

Academic Licensing to Global Health Product Development Partnerships



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With the assistance of several volunteers involved in the work of the Technology Managers for Global Health (TMGH), a special interest group within the Association of University Technology Managers, this booklet project was primarily managed by Usha R. Balakrishnan, founder of TMGH and Executive Director of MIHR-USA.

Nalini Anand (NIH Fogarty International Center) and Sandra Shotwell and Lisa Primiano (Alta Biomedical Group) contributed new content for this booklet, in addition to the large sections that were derived from meeting reports prepared by Tari Suprpto (Rockefeller University) and Karen Blöchlinger (Seattle Biomedical Research Institute). Rachelle Harris (MIHR) and Henry Lowendorf (Yale University) provided useful comments to early drafts of the booklet. This booklet would not have been possible without the input of officials from several global product development partnerships, and the enthusiastic participation of several colleagues at various conference sessions organized by TMGH in 2005-2006. The names of all session organizers and speakers are listed in the back cover of this booklet.

Foreword

Promotion of global health equity can occur by academic technology managers teaming up creatively with other professionals, organizations, and sectors to foster health product development that will be appropriate, affordable, and ultimately accessible to the global poor. We are pleased to share with you a booklet that is intended to foster such relationships and alliances. *Academic Licensing to Global Health Product Development Partnerships* is a sequel to the booklet titled *Global Health Partnerships and Academic Technology Transfer* produced and distributed in 2005. It expands the topic with descriptions of successful partnerships that are improving global health, sharing details of how they work in the hopes that others can build on their example.

Global health is a challenging and complex environment, particularly with regard to intellectual property management and alliance-building. Viewed as the “next frontier” for the technology transfer profession, global health is proving to be a dynamic landscape of potential partners, licensees, and funding sources. Technology managers can construct creative partnerships and encourage sharing and leveraging of resources to improve the lives of the poor in developing countries. They can facilitate R&D and technology transfer in global health areas in economically viable ways, working with new partners to further develop technologies of particular relevance to developing countries. In this context, a group of global nonprofit organizations that are targeting “neglected disease” treatments are valuable partners to university technology managers. This booklet focuses on these public-private, product-development partnerships (PDPs) and their effective role in developing new drugs, vaccines, and diagnostics.

The content for this booklet builds on a series of conference sessions held in 2005-2006. It is primarily directed at technology licensing professionals wishing to:

- (a) Manage new inventions generated from research that may lead to treatments for neglected diseases and other diseases that disproportionately affect the poor in developing countries, and
- (b) Ensure access to, and promote further development and/or utilization of, such technologies for the benefit of the poorer populations in developing countries.

Several professionals came together to prepare this booklet. They are all interested in the work of the Technology Managers for Global Health (TMGH), a special interest group within the Association of University Technology Managers. We are grateful to the Rockefeller Foundation and the Ewing Marion Kauffman Foundation for providing financial support for efforts undertaken by the MIHR-TMGH partnership. We hope that this booklet is useful to you and can be included within educational materials and in training programs. We encourage you to share your feedback about this booklet. Send your comments to rachelle.harris@mihhr.org.



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The Global Forum for Health Research (www.globalforumhealth.org) recently published a two-volume report titled “Global Forum Update on Research for Health 2005.” As noted in this publication, the impressive advances in health by the world’s population in the last century have been very unevenly distributed. For example, children under the age of five accounted for roughly 20% of the 57 million deaths in 2002, and 97% of these children lived in low- and middle-income countries. According to the report, this kind of inequality in health is accompanied by a significant imbalance in the focus of health research worldwide. Most research funding has been applied towards the needs of populations in high-income countries. Many inventions, especially in the new age of including biotechnology, have great potential to improve and save lives, but they need to be applied to the problems of poor populations around the globe as well as more developed countries. This is particularly true for diseases that affect primarily developing countries, such as HIV/AIDS and tuberculosis, as well as diseases that occur almost exclusively in developing countries, such as malaria, Chagas’ disease, and leishmaniasis. The impact of these diseases on global health, stability and economic development should not be underestimated. By reducing growth, destroying human capital, discouraging investment and eroding productivity, HIV/AIDS and other diseases prevalent in the developing world seriously undermine countries’ efforts to develop their societies and rise out of poverty. Without a significant research effort, there will be very little innovation to develop effective interventions for these diseases, including better vaccines, drugs, diagnostics, and medical devices. Even with increased research effort, creative licensing approaches will need to be employed to manage research outcomes since these innovations do not carry the promise of high financial returns.



To be sure, there are numerous factors that contribute to global health disparities, such as the lack of food, clean water, sanitation and the need for better public health infrastructure, trained health workers to deliver healthcare services, disease surveillance, and policy formulations. However, new and effective health technologies are critical to improving health around the world, and increased parity in research and development (R&D) related to diseases afflicting the poor is essential in generating such interventions.

Modern research universities play an increasingly important role in assuring research, development, access, and affordability of health product innovations for poorer populations in developing countries. Academic technology managers play a key “gatekeeping” function in fostering new partnerships and facilitating timely interactions within the continuum of scientific R&D, discovery, and product development to improve the lives of the poor. Invention evaluation, patent filing decisions, and other licensing tactics and negotiating strategies employed by technology managers can greatly impact the translation of university-based discoveries into products that benefit society.

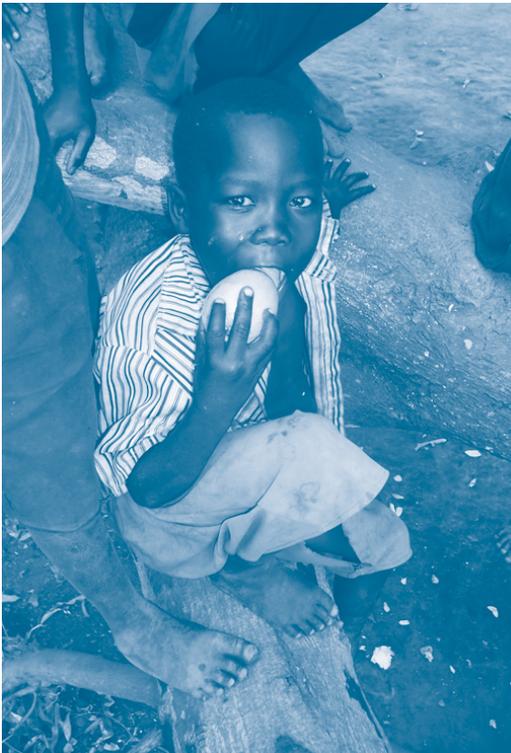
Most university technology transfer offices operate fairly autonomously, allowing for creativity in licensing for global health purposes. The key issues include practical mechanisms and partnering strategies that (a) enhance both the economic and social impact of university innovations; (b) extend these impacts to broader global settings; and (c) ensure fair access for the world’s poor within an evolving framework of licensing practices, legal concerns, business opportunity, and time constraints. To expand opportunities for technology managers to impact global health, several university-based technology managers came together in 2003 to form the Technology Managers for Global Health (TMGH) as a special interest group within the Association of University Technology Managers (AUTM). This booklet is one of the tools to expand those opportunities. TMGH efforts have brought a new appreciation for what could be accomplished via collegial sharing among technology managers: a deeper caring about science, research, and its impact both in terms of economic and social good around our world.

Working with Global Health Product Development Partnerships

The formidable challenge of developing health products for neglected diseases in the absence of much profit opportunity has led to the emergence of public-private product development partnerships, so-called PDPs, supported by philanthropic organizations such as the Rockefeller Foundation and the Bill & Melinda Gates Foundation as well as national governments and international organizations.

PDPs receive R&D support, both financial and in-kind, from a variety of sources both public and private, and focus on acquiring, developing and managing a portfolio of candidate products. Their priorities are based on health inequities, social demand, and the maturity of the science. PDPs follow a non-profit business model, including a clearly articulated business plan based on market analyses, a portfolio management approach, and an access and advocacy strategy. PDPs are critical licensing and drug development partners for university technology managers as they strive to promote global health equity and formulate university-generated R&D and technology transfer alliances.

For example, one well-established PDP, the Global Alliance for TB Drug Development, has an operating model which includes:



- * **Creating a portfolio of R&D investments by acquiring, in-licensing or co-developing promising compounds;**
- * **Developing these drug candidates by outsourcing to public and private partners to whom the TB Alliance provides staged funding and expert scientific and management guidance;**
- * **Managing its portfolio with dedicated project management, predefined and measurable milestones, and clear go/no-go decision points and common evaluation criteria;**
- * **Designing innovative agreements leveraging intellectual property to ensure the affordability of the developed drugs, especially in poorer, high-endemic countries; and**
- * **Enlisting scientific capacity and resources worldwide.**

Most of the PDPs follow a similar operating model. In her recent article, Mary Moran (“A Breakthrough in R&D for Neglected Diseases: New Ways to Get the Drugs We Need.” *PLoS Med* 2(9): e302) illustrates how PDPs have expanded the development pipelines for drugs for neglected diseases: in the 25-year period between 1975 and 2000, there were 21 drug development projects in industry; in the 5-year period since 2000 (when many of the PDPs began their work), there were 63 drug development projects—16 exclusively multinational corporation projects, and 47 in PDPs. Approximately half of the PDP projects are being conducted in partnership with small and medium-scale organizations.

This increased attention to drug development for neglected diseases could be further fueled by more involvement of university technology managers. A 2005 survey of U.S. and Canadian university technology licensing offices (TLOs) found that although financial and economic considerations are an important factor in the invention evaluation and patent licensing

process, this does not close the door to the pursuit of global public health technology transfer that aims to increase the public benefits arising from the technology transfer process. Only a handful of TLO managers have experience in global health technology management issues; if appropriate multidisciplinary training and professional relationships are developed, there is ample opportunity to increase awareness of global health technology management, and thereby improve opportunities for new product development (U. Balakrishnan, L. Troyer, and E. Brands, 2006 AUTM Journal article. Surveying the Need for “Technology Management for Global Health” Training Programs).

An evolving set of partnering strategies and best practices is reflected in the work of university technology managers as they seek to construct relationships with the private and non-profit sectors. These approaches can be driven by entrepreneurial thinking and with a view to reducing “transactions costs” in technology licensing negotiations. However, there are no easy and straightforward or standardized solutions to some of these challenges. For example, decisions regarding whether and where to patent an invention can be complex. For some projects, transfer of technology and know-how to developing countries may be more effective than obtaining patent rights. A thoughtful assessment on a case-specific basis may be required based on the disease and its epidemiology, the pertinent technology, or the region.

How can university technology managers leverage their technologies through partnerships with PDPs to catalyze the development of therapeutics, diagnostics, or vaccines? As we seek to harness science and develop new management frameworks to improve global health, technology managers are coming to appreciate the nuances of working with non-traditional partners such as global PDPs, and have begun to develop new and innovative intellectual property (IP) management strategies and practices. Case studies based on their experiences show how PDPs bring together significant resources for drug development from multiple sectors and regions. PDPs have teamed up with universities, government laboratories, and biotech and pharmaceutical companies to bring together various resources. Some case studies were gathered recently, and are included in later sections of this booklet, and also posted at www.tmggh.org. These case studies also foster appreciation of the constraints faced by universities and PDPs in forming collaborations – constraints that stem from the economic realities of developing products for markets with little or no profit potential in the traditional sense. This requires clear management of expectations, opportunities, and challenges on both sides. PDPs also bring certain advantages to the table for technology managers that other traditional partners might not have – flexibility, broad capacity to identify and work with partners in all sectors (academic, private, NGO, government), and strong focus on rapid product development unfettered by traditional market realities. In some cases, where there are associated profitable markets, there will be opportunities to generate a profit through these partnerships. In other cases, there will be largely the satisfaction of shared mission fulfillment – improving global health through development of university technology.





4 Case Studies



Case Study 1

August 2006

A Better Tuberculosis Vaccine

Overview

Tuberculosis (TB) is a contagious disease caused by the bacterium *Mycobacterium tuberculosis*. Approximately 2 billion people (1/3 of the world's population) are infected. A TB infection causes active disease in only about 5 – 10% of these individuals. The remaining individuals have latent disease which causes no obvious symptoms and cannot be passed on to others. The disease can become active when the immune system is weakened (most commonly when individuals contract HIV/AIDS). TB caused an estimated 1.7 million deaths in 2004, with the highest number of deaths occurring in Africa.

In 1921, BCG (Bacille Calmette-Guerin), the current TB vaccine, was developed using *Mycobacterium bovis*, a bacterium related to *M. tuberculosis*. (See, for example, <http://www.metrokc.gov/health/tb/bcgvacine.htm>). However, epidemiological evidence indicates that BCG is not highly effective over a lifetime. In addition, the current TB treatment regimen is complicated. It requires patients to take as many as four different drugs for at least six months. Of even more concern, a multi-drug resistant (MDR)-strain of the bacterium is emerging. Therefore, an improved TB vaccine would be highly valuable in the effort to stop TB.

The Aeras Global Vaccine Foundation (Aeras) was founded in 1997 with a mission to develop and ensure access to new effective TB vaccines. Aeras adheres to an industrial model of vaccine development, with a pipeline of lead and back-up TB vaccine candidates. These include vaccines for initial vaccination and boosters for infants and adolescents. Aeras is also developing vaccines to protect against the activation of latent infections, and second generation technologies with improved product profiles. Aeras has established infrastructure for both pre-clinical development and clinical trials, and recently opened a manufacturing facility in Maryland capable of providing 150 million annual vaccine doses by 2010. The Bill & Melinda Gates Foundation recently awarded Aeras a grant of \$82.9 million to develop a new TB vaccine. Aeras' goal is to obtain regulatory approval for a new vaccine regimen in 7-10 years.

On May 4, 2006 Aeras and Vanderbilt University announced an exclusive license agreement for a TB vaccine based on technology developed at Vanderbilt. The technology enhances the ability of the BCG vaccine to trigger immune system responses. Under the agreement, Aeras will use the technology to modify the BCG vaccine and will guide the new vaccine through clinical trials. The license agreement grants Aeras exclusive rights for developing a TB vaccine. If a successful vaccine results from the use of this technology then Aeras will manufacture the new vaccine at its facility in Rockville, Maryland. Vanderbilt retains rights to the technology as a delivery system for other uses. This could potentially include new vaccines or immunotherapies against other diseases from HIV and malaria to cancer.

The Vanderbilt technology, called "pro-apoptotic BCG," is designed to weaken the BCG virus. It is a version of BCG with genetic modifications designed to inhibit the bacterium's ability to stop the programmed cell death of a patient's immune cells. These modifications are likely to result in a vaccine that provides better, longer lasting protection against TB, and may prevent progression to active TB among people with compromised immune systems.

Partners

Research – Vanderbilt University

PDPs – Aeras Global TB Vaccine Foundation

Progress, Current Status and Goals

The goal of the project is to develop a new TB vaccine to be shepherded through clinical trials toward regulatory approval. Aeras has established test sites for the vaccine near Bangalore, India, and Cape Town, South Africa. Aeras' goal is to obtain regulatory approval for a new vaccine regimen in 7-10 years (with either the pro-apoptotic BCG or another candidate).

Deals

- Grant – Aeras obtained an exclusive license in its field of use
- Field of Use – Aeras has an exclusive license to the TB field, Vanderbilt retains rights in other fields
- Payments/Royalties – The license is royalty bearing (including stacking terms) along with milestone payments
- Patents – patent costs paid by Aeras

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Case Study 2

August 2006

Improved Production of a Natural Product Treatment for Malaria

Overview

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

Malaria is a parasitic blood disease that strikes up to 500 million people annually. About 1.5 million people a year die 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 \$2.40, which places it out of reach 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 Foundation-funded project hopes to eliminate the need for plant extraction by utilizing a platform technology of "synthetic biology" developed by Dr. Jay Keasling at UC Berkeley. 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 \$42.6 million grant was divided among the three parties: \$8 million to UC Berkeley for continued basic research; \$12 million to Amyris for applied research on the fermentation and chemical processes; and \$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 from engineering of the production microbe to optimizing the semi-synthesis of the drug through fermentation and novel downstream synthetic chemistry. iOWH's role 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 of partners, each applying its expertise to streamline translation from bench to bedside.

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 intellectual property that is developed during the collaboration for the treatment of malaria in the developing world, with the goal to significantly reduce the price of ACT products, and reduce the use of artemisinin monotherapies per the WHO recommendations for uncomplicated malaria.

This arrangement has benefits for all the parties. The University benefits from the research funding as well as 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 non-profit pharmaceutical company, iOWH is able to make malaria treatments more affordable for people in the developing world.

Partners

Academia– University of California, Berkeley

Non-profit pharmaceutical company– Institute for OneWorld Health

For-profit pharmaceutical company– Amyris Biotechnologies, Inc.

Funding – The Bill & Melinda Gates Foundation

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 – 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 multi-step process in bacteria. 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 will carry out the following activities:



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 scalable, 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

License Grant(s):

- 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. iOWH 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, non-malaria indications of artemisinin, and alternative uses of the platform worldwide. UC Berkeley further shall grant similar licenses to Amyris for IP 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 royalty bearing for the developed world and non-malaria 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 a UC spin-out company, is seeking venture funding to leverage applications in other markets
- iOWH to establish partnerships for ACT manufacture and distribution using the process developed by Amyris and UC Berkeley
- iOWH plans to obtain similar licenses to all relevant third-party IP as the need arises as the project progresses

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The partnership: www.artemisininproject.org

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Case Study 3

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Research Consortium to Fill Critical Gap in AIDS Vaccine Development

Overview

A 2005 report from The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization estimated that there are 40.3 million people living with HIV. There were an additional five million new infections in 2005, 64% of which occurred in sub-Saharan Africa. Over 20 million men, women and children have died of AIDS-related illnesses since the epidemic began. AIDS now kills more people worldwide than any other infectious disease.

Prevention programs have slowed the spread of HIV, but have not stopped it. AIDS treatment options are not accessible for most people in the countries where they are needed most. Also, side effects and increased rates of viral infection have raised concerns about long term use of these treatments. An HIV/AIDS vaccine has the potential to end the pandemic.

The mission of the International AIDS Vaccine Initiative (IAVI) is to ensure the development of safe, effective, accessible, preventive HIV/AIDS vaccines for use throughout the world. Central to IAVI's mission is to improve access to a vaccine for the developing world. This includes speed of development, availability and price. A large portion of IAVI's resources are used to conduct research & development to design, manufacture and test promising HIV/AIDS vaccine candidates.

In July 2002, IAVI announced the formation of the Neutralizing Antibody Consortium (NAC), a five-year, multi-million dollar research program to develop a preventative HIV/AIDS vaccine that fills a critical gap not addressed by most HIV/AIDS vaccines currently in clinical trials. The original NAC consisted of four founding institutions. Today, the NAC includes an international group of 15 laboratories funded by IAVI representing academia, government, and not-for-profit research organizations.

The R&D Challenge

NAC is developing vaccine candidates with the ability to stimulate the human immune system to make broadly neutralizing antibodies. A neutralizing antibody is an antibody that prevents virus from infecting a cell, usually by blocking viral entry points (receptors) on the virus. Such antibody responses are the basis for existing vaccines against measles, polio, hepatitis B and hepatitis A. Most HIV/AIDS vaccines being tested in clinical trials rely on a different mechanism - triggering the body's cell-mediated immunity. However, it is likely that neutralizing antibodies will be necessary to provide a high degree of protection across a large population.

Using a strategy of rational immunogen design, vaccine candidates from the NAC program are generated by an iterative process that moves from crystal-structure, to re-engineered protein, to production and purification, to preclinical testing. NAC scientists conduct specialized research projects integrated into the overall NAC scientific program. They collaborate in study designs and problem solving, and regularly share research findings.

IAVI provides program management, procures common reagents, and conducts animals studies and high throughput assays. In addition, IAVI provides business development and intellectual property (IP) support to the individual scientists and their institutions. IAVI licenses IP developed under the scientific program by any of the NAC institutions and is responsible for the licensing-out of Program Inventions on behalf of the NAC. The collaboration agreement provides for the distribution of licensing revenues to the inventing institutions and the other NAC members. IAVI is also responsible for the patent costs for Program Inventions selected for licensing. The licensing provisions are consistent with global access principles, i.e., the distribution of a vaccine in developing countries promptly, at appropriate prices, and in adequate quantities to meet demand.

In addition to IAVI's program management role, the consortium director ensures that the overall effort of the NAC is focused on the creation of useable data leading to the selection of the best candidates for preclinical testing and clinical evaluations. The scientific research director works with each individual NAC scientist to maintain a dialogue on scientific issues to foster innovative problem-solving.

The Upside

The NAC institutions benefit from participation in a cutting-edge R&D effort, research funding and centralized research-enabling programs. These collaborative mechanisms enhance the likelihood that a vaccine candidate will be identified, evaluated, developed and delivered. IAVI is responsible for ensuring that commercialization occurs in a manner consistent with global access principles. IAVI anticipates engaging industrial partners to further develop, manufacture and distribute promising vaccine candidates.

Partners

Research Institutions – The initial NAC institutions were from The Scripps Research Institute, the University of Pennsylvania School of Medicine, Weill Medical College of Cornell University, and Dana Farber Cancer Institute. Other institutions currently in the NAC are Harvard Medical School, University of Wisconsin, Center d’Immunologie de Marseille, University of Oxford, University of Minnesota, The Children’s Hospital of Philadelphia, Global Vaccines, Inc., and Oregon Health and Science University.

Government Research Institutions – Scientists at the Dale and Betty Bumpers Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (part of the US National Institutes of Health) have provided advisory support for the NAC since its inception in 2002; they are now actively participating in the NAC through a Cooperative Research and Development Agreement (CRADA) with IAVI.

Sponsor – IAVI provides the funding for the NAC institutions, technical expertise to manage the scientific program, support research and the IP management and licensing-out of Program Inventions.

Industrial Partners – IAVI anticipates engaging industrial partners to secure additional funding of NAC research activities, provide scientific and development expertise, and manage downstream development, manufacturing and distribution.

Progress, Current Status and Goals

In 2004, the NAC scientists agreed that the consortium’s objectives should be expanded to include multiple research programs covering: a) design of immunogens capable of inducing broadly cross-reacting antibody responses against the globally diverse circulating isolates of HIV; b) elucidation of the mechanism of protection by live attenuated SIV, and harness this mechanism to design more effective HIV/AIDS vaccines; c) design and evaluation of T cell vector vaccines and related technology; and, d) other vaccine research approaches to design more effective HIV/AIDS vaccines capable of protecting humans from HIV/AIDS. IAVI and the consortium scientists are carefully considering the addition of new institutions and principal scientists to broaden the consortium’s science program in order to expedite the generation of data and vaccine candidates.

As of 2006, NAC researchers solved the structures of all the currently known broadly neutralizing antibodies and characterized their breadth of neutralization; established the membrane proximal external region of GP41 as well as carbohydrate-covered regions of GP120 as major targets for vaccine design; advanced understanding of the mechanism of neutralization of HIV; and established hybrid HIV/SIV to help define HIV vaccine targets.

Deals

- IAVI funds individual research work plans for NAC principal scientists; in some cases restricted grant monies are used for selected research projects which carry special compliance terms that apply specifically to that project.
- IAVI manages intellectual property (IP) on behalf of the NAC. IAVI rights include:
 - o option for exclusive license to Program IP in the Field
 - o option for non-exclusive license to Background IP
- IAVI pays for certain patent costs related to Program Inventions and Background Inventions
- Predetermined sharing of revenues among all Collaborators
- Other provisions include diligence, governance, publications, patent management and process for adding new members.

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Case study 4

August 2006

Working on Reducing Treatment Time for Tuberculosis Patients

Overview

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*, slow-growing bacteria that thrive in areas of the body that are rich in blood and oxygen. TB in the lungs is easily spread to other people through coughing or laughing. *Mycobacterium tuberculosis* infects one-third of the world's population, resulting each year in nine million new cases of active TB and two million deaths, 90% of them in developing countries. China and India alone account for 35% of all estimated new TB cases each year. An estimated 1 billion people will be newly infected between 2000 and 2020, 200 million will fall ill and 35 million will die. TB is a leading cause of death among people living with HIV/AIDS, and multi-drug resistant strains are spreading at a rate of 300,000 newly diagnosed cases a year.

The R&D Challenge

The TB drug market will require sufficient incentives to support the research needed to develop a pipeline of continually improving drugs. Even with the market potentially reaching \$700 million by 2010, it is concentrated in poor countries and no single industry player has been able to pursue the full development of an anti-TB drug. The Global Alliance for TB Drug Development (TB Alliance) was designed by the international community as the primary instrument to fill this vacuum and to ensure that new anti-TB drugs are affordable and accessible in endemic countries.

Current TB therapy is based on four drugs to prevent multidrug-resistant TB. These drugs were discovered forty or more years ago and must be administered for six to eight months, often under the direct observation of a healthcare provider. The four-drug regimen consists of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). There is a real need for new treatments that are less expensive, of shorter duration and easier to manage.

Moxifloxacin is an antibiotic first approved in 1999 and currently used in 104 countries to treat certain bacterial respiratory, skin and intra-abdominal infections. It has been used by over 47 million patients worldwide. Moxifloxacin is generally well tolerated but treatment may result in certain side effects that are usually mild including nausea, diarrhea and dizziness. *In vitro* and *in vivo* studies have demonstrated moxifloxacin activity against *Mycobacterium tuberculosis*. Investigators at Johns Hopkins discovered that substitution of moxifloxacin for isoniazid in the TB treatment regimen reduced treatment time by 2 months in mice. The treatment regimen included rifampin, pyrazinamide, and either moxifloxacin or isoniazid.

In October 2005, the TB Alliance and Bayer Healthcare AG announced a partnership to coordinate a global clinical development program to study the potential of moxifloxacin to shorten the standard 6-month treatment of TB by 2-3 months. The trials will evaluate whether the substitution of moxifloxacin for one of the standard TB drugs (ethambutol or isoniazid) eliminates TB infection faster than the current standard therapy. If successful and approved by the respective regulatory agencies, a new, shorter regimen could be available in the next five years.

The Phase II/III clinical trial program spans four continents and will enroll close to 2,500 patients with TB. The trials will take place in Brazil, Canada, South Africa, Spain, Tanzania, Uganda, the United States and Zambia. If the trials are successful, the partnership aims to register moxifloxacin for a TB indication. Upon regulatory approval, the partnership is committed to making it affordable and accessible in developing countries where TB patients need it most.

For this project, Bayer will donate moxifloxacin for each trial site and will cover the costs of regulatory filings, and the TB Alliance will coordinate and help cover the costs of the trials, seeking to leverage support from the U.S. Centers for Disease Control and Prevention (CDC), the Orphan Products Development Center of the U.S. Food & Drug Administration (FDA) and the European and Developing Countries Clinical Trials Partnership (EDCTP). In May 2006 the TB Alliance received a \$104 million grant from the Bill and Melinda Gates Foundation. The grant will be used in part to fund Phase II and III trials of moxifloxacin with the goal of showing the efficacy of moxifloxacin in reducing TB treatment times by 2 months by 2010.

The Upside

Public health experts note that a shorter TB regimen would help ease the economic burden of the disease, estimated at \$16 billion a year, and enable healthcare workers to treat more patients. A shorter treatment protocol may improve patient adherence to therapy, and thereby help save lives. Recovery, when patients complete treatment successfully, has a lower chance of relapse or the emergence of drug resistance.

Partners

Pharmaceutical – Bayer Healthcare AG

PDPs – Global Alliance for TB Drug Development

Clinical studies - Tuberculosis Trials Consortium (TBTC) of the CDC, Columbia University, Johns Hopkins University, University College London, British Medical Research Council

Government – US Centers for Disease Control and Prevention, US Food and Drug Administration, European and Developing Countries Clinical Trials Partnership (EDCTP)

Funding – For the TB Alliance, Bill and Melinda Gates Foundation and US Agency for International Development

Progress, Current Status and Goals

Goals of the Alliance:

- In partnership with Bayer, devise, coordinate and support a global clinical development program to register a moxifloxacin-based regimen for TB treatment-shortening at an affordable price.
- ICH and FDA cGCP/cGLP/cGMP-compliant clinical trial standards
- Unified global safety data base
- Clinical data-sharing
- Affordability- for patients most “in need”

Clinical trials and their development status:

- CDC TBTC Study #27: Moxifloxacin replaces Ethambutol in US, Canada, Uganda, and South Africa. 336 patients. Status: Completed in June 2005.
- CDC TBTC Study #28: Moxifloxacin replaces Isoniazid in US, Canada, Uganda, South Africa, Brazil, and Spain 410 patients. Status: Enrollment initiated February 2006.
- JHU: Moxifloxacin replaces Ethambutol in Brazil 170 patients. Status: Trial initiated in February 2005.
- UCL-BMRC: Moxifloxacin replaces Ethambutol and Moxifloxacin replaces Isoniazid in Tanzania, South Africa, and Zambia. 1500 patients. Status: Recruiting to commence in late 2006.

Deals

Field of Use – Tuberculosis drugs

Payments/Royalties - Will be made available in developing countries at cost, for use against tuberculosis.

Patent strategy – Patents previously issued

Contacts

Global Alliance for TB Drug Development

Maria Freire, President and CEO

New York City, New York

www.tballiance.org

Web Sites

Bayer Healthcare AG

www.bayer.com



PDPs are relatively new players in global health, charting untested waters. Although there are numerous promising vaccine and drug candidates in PDP pipelines, the success and overall sustainability of PDPs in general remains uncertain. But foundations, governments, universities and the private sector have all recognized the incredible promise of these entities, and have invested substantial financial, technological, and human resources in them. There is much at stake in promoting the success of the PDP model and improving the health of millions across the globe. Universities can play a critical role in making this happen.



Specific ways in which you can help as a university technology manager:

- ↳ Expand marketing and partnering strategies to reach beyond traditional licensees to include the global public-private, product development partnerships and new R&D players in global health. *Check out the listing of global health partners in technology transfer provided on the TMGH website (www.tmgh.org) and include global health components in educational training seminars to faculty, students and administrators on your campus.*
- ↳ On an ongoing basis, examine current inventories of technologies with the intent of assessing whether any of these technologies might be useful to global PDPs that target health products primarily for the developing world. *TMGH is currently developing an information clearinghouse and repository to foster exchanges of such technologies.*
- ↳ Incorporate creative licensing terms and conditions that would support development for high impact/low profit technologies. *Share with TMGH the ways in which you have licensed to global PDPs and/or developed the Global Access Plan under the Grand Challenges for Global Health initiative from the Gates Foundation.*
- ↳ Seek out resources that may provide guidance in developing and crafting new licensing strategies. *Examine the collection of case studies about university licenses to PDPs posted on the TMGH website.*
- ↳ Foster regional global health technology transfer forums. *TMGH encourages you to form cross-sector collaborative networks that would help leverage research investments and outcomes in local, regional, national, and transnational settings.*
- ↳ Share your experiences in these emerging IP management settings that may be valuable to other professional colleagues. *TMGH is always looking for speakers to share their perspectives at conference sessions and also invites you to submit your case study to be considered for inclusion in the growing collection.*

Conference Sessions organized by TMGH, 2005 - 2006

Global Health Council annual conference session, June 1, 2006, Washington DC

“New Technologies: The Role of the Private Sector”, Approximate Number of Attendees: 110

Usha Balakrishnan, MIHR-USA
Peter Young, AlphaVax
Wendy Taylor, BIOVentures for Global Health
Charles Gardner, The Rockefeller Foundation
John Fraser, Florida State University

LES-AUTM 2006 Spring Meeting Workshop, May 12, 2006, Philadelphia

“Perspectives and Issues in Building Global Health Alliances”, Approximate Number of Attendees: 30

Tari Suprpto, Rockefeller University
Richard Wilder, Sidley, Austin, Brown & Wood LLC
Kevin Kuehm, Bayer Healthcare

AUTM 2006 annual conference Educational Track session, March 2, 2006, Orlando

“Licensing to Global Product Development Partnerships”, Approximate Number of Attendees: 70

Usha Balakrishnan, MIHR-USA
Ximena Ares, Stanford University
Gennaro Gama, University of Georgia Research Foundation
Karen Blöchlinger, Seattle Biomedical Research Institute
Charles Gardner, The Rockefeller Foundation
Rita Khanna, Aeras Global TB Vaccine Foundation
Labeeb Abboud, International AIDS Vaccine Initiative
Linda Nyari, PATH
Patricia Vaughan, Population Council
Katherine Woo, Institute for OneWorld Health
Paul Model, International Partnership for Microbicides
Gregory Graff, Public IP Resource for Agriculture
Robert Johnston, Global Vaccines, Inc.
Rachelle Harris, MIHR
Sandra Shotwell, Alta Biomedical Group
Lita Nelsen, Massachusetts Institute of Technology
Carol Mimura, University of California at Berkeley
Cale Lennon, Emory University

LES 2005 annual conference session, October 20, 2005, Phoenix

“Emerging Strategies & Structures in Global Health Partnerships”, Approximate Number of Attendees: 30

Usha Balakrishnan, MIHR-USA
Julie Tan, Health Canada
Tari Suprpto, Rockefeller University
Gordon Comstock, University of Illinois at Chicago
Heather Lauver, Pfizer
Richard Mahoney, Arizona State University
Rita Khanna, Aeras Global TB Vaccine Foundation
Labeeb Abboud, International AIDS Vaccine Initiative
Gerald Siuta, Global Alliance for TB Drug Development
Wendy Taylor, BioVentures for Global Health
Mark Rohrbaugh, NIH-Office of Technology Transfer
Ashley Stevens, Boston University
Charles Gardner, The Rockefeller Foundation
Erik Iverson, Bill & Melinda Gates Foundation
Mukul Ranjan, NIAID
Robin Krause, Patterson, Belknap, Webb & Tyler, LLP

Biotechnology Industry Organization (BIO) 2005 session, June 15, 2005, Philadelphia

“Innovative Approaches in Technology Transfer for Global Health”, Approximate Number of Attendees: 40

Usha Balakrishnan, MIHR-USA
Hannah Kettler, Bill & Melinda Gates Foundation
Erik Iverson, Bill & Melinda Gates Foundation
Lisa Conte, Napo Pharmaceuticals
Gregg Alton, Gilead Sciences



**Be sure to check out the listing of
Global Health Product Development Partnerships
at www.tmgh.org/global-partners.php**

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