conferring viral resistance to groundnut plants.

The CP technology for conferring resistance to viral infection is owned by Monsanto Company. A patent nonassertion agreement[2] from Monsanto for the CP technology to be used for nonprofit public good was obtained by the Danforth Center. This non-assert was facilitated by the ABSPII project. The Danforth Center further developed the technology for TSV-CP-mediated-resistance in groundnut to be deployed in South Asia and Southeast Asia.

A consortium of public institutions was formed by ABSPII with International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) and Acharya N. G. Ranga Agricultural University (ANGRAU) in the state of Andhra Pradesh. These institutions were the primary licensees of the technology developed by the Danforth Center for TSV-resistant groundnut cultivars.

With Sathguru Management Consultants as facilitator of the technology transfer, a nonexclusive licensing agreement was penned for nonexclusive licensing of the CP technology, free of royalties and upfront payments, to public institutions planning to develop the varietal groundnut. A tripartite agreement was arranged, with the Danforth Center as the technology licensor and Sathguru Management Consultants and ICRISAT as licensees. Development efforts of TSV-resistant groundnut by the public research institutions are underway and slated for commercialization in 2009.

Medakker A and V Vijayaraghavan. 2007. The Groundnut Story: A Public-Private Initiative Focused on India. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

Similar nonexclusive licensing arrangements have been made with private organizations for the development of hybrid groundnut cultivars. These licenses include upfront and royalty payments and an understanding with regard to benefit sharing.

POLICY COMPONENTS

Because groundnut is a so-called orphan crop, there was little interest in producing and selling open-pollinated varieties owing to their susceptibility to viral infection. Moreover, private industry lacked the motivation to commercialize hybrid varieties. Key policy makers for the ABSPII project secured financial support for developing and distributing the TSV-resistant groundnut and for facilitating the project through planning and implementation.

KEY LESSONS LEARNED

Technology can be a major force in alleviating poverty and increasing food security in developing countries. Moreover, investment gains can be multiplied by adopting technologies in different regions through the creation of synergic partnerships for product development, implementation, and commercialization. ■

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1 www.absp2.cornell.edu.

2 See also, in the *Handbook*, Chapter 7.6 by Anatole Krattiger titled, The Use of Nonassertion Covenants: A Tool to Facilitate Humanitarian Licensing.

Golden Rice: A Product-Development Partnership in Agricultural Biotechnology and Humanitarian Licensing

IP (intellectual property) constraints are often perceived as barriers to market entry, especially when it comes to developing countries. This case study examines the IP management component in the development of Golden Rice[1] (or beta-carotene-containing rice) and the transfer and introduction of Golden Rice to developing countries.

Rice, one of the most widely grown food crops, contains neither vitamin A nor beta-carotene, yet it is a staple food crop for billions of people, especially in Asia. Here, and in other developing countries, vitamin A deficiency (VAD) is a major problem affecting primarily children under age five and pregnant and lactating women. Thousands of impoverished people lose their eyesight because of VAD. Severe VAD (xerophthalmia, or night blindness) leads to permanent blindness: 500,000 people, 250,000 of them children, lose their sight every year due to VAD.[2] The deficiency also leads to a depressed immune system that increases the incidence and severity of infectious diseases and infant mortality rates.

There are several avenues for mitigating VAD, including programs to fortify food with vitamin A and beta-carotene and to distribute vitamin A supplements to affected populations. For the supplement distribution, more than US$100 million are spent every year. An alternative, and complementary, approach is to insert relevant genes in rice. This allows farmers to grow beta-carotene-rich rice. By enhancing those varieties primarily grown or consumed by poor people, beta-carotene can be delivered at essentially no cost once the Golden Rice has been developed and bred into local varieties.

Interestingly, rice plants synthesize beta-carotene in foliage and other parts of the plant, but not in the grain, and all but two steps of the biosynthetic pathway are present in the grain. By the addition of only two genes, phytoene synthase (*psy*) and phytoene desaturase (*crt* I), the pathway is reconstituted and beta-carotene accumulates in the endosperm (the endosperm being the edible part of the grain).[3]

INTELLECTUAL PROPERTY FEATURES OF THE CASE

The development of Golden Rice led to a significant change in the relationship between the public sector and intellectual property. A freedom to operate (FTO) review of pro-Vitamin A-containing Golden Rice was commissioned by the International Rice Research Institute, a center of the Consultative Group on International Agricultural Research (CGIAR), with funding from the Rockefeller Foundation (led by one of us [AK]). The review showed that about 70 patents and patent applications were applicable to the improved rice when *all* patents issued in or applied for in *all* countries, including patents on commercially accessed research tools, were considered.[4] The published analysis also showed, in accordance with analysis by Zeneca (which later merged with Novartis to form Syngenta) that, in practice, only a few, if any, patents pertaining to Golden Rice were applicable in developing countries, together with a few material transfer agreements.

Obtaining Freedom to Operate

Fortunately, these potential—and arguably perceived—constraints were resolved in a few months in the year 2000 by a straightforward IP management strategy comprising four goals:

- identification of major IP components (the above-mentioned FTO review)
- interpretation, with Zeneca, of the relevance of the FTO review to the proposed humanitarian use in developing countries

Krattiger A and I Potrykus. 2007. Golden Rice: A Product-Development Partnership in Agricultural Biotechnology and Humanitarian Licensing. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

- in licensing for humanitarian use, led by Zeneca, of IP components it did not already own
- licensing by Zeneca, as Syngenta, via the inventors of the assembled (or bundled) intellectual property to public sector institutions in developing countries that could use the rights for the benefit of resource-poor farmers, and others, deficient in vitamin A

The patented key technologies for Golden Rice production include core patents related to the specific biosynthetic pathway. These patents were filed by the inventors, Potrykus and Beyer. Their work built on myriad other technologies that were published in issued patent documents and scientific literature. These core patents were licensed to Zeneca, which already owned its own plant-biotechnology-related patents. Zeneca then negotiated access to all possibly necessary patents, including intellectual property from Bayer AG, MonsantoCompany, Novartis AG, Orynova BV, and Zeneca Mogen BV.

All of these companies, including Zeneca (which, coincidentally, almost immediately merged with Novartis Agribusiness to form Syngenta), provided access to their technologies, free of charge, for defined humanitarian research and use of Golden Rice in developing countries. It is important to note that, contrary to what many commentators state, the licensing process was relatively uncomplicated, with the involvement of commercially experienced people.

Licensing

Within a short time, 16 further licenses, including licenses with the right to further sublicense (for example, the license issued to IRRI), were issued to public sector licensees. Thus national programs in Bangladesh, China, India, Indonesia, the Philippines, South Africa, and Vietnam obtained licenses for use of the technology in local rice varieties important in VAD areas.

Terms of the humanitarian license agreement

The Golden Rice Humanitarian Board, although not a legal entity, provides a forum for discussion of strategic and tactical issues relating to the humanitarian project. Both Potrykus and Beyer have the right to issue licenses. Two licensees also have that right, as does Syngenta, which has not exercised its right. All the licenses are in the same form, as proposed by Syngenta and agreed to by the inventors.

The essential elements of the licenses include the following points:

- Syngenta retains commercial rights, although it has no current plans to commercialize Golden Rice. Humanitarian use, and research leading to it, is allowed.
- Humanitarian use is defined as use in developing countries by resource-poor farmers (earning less than US$10,000 per year from farming).
- The technology must be introduced into public seed varieties, as a way to optimize public sector benefit and use.
- No technology fee (or surcharge) may be charged for Golden Rice, as a way to optimize public sector benefits.
- Sale of Golden Rice is authorized by farmers, as a way to reach urban poor.
- Farmers are allowed to reuse harvested seeds.
- Golden Rice may not be released in a country that lacks biosafety regulations and where official government review has not been made to ensure health and environmental safety.
- Export of Golden Rice is not permitted, except to other licensees for humanitarian research and subsequent use. (Export of crops is a commercial activity. The purpose of the humanitarian project is to assist resource-poor people in overcoming VAD).
- With regard to improvements to the Golden Rice technology:
  - Humanitarian use of any improvements to Golden Rice is guaranteed under the same terms of the original agreement (and thus any improvements to the technology will serve the humanitarian purpose). Syngenta has acted on this—donating to the humanitarian project new transformations, including the intellectual property and results reported in Paine and colleagues.[5]
  - Commercial rights to improvements of the technology are granted back to Syngenta.
- No warranties are given by the licensor or licensors (as is common for licenses), and each party is responsible for what it controls.

KEY LESSONS LEARNED

The rapid resolution of the IP constraints surrounding Golden Rice demonstrated, first of all, how effective IP management, coupled with strong collaborations between the public and private sectors, can help achieve global access to new technologies and products for humanitarian goals. The IP constraints identified by Kryder and colleagues[6] did not delay the development of the product, and their clarification and resolution required only managerial and influencing skills and the resulting goodwill of IP owners.

More specifically, three specific lessons have been learned:

1. Intellectual property and patents did not delay the development and introduction of Golden Rice by a single day. Notwithstanding this, the resolution of the potential IP constraints could not be ignored.
2. Other constraints are much more critical to the introduction of Golden Rice, in particular, and to potentially life-saving food biotechnology

applications, in general. These constraints are, in decreasing order of importance:

- the necessity of governments to establish a sustained and positive policy priority for the adoption of all relevant, including novel, technologies in agriculture
- the importance of the establishment of affordable, workable, and science-based regulatory systems designed to comply with international obligations *and* to address local needs and concerns (The unnecessarily burdensome, overly politicized regulatory requirements for genetically modified organisms [GMOs] and the absence of consideration of benefit has led to years of delay in the introduction of Golden Rice technology. Yet there is no evidence to justify such a burdensome regulatory system.)
- the need for the capacity and funding of national agricultural rice research institutions to keep segregated different versions of genetically modified crops, including conducting field trials with them
- the anticipated need to develop effective seed distribution systems for reaching farmers in remote areas, including the presence of private sector entities willing to invest in seed distribution systems (However, a major aim is also to have farmers pass the seed on to neighboring farmers to reach "infrastructure remote" areas often associated with VAD.)

3. Recognizing that universities are not set up to develop products, Syngenta was instrumental in converting the proof-of-concept results generated at ETH Zurich and University of Freiburg into deliverable products. Although Syngenta retained commercial exclusivity for the technology, the company decided not to develop a commercial product of Golden Rice for markets in developed countries. Syngenta's continued support of the project with advice and scientific know-how has proven absolutely essential for the success of the product-development partnership.

From a broader perspective, the FTO review of Golden Rice, in particular before "commercial analysis," served as a wake-up call to the public sector to pay more attention to IP management as a powerful tool for meeting public sector goals. Concern about potential constraints on public sector research and innovation in agriculture spurred the public sector's interest in intellectual property. One important response was work that led to the formation of the Public Intellectual Property Resource for Agriculture (PIPRA). Supported by, among others, the Rockefeller and McKnight foundations, PIPRA is a public sector initiative that recognizes that continuing and enhancing relationships with the private sector, and between the public sector institutions, are critical components of the utilization of intellectual property to meet public sector goals. As part of its initial work, PIPRA began a study of the structure of IP ownership in agricultural biotechnology. In the words of the study's authors, Richard C. Atkinson and colleagues: *This study found that roughly one-fourth of the patented inventions were made by public-sector researchers, which is substantially larger than the IP portfolio held by any single agricultural biotechnology company. It is, however, highly fragmented across institutions and across technology categories. And much of this IP has been licensed, often under terms that are confidential but which have likely resulted in greatly restricted access to the underlying technologies.*[7] *This study suggested that, apart from a few important exceptions, public-sector scientists have invented many of the types of technologies that are necessary to conduct basic biological research and develop new transgenic plant varieties. For instance, they have developed technologies to transfer genes into plant cells; have characterized specific DNA elements that drive unique patterns of gene expression; and have identified many genes that confer important plant traits. Such discoveries underscore the fact that public-sector research institutions have been significant sources of technological innovation.*[8]

We believe that this study involving Golden Rice shows how public and private sector innovations can be put to work directly to help the poor with more focused public sector IP management. Indeed, IP management is merely one of the components needed to bring innovation to the poor.[9] Other factors, such as regulatory requirements, can be much more costly and do constitute tremendous barriers to the poor benefiting from innovations that are becoming commonplace in much of the world. ■

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1 Golden Rice was invented by Ingo Potrykus, then at ETH in Zurich, Switzerland, and Peter Beyer of the University of Freiburg, Germany. See also www.goldenrice.org.

2 childinfo.org/areas/vitamina/ .

3 Potrykus I. 2001. Golden Rice and Beyond. *Plant Physiology* 125:1157–1161.

4 Kryder D, SP Kowalski and AF Krattiger. 2000. The Intellectual and Technical Property Components of pro-Vitamin A Rice (GoldenRice™): A Preliminary Freedom-to-Operate Review. ISAAA Briefs No 20. ISAAA: Ithaca, NY. www.isaaa.org/kc/bin/isaaa_briefs/index.htm.

5 Paine JA, Shipton CA, Chaggar S, Howells RM, Kennedy M, Vernon G, Wright SY, Hinchcliffe E, Adams JL, Silverstone a, Drake R. 2005. Improving the nutritional value of Golden Rice through increased pro-vitamin A content. Nature Biotechnology 23(4):482–487.

6 See *supra* note 4.

7 Only within the temporal and spatial limits allowed by the patent system (note added by the authors of this case study).

8 Atkinson RC, RN Beachy, G Conway, FA Cordova, MA Fox, KA Holbrook, DF Klessig, RL McCormick, PM McPherson, HR Rawlings III, R Rapson, LN Vanderhoef, JD Wiley and CE Young. 2003. Public Sector Collaboration for Agricultural IP Management. *Science* 301(5630):174–175.

9 Current Golden Rice transformation events in the humanitarian project's development process were all designed and made by Syngenta to need access to no third party intellectual property.

Saving Forests and Creating a New Cash Crop in the Middle East and Asia: University of Minnesota

The high demand for agarwood—wood soaked with a resin produced by a small portion of Aquilaria trees in southeast Asia and Indonesia—nearly decimated the species. The trees produce the resin only when injured and, before researchers stepped in, usually when the trees were 50 or more years old.

Agarwood and its resin are highly prized in the Middle East and Asia, particularly in Islamic and Buddhist cultures, where the wood and resin are used in perfumes, ceremonial incense, traditional medicine, and other applications. Unfortunately, determining whether a particular standing Aquilaria tree contains agarwood is nearly impossible, so harvesters were felling and sawing up Aquilaria trees until they were close to extinction in much of their natural range.

Robert Blanchette, Ph.D., of the University of Minnesota, and the nonprofit organization Rainforest Project, based in the Netherlands, have jointly developed an easy and inexpensive method to induce agarwood formation in trees that are only three to six years old. Now, instead of cutting down trees found in the forest, farmers can grow stands of Aquilaria trees on plantations, induce production of agarwood in those trees, and sell them as a new cash crop.

This practice will benefit regional farmers and their local economies, reduce the threat of extinction to native populations of Aquilaria trees, and ensure a long-term supply of agarwood for centuries-old cultural and religious uses. The University of Minnesota has licensed the technology to the Rainforest Project, which is leading distribution efforts beginning in Southeast Asia. ■

AUTM. 2007. Saving Forests and Creating a New Cash Crop in the Middle East and Asia: University of Minnesota. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

Editors' Note: We are most grateful to the Association of University Technology Managers (AUTM) for having allowed us to adapt this case study for inclusion in this *Executive Guide*. The original was published by AUTM. 2006. *Technology Transfer Works: 100 Cases from Research to Realization* (Reports from the Field). Association of University Technology Managers, Northbrook, IL. www.betterworldproject.net.

Building Healthy Forests with Early-Stage Propagation: University of Saskatchewan

Forestry is among the world's largest industries; it has a significant impact on people's lives around the world. One of the industry's greatest challenges is increasing the efficiency of land areas designated for commercial forestry by improving their productivity. Another challenge is complying with environmental standards, which provide guidelines for reforestation, production in environmentally sensitive areas, and long-term sustainable forest management.

A crucial step toward increased efficiency is growing stronger trees. With many plant species, horticulturalists can create new varieties by taking cuttings from plants with desirable characteristics and encouraging the cuttings to root. This propagation method has yielded scores of different kinds of plants including orchids, roses, grapevines, and fruit trees. But the method doesn't work well with most forest trees because the cuttings are less likely to take root.

Researchers at the University of Saskatchewan developed a technology called somatic embryogenesis (SE), a complex propagation process that relies on the splitting of one embryo into two or more identical embryos. The method allows scientists to grow two or more plants that have the same genetic makeup. With SE, propagation occurs earlier in the plant's lifecycle and rooting is more likely to be successful.

SE offers several economic benefits to the forestry industry including greater success in propagating desirable trees and the ability to grow seedlings year-round. The University of Saskatchewan licensed the patent-protected technology to CellFor based in Vancouver, British Columbia, Canada. In 2003, the company began working with timberland managers to plant loblolly pine seedlings propagated from fast growing, disease-resistant varieties in the southeastern U.S. states including Georgia and Mississippi.

Today the company maintains more than 3,000 unique genetic lines and has an extensive network of field trials aimed at testing and further refinements. The technology allows CellFor to produce seedlings that grow faster, generate a higher yield, and produce superior wood, while reducing production costs and enhancing resistance to disease and pests.

Read more about SE at www.cellfor.com. ■

AUTM. 2007. Building Healthy Forests with Early-Stage Propagation: University of Saskatchewan. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

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DNA Hepatitis B Vaccine: International Vaccine Institute, Korea

Intellectual property as a barrier to market entry is examined through a study of the development and introduction of recombinant DNA (rDNA) hepatitis B vaccine (HBV) in developing countries. The most widely used vaccines in the mid-1980s were produced by Merck and GlaxoSmithKline, which were the first two companies to introduce the rDNA HBV. Almost a decade later, Korean and Indian manufacturers entered the rDNA HBV vaccine market. However, the price remained relatively high (>US$7 per dose) until the Global Fund for Children's Vaccine (today amalgamated with the GAVI Alliance) was established with seed funding from the Bill and Melinda Gates Foundation. With this funding the price dropped to less than US$0.30 per dose. This study sought to identify factors that affected supplying low-cost vaccine to the public sector.

Merck and GlaxoSmithKline licensed three key patents assigned to Institut Pasteur, Biogen, and the University of California. These patents were filed in the United States, Europe, and a few other developed countries. The companies stated that licenses to more than 90 other patents relating to manufacturing processes such as isolation and purification were also needed.

The Korean companies pursued collaborations or joint ventures but chose not to focus on the United States and European markets mainly due to regulatory and market entry costs. These companies sought World Health Organization prequalification for their production facilities and approval for the vaccine from several governments in Asia and other countries in the developing world.

A Korean company, LG Chem, formed a joint venture with Chiron. Chiron had a license from the University of California (key scientists at Chiron were inventors on the University patent). Through the joint venture, LG scientists could learn how to make the vaccine. Korea Green Cross entered into a joint venture with Rhein Biotech, which had developed and patented its own method for making the vaccine. Having surveyed globally for a partner to exploit its technology, the German company chose Korea because of the low cost of production achieved by Korea Green Cross. The Korean company Cheil Sugar also sought to enter the market for the vaccine and attempted to develop its own technology. After nearly 20 years of effort, Cheil Sugar (now CJ Corp.) abandoned the effort.

These LG Chem and Korea Green Cross alliances were formed in an environment that was supportive of biotechnology innovation. The Korean government accorded high priority to R&D in biotechnology and provided strong support for overseas training and domestic research. The biotech industry received the backing of private sector investment, and domestic and export markets were encouraged by the government. High priority was given by the Korean government to hepatitis B immunization thereby ensuring an initial market for the companies.

This case study concludes that intellectual property was not a major barrier to market entry. Korean companies took several years to enter the market because of lack of resources, including a small cadre of scientific staff, the need to improve national regulatory systems, and, importantly, the small size of the global market. The international public sector market remained underdeveloped in part because of its low priority for large pharmaceutical companies, lack of demand by

Mahoney R. 2007. DNA Hepatitis B Vaccine: International Vaccine Institute, Korea. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

Editors' Note: This case study was originally presented at the MIHR conference Using Intellectual Property for Improved Health in Developing Countries: An Evidence-Based Approach to Good Practice, Bellagio, Italy, June 14–18, 2004.

developing countries, and little procurement by international donor agencies.

Each company sought to secure intellectual property in order to bring its vaccines to market, but patents did not hinder developing the vaccine because the companies focused on markets in countries where the three key patents were not filed. Intellectual property had some affect on access but was much less important than regulatory and manufacturing issues, and market development. However, the situation might be different post-2005 when most developing countries are required to be TRIPS compliant. In the TRIPS era, patents may be routinely filed in many countries such as Brazil, China, India and Korea thereby making it more difficult for second comers to produce in and sell to those large and important markets.

FEATURES OF THE CASE

Types of agreements

Merck and GlaxoSmithKline obtained licenses to three key patents assigned to Pasteur Institute, the University of California, and Biogen. These patents were filed in the United States, Europe, and a few other developed countries. Both companies obtained licenses to numerous other patents having to do with manufacturing processes, including isolation and purification. The Korean companies took three different routes. Cheil sought to develop the technology on its own. LG Chem (previously Lucky Gold Star) formed a joint venture through which it obtained know-how for the production of the vaccine. Korea Green Cross entered into a joint venture with a foreign company, Rhein Biotech of Germany, which had developed an alternate production method.

Patent and IP rights decisions

Merck and, to a lesser extent, GlaxoSmithKline were primarily interested in markets in developed countries and obtained all necessary licenses to patents filed in those countries. The Korean companies opted not to pursue the same markets as Merck and GlaxoSmithKline because of the costs of obtaining regulatory approval and establishing a market presence associated with those markets. LG Chem decided to proceed simply by obtaining know how and relying on its low cost of manufacture and aggressive marketing skills. Korea Green Cross and Rhein Biotech formed a joint venture in which they exploited the Rhein Biotech patent for a manufacturing method different from that used by Merck and GlaxoSmithKline. Cheil sought to develop its own proprietary technology but eventually abandoned this effort.

Policy implementation

All five companies complied with the laws and regulations applicable in their legal jurisdictions. Each company sought a clear IP path to marketing the vaccines. To the author's knowledge, no infringement lawsuits were brought against any of the companies.

EXTERNAL FACTORS THAT AFFECTED DECISION MAKING

Key factors that affected decisions made by the Korean manufacturers were the costs of regulatory compliance with respect to and market entry into the United States and Europe. In addition, the Korean Food and Drug Administration had been undertaking certain improvements, and until those improvements were completed, the Korean manufacturers could not supply United Nations agencies. The Korean manufacturers also had to obtain World Health Organization prequalification for their production facilities, which LG Chem and Korea Green Cross succeeded in accomplishing in the late 1990s. The key factor in allowing the Korean manufacturers to supply low-cost vaccine to the public sector was the establishment of a market through the Global Fund for Children's Vaccine, initially funded by the Bill and Melinda Gates Foundation.

LESSONS LEARNED AND HEALTH-ACCESS ISSUES

Intellectual property was an important issue for all the companies involved in the DNA hepatitis B vaccine project, but IP issues did not significantly impede the pace at which the Korean manufacturers were able to enter the market. The key factors were (in approximate order of importance):

- requirement for a global market
- need to meet international regulatory standards
- need to undertake in-house R&D or obtain know-how from a joint-venture partner
- time it took to construct and improve production facilities that would meet WHO requirements

Further, the ability of Rhein Biotech and Korea Green Cross to exploit the Rhein Biotech patent on an alternate production method provides support for the argument that it is easier to develop and market vaccines in a complex IP environment than it is to develop and market new defined chemical entities that have been patented. Vaccines are complex biological products that can be made through a diversity of procedures while defined chemical entities are single molecules that may be easy to produce only through one process. ■

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HIV/AIDS Vaccine: Indian Council of Medical Research

This HIV/AIDS initiative is a collaborative venture between the Indian Council of Medical Research (ICMR), New Delhi, the International AIDS Vaccine Initiative (IAVI), New York, National AIDS Control Organization (NACO/Indian Ministry of Health), New Delhi and Therion Biologics, Cambridge, Mass. The project aims to develop a safe and effective HIV/AIDS vaccine—such development has been mandated by the Indian government—for India and other developing countries. The vaccine has now been developed by ICMR in collaboration with Therion and is undergoing clinical trials.

Under the terms of this public-private partnership (PPP), ICMR will provide technical expertise, obtain all necessary permissions and permits, conduct R&D to develop the vaccine in collaboration with Therion, prepare the community (in India) for clinical trials, and conduct the trials. ICMR will select an Indian partner for the manufacture of vaccine and has overall responsibility for ensuring that the project is executed according to its objectives. NACO will facilitate the execution of the project. IAVI will support the project, facilitate development of an appropriate vaccine through transfer of technology from Therion, engage in capacity building and advocacy, and facilitate technology transfer for the local manufacture of the vaccine. Therion will assist ICMR with the vaccine development and help transfer technology to the selected Indian manufacturer.

The project involved an overall agreement between ICMR and IAVI, a patent and technology transfer agreement between ICMR and IAVI, and an IP (intellectual property) rights and confidentiality agreement between ICMR and Therion Biologics. A project management committee was set up, comprising representatives from ICMR and IAVI, to coordinate and monitor all activities and assessments of the R&D programs. The committee is also responsible for strategic IP management.

All new intellectual property generated will be jointly held by IAVI and ICMR, and the Indian government shall have the exclusive right to use all patent and other new IP rights to inventions arising out of the program to benefit India and its neighboring countries. The ICMR will grant nonexclusive royalty-free and sublicensable licenses to all new intellectual property arising out of the project to selected third parties in order to make, use, sell, and import the HIV/AIDS vaccine in countries other than those indicated in the agreement (to the extent ICMR has the right to permit this use). The IAVI shall have IP rights for rest of the world.

Initially, the program was to be implemented only in India, but the Government of India, realizing that the program could benefit other developing countries as well, asked for licensing rights. In arriving at this realization, policymakers (bureaucrats) of the government needed to be educated about intellectual property and its role in technology transfer. This case has highlighted the importance of keeping government officials involved in order for an international PPP to be successful.

Although no patents were filed in India, a significant amount of clinical trial data was generated. From an IP perspective, it was crucial to recognize private sector interests. Therion has global rights for the technology needed for the vaccine construct, but India

Satyanarayana, K. 2007. HIV/AIDS Vaccine: Indian Council of Medical Research. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

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will have rights to improvements made to the vaccine. Therion's stringent IP regulations meant confidentiality agreements were imposed on collaborating scientists, which the Government of India appreciated.

The recruitment process for the vaccine trials envisages serious ethical concerns as well as potential liability issues, as the vaccine is for HIV/AIDS. It was recognized that clinical trials must be conducted in a fair and transparent manner and the interests of participants protected through informed consent as per the ICMR's Ethical Guidelines and that all necessary safeguards to protect subjects of the study had to be built into the system.

The case study recognizes (1) the role of "honest broker" that international nongovernmental organizations like IAVI can play in a PPP, providing funding and access to high technology from a private company; (2) the need to educate policymakers (bureaucrats) from the beginning of a project to ensure smooth progress; and (3) the equally crucial need to involve policymakers, lawmakers, politicians, women's associations, and other civil society organizations in the execution of such projects that envisage clinical trials. This project is offered as an example of productive North–South collaboration and broad capacity building and a partnership in which the strengths of the partners complement each other.

TYPES OF AGREEMENTS

As part of the HIV/AIDS project, ICMR entered into the following types of agreements:

- an overall agreement between the ICMR and the IAVI for the entire project including provisions for development, upscaling, manufacture, and distribution of the vaccine in India, neighboring countries, and the rest of the world
- a separate technology transfer and manufacturing agreement between Therion and the manufacturer identified jointly by IAVI, the Government of India, and Therion

IP RIGHTS DECISIONS AND IP MANAGEMENT

The project has resulted in the following arrangements with respect to IP rights and strategic IP management issues:

- IAVI and the Government of India-ICMR will jointly hold the new intellectual property generated during the project.
- The Government of India-ICMR shall have exclusive rights to use all patent and other new IP rights to inventions arising out of the program in India and neighboring (SAARC) countries.
- ICMR grants IAVI a nonexclusive, worldwide, royalty-free sublicensable license to all new patents and other intellectual property arising out of the program that would permit IAVI or third parties selected by IAVI to make, use, sell, offer for sale, and import HIV/AIDS vaccines in countries other than those indicated in the agreement (to the extent ICMR has the right to permit the use of the same).
- Intellectual property is jointly managed by the ICMR and IAVI through the project management committee.

POLICY IMPLEMENTATION

Policy is implemented through a project management committee comprising representatives from the IAVI, ICMR and NACO, and jointly chaired by members appointed by ICMR and IAVI. The committee is responsible for the coordination and monitoring of all activities, periodic assessments and updates, and refinements and revisions of the R&D program.

EXTERNAL FACTORS THAT AFFECTED DECISION MAKING

A number of external considerations influenced ICMR's strategies and decision making. These include:

- the potential use of the vaccine(s) in India's neighboring countries
- the need to provide an effective and affordable vaccine to the people

KEY LESSONS LEARNED AND HEALTH-ACCESS ISSUES

The following items represent key lessons from ICMR's HIV/AIDS vaccine project, which may be applicable to other entities that aim to utilize intellectual property:

- Only through strategic public-private partnerships can such ventures succeed.
- Private sector's interests need to be considered.
- The role of an international nongovernmental agency such as IAVI is important and vital for the success of such a project.
- There is a need to educate government officials on issues relating to IP rights and technology transfer, as the government's role is crucial in the clearance and approval of projects of national interest.
- The importance of (1) ethics in carrying out clinical trials and (2) the need to involve policymakers, women's associations, and other civil society groups in the execution of the project cannot be overstated. ■

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Malaria Vaccine: Malaria Vaccine Institute and GlaxoSmithKline Biologicals

Malaria remains one of the world's deadliest killers. Every year, the disease takes the lives of more than one million people, mostly sub-Saharan African children under age five. Hundreds of millions more people fall ill from the mosquito-borne disease. Major hurdles to traditional prevention and treatment strategies include drug resistance by the malaria parasite and heightened resistance to insecticides by the mosquito that transmits it. Scientists have been working for decades to develop a preventive malaria vaccine. While they have successfully demonstrated that such a vaccine is possible, many challenges continue to impede progress on the road to an effective product. The complex life cycle of the malaria parasite (the most deadly being the *Plasmodium falciparum* species) represents a major hurdle. While each stage of the parasite's development offers an opportunity to attack it, the parasite's ability to evade people's immune responses has made the development of a malaria vaccine technically difficult.

PATH[1] is an international, nonprofit organization that creates sustainable, culturally relevant solutions, enabling communities worldwide to break longstanding cycles of poor health. The PATH Malaria Vaccine Initiative (MVI)[2] is a global program established in 1999 through an initial grant of US$50 million from the Bill and Melinda Gates Foundation, which has since awarded MVI an additional US$207.6 million, including US$107.6 million to complete development of the most promising malaria vaccine candidate. MVI's mission is to accelerate the development of promising malaria vaccines and to ensure that they are available and accessible in the developing world.

Among the candidates in MVI's portfolio, the RTS,S vaccine of GlaxoSmithKline (GSK) Biologicals[3] is the most advanced. Created in 1987, the pre-erythrocytic vaccine candidate's early development was undertaken by GSK Biologicals, in close collaboration with the Walter Reed Army Institute of Research. In January 2001, GSK Biologicals, MVI, and other partners—with support from the Bill and Melinda Gates Foundation—entered into an agreement to develop the vaccine for children in sub-Saharan Africa. Clinical evaluation of RTS,S began in 1992 and the results since then represent a breakthrough for malaria vaccine development. RTS,S has proved to be effective for at least 18 months in reducing clinical malaria by 35 percent and severe malaria by 49 percent. *Time* magazine highlighted this project as one of the most important health accomplishments of 2005.

PARTNERS

Partners in the malaria vaccine project are

- from academia, New York University
- from government, Walter Reed Army Institute of Research
- a nonprofit organization, PATH Malaria Vaccine Initiative
- a pharmaceutical company, GSK Biologicals
- two health-research centers, the Center for International Health (CIH), Hospital Clínic

MIHR/PIPRA. 2007. Malaria Vaccine: Malaria Vaccine Institute and GlaxoSmithKline Biologicals. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

Editors' Note: This case study was prepared by MIHR members of the Technology Managers for Global Health (TMGH), a special interest group of the Association of University Technology Managers (AUTM) (see www.tmgh.org) and adapted for this *Executive Guide*. The original version was published as part of a collection of case studies: MIHR/TMGH. 2007. *Academic Licensing to Global Health Product Development Partnerships* (ed. U Balakrishnan). MIHR: Oxford, U.K.

of the University of Barcelona and Centro de Investigação em Saude da Manhiça (CISM)

The Bill and Melinda Gates Foundation provided funding for the project.

TECHNOLOGY

This vaccine candidate is a recombinant protein that fuses a part of the *P. falciparum* circumsporozoite protein with the hepatitis B surface antigen molecule. Combined with a proprietary GSK adjuvant system, RTS,S induces the production of antibodies and white blood cells that are believed to diminish the capacity of the malaria parasite to infect, survive in, and develop in the human liver. In addition to inducing partial protection against malaria, the RTS,S vaccine candidate stimulates a protective immune response to hepatitis B, which commonly infects people in developing countries.

PROGRESS, CURRENT STATUS, AND GOALS

GSK Biologicals and MVI are currently conducting several small-scale trials in infants and young children, the groups most vulnerable to malaria and that would benefit most from an effective malaria vaccine. Working with in-country research institutions, clinical trials are ongoing in partner African countries, including Mozambique, Tanzania, Gabon, and Ghana. A variety of immunization schedules will be assessed, and the efficacy of the vaccine will be evaluated when administered with the Expanded Programme on Immunization. If these trials are successful, the partners will proceed to a large-scale Phase III clinical trial to determine the efficacy of the vaccine in the same age group. If all goes well, the RTS,S vaccine could be licensed as early as 2010.

ABOUT THE CLINICAL PARTNERS

The Center for International Health (CIH), Hospital Clínic of the University of Barcelona

The Center for International Health (CIH) is a pioneering structure within the University of Barcelona's Hospital Clínic, the leading Spanish biomedical research center.[4] The CIH is involved in health care, training, and research in global health issues. The collaborative programs in Africa, particularly the development of the Manhiça Health Research Center, which is in close partnership with Mozambican institutions, are a central component of the activities of the CIH.

THE CENTRO DE INVESTIGAÇÃO EM SAUDE DA MANHIÇA

Centro de Investigação em Saude da Manhiça (CISM) is the first peripheral health research center in Mozambique to undertake medical research into key health problems in that country. Founded in 1996, CISM was developed under a collaborative program between the Mozambique Ministry of Health, the Maputo School of Medicine (Universidade Eduardo Mondlane), and the Hospital Clínic of the University of Barcelona with core funding from the Spanish Agency for International Cooperation.[5]

MOZAMBIQUE'S MINISTRY OF HEALTH

The mission of Mozambique's Ministry of Health is to promote and preserve the health of the Mozambican population, to promote and provide quality and sustainable healthcare services, and to, with equity and efficiency, gradually increase access to sustainable healthcare for all Mozambicans. ■

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1 PATH: www.path.org.

2 Malaria Vaccine Initiative: www.malariavaccine.org.

3 GlaxoSmithKline Biologicals: www.gsk-bio.com.

4 University of Barcelona Hospital Clínic: www.hospitalclinic.org.

5 CISM: www.manhica.org.

Rotavirus Vaccine: NIH Office of Technology Transfer

The National Institutes of Health (NIH), as part of the U.S. Public Health Service (PHS), is dedicated to improving the public health of individuals worldwide through innovative research and the funding of critical medical research programs. Immunization against rotavirus disease is an important public health initiative supported by several organizations worldwide. This case study describes the partnerships between PHS and institutions in Brazil, China, India, and the United States that have been established to facilitate development of a safe, effective, and affordable vaccine for arresting the overwhelming mortality associated with rotavirus infection in the developing world.

PARTNERS

Partners in the rotavirus vaccine project are:

- from government: the National Institutes of Health/U.S. Public Health Service
- nonprofit organizations: Fundação Butantan (Sao Paulo, Brazil), Chengdu Institute of Biological Products (Chengdu, China), and Wuhan Institute of Biological Products (Wuhan, China)
- for-profit companies: Aridis Pharmaceuticals (United States), Bharat Biotech International, Ltd. (Hyderabad, India), Biological E., Ltd. (Hyderabad, India), Shanta Biotechnics, Ltd. (Hyderabad, India), and Serum Institute of India, Ltd. (Pune, India)

EPIDEMIOLOGICAL FEATURES OF ROTAVIRUS

Rotavirus is the leading cause of severe dehydrating diarrhea in infants and children worldwide. According to a report issued by the World Health Organization (WHO), each year, the disease is responsible for about 25 million clinic visits, two million hospitalizations, and between 352,000 and 592,000 deaths in children age five and under. As one can imagine, the worldwide economic burden associated with rotavirus disease is staggering, exceeding $1 billion each year in medical costs. Children in developing countries are disproportionately at risk of dying from rotavirus-related infection. In India alone, rotavirus is blamed for the deaths of approximately one out of every 250 children each year, and in China, the disease accounts for more than 34,000 deaths per year. This rotavirus-associated mortality is due in part to inadequate sanitation and to inadequate access to intravenous rehydration therapy in poor countries.

THE TECHNOLOGY

The human-bovine reassortant rotavirus vaccine is an invention of Dr. Albert Kapikian and his colleagues at the National Institutes of Allergy and Infectious Disease (NIAID) of the NIH. The invention was further developed through collaboration with Wyeth Pharmaceuticals. The vaccine technology is based on multivalent immunogenic compositions comprising four human-bovine reassortant rotaviruses and involves the insertion of the gene-encoding VP7 protein of G1, G2, G3, and G4 human rotavirus strain into a bovine rotavirus backbone. These VP7 serotypes represent the clinically most prevalent human rotavirus serotypes. Additionally, the basic quadrivalent vaccine formulation can be augmented with G9 and G8 strains (or one of these additional strains for a pentavalent formulation) to make a hexavalent formulation. Serotype 9 (G9) has emerged as an important strain in Latin America and the most important

MIHR/PIRPA. 2007. Rotavirus Vaccine: NIH Office of Technology Transfer. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

strain in Brazil, whereas G8 is prevalent in many African countries.

Originally, the human-bovine reassortant rotavirus vaccine was intended as a second-generation rotavirus vaccine. It was developed alongside the human-rhesus reassortant vaccine, RotaShield, an earlier invention of Dr. Kapikian that was commercialized by Wyeth following U.S. Food and Drug Administration approval in 1998. RotaShield was voluntarily removed from the market in 1999 after the vaccine was suspected of being linked to an increased risk for intussusception in children. After the withdrawal of RotaShield from the market, interest in the human-bovine reassortant technology increased, which led to multiple applications for commercial licensing as detailed below.

LICENSE AGREEMENTS

Published reports and presentations by NIH NIAID investigators generated significant interest in the human-bovine rotavirus vaccine technology from companies and institutions worldwide. In 2005, eight organizations, one in the United States and seven based in the developing world, were granted licenses from PHS to manufacture and distribute the rotavirus vaccine. The licensees are U.S.-based Aridis Pharmaceuticals; Fundação Butantan, a Brazilian government institution; Bharat Biotech International, Biological E., Ltd., Shantha Biotechnics, Ltd., and Serum Institute of India, Ltd., all India-based companies; and Chengdu Institute of Biological Products and Wuhan Institute of Biological Products, both funded by the government of China. The vaccine technology is covered by issued patents (and pending patent applications) in the United States, Europe, Canada, Japan, China, India, Korea, Brazil, and Australia, thus NIH decisions regarding the license agreements were based on thorough evaluation of the applicants and their capabilities with regard to vaccine research and manufacturing. The license agreements with all parties are based on territorial rights and include both rights for the intellectual property and to biological materials. The biological materials include all the vaccine strains, as well as the analytical reagents necessary to develop the vaccine.

Butantan was awarded an exclusive license to practice the invention for development of a rotavirus vaccine in Brazil and Latin America. In cooperation with the Brazilian Ministry of Health, Butantan plans to introduce the vaccine into Brazil's child immunization program, which provides free vaccines for all children of Brazil. Similarly, Chengdu and Wuhan will manufacture and supply the rotavirus vaccine to China's expanded program of immunization (EPI). The Office of Technology Transfer (OTT) at NIH granted to the four Indian companies licenses to the IP rights in India and rights to manufacture and distribute the rotavirus vaccine in India and other developing countries, excluding Brazil and other Latin American countries and China. Finally, Aridis was granted an exclusive license to IP rights covering the rotavirus vaccine in the United States, Europe, and Canada. By using this multipronged approach and carving out territory-specific agreements, PHS ultimately set the stage for global distribution of the rotavirus vaccine. The terms of the agreements were structured according to each licensee's mission to provide free or affordable vaccines to children in their specific territories.

PROGRESS, CURRENT STATUS, AND GOALS

The human-bovine reassortant rotavirus vaccine is expected to reach the market in developing countries in five to six years. All the licensees are currently in a stage of organization, preparing all the necessary facilities and infrastructure for manufacturing the vaccine and for clinical trials. The licensees plan to receive training in the technology involving the vaccine at the laboratory of Dr. Kapikian at NIH. It is anticipated that the Codevelopment will include collaboration with the NIH. OTT staff was recently notified by its partners and the staff of the Bill & Melinda Gates Foundation that the latter will support partial development of clinical trial procedures for screening the technology at specific institutions in developing countries. ■

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Gastrointestinal Medicines from African Aloe: Baylabs (Pty) Ltd.

The plant species *Aloe ferox*, indigenous to the eastern and southeastern Cape regions of South Africa, has sustained an aloe tapping industry for more than 250 years. However, the industry has failed to substantially improve the economic conditions of communities in the region. Between 1,600 and 3,000 aloe tappers earn, on average, $150 per month.

In 1998, a method for producing a novel fiber in powder form from the discarded leaves of the plant was patented by South Cape Aloe (SCA). A virtual startup company with a strong emphasis on technology and intellectual property (IP) was subsequently formed in South Africa to develop a product to treat irritable bowel syndrome (IBS) and AIDS-related diarrhea (ARD).

The company, Baylabs, aims to form local partnerships to develop, manufacture, and distribute the product to both developed and developing countries. Baylabs' strategy is to focus on R&D to generate and protect intellectual property and products, while outsourcing noncore functions such as manufacturing, sales, and distribution.

SCA granted the manufacturer African Aloe exclusive rights to make the powder and gained a share hold in Baylabs in exchange for exclusive, royalty-free, worldwide rights to exploit the powder. Baylabs filed a Patent Cooperation Treaty application for the novel powder formulation, with national filings in 13 European countries and prosecutions in the United States, Japan, Australia, and China.

Baylabs has developed four over-the-counter natural remedies from *A. ferox* that are distributed to pharmacies. The revenue generated is used to file patents and obtain scientific evidence of efficacy for gastrointestinal (GI) problems. The products will continue to be marketed and regulated as a dietary supplement while scientific evidence is being gathered and until the product is registered as a medicine.

The company's value has grown through its intellectual property and clinical trials of IBS and infantile diarrhea disease (IDD). Discussions are underway with international strategic partners regarding exclusive license agreements; efforts to secure government or venture capital funding are in progress. Baylabs plans to build preprocessing field plants and a facility to manufacture the powder, with the aloe tapper community as an equity partner, which could lead to increased salaries (almost double) for aloe tappers.

There is no traditional knowledge (TK) involved in using the waste leaf but TK exists in using the *A. ferox*. A key feature of this case study is the potential for other treatments; the formulation can be used for IBS in developed countries and ARD in developing countries. Once clinical trials have been completed, Baylabs plans to register the product as a medicine. However, the advantages of registering the product as a drug rather than as a food supplement have been questioned. Such registration would require, among other things, strict manufacturing quality standards and could be fraught with regulatory difficulties. Many intended herbal remedies, if subjected to full clinical trials and toxicity (as required by regulation), would not meet these standards.

In natural products a key issue is long-term planning and supply. If the product were to become a blockbuster, arrangements would have to be made for the community to benefit, such as through a trust fund. It is important to recognize traditional harvesters and

Bunn AE. 2007. Gastrointestinal Medicines from African Aloe: Baylabs (Pty) Ltd. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

Editors' Note: An earlier version of this case study was presented at the MIHR conference Using Intellectual Property for Improved Health in Developing Countries: An Evidence-Based Approach to Good Practice, Bellagio, Italy, June 14–18, 2004.

traditional plant users and their stake in bioprospecting. Baylabs is set to give the aloe tapping community a stake in the project.

The Baylabs example illustrates how the development of a technology can have positive commercial and positive moral outcomes. Through the creation of strategic alliances and partnerships, there can arise opportunities for securing and developing intellectual property for the benefit of underserved communities in both developed and developing countries.

TYPES OF AGREEMENTS

As part of the GI medicines from African aloe project, Baylabs has entered into the following types of agreements:

- exclusive patent license agreement
- exclusive supply agreement

IP RIGHTS DECISIONS AND IP MANAGEMENT

Baylabs has faced key areas of IP rights decision making and strategic IP management issues including:

- securing a strong IP portfolio through international filings, scientific proof-of-concept, and rigorous clinical trials
- securing ownership of intellectual property and outsourcing noncore functions

POLICY IMPLEMENTATION

The SA Medicines Control Council (MCC) is presently formulating policy on traditional and herbal medicines. Companies are therefore able to place over-the-counter products in the market without clinical trials. These may not make any medicinal claims. This enabled Baylabs to place four elementary products (aloe gel, a high fiber tablet, a laxative tablet, and an antiarthritic tablet containing aloin as the active ingredient) on the market and to secure income from their sale. These products had to be submitted to the traditional medicines registry at the MCC to enable continued manufacturing and sales.

EXTERNAL FACTORS THAT AFFECTED DECISION MAKING

A number of considerations influenced Baylabs' strategies and decision making. These include:

- burden of disease from ARD in developing countries
- burden of disease from IBS in developed countries
- commercial opportunity from IBS
- indigenous occurrence of *Aloe ferox*
- opportunity to exploit a by-product of the aloe tapping industry
- regulatory issues relating to aloe mixture
- opportunity to alleviate IDD

KEY LESSONS LEARNED

The following items represent key lessons from the Baylabs GI Medicines/Aloe project, which may be applicable to other companies that aim to utilize intellectual property:

- have a moral as well as a commercial reason for existence (improve living standards of aloe tappers and alleviation of ARD, IBS, and IDD)
- have a global commercial opportunity, which big pharma has been unable to effectively address (IBS—a US$15 billion annual industry)
- create and protect intellectual property (registers serious intent)
- create alliances and partnerships
- a startup can be successful operating as a virtual company and securing IP ownership
- choose partners with a shared value system
- have a good IP attorney (preferably in-house)—there are always issues! ■

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Lapdap™ Antimalarial Drug: GlaxoSmithKline, WHO-TDR, and the U.K. Department for International Development

Lapdap™ is a new combination of two off-patent malaria drugs. The U.K. Medicines and Healthcare Products Regulatory Agency approved the drug in 2003 for the treatment of malaria caused by *Plasmodium falciparum*, which kills one to two million people every year. The combination drug was developed in response to the growing resistance among patients to malaria drugs, with failure rates in Africa as high as 40 percent.

Lapdap came out of early research funded by the Wellcome Trust and was brought to market by a public-private partnership (PPP) involving GSK (GlaxoSmithKline), WHO-TDR (a WHO/UNDP/World Bank Special Program in Research and Training in Tropical Diseases), and the U.K. Department for International Development (DfID). This was done in collaboration with scientists from the University of Liverpool and the London School of Hygiene and Tropical Medicine, African researchers and clinicians, and the Wellcome Trust.

Under the terms of a funding partnership, GSK, WHO-TDR, and DfID each paid one-third of the development costs. Their agreement covered the ownership of nonpublished data and the establishment of a product-development team to continue development and obtain regulatory approval.

Early patent applications filed on the basic biological work underlying the combination of the two existing drugs were abandoned after filing because it was later found that the work had already been published in scientific literature and so there was 'prior art.' There are currently no patents protecting the Lapdap™ product in any country.

Lapdap™ was developed to be as inexpensive as possible, with a public sector target of less than US$0.30 per dose. It is currently sold only through private sector pharmacies, with the commercial sale price varying by country. The drug is available in South Africa, Nigeria, Kenya, and Ivory Coast.

Lapdap's™ role in public health is still being assessed; Phase IV studies are ongoing and the WHO has stated that after reviewing available clinical and preclinical data, it will identify strategies for optimal and safe use. Lapdap™ has potential for future public health initiatives; a collaborative agreement was signed in April 2004 between GSK, WHO-TDR, and MMV to develop a new fixed-dose artemisinin combination-therapy drug combining chlorproguanil, dapsone, and artesunate for treatment of malaria.

Successful collaboration to ensure that developing countries benefit from the fruits of intellectual property requires an integrated approach toward networking and capacity building, involving innovation, regulatory approval, market creation, licensing, and distribution.

The lack of formal health infrastructure in rural Africa, where there are few physicians and where the drug is sold over the counter, has led to great importance being attached to the packaging and distribution, as well as education to ensure proper dosage. The establishment before registration of a public health group, under the WHO's auspices, provided a useful forum for discussing how Lapdap™ would be accessed. This case highlights the need for consensus regarding

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MIHR/PIPRA. 2007. Lapdap Antimalarial Drug: GlaxoSmithKline, WHO-TDR, and the U.K. Department for International Development. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

Editors' Note: An earlier version of this case study was presented at the MIHR conference Using Intellectual Property for Improved Health in Developing Countries: An Evidence-Based Approach to Good Practice, Bellagio, Italy, June 14–18, 2004.

public sector use of the product between all parties involved in national malaria control.

This case study was considered 'IP neutral,' since the academic and public health mission was neither impeded nor driven by IP considerations. However, the Wellcome Trust, as part of its mission, recognizes the important role of industry and its investors (including non-commercial funders) in translating research innovations into new health products. It therefore encourages and supports the responsible use of IP rights to protect research findings where commercialization or further funding which could benefit from the existence of that underlying IP is necessary to achieve the greatest public benefit.

It could be argued that the lack of underlying intellectual property in this case, specifically patents, may have accelerated the research project and reduced transaction costs. On the other hand, the absence of patents may have slowed this process, particularly the attainment of Phase IV studies because a patent-driven time schedule did not drive the development process.

It was generally agreed, however, that intellectual property other than patents was generated in the form of regulatory dossiers (clinical trial data), know how, terms of codevelopment agreements, and trademarks. Recognizing the multiplicity of intellectual property can contribute to a more comprehensive understanding of the IP management aspects of product R&D, post-development, and manufacturing.

Lapdap's™ pursuit of WHO endorsement raised the broader policy issue of the global health body's role as a certificatory of treatment regimes. WHO approval is a vital step in products reaching developing countries and gaining public sector acceptance. However, responsibility within a PPP for securing such endorsement is not always clear.

Regulatory endorsement is but one aspect of product sustainability. Royalty streams should be examined for how their use and management can contribute to product support. Although often treated as undesirable additional costs, the generation of royalties on public sector sales is an effective IP management tool for keeping a product on the market.

The involvement of universities in this public health initiative drew attention to the role of university technology transfer offices (TTOs). It appears that TTOs are frequently given competing missions by their institutions, with no clear priority as to whether making money or delivering applications of research regardless of returns is the most important goal. Declining revenue of universities has pressured cash-strapped TTOs to increase their contribution, compelling them to turn to intellectual property. Although exploiting university research is a legitimate goal, it may be short-sighted to focus solely on patents; the transfer of know-how and trade secrets is just as important, and an overemphasis on revenue generation using IP rights may limit the potential of certain research outcomes.

In attracting commercial interest, TTOs must be mindful of overvalued patents and overestimated royalties, and must know how to manage hurdles and prevent unreal expectations. Alongside the need for flexibility in negotiations, education about technology management is required.

The challenge therefore is to use PPPs as an effective means of bringing drugs to the poor by drawing on the expertise and synergies between sectors. These partnerships afford the opportunity to segment the market in a way in which the public body can benefit from having an exclusive license for its stakeholders while satisfying commercial partners.

TYPES OF AGREEMENTS

An agreement was signed relating to establishment of the product-development team and ownership of nonpublished data. Under the funding partnership between GSK, WHO-TDR, and the U.K. DfID, each partner contributed one-third of the development costs.

PATENT AND IP RIGHTS DECISIONS

Early patent applications were filed between 1994 and 1996 by GSK (then SmithKline Beecham) on the basic biological work underlying the combination of the two existing drugs, with Dr. Bill Watkins (University of Liverpool & Wellcome Trust Research Laboratories, Kenya) as named inventor. These applications were later abandoned, because after filing it became clear that the combination had already been published in the literature and therefore was no longer novel. There are therefore no patents protecting the Lapdap™ product in any country.

POLICY IMPLEMENTATION

Lapdap™ at present is being sold only through the private sector (pharmacies). WHO does not currently recommend the use of chlorproguanil-dapsone alone as an option for national treatment policy in countries where malaria is endemic. The role of the drug in public health is still being assessed—Phase IV studies are ongoing, and pharmacovigilance activities in specific patient groups are planned. WHO has stated that after reviewing available clinical and preclinical data, it will shortly identify strategies for the optimal and safe use of Lapdap™ in malaria-endemic countries.

Because of Lapdap's™ reported efficacy, relatively short half-life, and low production cost, it has potential for future public health use in combination with an artemisinin compound. In April 2004, a collaborative agreement was signed between GSK, WHO-TDR, and MMV to develop a new fixed-dose artemisinin combination-therapy drug combining chlorproguanil, dapsone, and artesunate for treatment of malaria.

EXTERNAL FACTORS THAT AFFECTED DECISION MAKING

In the case of Lapdap™, where IP considerations did not drive the later development of the project, some external factors of relevance were:

- nature of the end market for Lapdap™ (poor countries in Africa)
- multiparty cooperation and synergy

KEY LESSONS AND HEALTH-ACCESS ISSUES

The following lessons were learned during development of the Lapdap™ drug and subsequent distribution:

- Pharmaceutical industry expertise in clinical trials, the regulatory process, and marketing are necessary to accelerate product development.
- Establishment of a public health group under WHO auspices *in advance of registration* was a useful forum for discussing how the product would be accessed.
- Consensus on the use of the product in Africa is necessary at the country level between parties involved in malaria control. ■

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Cyclofem® Contraceptive: Upjohn, WHO, and the Concept Foundation

The case study of the development and distribution of Cyclofem® contraceptive as a project of Upjohn and the World Health Organization (WHO) is an example of innovative intellectual property (IP) management in which a collaboration between a public sector institution and a private pharmaceutical company led to the establishment of a new nonprofit organization that brought the product to developing country markets. The venture described in this case study was also new type of undertaking for WHO.

Upjohn pharmaceutical company developed the once-a-month injectable contraceptive Cyclofem®. Despite successful Phase III trials undertaken jointly by WHO and Upjohn, the drug company decided there was an insufficient market for the contraceptive and donated the clinical trial data to WHO. When no U.S. or European commercial partner could be found to take the product forward, WHO invited the nonprofit organization PATH (to which it licensed the clinical data rights) to come up with a viable solution.

PATH proposed establishing a new nonprofit organization, the Concept Foundation, which would focus on developing countries. Intellectual property and know-how was transferred via PATH to the Foundation, which licensed developing country producers on an exclusive basis in defined private sector markets and on a nonexclusive basis for public sector markets to ensure competition. A royalty stream of 4% was paid to the Foundation to support continued production and distribution. Manufacturers were expected to meet national and international (current good manufacturing practices, or cGMP) regulations. Milestones were an important part of the package, and were linked to territories, regulatory matters, and market penetration.

Production was established in Mexico and Indonesia, supplying private and public sectors with an affordable quality product that had been dropped by its developer. This was the first pharmaceutical product to result from successful WHO product R&D. The Concept Foundation is now self-sufficient and provides valuable technical assistance and introduction support, alongside economic development and technology transfer.

EXTERNAL FACTORS THAT AFFECTED DECISION MAKING

Establishing a nonprofit organization in a developing country was an appropriate option because WHO could not own, manufacture, distribute, or manage the product. PATH did not want to jeopardize its own neutral role in improving public health. Another consideration was liability. PATH, with assets in the United States, could not afford to risk its well being. Ultimately, after much discussion it was realized that the liability risk should rest in a jurisdiction that reflected the environments in which the product would be used.

The Foundation's aim was to on-license to producers and distributors in developing countries. If a government wanted to buy the product, it could go to any of the manufacturers and ask for a bid on cost prices. As time passed, the Concept Foundation identified the need to update the regulatory dossier for Cyclofem®. It carried out this updating and made the new dossiers available to current and prospective licensees.

Mahoney R. 2007. Cyclofem Contraceptive: Upjohn, WHO, and the Concept Foundation. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

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LESSONS LEARNED AND HEALTH-ACCESS ISSUES

This case study is an example of innovative IP management where collaboration between WHO and Upjohn led to the establishment of a new nonprofit organization with the purpose of bringing the Cyclofem® contraceptive to developing country markets. This case demonstrates that clinical trial data can be important IP that can help ensure availability of products in developing countries. Putting it simply, without clinical trial data, the product can not be marketed; thus the data are of great value. The goal of the Concept Foundation and similar ventures is to ensure availability of products to the poorest of the poor. It is not enough to ensure that the private market helps public sector distribution. As this case study shows, investing time in updating a dossier to meet the requirements of other countries and therefore helping to encourage producers to go into markets that have not been served is important. Similarly, having solid and enforceable milestones is not an indication of lack of trust; it is rather being serious about business and wanting to succeed. ■

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Improved Production of a Natural Product Treatment for Malaria: OneWorld Health, Amyris, and the University of California at Berkeley

In December 2004 the Bill and Melinda Gates Foundation[1] awarded a five-year product development grant to the Institute for OneWorld Health (iOWH),[2] a nonprofit pharmaceutical company, to create a unique three-way partnership between iOWH, a university (University of California at Berkeley),[3] and a for-profit company (Amyris Biotechnologies, Inc.).[4] The goal of this project[5] is to significantly reduce the cost of artemisinin, a key precursor in the production of Artemisinin Combination Therapies (ACT), through synthetic biology, industrial fermentation, and chemical synthesis. Artemisinin is chemically converted to one of several derivatives and then combined with other drugs to make an ACT for the treatment of malaria.

Malaria is a parasitic blood disease that inflicts as many as 500 million people annually. About 1.5 million people die each year from the infection, primarily children in Africa and Asia. More than half of the deaths occur among the poorest 20 percent of the world's population. Studies in Vietnam have shown that the botanically derived medicine, artemisinin derivatives, can reduce deaths from the illness by 97 percent. However, the current cost of a three-day course of drugs containing artemisinin is US$2.40, which places it out of reach for people in many nations where the disease is most prevalent. Reducing the price would make the treatment more widely accessible.

Artemisinin is currently extracted from the wormwood plant, which is supplied by farmers in Vietnam and China (and more recently, Africa). Seasonality and availability of the plant contribute to the high price of the drug. The Gates-funded project hopes to eliminate the need for plant extraction by utilizing a platform technology of synthetic biology developed by Dr. Jay Keasling at the University of California (UC), Berkeley.[6] The goal is to lower the cost of artemisinin-containing drugs ten-fold by producing a consistent, reliable, high-quality supply of artemisinin in microbes.

The US$42.6 million grant was divided among the three partners: US$8 million to UC Berkeley for continued basic research, US$12 million to Amyris for applied research on the fermentation and chemical processes, and US$22.6 million to iOWH to perform the required regulatory work and lead the implementation of the product development strategy for the developing world. UC Berkeley's role focuses on the engineering of drug-precursor-producing microbe. Amyris' efforts span engineering of the production microbe to optimizing the semisynthesis of the drug through fermentation and novel downstream synthetic chemistry. The role of iOWH includes developing a commercialization strategy based on a thorough understanding of the worldwide regulatory requirements and an analysis of the current ACT manufacturing supply-chain and distribution models. This one grant enables activities in all three areas of development and creates an integrated team, each of the partners applying its expertise to streamline translation from bench to bedside.

MIHR/PIPRA. 2007. Improved Production of a Natural Product Treatment for Malaria: OneWorld Health, Amyris, and the University of California at Berkeley. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

Editors' Note: This case study was prepared by MIHR members of the Technology Managers for Global Health (TMGH), a special interest group of the Association of University Technology Managers (AUTM) (see www.tmgh.org) and adapted for this *Executive Guide*. The original version was published as part of a collection of case studies: MIHR/TMGH. 2007. *Academic Licensing to Global Health Product Development Partnerships* (ed. U Balakrishnan). MIHR: Oxford, U.K.

To ensure accessibility and affordability, the partners have committed to reduced returns in the malaria field. UC Berkeley has issued a royalty-free license to iOWH and shall grant royalty free licenses to Amyris for IP that is developed during the collaboration for the treatment of malaria in the developing world with the goal of significantly reducing the price of ACT products, and reducing the use of artemisinin monotherapies per the World Health Organization's recommendations for uncomplicated malaria.

This arrangement has benefits for all the parties. The university benefits from the research funding as well as from any royalties that may be realized on profit earned from sales by Amyris in areas outside of malaria in the developing world. As a for-profit company, Amyris can apply the innovations developed for the artemisinin project to other projects that rely on the same platform technology. As a nonprofit pharmaceutical company, iOWH is able to make malaria treatments more affordable for people in the developing world.

PARTNERS

Partners in this project are:

- from academia, the University of California, Berkeley
- the nonprofit pharmaceutical company Institute for OneWorld Health (iOWH)
- the for-profit pharmaceutical company Amyris Biotechnologies, Inc.

The Bill and Melinda Gates Foundation provided the funding for the project.

THE TECHNOLOGY

The preferred and most effective treatments for malaria today are artemisinin-based combination therapies (ACT). Artemisinin, a complex natural product known as an herbal remedy for thousands of years, is typically derived from the wormwood plant. Plant sources of the chemical are variable and crop shortages contribute to increased cost. Chemical synthesis of the molecule would require 30 to 40 steps and is therefore impractical on a commercial scale.

Dr. Jay Keasling, a UC Berkeley professor of chemical engineering, developed a process of "synthetic biology" to produce an artemisinin precursor through a multistep process in bacteria.[7] The precursor can then be chemically converted to artemisinin through synthetic chemistry developed at Amyris. Producing the drug precursor in microbes would lead to a more consistent and reliable supply and therefore reduce the cost of production.

The synthetic biology platform may also be used to produce other drugs, nutraceuticals, and flavors and fragrances.

PROGRESS, CURRENT STATUS, AND GOALS

During the five-year granting period, which began in 2005, the partners would carry out the following activities shown in Figure 1.

UC Berkeley researchers are working to identify the genes involved in the artemisinic acid biosynthetic pathway in the wormwood plant, *Artemisia annua*. Using their expertise in synthetic biology, they are inserting this biosynthetic pathway into microbes to create hosts that manufacture this direct precursor to artemisinin. Optimizing artemisinic acid production in these host cells is being achieved through cutting-edge techniques in metabolic engineering, in collaboration with scientists at Amyris Biotechnologies.

Amyris Biotechnologies is collaborating with the Center for Synthetic Biology to build a better microbe. Amyris will optimize the microbial strain developed with UC Berkeley for commercial production. In addition, Amyris will develop a fermentation and purification process for the precursor. Simultaneously, Amyris is developing a scaleable, inexpensive chemical process to convert the precursor to artemisinin.

OneWorld Health is the product development lead and has responsibility for directing this collaborative effort. In addition, the organization is leading the project's regulatory and commercialization strategies and is conducting a risk-benefit analysis surrounding the use of artemisinin derivatives in malaria-endemic regions.

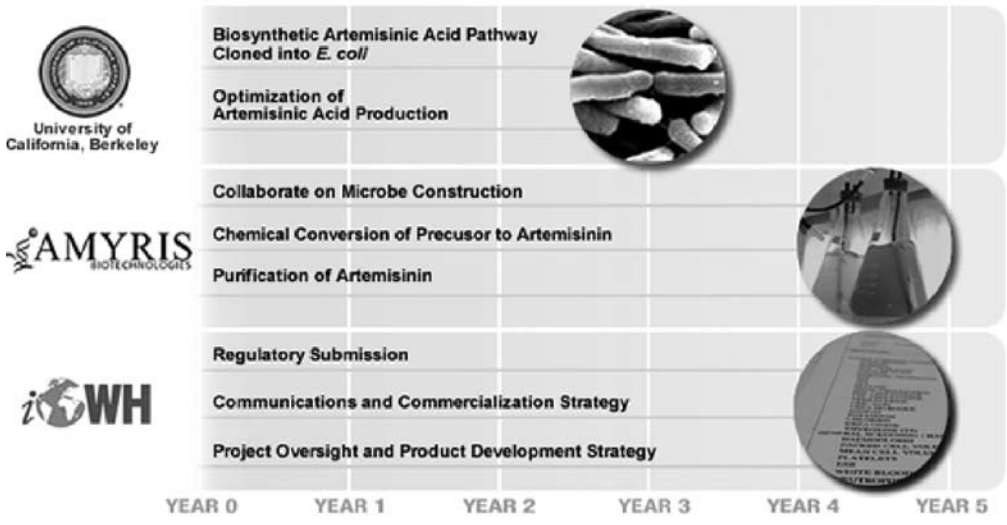
DEALS

Agreements between the partners include the following:

License Grants:

- The arrangement is governed by a three-party collaboration agreement and two license agreements (from UC Berkeley to each of Amyris and iOWH).
- UC Berkeley granted iOWH a royalty-free license for the manufacture of artemisinin-based malaria treatments used in the developing world. UC Berkeley further shall grant royalty-free licenses to iOWH for IP developed under the three-party collaboration agreement for use in manufacturing artemisinin-based malaria treatments used in the developing world. OneWorld Health is to establish partnerships for ACT manufacture and distribution.
- UC Berkeley granted Amyris licenses to develop the manufacturing process for the developing-world malaria market. Amyris also has licenses for the developed-world malaria market, nonmalaria indications of artemisinin, and alternative uses of the platform worldwide. UC Berkeley further shall grant similar licenses to Amyris for IP

Figure 1: Activities of Project Partners
(to be carried out by the end of the grant period)



developed under the three-part collaboration agreement.
- Amyris shall grant iOWH a royalty-free license for IP developed under the three-part collaboration agreement for the manufacture of artemisinin-based malaria treatments used in the developing world.

Royalties:
- The license from UC Berkeley to iOWH is royalty free.
- The license from UC Berkeley to Amyris is royalty free for the developing-world malaria market (development for iOWH) and is royalty bearing for the developed world and nonmalaria indications in the developing world.

Patents:
- Patent costs for UC Berkeley's pre-existing patents are shared between iOWH and Amyris.
- UC Berkeley patents on IP arising from the collaborative research may be filed by UC Berkeley and licensed to iOWH and/or Amyris under the pre-arranged terms mentioned above. Costs are shared by the licensee on a pro rata basis. UC Berkeley has no obligation to file an application if it does not have a commitment by a licensee to pay patent costs.
- Patents that are the sole property of Amyris and/or iOWH may be filed by Amyris and/or iOWH, as the case may be, at their own expense.
- Logistics of filing and payment of costs on jointly owned IP will be negotiated in good faith by the joint owners when such joint IP arises. If the joint owners cannot agree and if iOWH has an ownership interest in a joint property, then iOWH may file and prosecute on behalf of the owners at its own expense.

Other:
- Amyris, as UC spinout company, is seeking venture funding to leverage applications in other markets.
- Using the process developed by Amyris and UC Berkeley, iOWH is to establish partnerships for ACT manufacture and distribution
- Similar licenses to all relevant third-party intellectual property will be obtained by iOWH as the need arises. ■

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INSTITUTE FOR ONEWORLD HEALTH, *Katharine Woo, Director, Scientific Affairs, 50 California Street, Ste. 500, San Francisco, CA 94111, U.S.A. kwoo@oneworldhealth.org*

AMYRIS BIOTECHNOLOGIES, INC., *Neil Renninger, Vice President–Development, 5980 Horton Street, Ste. 450, Emeryville, CA 94608, U.S.A. renninger@amyrisbiotech.com*

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1 Bill and Melinda Gates Foundation. www. gates foundation.org.

2 Institute for OneWorld Health. www.oneworldhealth.org/.

3 Office of Intellectual Property and Industrial Research, UC Berkeley. ipira.berkeley.edu/index.php.

4 Amyris Biotechnologies, Inc. www.amyrisbiotech.com.

5 The Artemisinin Project. www.artemisininproject.org.

6 Keasling Laboratory, UC Berkeley. www.cchem.berkeley.edu/%7Ejdkgrp/.

7 Martin VJ, DJ Pitera, ST Withers, JD Newman and JD Keasling. Engineering a Mevalonate Pathway in *Escherichia Coli* for Production of Terpenoids. *Nature Biotechnology*. 21 July 2003. (7): 796–802.

Nontoxic Drug Therapy for Chagas' Disease and Malaria: University of Washington and Yale University

Some of the world's most intractable diseases are predominantly in the developing world. These illnesses are known as neglected diseases because they receive little attention from the medical community and the pharmaceutical industry, even though they have a significant impact on vulnerable populations. One of these neglected killers is Chagas' disease.

According to the World Health Organization, Chagas' disease is an insect-borne, parasitic illness that infects and kills millions of people every year. Chagas' disease is endemic in 21 Latin American countries and is a major cause of heart failure in the region. Caused by the parasite *Trypanasoma cruzi*, Chagas' disease is most often transmitted by an insect known as the kissing bug, which tends to feed on people's faces. Humans, as well as wild and domestic animals, carry the parasite, and insects infected with *T. cruzi* frequently live in the thatched walls and roofs of homes, making it especially challenging to eradicate.

Controlling the disease is difficult, costly, and risky: it depends largely on treating homes in affected areas with residual insecticides and, in general, improving housing by replacing traditional thatched-roof dwellings with more modern, plastered walls and metal roofs. Management of the illness now involves blood screening to prevent transmission through transfusion. Some drug treatments are available as well.

COLLABORATING TO FIND A TREATMENT

But the standard drug treatments for Chagas' disease leave much to be desired. Most are aimed at fighting the infection, which spreads inside the heart and gastrointestinal tract of the victim. Drugs are difficult to administer and highly toxic, leading to severe side effects in many patients. And no existing medicines have consistently cured patients, according to a report from the Institute for OneWorld Health, a nonprofit pharmaceutical company the goal of which is to develop affordable treatments for neglected infectious diseases around the world.

A collaborative research effort among scientists at the University of Washington and Yale University recently brought forth a nontoxic drug therapy for Chagas' disease. The team included Andy Hamilton and Junko Ohkanda, both chemists at Yale, and Fred Buckner and Wesley Van Voorhis, infectious disease experts, and Michael Gelb and Kohei Yokoyama, chemists, at University of Washington.

"It was a wonderful collaboration between organic chemists and parasite biologists that came about through reading the literature and recognizing potential connections," said principal investigator Hamilton, who has since become a provost at Yale. "Big problems nearly always involve collaborative solutions because no one person or institution can have all the answers."

Buckner, of the University of Washington Medical School, agreed. He has worked for years with a group of chemists led by Gelb to develop compounds to treat infectious diseases caused by protozoan pathogens.

"They would make the compounds and we would test them against the parasites to see if they would do

AUTM. 2007. Nontoxic Drug Therapy for Chagas' Disease and Malaria: University of Washington and Yale University. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

Editors' Note: We are most grateful to the Association of University Technology Managers (AUTM) for having allowed us to adapt this case study for inclusion in this *Executive Guide*. The original was published by AUTM. 2006. *Technology Transfer Works: 100 Cases from Research to Realization* (Reports from the Field). Association of University Technology Managers, Northbrook, IL. www.betterworldproject.net.

anything," Buckner said. "Some turned out to be active against targets that were different than what we designed them to do, but we determined the mechanism of action and showed them to be active in an animal model."

APPROACHING THE PROBLEM FROM DIFFERENT ANGLES

The original patent application described "compounds and methods for treating infections caused by bacterial protozoal and fungal agents," said Aline Flower, of University of Washington TechTransfer Invention Licensing.

When asked about the potential application of the compound, Hamilton said, "we developed, in collaboration with parasitologists, compounds that target the Chagas' disease agent in animal models, and we are seeing some very encouraging data."

Buckner and his colleagues had made inroads targeting these diseases, working toward cures or vaccines. "We had discovered that protozoan parasites contain the enzyme protein farnesyltransferase," said Buckner. "This same enzyme plays an important role in cancer cells, which meant a lot of research laboratories were developing drugs against it. We were working on the hypothesis that protein farnesyltransferase inhibitors might work against parasites."

In the meantime, Hamilton and Ohkanda were working on a similar problem from another angle. "This was the result of many years of fundamental research in trying to get a novel molecular structure to target a specific enzyme," Hamilton said. "It's a question of how one synthetic molecule could recognize a biological molecule in a process called molecular recognition."

According to Hamilton, the two universities and the nonprofit pharmaceutical company developed an integrated model for drug development, perhaps just as important as the chemical compound the researchers had discovered. "We hope, as we make progress in the pre-clinical stage, OneWorld Health will help us pull together the necessary funding to allow the clinical and preclinical development of these compounds," said Hamilton.

The Yale Office of Cooperative Research senior licensing associate Alan Carr explained that an interinstitutional agreement between the University of Washington and Yale University enabled the institutions to structure a deal with OneWorld Health to license the compound affordably.

Like the drug compound, the model for drug development, borne of innovative university technology transfer, could well have a lasting impact on people around the world. ■

Diagnostic Tests for Cervical Cancer: PATH

The public sector institution PATH aims to improve global health by advancing technologies, strengthening systems, and encouraging healthy behaviors through effective collaborations with the private sector. PATH tries to reduce risks for a commercial company developing products for resource-poor countries by identifying gaps in the market that existing technology can fill, demonstrating value, and partnering in development and sustainable supply. In addition, PATH adapts products to different markets, provides training, and engages in advocacy with WHO and other public bodies. PATH is both a recipient and a provider of funding.

As a nonprofit organization that creates and manages intellectual property in house, PATH recognizes that working with private companies requires sensitivity to and awareness of commercial incentives. PATH believes that intellectual property is just one element of the economic environment of the technology. Successful collaborations with private sector companies impact positively the availability, accessibility and affordability of products in public sector health programs in developing countries.

During product development and distribution, PATH works to change behavior and to open or improve communication. It worked with India's Ministry of Health to launch a hepatitis B vaccine on a project that involved community education and communication in preparation for the vaccination program. The program's success has ensured national expansion of the program.

Diagnostics is a large field with a number of disparate groupings of intellectual property generated by scientists around the world; it is common for multiple parties to hold key pieces of intellectual property. PATH routinely conducts market and industry feasibility studies to determine the type of industry partner to pursue, to determine which is best positioned to take PATH into the target segments it is interested in, and to identify IP issues. The public sector needs to recognize that securing the necessary IP rights for diagnostic products is imperative before moving ahead with development and commercialization.

Procurement in diagnostics is not as centralized as other public health products, such as vaccines and drugs. This makes it more difficult to plan for the global public health sector. Marketing is generally on a country-by-country basis, unlike family planning products, for example, that have regional or global distribution agencies for the public sector markets.

THE CERVICAL CANCER DIAGNOSTIC TEST PROJECT

PATH is engaged in ongoing work with industry partners to develop rapid diagnostic tests for cervical cancer for use in developing countries. In addition, two major institutes, in India and China, are screening 30,000 women for cervical cancer and will then conduct the clinical trials to validate the efficacy of these these simple and inexpensive tests. In addition, this work will generate useful information on viruses that have not yet been examined in detail in these countries.

Under the terms of the R&D agreements between PATH and the industry parnters, PATH's obligations include funding a portion of the industry partner's direct R&D costs, conducting market and industry assessments, developing an evaluation framework

Brooke S. 2007. Diagnostic Tests for Cervical Cancer: PATH. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Krattiger A, RT Mahoney, L Nelsen et al.). MIHR (Oxford, UK), PIPRA (Davis, USA), Oswaldo Cruz Foundation (Fiocruz, Rio de Janeiro, Brazil), and *bio*Developments-International Institute (Ithaca, USA). Available online at www.ipHandbook.org.

Editors' Note: An earlier version of this case study was presented at the MIHR conference Using Intellectual Property for Improved Health in Developing Countries: An Evidence-Based Approach to Good Practice, Bellagio, Italy, June 14–18, 2004.

for public-health use of the new test, and conducting multicountry clinical evaluation of the new tests' performance for registration purposes. The industry partner is responsible for development of the products, management of the intellectual property (patenting costs and prosecuting infringement), manufacture and supply for clinical evaluations, and finalizing the product for registration and commercial supply.

PATH retains ownership of specimens, but data are either jointly or individually owned. A product-development committee was formed, and PATH only provides funding sufficient to reach the next agreed-upon milestone. During the R&D phase PATH can terminate, without cost, at key milestones, although industry partners terminate at a cost.

The commercialization period of the agreement runs for ten years from the first sale of a registered product. Both industry partners are required to provide preferential public sector pricing. If these specific products are sold in developed countries, PATH will earn a royalty, however PATH has forgone all royalties on developing country sales. Termination clauses covering one industry partner involve repayment of PATH's direct funding and the transfer of distribution and/or manufacturing to a third party; the other industry partner is only required to grant PATH a nonexclusive license to the product and underlying reagent.

Both companies are working on products that are different from those they will launch in the United States and Europe. Developing a product with PATH could potentially jeopardize products in other developed countries; it is therefore critical for participating industry partners to be able to segment markets.

PATH's success in being able to attract industry partners to collaborate in its effort to develop a diagnostic test for cervical cancer is an example of creating an overarching cervical cancer prevention initiative that made collaboration attractive and worthwhile—in this case, a program of cervical cancer screening including clinical work, advocacy, and policy issues. PATH does not expect to be providing the product in the future; its industry partners have the intellectual property, are developing it, and are responsible for its management.

This case study illustrates that intellectual property and technology transfer are not enough to create a broad and lasting health impact. PATH believes it is possible to attract top-tier industry partners, especially if there is a comprehensive public health initiative and not just a technology development project. Issues to consider in developing a public health initiative include determining the value of know-how, deciding whether to grant an exclusive or a nonexclusive license, dealing with key reagent IP holders, and influencing the final product price.

TYPES OF AGREEMENTS

Over the years of diagnostic-test development and commercialization, PATH has:

- in-licensed key diagnostic reagents to PATH from academic, government, and private company sources
- out-licensed diagnostic test and reagent production know-how from PATH to diagnostic manufacturers
- some with geographically defined exclusive territories
- some on global nonexclusive basis
- materials transfer agreements
- supply agreements
- confidentiality agreements
- codevelopment agreements

IP RIGHTS DECISIONS AND IP MANAGEMENT

PATH has faced key areas of IP rights decision making and strategic IP management issues including:

- managing freedom to practice risks associated with other parties' intellectual property for certain diagnostic platforms and reagents
- determining the value of know-how developed for efficient production of certain diagnostic reagents even when the know-how was not patentable
- determining whether to provide downstream licensees with a greater or lesser level of market exclusivity, or whether to license only on a nonexclusive basis
- dealing with holders of key intellectual property involving particular antigens or antibodies necessary to develop particular diagnostic tests
- deciding whether to patent incremental in-house innovations in the face of uncertain demand and usefulness
- considering how to achieve or at least positively influence final product pricing and access when third-party diagnostics importers/distributors (not the PATH-licensed diagnostic manufacturer) will be the party making the sales transaction to a developing country government

POLICY IMPLEMENTATION

On an overall policy basis PATH works under its Guiding Principles for Private Sector Collaboration, endorsed by the board of directors, which is most often relevant to PATH's intellectual property and licensing activities with diagnostics. To conform to key elements of these guiding principles, a license (and overall collaboration) between PATH and a commercial diagnostics producer must:

- exhibit a clear link to PATH's mission by improving the availability, accessibility, and affordability of important products for public health programs in developing countries
- recognize that the commercial partner must achieve commercial benefit to ensure their sustainable commitment to supplying the technology
- provide a clear definition of the roles, responsibilities, and expectations of both PATH and the commercial producer
- balance PATH's need for transparent collaboration with the commercial producer's need to protect proprietary information
- reflect a rigorous process of due diligence on PATH's part before executing an agreement

The IP elements, working relationships, and technology economics of every project or program can vary from one extreme to the other. Because of this, PATH has found it counterproductive, for the most part, to make broad institutional policies about specific individual elements of complex intellectual property and collaborative development agreements. For example, there is no PATH-wide policy that states "all licensed manufacturers must sell to public sector at cost plus 10%." In some cases that structure might be appropriate, in others it might prevent the technology from ever coming to market. In cases where PATH has developed significant technology that may have value in developed country markets, PATH maintains the flexibility to negotiate for a royalty on developed country market sales. PATH forgoes royalties on sales of licensed technologies for developing country public sector use.

EXTERNAL FACTORS THAT AFFECTED DECISION MAKING

The diagnostics arena has a number of characteristics that have historically influenced PATH's strategies and decision making. These include:

- extremely competitive nature of global diagnostic industry
- relative ease of entry into global diagnostics industry
- proprietary control (whether through formal patents or, simply, sole possession of key clones) of key diagnostic reagents by individual companies or institutions
- multilevel manufacturing and distribution channels typical for diagnostic products
- distributed nature of global public sector procurement of diagnostic reagents—no single, huge, vertical procurement mechanism as exists for vaccines and, to a degree, family planning products

KEY LESSONS LEARNED AND HEALTH ACCESS ISSUES

The proprietary control of a single key diagnostic test reagent can give some parties control and power seemingly disproportionate to their contributions to an overall diagnostic test development project. It is critical to have either IP access and/or reagent supply agreements in place early in the product-development cycle, so that access uncertainty is reduced and cost of access is fully understood. The private sector understands this well, while we (at PATH and in the broader public sector) have not always done our homework in this area.

Noncommercial development and/or stewardship of diagnostic platform intellectual property or key component intellectual property can create a positive impact. For example, PATH enhanced the local production of key rapid-test raw materials (nitrocellulose filters and colloidal gold signal reagents) in India, which created an impact beyond the transfer of technology for individual tests to specific companies. Materials suppliers are now serving additional emerging diagnostic producers.

Intellectual property and technology transfer alone are rarely enough to create a lasting impact on public health. We are all working on solutions to health problems that have fundamentally less promise as a "business opportunity," from a commercial manufacturer's standpoint, than do other health problems. To make a new diagnostic test that will deliver profit to the manufacturer and be beneficial and accessible to patients, there needs to be policy change, advocacy work, and extensive evaluations. The diagnostic manufacturer will rarely fund these types of activities, especially for price-sensitive public health markets, so it is critical to involve others who will undertake this work. Intellectual property and technology transfer are certainly important. However, for maximum lasting health impact they should be managed as components of a comprehensive public health initiative rather than as independent activities. ■

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