Global Health Innovators:  
A Collection of Case Studies

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"I remain committed to global health for a simple reason: once you realize the impact of these diseases on the people of developing countries, it becomes very difficult to neglect what you have learned."

YVES RIBEILL, CEO, SCYNEXIS, INC.
The need for new treatments: Each year infectious diseases — many of them potentially preventable or treatable — imperil families throughout the developing world. The impact of disease is difficult for those in affluent societies to imagine. Rich countries have access to effective treatments for many acute infections. But in the developing world, not only are today’s medicines out of reach, there are many tropical diseases for which there is no effective prevention or cure.

Diseases such as malaria, tuberculosis, diarrheal diseases, systemic worm infections, and trypanosomal parasites such as African sleeping sickness kill as many as 10 million people each year and disable millions more. Some lose their ability to work, many lose their loved ones, and others lose their lives. Despite the progress that has been made in improving delivery of existing medicines for infectious diseases of the developing world, there remain major gaps in prevention, diagnosis, and treatment.

An innovation gap exists for global health products: As BIO Ventures for Global Health (BVGH) elucidated in Closing the Global Health Innovation Gap:

2 Some of the major issues related to infectious diseases include:

Vaccines: Vaccines have long been recognized as one of the most cost-effective public health interventions; yet, nearly 20 years since it was first identified, there are no available vaccines against HIV. Similarly, vaccines do not exist to prevent disease caused by any parasitic protozoan (e.g., malaria, Chagas disease) or soil-transmitted helminth (worm).

Diagnostics: A number of infectious diseases are treated on the basis of a clinical diagnosis, rather than through a modern test capable of identifying the infectious agent. This leads to the inappropriate use of drugs, which is expensive and fuels the rise of resistance. Rapid, robust point-of-care diagnostics are needed to counter these problems.

Therapeutics: Many of the drugs to treat infectious diseases of poverty are decades old, highly toxic, and require hospitalization to be administered. Older drugs are also losing efficacy due to the rise of resistance. Even for diseases for which treatments exist, such as tuberculosis (TB) and malaria, improvements are sought in treatment efficacy, safety, cost, and activity against drug-resistant organisms.

A Role for the Biotechnology Industry, increased funding for neglected diseases and the evolution of new public-private research and development (R&D) partnerships has not been sufficient to create a full pipeline of innovative new products that will fully address key treatment goals. The investment in product discovery and “translational” research for neglected diseases remains at a fraction of the level necessary to capitalize on promising discoveries made in academic laboratories (such as identification of new molecular targets). This is largely because most global health products lack a profitable market that would justify investing the millions of dollars needed to develop new medicines. The lack of substantial funding for early-stage product innovation, combined with a lack of broad-based market-like incentives, has prevented widespread participation by the private-sector players that drive pharmaceutical innovation in the developed world. Incentives that compensate for risk that are paid upon success and emulate the rewards that can be achieved in the marketplace are essential if we want to garner additional private-sector participation in global health.

The biotechnology industry has resources to help bridge the innovation gap: With over 1,400 biotechnology companies in the United States alone, more than 200 FDA-approved products on the market, and exceptionally diverse high-tech platforms for vaccine and drug discovery, the biotechnology industry has the resources and capability to take on the challenges of global health. Furthermore, drug discovery platforms focused on targets such as proteases, kinases, and cell motility factors that control diseases such as cancer and cardiovascular disease can be applied to analogous targets in neglected diseases. Biotechnology resources must play a key role in building the global health R&D pipeline and closing the existing innovation gap.

“The advanced technologies applied to developed world diseases are only now being applied to neglected diseases. I don’t want to minimize the challenges, but it is encouraging that these are not intractable scientific problems...With more focus and resources these are completely solvable problems.”

DAVID P. PERRY, PRESIDENT AND CEO, ANACOR PHARMACEUTICALS
There are significant barriers to biotechnology industry engagement in global health R&D:

Extensive discussions with top management at leading biotechnology companies have led BVGH to identify three types of barriers that keep companies from engaging in global health product development:

- **Market barriers:** For most global health products, there is a lack of a profitable market to generate sufficient return to justify investing the millions of dollars required to develop a new vaccine or therapeutic. There are also too few market-like incentives that can defray product development costs, compensate for risk, or increase the reward for successful product development.

- **Information barriers:** Most biotechnology companies lack experience with pathogens that afflict poor populations. They are also unfamiliar with medical practice and pharmaceutical distribution in the developing world. As a result, they are unsure of how company assets can best be deployed to address neglected diseases. Lacking familiarity with the pathogens and the underlying science, companies also struggle to identify academic partners with disease-specific expertise.

- **Managerial barriers:** Biotechnology companies are unable to devote substantial management time to non-core activities.

Despite these barriers, many biotechnology companies are seeking ways to engage in global health R&D in a manner consistent with their broader commercial strategy:

Many biotechnology companies are inspired by the opportunity to address tremendous unmet needs in global health. A number have been willing to go to considerable lengths to access public and donor funding for R&D targeted to these diseases. Having identified possible ways their technology platforms could be relevant, many are seeking ways to participate that are compatible with their business strategies and limited cash resources. Companies have also expressed interest in applying their capabilities through R&D collaborations with disease experts in product development partnerships (PDPs) and academia.

Nonetheless, only a few dozen companies have followed through and invested substantial management time and discovery resources in global health R&D. This commitment on the part of the leadership of a select number of biotechnology companies has overcome the barriers that have kept other “capable innovators” from participating in the field. This study examines how these pioneering companies have crafted successful business models around global health, and how they have engaged with a wide range of public sector partners.
CASE STUDY OBJECTIVES
AND APPROACH

At BIO Ventures for Global Health (BVGH), our goal is to help companies find ways to participate in global health. There is no scientific reason why technologies that have led to breakthroughs for diseases of the industrialized world cannot yield new cures for diseases of the developing world. We believe it’s essential to engage private-sector innovators, particularly entrepreneurial biotechnology companies, who have the expertise and track records of inventing, developing, and testing new medicines. Today, these companies are the principal originators of new pharmaceuticals, as many pharmaceutical companies source their new product pipelines from smaller companies. Biotechnology companies have an integral role to play in the fight against diseases that primarily affect the developing world.

BVGH is constantly exploring new ways to break down the market, information, and managerial barriers that have kept biotechnology companies out of global health, and to create new incentives that would draw them in. BVGH undertook these case studies to understand the motivations and incentives underlying existing global health efforts of leading biotechnology companies. These case studies analyze how the mainstream biotechnology companies seek out opportunities to contribute to global health, despite market and funding constraints.

The case studies highlight program objectives, milestones, and expected impact on patients in the developing world. We analyzed six partnership arrangements and the roles and responsibilities of each of the partners. We further explored the ways in which such efforts support the core commercial strategies of these companies and the strategic value the companies and their partners gain from their involvement. We also examined how the partners overcame barriers that arose when deciding to engage in global health and during negotiations over terms of research and development (R&D) agreements. Recognizing that experiences vary not only across companies but also across products (e.g., vaccines vs. drugs), we selected a range of examples that had the following features:

- Both the private-sector and public-sector partners were well funded, highly capable, and well respected among their peers
- The companies and their leadership teams had demonstrated track records of successfully innovating new products.
- The companies had diverse business models that could offer a range of possible avenues to participate in global health product development.

Our initial screen led to the selection of the following six collaborations, involving seven companies, to evaluate in detail:

1) The collaboration between Advinus Therapeutics Pvt. Ltd., the Drugs for Neglected Diseases initiative (DNDi), and the Central Drug Research Institute (CDRI) to develop new treatments for visceral leishmaniasis (VL).
2) The recent joint venture launched by Emergent BioSolutions Inc and the University of Oxford/Isis Innovation Ltd. in partnership with the Wellcome Trust and Aeras Global TB Foundation to develop a vaccine for tuberculosis (TB).
3) The collaboration between Genzyme Corporation, Medicines for Malaria Ventures, and the Broad Institute of MIT and Harvard to develop new treatments for malaria.
4) The collaboration between Anacor Pharmaceuticals, Scynexis Inc., DNDi, the Haskins Laboratory at Pace University, and the Swiss Tropical Institute to develop new treatments for human African trypanosomiasis (HAT).
5) The efforts of Vertex Pharmaceuticals (and partners within its Global TB Research Network) to develop new treatments for tuberculosis (TB).
6) The efforts of Acambis (now a subsidiary of Sanofi Pasteur) to develop a vaccine for Japanese encephalitis (JE).
We conducted in-depth interviews with more than 35 individuals, both senior leadership and day-to-day project managers at the biotechnology companies and each of their partners. We also fact-checked the content of this document to ensure that these global health programs and the perspectives of each of the stakeholders are reflected accurately.

In highlighting the efforts of these seven biotechnology companies and exploring the circumstances under which global health R&D projects were developed and the manner in which they are executed, we found extensive evidence that 1) biotechnology companies have a critical role to play in global health R&D partnerships, 2) global health R&D can support a biotechnology company’s core commercial strategy, and 3) challenges faced by parties exploring such partnerships can be overcome, and dissimilar stakeholders can work together for mutual benefit and significant global health impact.

**KEY FINDINGS**

**Biotechnology companies have employed three principal business models to engage in global health R&D.** The case studies contained in this report provide insight into three distinct business models that companies have used to engage in global health R&D while also pursuing a commercial return:

- **Biotechnology companies have found value in niche global health markets, targeting endemic neglected disease markets even before developed world markets:** Large and small vaccine companies have invested in R&D for niche global health markets with the expectations of future returns based on paying markets—often ones not visible to the biopharmaceutical industry at large. Some target developed world travelers’ markets, while others target the market in endemic countries, an opportunity that is not always widely understood.

- **Dual market opportunities can be pursued in partnership to defray the cost of product development:** Some vaccine and small molecule drug developers have found a way to engage in global health through pursuing dual market opportunities in partnership with public-private collaborations called product development partnerships (PDPs). In these cases, the cost of product development is jointly funded by both organizations and the biotechnology company is able to pursue commercial value in markets where patients are able to pay.

- **Contract research organizations (CROs) can conduct global health R&D within an existing “fee-for-service” business model:** Certain contract research organizations such as Advinus and Scynexis have successfully made global health R&D a significant part of their core “fee-for-service” business by partnering with PDPs at a reduced but still profitable rate. While there is an opportunity cost to working on these projects rather than projects with higher returns, CROs find that it is sustainable to continue working on global health within a broader portfolio of more profitable projects.

**The strategic value realized from global health R&D can support a company’s commercial strategy:** Even those companies that do not seek profit from their global health projects (e.g., by donating their technology or expertise to PDPs and other collaborators) view this engagement within the broader context of the companies’ commercial strategy. It is worthwhile to consider the types of strategic value that are not directly related to profits, but are nonetheless core to a company’s ability to expand and prosper. Some of these include:

- **Staff recruitment, motivation, and retention:** Providing employees the opportunity to work on neglected disease projects has aided recruitment efforts and improved staff morale. This is a benefit that has been highlighted by all seven of the biotechnology companies surveyed for this report.
A firm commitment from senior management is a prerequisite for engagement: All of the companies highlighted in this document have made a commitment to global health that begins at the very top levels of management. Consistently, it is the CEO’s motivation to address the unmet medical needs of poor patients in the developing world that enables commitment to flourish more broadly throughout the company. Without this commitment, the barriers to engagement in global health R&D are simply too high for the majority of cash-strapped biotechnology companies.

Negotiating ownership of intellectual property rights has not been a major challenge for these partnerships: Interviews with seven biotechnology companies and their partners on their efforts related to global health R&D indicated that negotiating intellectual property agreements has not been as challenging as anticipated. For the most part, those involved in partnerships highlighted in this document claim that the formation of the partnership itself was relatively straightforward and without major challenges.

Cultural differences between industry, academics, and PDPs are both a challenge and a potential strength: One challenge frequently raised by partners involved in collaborative R&D efforts to develop products for neglected diseases is that of working with a diverse group of organizations. According to those who have overcome these challenges, however, these cultural differences eventually became a strength. For example, chemists from industry take an interest and see value in academic precision and search for knowledge, while scientists at an academic institution see value in the way industrial scientists manage projects, particularly in areas such as establishing and adhering to strict testing protocols that the collaboration has put into place, as well as the importance of timelines.
IMPLICATIONS

These case studies demonstrate that it is feasible for biotechnology companies to engage in global health R&D in a way that enhances their core business strategies and the growth of their businesses. Each of the companies has built its global health R&D activity through collaborations with experts in the target disease areas — whether with academic institutions or through partnerships with PDPs and others who can defray costs. They also demonstrate that even if the ultimate products are not expected to be profitable, companies can derive significant strategic value from these projects.

These case studies present several paths by which other biotechnology companies can engage in global health R&D. These interviews identified three business models that are consistent with efforts to generate shareholder value. Nonetheless, biopharmaceutical R&D is inherently risky, and R&D for neglected diseases may be even more so. Industry analysts estimate that roughly one in 250 candidate molecules entering preclinical studies eventually becomes an FDA-approved drug, and fewer than one in 10 candidates that enter phase 1 human clinical trials is ever approved. Together, this means that the cost of developing a new therapeutic or vaccine can run into the hundreds of millions of dollars, and the timeline from discovery through clinical development to regulatory approval can extend over a decade or more. The constraints for global health products, such as inexpensive manufacture, potentially increase the difficulty of achieving success.

Biotechnology companies will resist dedicating more substantial resources to R&D unless a viable commercial or donor-generated market exists that has the potential to yield a significant return on investment. These case studies have demonstrated that there are global health products for which a viable commercial market exists, such as Japanese encephalitis and tuberculosis vaccines. However, it must be acknowledged that these markets are limited in number. For many other neglected diseases, no such market exists. This is the reason why many policy experts, along with BVGH, advocate the creation of new market-driven incentive mechanisms to compensate innovators for taking risk and investing in product development for global health commodities. Where a viable commercial or donor-generated market is lacking, such incentives can overcome the opportunity cost associated with working in global health.

Despite the barriers, it is remarkable what the following companies have already accomplished with comparatively modest budgets. Anacor Pharmaceuticals is working closely with Scynexis and DNDi to evaluate preclinical candidate molecules for African sleeping sickness with the intention of initiating clinical trials within a year. Acambis (now a subsidiary of Sanofi Pasteur) has a phase 3 vaccine for Japanese encephalitis in the clinic. Vertex Pharmaceuticals and its strategic alliance partners have identified initial compounds that point to new chemical classes with completely novel mechanisms of action for treating TB. Emergent BioSolutions and the University of Oxford have launched a new joint venture that will take a TB vaccine candidate into phase 2b trials and has partnered with Aeras Global TB Foundation to ensure that both commercial and humanitarian aims are met. Genzyme Corporation, in collaboration with Medicines for Malaria Venture and the Broad Institute of MIT and Harvard, has identified two compound families with activity against malaria and has advanced them into the lead optimization stage with the goal of identifying a clinical candidate in 2009. The successes of these biotechnology companies and their partners are no small achievement, and such progress could not have taken place without the dedication of the CEOs of these companies and their scientific teams.

BVGH applauds the commitment of the biotechnology companies highlighted in this report. They are an inspiration to other companies and a clear statement to the global health community that industry can and will work collectively to contribute to global health R&D.
Disease Overview

There are 12 million people infected with *Leishmania* parasites worldwide, and 350 million people living in at-risk locations. Each year, there are 1.7 million new cases of the disease and 45,000 deaths due to lack of access to effective treatment.¹ There is a profound need for safe, effective therapeutics to combat leishmaniasis. The problem is particularly urgent given that over the past 10 years, regions endemic for leishmaniasis have been growing, and a sharp increase in the number of recorded cases of the disease has been observed.

Leishmaniasis is a widespread parasitic disease that affects the skin, mucosa, or internal organs and results in severe disfigurement, disability, or death. *Leishmania* parasites are a genus of protozoa related to the trypanosomes that cause human African trypanosomiasis (HAT, or sleeping sickness) and Chagas disease. There are four forms of *Leishmania* disease. The most serious form, visceral leishmaniasis (VL)—commonly known as Kala-azar—is fatal if left untreated. Approximately 90% of all VL cases occur in Bangladesh, India, Nepal, and Sudan.

Market Overview

While the number of people in need of treatment and prevention is large, most of those afflicted live in severe poverty. Thus, there is not a significant private or public commercial market. There is, however, a small military market to treat soldiers who have been deployed in endemic countries such as Iraq. This offers the possibility of collaborations with the U.S. Department of Defense in the development process, but is unlikely to yield a significant financial return on R&D investment.

Project Overview

The Drugs for Neglected Diseases initiative, a product development partnership (PDP) based in Geneva, the Bangalore-based drug discovery and contract research company Advinus Therapeutics Pvt. Ltd., and the Indian public research organization Central Drug Research Institute (CDRI) formed a partnership in 2007 and 2008, respectively, to initiate a drug discovery program to create effective treatments for VL.

The goal of the project is to take a multidisciplinary approach in developing an oral drug for VL to supersede the other treatments that are difficult to administer and present safety issues.

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1. BVGH Global Health Primer. BVGH, October 2007; 45.
Progress to Date
The target date for achieving the goal of delivering a viable clinical candidate is 2012. DNDi Senior Project Manager Denis Martin states that “though the partnership is still recent, we are pleased with the progress and we are on track to meet our goal of having a clinical candidate within the next three years.”

Partnership Roles and Responsibilities
Advinus supports the partnership in developing early leads into clinical candidates, a process that requires a multi-disciplinary approach. Advinus provides medicinal chemistry, pharmacokinetics, and toxicology, mainly out of its Bangalore location.

CDRI has advanced in vitro and in vivo models for VL. Under the management of DNDi, Advinus works closely with CDRI to leverage their expertise by screening compounds through their in vitro and in vivo models. CDRI receives compounds synthesized by Advinus and tests them for efficacy using relevant models.

DNDi funds this collaborative effort entirely, thanks to the support of Médecins sans Frontières (MSF), the Bill & Melinda Gates Foundation, and other public and private donors. DNDi plays a critical project management and leadership role, and provides the initial leads obtained from other collaborators. Once a candidate progresses past the point of pre-clinical safety into full-scale clinical trials, DNDi will be responsible for managing and financing these trials as well as for registration of the drug.

DNDi selects Advinus and CDRI as partners for VL drug discovery: DNDi initiated this partnership with Advinus after identifying some initial hits demonstrating activity against VL. DNDi Director of Research and Development Shing Chang describes the decision to partner with Advinus as follows: “If you know Advinus CEO Rashmi Barbhaiya, then you know and believe in his commitment to working on neglected diseases. In Advinus’ mission statement, there is a full paragraph on neglected diseases and their commitment to provide therapeutic solutions—so it was natural to choose Advinus as a partner for our work on VL. Likewise, the expertise and commitment of CDRI in the field of VL made it an obvious choice to participate in the consortium. Furthermore, both Advinus and CDRI are located in India where VL is still endemic in the northern part of the country. This is an important motivating factor for the scientists working in India.”

Advinus commits to working with DNDi: Advinus was quick to respond to DNDi’s request that they conduct the medicinal chemistry, pharmacokinetics, and toxicology work for this VL drug discovery project. Advinus states that formalizing a partnership with DNDi was a simple decision despite the opportunity cost of taking on this project versus a higher return project for a large pharmaceutical company. Advinus decided that working in global health is a good fit with the company’s philosophy of social responsibility and a differentiating feature that contributes positively to its long-term strategy.

Deal making: Partners claim that the formation of the partnership itself has been relatively straightforward and without major complication. DNDi characterizes the deal making as “very straightforward.” The deal was announced in October of 2007, and collaboration between DNDi and Advinus became fully operational in January of 2008.

Project Timeline and Evolution

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<td>Early 2006</td>
<td>DNDi approaches Advinus to run early toxicology experiments for ongoing projects.</td>
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<td>October 2007</td>
<td>Advinus and DNDi sign a partnership agreement on drug discovery and development for VL.</td>
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<td>January 2008</td>
<td>Advinus and DNDi begin collaborating on a concrete basis.</td>
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<td>May 2008</td>
<td>CDRI officially joins the consortium.</td>
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Partner Profiles

**Drugs for Neglected Diseases initiative**: DNDi is an independent, not-for-profit product development partnership (PDP) working to research and develop new and improved treatments for neglected diseases such as malaria, leishmaniasis, human African trypanosomiasis (HAT, also known as sleeping sickness), and Chagas disease. DNDi was established in 2003 by five public sector institutions — the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia, and France’s Pasteur Institute; one humanitarian organization, Médecins sans Frontières (MSF); and one international research organization, the UNDP/World Bank/WHO’s Special Programme for Research and Training in Tropical Diseases (TDR), which acts as a permanent observer to the initiative. DNDi works in partnership with industry and academia and has established the largest existing R&D portfolio for kinetoplastid (flagellate protozoa) diseases.

**Advinus Therapeutics Pvt. Ltd., a TATA Enterprise**, is a private biotechnology company located in India and supported by TATA. It houses two business centers in Pune and Bangalore with over 470 employees. The Pune location focuses on drug discovery on internal programs and collaborative research with large pharmaceutical companies whereas the Bangalore location provides services for drug development and drug discovery for neglected diseases. The company offers a range of services to clients including custom synthesis, preformulation, stability testing, safety pharmacology, exploratory and regulatory preclinical safety assessment, and clinical pharmacology. Advinus is open to innovative partnering opportunities. Advinus’s in-house discovery program focuses on three key disease areas: metabolic, inflammation, and neglected diseases. The company strives to be the leader in drug discovery in India as well as the first choice for clients seeking drug development services. Work in neglected disease areas is core to Advinus’s Vision & Mission, which states that “Advinus is committed to addressing these global public health issues,” and that “India is ideally suited for this activity due to public health issues of the country, availability of talent and cost effectiveness.”
Case Study 1

Mission driven: Advinus describes its motivation for engaging in global health very simply — being based in India gives the company an obligation to do drug discovery in disease areas that are endemic to India and affect the population in the country where it operates. Barbhaiya states: “We feel very proud that as a small company at such a young age, we have made such a commitment. We have created a positive image for the company by showing this sort of commitment despite not being profitable yet. We hope that this conveys something about our character and management.”

Attracting, retaining, and motivating talent: Advinus has found that providing employees the opportunity to work on neglected disease projects has aided recruitment efforts and boosted staff morale. Barbhaiya describes Advinus employees as feeling “very proud that they are working for a company that
is not only thinking about profits but also concerned with contributing to society. Our employees have an opportunity to do research that larger, more profitable companies don’t always provide, and this has been helpful in attracting and retaining talent.”

**DNDi Perspective**

**Results:** DNDi secures faster advancement of compounds using Advinus’ knowledge base and scientific talents. As DNDi’s June 2008 newsletter explains, “The process of drug discovery and development has been likened to that of building a jet airliner. No single partner has all of the skills, and the final product must be safe for millions of people — partnerships are essential. DNDi has had to build effective partnerships between scientists from a number of different disciplines to adequately address all the skills necessary for lead optimization.” This partnership is a good example of just such an effort to bring all relevant skills to the table.

**Ownership over IP:** Because Advinus is funded as a fee-for-service contractor and makes no claim to any intellectual property generated during the lead optimization program, “DNDi remains free to manage the intellectual property in a manner the organization deems to be most appropriate in order to guarantee access by those suffering from neglected diseases.”

**Lower costs:** Advinus offers the benefit of being able to conduct drug discovery and development cost-effectively because of its location in India. Research is performed at one-third of costs in the United States or in Europe, without sacrificing quality or timelines. Many of Advinus’ staff has had international training and experience in the United States or Europe.

**Overcoming Key Challenges**

**Structuring the project to be financially viable:** As noted, Advinus engages in this partnership via its existing fee-for-service model. Barbhaiya states that a key challenge faced is “the opportunity cost of doing this work,” as the company utilizes resources for these projects that could be devoted to higher return engagements. Yet he maintains that because such work on neglected diseases “occurs as part of an organization where there are larger revenue streams elsewhere, it becomes sustainable, especially if management is passionate about the work, as we are at Advinus.” Thus, Advinus has utilized a mixed model, where approximately 10% of staff work on neglected diseases and the remainder focus on higher-return projects. Furthermore, Advinus acknowledges that its position as a private company has also been a key factor in making it possible to work on global health projects for lower profit. CDRI, like Advinus, is funded by DNDi for the screening work it provides the project. DNDi, as the major funder of this project, secures its funding from the Bill & Melinda Gates Foundation and other public and private donors.

**Cultural barriers:** Advinus’s CEO states that “one of the major problems faced and still faced is the mind-set of some in the U.S. or Europe that innovation-driven R&D can be done well only in the United States or Europe. Many [potential clients] have refused to even meet us. We are working to overcome the challenges of accessing companies and people who are willing to work with us in India.” DNDi’s initiative for this project contributes to overcoming these barriers as Advinus has the chance to demonstrate its expertise and ability to serve the needs of a very visible European client.
The only currently available vaccine for TB is Bacille Calmette-Guérin (BCG), which is the most commonly administered vaccine in the world. Although BCG is safe and inexpensive, it has variable and limited efficacy. Also, while BCG appears to reduce the risk of severe childhood TB disease, it may provide limited or no protection against TB in adults or adolescents. BCG is not recommended for people who are HIV-positive, and does not appear to protect against pulmonary TB at any age. BCG is therefore targeted at newborn infants, high-risk older children, and adolescents.

There is a need for a new TB vaccine that would protect against TB in adults and adolescents and that would be safe to administer to HIV-positive patients.

Market Overview

BIO Ventures for Global Health (BVGH) showed in its TB vaccine business case, *Tuberculosis Vaccines: The Case for Investment*, that there is a viable worldwide market for an effective tuberculosis vaccine. The report found that potential TB vaccine manufacturers could generate a return on investment with developed countries as a market. It also found that even if the doses were sold at cost to developing countries, the volume of production would yield significant beneficial manufacturing efficiencies. The report estimated that the market for a booster vaccine which boosts the existing BCG vaccine is nearly $800 million (about 40 million doses) with high-income markets driving revenues.

BVGH highlighted that the timelines, cost, and risk of phase 3 trials for a TB vaccine are likely deterrents to for-profit companies. We noted that a major incentives program (such as an Advanced Market Commitment),
or risk-mitigating financial support from donors is likely to be important in attracting for-profit investment in the full-scale development of a new vaccine.

**Project Overview**

In 2008, Emergent BioSolutions Inc. (Emergent) and the University of Oxford (Oxford) /Isis Innovation Ltd. (Isis) formed a joint venture known as the Oxford Emergent Tuberculosis Consortium (OETC) to develop the TB vaccine candidate MVA85A/AERAS-485 (MVA85A). The vaccine candidate was originally developed at the Jenner Institute and the University of Oxford by Dr. Helen McShane, a Wellcome Trust Senior Research Fellow, who worked with Dr. Sarah Gilbert, a Reader in Vaccinology and Professor Adrian Hill, a Wellcome Trust Principal Research Fellow. Dr. Helen McShane continues to be involved in the development of the vaccine, and Dr. Jacqui Shea from Emergent is now the general manager of the OETC. The OETC is set up as a private company limited by shares incorporated in England and Wales.

The OETC signed an agreement with Aeras Global TB Vaccine Foundation (Aeras) that provides Aeras the rights to distribute the vaccine in developing countries. It also entered into a commercial supply agreement with Emergent that enables the company to sell in developed countries and some countries in Asia.

The Wellcome Trust and Aeras are each providing £4 million to support phase 2b clinical trials. Emergent is contributing additional funding to the partnership to support a product development package.

The goal of the collaboration is to utilize a joint-venture structure that enables the stakeholders to collectively take the MVA85A through phase 2b proof-of-concept clinical trials and to prepare a product development package that plans for the development of the vaccine through phase 3 and beyond. All partners believe the joint venture structure is the optimal structure to meet both commercial and humanitarian objectives, as funding and expertise from both sets of parties are required for the development and commercialization of the vaccine. Because the potential for profitability in the developed world and private markets in endemic countries provides the incentive for Emergent to jointly fund the development and commercialization of the vaccine (a pre-requisite to making the vaccine available for humanitarian purposes to low-income markets), partners believe that the joint venture structure ensures that the product development package will serve both commercial and humanitarian interests.

Following the formalization of the Consortium and related agreements, the phase 2b clinical trial commenced in early June 2009 and is currently underway in collaboration with the South African Tuberculosis Vaccine Initiative (SATVI) of the University of Cape Town in the Western Cape Region at its study site 100 kilometers from Cape Town in Worcester, South Africa. This is the first proof-of-concept trial of a new preventative TB vaccine in infants in more than eighty years.

**Progress to Date**

MVA85A is a recombinant viral vaccine. It is a recombinant strain of MVA (modified vaccinia virus Ankara) which is an attenuated (weakened) strain of vaccinia, the smallpox vaccine. The MVA expresses antigen 85A, an immunodominant antigen from Mycobacterium tuberculosis. The MVA85A vaccine relies on enhancing an immune response against the mycobacterial mycolyl transferase enzyme. It has been shown to enhance BCG-induced protection in four preclinical animal models of tuberculosis, even when animals have already been exposed to mycobacteria. This is important considering that people in the developing world will have a broad range of prior exposure to mycobacteria. Importantly, the immune response to antigen 85A does not interfere with new diagnostic tests.

Until the formation of the Consortium in July 2008, Oxford had been leading the development of the MVA85A vaccine candidate, supported by funding provided by the Wellcome Trust and other groups. To date, MVA85A has been evaluated in phase 2a clinical
Partner Profiles

Emergent BioSolutions Inc. is a publicly traded biotechnology company focused on the development, manufacture, and commercialization of vaccines and therapeutics that assist the body's immune system to prevent or treat disease. Emergent’s marketed product, BioThrax® (Anthrax Vaccine Adsorbed), is the only vaccine licensed by the U.S. Food and Drug Administration for the prevention of anthrax. Emergent’s development pipeline includes programs focused on anthrax, botulism, typhoid, hepatitis B, chlamydia, and tuberculosis.

Isis Innovation Ltd. is a wholly owned subsidiary of the University of Oxford. Isis was established by Oxford University in 1988 as its technology transfer company and has developed substantially over the years as the technology transfer activity has grown. Isis manages the university’s intellectual property portfolio, working with university researchers on identifying, protecting, and marketing technologies through licensing, spin-out company formation, consulting, and material sales. Isis funds patent applications and legal costs, negotiates exploitation and spin-out company agreements, and identifies and manages consultancy opportunities. Isis works on projects from all areas of the university’s research activities: life sciences, physical sciences, social sciences, and humanities. Isis provides access to Oxford’s expertise and provides researchers with advice on commercialization.

Aeras Global TB Vaccine Foundation is a non-profit product development partnership (PDP) dedicated to the development of effective TB vaccine regimens that will prevent tuberculosis in all age groups and will be affordable, available, and adopted worldwide. The goal of the Aeras Global TB Vaccine Foundation is to develop, test, characterize, license, manufacture, and distribute at least one new TB vaccine regimen for infants and another for adolescents and ensure their availability to all who need them. Major donors of Aeras include the Bill & Melinda Gates Foundation and the Netherlands Ministry of Foreign Affairs.

The Wellcome Trust is an independent charity funding research to improve human and animal health. Established in 1936 and with an endowment of around £12 billion, it is the UK’s largest non-governmental source of funds for biomedical research, spending around £600 million every year both in the UK and internationally, supporting and promoting research to improve the health of humans and animals. As well as tackling immediate priorities, its independence and long-term perspective enable the Trust to support research that will benefit future generations. To achieve its mission, the Wellcome Trust supports research in universities and other academic centers in the United Kingdom and overseas. The Wellcome Trust also supports public debate about biomedical research and its impact on health and well-being.

The Jenner Institute was founded in November 2005 to develop innovative vaccines against major global diseases. It focuses on diseases of humans and livestock and tests new vaccine approaches in parallel in different species. A major theme is translational research involving the rapid early-stage development and assessment of new vaccines in clinical trials. The institute is a partnership between the University of Oxford and the Institute for Animal Health and is supported by the Jenner Vaccine Foundation, a UK registered charity, and advised by the Jenner Institute Scientific Advisory Board.

The South African Tuberculosis Vaccine Initiative (SATVI) was established in 2001 and is located within the Institute of Infectious Disease and Molecular Medicine of the University of Cape Town. SATVI is the largest dedicated TB vaccine research group on the African continent. SATVI’s long-term aim has been to develop capacity to conduct registration standard trials of novel TB vaccines, and it has embarked on clinical, epidemiological, and immunological research critical for clinical testing of new TB vaccines. In addition, SATVI has completed a number of phase 1 and 2 trials of new TB vaccines.
trials, including in: *M. tuberculosis*-infected adults in the United Kingdom and South Africa; in HIV-infected adults in the UK and South Africa; infants in Gambia; and adolescents, children, and infants in South Africa.

The OETC was formed for the development and commercialization of the MVA85A TB vaccine candidate through phase 2b proof-of-concept clinical trials, which commenced in early June 2009. The phase 2b trial will take place at a clinical trial site developed by Aeras and SATVI. The trial has been approved by the Medicines Control Council of South Africa and will test MVA85A in approximately 2,784 children under one year of age, all of whom have received BCG at birth. It is expected that the trial will generate important safety, immunogenicity, and preliminary efficacy data about the vaccine candidate.

Eight million pounds has been secured from the Wellcome Trust and Aeras to fund this trial. Emergent has contributed additional funding to develop a product development package and prepare for future phase 3 trials. This is the first proof-of-concept trial of a new preventive TB vaccine in infants in more than eighty years, and the direction of this joint venture will be reassessed pending the results of these trials, but partners are highly optimistic. Rita Khanna, general counsel at Aeras states: “There is an urgent need for a new TB vaccine, and we are very pleased to be working on the clinical development of MVA85A/AERAS-485. This is an important milestone toward finding a solution for this terrible disease.”

### Partnership Roles and Responsibilities

**Emergent:** Emergent is providing funding for product development and support for the phase 2b clinical trials expected to take two years. Emergent provides product development expertise and a commercial perspective to the partnership; it is responsible for development of commercial-scale manufacturing processes, and commercialization in the developed world, including India and China. Emergent manages its participation in the OETC through two separate teams — a product development team headed by Dr. Stephen Lockhart, senior vice president of product development, and a commercial team led by Vice President of Business Development José Ochoa, as well as staff from legal and finance departments.

**Oxford/Isis:** The Jenner Institute at the University of Oxford is the innovator of TB vaccine candidate MVA85A and led its development through phase 2a, with the support of the Wellcome Trust. The University of Oxford and Isis together provide the partnership with intellectual property and know-how, clinical data, seed stocks, and tuberculosis vaccine clinical development expertise. They are responsible for the phase 2b infant efficacy trial in collaboration with Aeras and the University of Cape Town’s South African TB Vaccine Initiative (SATVI), and they contribute to oversight of the product development plan.

**Aeras Global TB Vaccine Foundation:** Aeras has made substantial investment in the development of clinical sites, in collaboration with SATVI, for conducting TB trials. In the past, Aeras has invested heavily in SATVI to build capacity at the organization required to conduct large scale clinical trials for TB vaccines. During this next phase of development, Aeras is providing a £4 million contribution that matches that of the Wellcome Trust to support phase 2b trials. Aeras is the clinical trial sponsor of phase 2b. Aeras has also taken responsibility for supply and distribution of the vaccine in the developing world through an agreement with the Consortium.
The Wellcome Trust: The Wellcome Trust had already been a key funder of Oxford’s efforts to develop MVA85A through phase 2a. During phase 2b, the Trust is contributing an additional £4 million.

Project Timeline and Evolution

1997
Dr. Helen McShane at the Jenner Institute is funded as a Clinical Research Fellow to conduct promising early stage research for a TB vaccine.

2001
The Wellcome Trust funds a translational program to conduct early-stage clinical safety studies with one of the candidate vaccines, MVA85A.

2002-2006
Promising safety and immunogenicity data from the clinical trials conducted with MVA85A in the UK and Africa.

Late 2004
Aeras and Oxford have initial conversations about the potential for collaboration based on Aeras’ familiarity with Oxford scientists and publications.

January 2005
Oxford presents data on MVA85A to Aeras’ Vaccine Selection Assessment Committee.

Late 2006
BIO Ventures for Global Health (BVGH) develops and presents a TB business case titled “Tuberculosis Vaccines: A Case for Investment.”

January 2007
Emergent learns of BVGH’s TB business case and expresses interest in Oxford’s MVA85A vaccine candidate.

April 2007
Emergent and Oxford/Isis initiate discussions on the development of the MVA85A vaccine candidate. Separately Aeras and Oxford/Isis continue discussions.

May 2007
Three-way discussions/negotiations begin between Emergent, Aeras, and Oxford.

August 2007
A preliminary agreement is reached between Emergent and Oxford/Isis.

January 2008
Collaborative work begins between Emergent and Oxford/Isis based on mutual trust and understanding, as the details of the joint venture are agreed and finalized.

July 2008
The OETC is finalized and formally announced. Separate agreements are signed between the OETC and Emergent and the OETC and Aeras.

April 2009
Phase 2b clinical trials are launched in South Africa by Oxford and Aeras in collaboration with SATVI.

The Jenner Institute and the University of Oxford, funded by the Wellcome Trust, innovate and develop TB vaccine candidate MVA85A through phase 2a: The MVA85A vaccine candidate was originally developed at the Jenner Institute and the University of Oxford by Dr. Helen McShane, a Wellcome Trust Senior Research Fellow, who worked with Dr. Sarah Gilbert, a Reader in Vaccinology, and Professor Adrian Hill, a Wellcome Trust Principal Research Fellow. The hope was that if licensed, MVA85A would act as a “boost” vaccine to enhance the existing BCG vaccine. Rather than replacing BCG, it would be given to those who have already received the BCG vaccine in order to improve protection against TB in childhood, adolescence, and adulthood. Clinical trials for MVA85A began in 2002 in the United Kingdom and continued in Gambia, South Africa, and Senegal. As noted, MVA85A has been found to be safe and highly immunogenic in all clinical trials to date. It has been found to improve BCG protection in mice, guinea pigs, non-human primates, and cattle.

BVGH presents a market case for investment in TB vaccines: In 2006, BVGH evaluated the global market opportunity for TB vaccines and released its report, *Tuberculosis Vaccines: The Case for Investment*, which presented a strong financial and social case for investment in TB vaccines. The report demonstrated that the market for TB vaccines should be sufficient to attract innovators and that a positive return on investment was possible due to the market in both the developed world and emerging economies. It also highlighted that the potential value for the developing world justifies substantial public-sector investment in TB vaccine development. The BVGH TB vaccine business case was presented in January 2007 at an international conference on tuberculosis and sparked the interest of a number of companies, including Emergent. BVGH helped interested parties understand the market opportunity, evaluated the pipeline and matching of interests, and ultimately introduced Emergent and the University of Oxford to one another.
(1) Emergent provides funding and staff to the OETC and has 51% ownership. The OETC has licensed to Emergent the right to become the commercial market supplier (including India and China) of any products developed by the OETC.

(2) Oxford, through its technology transfer office Isis, licensed the TB vaccine candidate MVA85A to the OETC in exchange for future milestone and royalty payments and 49% ownership in the OETC. The OETC works closely with Oxford scientists to develop MVA85A through phase 2b trials. The OETC will conduct product testing.

(3) The Wellcome Trust provides the OETC with funding (£4M) to conduct phase 2b clinical trials.

(4) Aeras provides the OETC with funding (£4M) as well as with developing world clinical trial sites. Aeras has licensed the supply rights for any developing world (non-commercial) distribution of MVA85A for humanitarian purposes.

(5) Both Emergent and Aeras, in addition to the OETC, will conduct product testing.
Emergent and Oxford discuss partnering to further develop TB vaccine candidate MVA85A: As noted, BVGH’s TB Business Case illustrated that Oxford’s vaccine was clinically advanced and as yet had not completed a commercial partnership agreement. After learning this, Emergent management met with Oxford in April 2007 and had good initial conversations with Oxford scientists. Through Oxford’s technology transfer office, Isis, negotiations began to license MVA85A to Emergent for commercialization. The key question remaining is whether MVA85A will prevent disease in humans. This will be evaluated during ongoing phase 2b and future phase 3 trials. When Oxford reached phase 2a, however, a commercial partner was required to move the vaccine forward quickly. At this time, Emergent conducted due diligence on this potential partnership. The company reviewed patent filings and standard operating procedures and protocols for the clinical trials to assure itself that the program it would be investing in met product development requirements. Ultimately, Oxford selected Emergent as its preferred partner. A preliminary agreement was reached in August 2007, and Emergent made an initial monetary commitment. As negotiations progressed, however, a joint-venture model was proposed as the optimal business structure to meet both commercial and humanitarian objectives for the program, and the idea of the OETC was born. The Consortium was finalized in July 2008, but collaborative working relationships had already been established by January.

Overview of Contractual Agreements
Oxford, through its technology transfer office, Isis, has exclusively licensed the MVA85A vaccine candidate and related technology to the OETC. Emergent has 51% ownership in the OETC, and Oxford has 49% ownership — 24.5% with the university itself and 24.5% distributed among various Oxford scientists. A total of £8 million (£4 million each from Aeras and the Wellcome Trust) has been provided for the phase 2b clinical trials. Emergent is providing additional funding to support the development of a product development package.

Emergent has a separate licensing agreement with the OETC giving it rights to commercialize the vaccine in the developed world including India and China. Aeras has its own licensing agreement with the OETC giving it rights to distribute the vaccine in the developing world for the humanitarian purpose of ensuring availability and access to the vaccine for those who need it.

Strategic Value Realized
Emergent Perspective
Financial profit: From a commercial perspective, Emergent has expectations of commercial returns. These expectations were a key driver in the decision to engage in TB vaccine development. José Ochoa states that “this is an interesting commercial opportunity, particularly in Eastern Europe, India, and China.”

Fit with mission: Working on tuberculosis vaccine development is a strong fit with Emergent’s broader company mission: “to protect life.” As one Emergent employee explains, “everybody is excited to be supporting a vaccine this clinically advanced to prevent this deadly disease. Our corporate mission statement ‘to protect life’ was obviously crafted in context of our biodefense product portfolio, but really resonates with this project.”
**Establishing expertise:** Emergent’s decision to engage in TB vaccine development was viewed as part of its core strategy, as it is viewed as a fitting expansion within infectious diseases — an area in which Emergent can claim expertise based on its work on typhoid, hepatitis B, and anthrax. Emergent also has considerable experience through its typhoid vaccine in performing clinical trials in less developed countries; field studies in endemic regions will also be required for MVA85A. In this way, working on TB is seen as a logical expansion in an area where Emergent is an expert. Emergent characterizes this effort as follows: “This expansion into more commercial vaccines demonstrated that we are more than only a biodefense company — it put us on the map.”

**Use of Consortium to facilitate acquisition of phase 2 product:** Emergent was able, through this consortium, to acquire a phase 2 product. José Ochoa explains that, in the end, all the parties wanted the same thing: to commence a phase 2b clinical trial in early 2009. He said, “The parties were able to put aside their differences and reached an agreement that preserves each participant’s vested interest and puts the focus on the upcoming clinical trial. All participants will share in the benefits of success and in the risks of the project. The product provides an important later-stage addition to the Emergent pipeline.”

**Reputation, access to key players in global health:** Emergent sees a public relations value in working on global health projects — but highlights that this is not simply “feel good PR, but rather, a reputational value that allows Emergent access to key players in the global health space.” Emergent sees having access to and credibility with these global health stakeholders as crucial to its long-term strategy and highlights this as an important benefit this partnership has provided.

**Oxford/Isis Perspective**

**Commercial perspective:** Oxford believes that the fact that the program was partnered so late in the vaccine candidate’s development reflects the lack of commercial interest in taking a TB vaccine forward. It became apparent to Oxford that it had taken the vaccine as far as it could on its own and that there was a need to begin considering factors such as virus manufacturing expertise, product formulation, mechanisms for sale, and distribution and supply chains — all issues for which having a commercial partner would be essential.

**Ability to continue TB research:** Oxford found the idea of the joint venture attractive in that it provided the ability to retain significant input into the development of the vaccine. Oxford has an expertise in cellular immunology that is critical to the successful development of MVA85A. Emergent, on the other hand, had an expertise in MVA manufacturing, product development, and running clinical trials, but required Oxford’s deep understanding of the clinical stages of TB. Had Oxford partnered with a large pharmaceutical company, management believes that there might have been less willingness to keep the researchers involved than the partnership with Emergent provides. Furthermore, the agreement made it possible for Oxford to continue to contribute to the vaccine’s development, which can be unusual when a commercial partner licenses a product.

**Certainty of product development:** Oxford wanted a commercial partner who would guarantee that the vaccine candidate would not be marginalized. As Dr. Helen McShane of Oxford explains, “the last thing Oxford wanted was for the candidate to be purchased and stuck on a shelf without serious development efforts. It was clear to us that this project would be important to Emergent and that they would work to develop the vaccine candidate.”
Case Study 2

The principal investigator at the University of Oxford, Dr. Helen McShane. Dr. McShane was funded as a Wellcome Trust Clinical Research Fellow within the research team of Dr. Adrian Hill at the University of Oxford. As Dr. McShane’s research evolved and Oxford filed patents on certain discoveries, the Wellcome Trust became interested in funding Dr. McShane’s work further — and expanded funding to early stage pre-clinical and clinical safety studies. This partnership enables the Wellcome Trust to work in partnership with other funders to push a research discovery enabled by its early support down a product development pathway with increased likelihood of success.

Overcoming Key Challenges

Meeting the needs of all partners through joint venture: The partnership began as a proposed straight licensing agreement from Oxford to Emergent. Though the possibility of a joint venture was discussed, Oxford’s initial preference was to take the more typical approach of a licensing agreement. Usually at phase 2 a licensing deal would have long since been signed. Oxford, however, wished to remain a participant in the development of the vaccine. Dr. Jacqui Shea, General Manager of the OETC states that “academic institutions fear that when they license a product to big pharmaceutical companies they have little influence over its destiny. Oxford is extremely pleased to remain an integral part of the continuing efforts to bring this product to market and has embraced the benefits of a public-private partnership.” As discussions between Oxford and Emergent moved forward, a joint venture became a real option that seemed to have potential to meet the needs of all parties — despite the fact that for the university being part of a joint venture was more complex than an arm’s length licensing agreement accompanied by a sponsored research agreement between Emergent and the university. And though “this was the most complex deal that Isis has ever done,” negotiations were successful and agreement was reached with all parties.

Geographic fit: The geographical distribution of the offices provided a good fit. As José Ochoa summarizes: “When discussions with Oxford launched, Emergent could offer them a product development company in Reading, UK, close to Oxford, a product development group in Germany with expertise in MVA, and an office in Rockville, MD just down the street from Aeras.”

Aeras Global TB Vaccine Foundation Perspective

Fit with Mission: Aeras is dedicated to developing and delivering new TB vaccines and ensuring that they are made available and accessible at an affordable cost to developing country populations most in need. Toward that end, Aeras has assembled a robust vaccine product pipeline through its in-house vaccine development program and in collaboration with its global development partners. This collaboration with the OETC to move the MVA85A vaccine candidate into phase 2b clinical trials is a natural collaboration for Aeras, who views the project as an important step toward developing a more effective TB vaccine. Aeras has the clinical expertise and has helped establish a world-class clinical field site in Worcester, South Africa, where the candidate will undergo clinical testing at the University of Cape Town’s South African Tuberculosis Vaccine Initiative (SATVI).

The Wellcome Trust Perspective

Long-term relationship: The mission of the Wellcome Trust is to improve human and animal health through funding basic scientific research, which accounts for 70% to 80% of the Wellcome Trust activities, and through funding translational research that pushes research discoveries along a product development pathway. The Wellcome Trust, according to its head of business development in technology transfer, Dr. Richard Seabrook, is “in a fortunate position because as a UK charity with a substantial endowment we are able to take on early stage product development for neglected and tropical diseases.” Related to this project, the Wellcome Trust has been the key funder of the development of the MVA85A vaccine candidate for ten years. At that time, the Wellcome Trust funded
Project governance: In such a complex joint venture, all parties agree that clear and transparent project governance is critical to success. A board of directors was established to oversee the joint venture with a structure that allows for senior management at both Oxford/Isis and Emergent to be represented. Beneath the board, the project is managed via a steering committee that meets on a monthly basis and consists of representatives of Oxford/Isis Innovation Ltd., Emergent, and the Wellcome Trust. All parties have found that steering committee meetings are a good forum for airing any issues that emerge and for ensuring alignment among all partners. The joint venture also has its own independent general manager, Dr. Jacqui Shea, who works closely with Emergent and Oxford every day. Day-to-day project teams are divided into the following categories: clinical, manufacturing, quality, legal/commercial, marketing, and regulatory teams. Partners agree that the success of this project so far stems largely from clear definition of roles and responsibilities, representation of both Oxford/Isis and Emergent at every level of project management, and a governance structure that allows for the proactive identification of issues as they emerge.

Determining ownership: Coordinating with the Wellcome Trust and Aeras was necessary, as initially it was unclear if all parties would become part of the joint venture. Aeras reached a decision that it did not want to formally enter into the joint venture, opting instead to establish a developing world supply agreement with the Consortium. Yet as noted, the structure of the joint venture is flexible enough to allow for inclusion of additional parties moving forward, if desired.
Disease Overview
More than 40% of the world’s population is at risk for malaria, and between 300 million and 500 million new cases of malaria are recorded each year. Malaria is a parasitic disease transmitted by infected mosquitoes. Severe malaria can cause anemia, acute respiratory distress symptom, coma, and death. Young children and pregnant women, especially those living in sub-Saharan Africa where the more virulent *Plasmodium falciparum* parasite is dominant, are most vulnerable to malaria. They account for the majority of the nearly one million deaths estimated to occur annually.

Commonly used antimalarials are increasingly ineffective because of widespread drug resistance. To combat the emergence of resistance to the drugs remaining in the antimalarial arsenal, use of combination therapies has been urged. Artemisinin-based combination therapies (ACTs) have proven especially efficacious. Artemisinin, a structurally complex natural product, is comparatively expensive to manufacture. This, until recently, precluded the use of ACTs in many impoverished countries. With the recent reduction in artemisinin costs and the advent of the Affordable Medicines Facility for Malaria (AMFm), which will provide a subsidy for public and private first-line wholesalers when purchasing ACTs from manufacturers, access to effective antimalarial treatments may improve. The initial costs of $225 million to $233 million for medicines forecasted to be procured through the AMFm in the first two years will be shared by UNITAID (an international mechanism to finance quality-assured medicines and diagnostics against HIV/AIDS, malaria, and tuberculosis, created by France and supported by Norway and twenty-six other nations), and the UK government. Several other organizations and governments have indicated willingness to contribute additional funding to the initiative. Yet as medical resistance is expected to develop to ACTs, there is a need to begin developing the next generation of antimalarial treatments today.

Market Overview
While there is a small developed-world market for prophylactic antimalarial drugs, compounds developed to treat an established infection primarily address developing world needs, particularly in areas of dire poverty. As the creation of the AMFm indicates, the patients and their governments have insufficient resources to purchase needed antimalarials. Although the AMFm and other programs for purchasing antimalarial drugs will allow the purchase of potentially millions of doses, they intend to purchase these products on a “no profit, no loss” basis. As a result, for-profit drug developers, even if they can find “push” funding for research and development (R&D), lack a profit motive to allow malaria programs to compete for resources on a par with their other developed world initiatives.
Project Overview

The Broad Institute of MIT and Harvard (the Broad Institute), Genzyme Corporation (Genzyme), and the Medicines for Malaria Venture (MMV)—formed a partnership in 2006 to address the significant need for novel malaria treatments. The goal of the partnership is to sustain a large-scale drug discovery effort that would discover novel antimalarial compounds and to advance them to the point of investigational new drug (IND) applications. The program aspires to deliver a new antimalarial drug to the clinic every four years, if sufficient financial support can be established.

Applying roles that have traditionally proven effective in industry-biotech collaborations, the Broad Institute conducts research on the biology and pathology of the disease along with high throughput drug screening, while Genzyme donates its expertise in drug discovery, including high throughput screening, medicinal chemistry, drug metabolism, preclinical development, and project management to prepare clinically viable products. Genzyme also contributes financially to the collaboration. MMV is the principal financial sponsor of this project and serves as scientific expert advisers. It provides a project director, who is part of the project team (PDT) and expert review from its External Scientific Advisory Committee (ESAC). The project is overseen by a Joint Steering Committee, containing one senior person from the Broad Institute, Genzyme, and MMV. Genzyme conducts some of the R&D activity itself but also outsources some of chemistry and drug metabolism and pharmacoki-

Partner Profiles

Medicines for Malaria Venture is a not-for-profit public-private partnership that was established as a foundation in Switzerland in 1999. It is dedicated to reducing the burden of malaria in disease-endemic countries by discovering, developing, and facilitating delivery of new, effective, and affordable antimalarial drugs. MMV works to create a world in which innovative medicines will cure and protect the vulnerable and under-served populations at risk of malaria, and help to ultimately eradicate this terrible disease. Its mission is to bring public, private, and philanthropic partners together to fund and manage the discovery, development, and delivery of new medicines for the treatment and prevention of malaria in disease-endemic countries.

Genzyme is a public biotechnology company headquartered in Cambridge, Mass., with annual revenues exceeding $4.6 billion and 11,000 employees in locations spanning the globe. With many established products and services helping patients in nearly 100 countries, Genzyme is a leader in the effort to develop and apply the most advanced technologies in the life sciences. The company’s products and services are focused on rare genetic disorders, kidney disease, orthopedics, transplants, cancer, and diagnostic testing. Genzyme’s commitment to innovation continues today with a substantial research and development program focused on these fields, as well as immune disease, infectious disease, and other areas of unmet medical need.

The Broad Institute of MIT and Harvard is an American research institute dedicated to the transformation of medicine with genomic knowledge. The Broad Institute was launched in 2004 with the visionary philanthropic investment of Eli and Edythe Broad, who joined with leaders at Harvard and its affiliated hospitals, MIT, and the Whitehead Institute to pioneer a “new model” of collaborative science bringing together world-class faculty, professional staff, and students from throughout the MIT and Harvard communities and beyond, empowering them to work together to identify and overcome the most critical obstacles to realizing the full promise of genomic medicine.
netics (DMPK) activities to the Indian-based contract research organization Advinus Therapeutics Pvt. Ltd. (Advinus). Genzyme also contracts Shanghai ChemPartner Co. Ltd. (ChemPartner), a contract research organization (CRO) in China, to conduct medicinal chemistry in one of the partnership’s lead optimization projects.

**Progress to Date**

In the three years since its launch, the program has yielded two compound families that have advanced into lead optimization. This is the stage of drug discovery at which serial cycles of biochemical and biological testing are applied to a set of similar compounds based on a common core “scaffold” believed to have promising drug-like properties. The process is designed to identify the molecule(s) with optimal potency, safety, and pharmacokinetic properties to enable the formal identification of a product candidate that can be taken to preclinical and clinical development. The project’s goal is to identify the first candidate for pre-clinical assessment by the end of 2009 and to be ready to enter human volunteer studies by the end of 2011. This would mean that the program will have taken less than five years to reach its first dose in humans. The program has multiple targets behind this one that may have additional resources dedicated to them if they are deemed worthy of additional investment.

The project’s staffing and funding has also expanded. As Roger Wiegand, associate director of the Infectious Disease Initiative at the Broad Institute, explains early on, the project was run by only one person at the Broad Institute: Professor Dyann Wirth from the Harvard School of Public Health, alongside a few students and two or three scientists at Genzyme. Today, the team includes ten people (FTE) at the Broad Institute, nine people (FTE) at Genzyme, and approximately fifteen outsourced FTEs contracted through Genzyme. There are an additional four individuals at Genzyme and six people at the Broad Institute/Harvard School of Public Health who contribute significantly to the project but are not supported directly by the grant. The majority of the funding comes from MMV, although there is a substantial donation from Genzyme.

**Partnership Roles and Responsibilities**

The Broad Institute, in collaboration with Harvard School of Public Health, is engaged in malaria biology research and novel target identification. Using its own proprietary compound libraries as well as those of Genzyme, the Broad Institute conducts high throughput screening and early stage medicinal chemistry on some of the active compounds. There is also an effort directed at identifying the mechanism of action of any products that show activity against malaria parasites. The Broad Institute has ten FTEs devoted to the project with additional support provided by six individuals who are not directly supported by the grant.

Genzyme is responsible for downstream aspects of drug discovery, including the management of the hits-to-leads and lead optimization programs. The original plan also involves using Genzyme’s extensive experience and capability in preclinical development, to help with the pharmacokinetic (PK), safety, and toxicology studies that are required as part of the preclinical dossier. High throughput screening, (both against the whole parasite and against molecular targets) has been shared between the Broad Institute and Genzyme. For the medicinal chemistry work, Genzyme outsources some of this work to Advinus Therapeutics and ChemPartner. Genzyme also hosts staff from the Broad Institute by providing office space and laboratory equipment for the project as necessary. Genzyme offsets approximately 50% of its own costs through MMV funding and has approximately nine FTEs devoted to the project with additional support provided by four other individuals who are not directly funded by the grant.

**MMV** is the central financial sponsor of this project, providing between 70% to 80% of the total costs of the project alongside a substantial donation from Genzyme. MMV provides expert advice to the drug
discovery efforts, through its own project director, as part of the project team, and also by providing a senior industry professional as a mentor for the medicinal chemistry. The project director participates in monthly project meetings and helps to provide connections to other MMV projects. The selection and funding of individual targets is reviewed annually by MMV’s External Scientific Advisory Committee (ESAC). The overall percentage contribution of MMV to the collaboration is strongly directed by the feedback from ESAC. Because of MMV’s global connections, MMV is also able to provide connections to other laboratories and provide access to resources for in vivo testing. Ultimately, MMV will be responsible for running clinical trials on any drug candidates developed.

**Project Timeline and Evolution**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Genzyme and the Broad Institute initiate conversations regarding a malaria collaboration.</td>
</tr>
<tr>
<td>Late 2005</td>
<td>Early research collaborations begin.</td>
</tr>
<tr>
<td>2006</td>
<td>Genzyme and the Broad Institute jointly approach MMV to seek funding for a large-scale drug discovery effort. MMV agrees to fund the collaboration.</td>
</tr>
<tr>
<td>2007</td>
<td>First year of significant funding by MMV — a total grant of $1.62 million.</td>
</tr>
<tr>
<td>2008</td>
<td>Expansion of the collaboration to bring on board external contractors for medicinal chemistry. Total funding from MMV of $3.73 million, with an additional $1.1 million from Genzyme. First family of compounds (based on a Genzyme compounds from whole cell screening) enters H2L chemistry.</td>
</tr>
<tr>
<td>2009</td>
<td>One project enters lead optimization; a second compound series enters H2L chemistry. Approaches to several early targets have been abandoned.</td>
</tr>
<tr>
<td>2010</td>
<td>Start of preclinical evaluation for most advanced project is planned.</td>
</tr>
<tr>
<td>2011</td>
<td>Leading candidates are expected to enter phase I volunteer studies.</td>
</tr>
</tbody>
</table>

**Genzyme and the Broad Institute initiate conversations in the field of malaria:** In mid-2005, the Broad Institute approached Genzyme to discuss possible collaborations in global health. These discussions progressed quickly to early research collaborations by the end of 2005, focused on discovering novel treatments for malaria.

**Genzyme and the Broad Institute together approach Medicines for Malaria Venture (MMV) to seek funding:** In 2006, after initial collaboration had begun, Genzyme and the Broad Institute jointly approached MMV to seek funding for a drug discovery effort with the goal of putting a new drug in the clinic every four years. The decision to expand the program and seek additional resources was made largely by leadership of both organizations. MMV agreed to fund the program in 2006.

Genzyme, the Broad Institute, and MMV work closely together. Today, this program is staffed by approximately thirty-five scientists from across the partner organizations and outsourced contractors. Though the project is managed by Genzyme by Dr. Edmund Sybertz, senior vice president of scientific affairs, there is daily coordination with both the Broad Institute and with MMV. As Sybertz explains, “This is a remarkable team effort and if you came to one of our team meetings you would not be able to tell who is from which organization.”

**Overview of Contractual Agreements**

According to Roger Wiegand of the Broad Institute, Genzyme determined early on in the process that “There’s no pot of gold at the end of this rainbow,” and therefore agreed to license all IP in the field of malaria related to this project to MMV on a charitable basis, with no expectation of financial return. Negotiations with the Broad Institute eventually led to a three-way agreement among Genzyme, the Broad Institute/Massachusetts Institute of Technology (MIT), and MMV by which each party maintains the rights to any non-malaria uses for their discoveries while all malaria applications flow to MMV.
(1) MMV funds Genzyme and the Broad Institute to conduct malaria biology research and novel target identification.

(2) Using its own proprietary compounds as well as compounds from Genzyme, the Broad Institute conducts high throughput screening with Genzyme and early stage medicinal chemistry on some of the active compounds. The Broad Institute contributes staff to work on the downstream preclinical research at Genzyme’s laboratories. Genzyme manages hits-to-leads and lead optimization programs and also helps with PK, safety, and toxicology studies. Genzyme outsources some of the medicinal chemistry activities to Advinus Therapeutics and ChemPartner.

(3) The IP rights to all products in the field of malaria stemming from the collaboration flow back to MMV for clinical development and eventual distribution. IP outside the field, whether developed at the Broad Institute or Genzyme, is retained by the inventors.
Strategic Value Realized

Genzyme Perspective

Corporate commitment to create impact: Genzyme believes that industry has a unique contribution to make by applying drug discovery and pharmaceutical development capabilities to create solutions for global health — filling a gap that currently has too little funding and activity. In partnership with others, Genzyme seeks to be a catalyst in advancing the development of novel therapies for neglected diseases, but does not seek to profit from the commercialization of these therapies. If a successful drug is developed through these research collaborations, Genzyme will grant the rights and intellectual property for use to non-profit organizations with no commercial interest for Genzyme related to neglected diseases. The work Genzyme does in global health is considered charitable. According to the company’s employees, Genzyme CEO Henri Termeer believes that Genzyme has a responsibility to make the infrastructure that exists at companies like Genzyme — but not anywhere else in the world — available. He believes that by not doing so, biotechnology as an industry runs the risk of being abandoned in terms of how society views it.

Supports commercial strategy: Genzyme’s CEO has publicly said that to be successful and expand commercial operations, it is essential to participate in the countries in which you wish to operate, particularly emerging markets. Genzyme works to be a socially responsible player in the culture of the countries in which it operates. It is part of Genzyme’s commercial strategy to be involved in global health because, as Associate Director of Communications Lori Gorski explains, “it builds the confidence of government officials and attracts the right employees in those regions. Genzyme’s commitment emerges from a sincere belief that to be commercially successful in a country, you need to demonstrate that you are a part of the region and its culture.”

Retaining talent: Genzyme believes that working on projects related to neglected diseases is an important motivator for its most talented scientists. As Sybertz summarizes: “Working on this is clearly a motivational factor because they see their labors going to some important societal causes. And scientifically, these are extremely interesting problems to try and solve.”

MMV Perspective

Fit with mission: MMV’s mission is to bring entities from the public, private, and philanthropic sectors together to fund and manage the discovery, development, and delivery of new medicines for the treatment and prevention of malaria in disease-endemic countries. This project is one of MMV’s three “miniportfolios.” Other miniportfolios include those being run at GlaxoSmithKline at its global health R&D facility in Tres Cantos, Spain, and at the Novartis Institute for Tropical Diseases in Singapore.

Shared funding: MMV has very few programs where it works with small biotechnology firms, in part because small to medium companies do not contribute any money themselves to the project, and therefore collaborations tend to be more expensive. Genzyme, as one of the largest biotechnology companies with more than $4.6 billion in 2008 sales and $400 million in net profit, is able, much like GlaxoSmithKline and Novartis, to make both in-kind and cash contributions to the project. However, MMV notes that despite this contribution, the effective FTE rate that MMV pays for this project is among the highest of its collaborations, as larger pharmaceutical companies such as Novartis and GlaxoSmithKline are able to make significantly larger contributions. As Timothy Wells, Chief Scientific Officer at MMV explains, “One factor for the future is how we can use Genzyme and the Broad Institute’s contacts to bring in local donors specifically for this project, or to find other ways of reducing the cost structure.”

The Broad Institute Perspective

Access to equipment and expert advice: Genzyme summarizes its value proposition to an organization such as the Broad Institute as follows: “Organizations like the Broad Institute are good at identifying targets by screening a library that could be effective against disease, and Broad has a special program devoted to
malaria — they have a library of targets. Broad has compound libraries that could be interesting, and they have innovative screening capabilities. They have identified early leads but don’t have the capacity or infrastructure to bring those forward to clinical candidates. That’s where Genzyme can come in and take the molecules and think about how to deliver them effectively, make them potent, make them safe, consider how their influence can be sustained, and so forth.” Dyann Wirth, the principal investigator at the Broad Institute, has a deep interest in conducting malaria research and, as Roger Wiegand puts it, “We get access to $20M of lab equipment and a pool of experts who really know their stuff when it comes to the more downstream aspects of drug discovery and development. This is a huge leverage point for us — for a fairly minimal investment we get a huge payback (as does MMV). We get a ton of expert advice for free.”

**Overcoming Key Challenges**

**Structuring IP agreements:** Partners insist that there was little challenge related to intellectual property rights, particularly as Genzyme committed from the beginning to contribute any intellectual property related to malaria to the public good. Licenses flow to MMV for the use of those compounds. However, to formalize these agreements, intervention was required at the highest levels of both Genzyme and MIT to secure such a commitment, and a three-way agreement was subsequently reached. It is significant that intervention was required at the highest level of the organizations, as it illustrates the buy-in that is required to navigate and finalize such contracts even between parties that are largely aligned.

**Cultural differences:** One of the challenges faced in the beginning was highlighted by both partners is the simple challenge of two very different organizations — the Broad Institute and Genzyme — working together. As one Genzyme employee notes, “The blending of academia with a corporate environment was difficult, because each side needed to understand the unique challenges that the other part of the program faced.” These cultural differences eventually became one of the program’s strengths, as chemists from industry have seen value in the way academics handle projects. Scientists at the Broad Institute saw the value of how industrial scientists think about science, particularly in areas such as, in the words of Wiegand at the Broad Institute, “establishing and adhering to a rigorous testing cascade that the collaboration has put into place.”

**Managing timelines:** The program’s goals include putting a new drug in the clinic every four years. To meet its product discovery timelines, the program has relied on screening techniques emerging from the Broad Institute and Harvard School of Public Health, synthetic chemistry techniques that reduce synthesis of certain compounds from seven steps to two, and a rigorous testing cascade with a clear order of testing, decision rules and a “kill early, kill often” philosophy. The partners stress that moving the program forward at a rapid pace relies on maintaining commitment and coordination on the part of each of the partners.

**Sustained involvement:** Sustaining this program is a challenge for Genzyme as there is no possibility of financial gain in engaging in this area. Genzyme supports approximately 50% of its own costs. MMV provides funding of 70% to 80% of total costs, and this funding makes the difference in Genzyme’s willingness to contribute significant resources. As explained by Dr. Edmund Sybertz: “We haven’t set up an institution or dedicated group to focus solely on neglected diseases, and we have sought outside funding to offset internal costs. This allows us to manage these efforts in the context of other organizational needs and priorities and makes working in global health a sustainable, long-term possibility.” In addition, the ability to collaborate with CRO partners such as Advinus and ChemPartner allows Genzyme to apply additional resources to these efforts where it would otherwise be difficult to commit its own FTEs to the project.
CASE STUDY 4

Scynexis Inc., Anacor Pharmaceuticals, the Drugs for Neglected Diseases initiative, the Haskins Laboratory at Pace University, and the Swiss Tropical Institute — Human African Trypanosomiasis Drug Discovery

Disease Overview
The few currently available treatments for human African trypanosomiasis (HAT), also known as sleeping sickness, can be toxic and prohibitively difficult to administer. Melarsoprol, which has long been the only drug available for stage 2 HAT (an advanced stage where the parasites move from the plasma into the central nervous system and the stage at which the majority of patients are diagnosed), is toxic and must be administered intravenously three to four times per day for three to four months. Despite being 80% to 90% effective, its toxicity leads to death in up to 5% of patients receiving the treatment. Recently eflornithine has replaced melarsoprol as the clinically preferred first-line medication but it is not available to the majority of patients because it is extremely difficult to administer, particularly in resource-poor settings where patients are most in need. Eflornithine requires fifty-six infusions, administered every six hours over two weeks, and each course of therapy requires that approximately sixty pounds of the solution must be transported to remote sites, often with limited road access and lacking electricity. As a result of these issues, approximately two-thirds of HAT patients are still treated with melarsoprol. Furthermore, according to Scynexis, “the difficulty of diagnosis, stage determination, and increasing numbers of treatment failures pose additional clinical challenges.” For all these reasons, there is an urgent need to develop new effective, affordable, and deliverable therapies for HAT.

HAT poses a devastating threat to the lives of sixty million people in thirty-six countries of sub-Saharan Africa where the disease is prevalent. The disease is caused by a single-cell parasitic protozoan called Trypanosoma brucei and transmitted by tsetse flies. The disease progresses from fever and fatigue (stage 1 — blood stage) to severe neurological conditions including extreme fatigue, major disturbances to patients’ sleep cycles, and coma (stage 2 — central nervous system or CNS stage). If left untreated, HAT always causes death. There are between 300,000 and 500,000 people infected with HAT, and each year an estimated 50,000 to 70,000 new cases are recorded. Approximately 66,000 people die from HAT every year.

Market Overview
As with diseases like leishmaniasis and schistosomiasis, most of those affected live in severe poverty. Thus, there is not a significant private or public commercial market for treatments for HAT. Indeed, HAT afflicts those in some of the poorest, least accessible areas of the world, in Central Africa. Research and development (R&D), manufacturing, and distribution of new thera-

1 Scynexis and DNDi Extend Collaboration to Identify Drug Candidates to Treat Sleeping Sickness. December 11, 2008. Source: Scynexis, Inc.
2 BVGH Global Health Primer. BVGH, October 2007; 24.
3 WHO Fact Sheet; http://www.who.int/mediacentre/factsheets/fs259/en/
4 SBRI http://www.sbri.org/diseases/african.asp
Partner Profiles

**Drugs for Neglected Diseases initiative: DNDi** is an independent, not-for-profit development partnership (PDP) working to research and develop new and improved treatments for neglected diseases such as malaria, leishmaniasis, human African trypanosomiasis (HAT, also known as sleeping sickness), and Chagas disease. DNDi was established in 2003 by five public-sector institutions — the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia and France’s Pasteur Institute; one humanitarian organization, Médecins sans Frontières (MSF); and one international research organization, the UNDP/World Bank/WHO’s Special Programme for Research and Training in Tropical Diseases (TDR), which acts as a permanent observer to the initiative. DNDi works in partnership with industry and academia and has established the largest R&D portfolio for kinetoplastid (flagellate protozoa) diseases.

**Anacor Pharmaceuticals** is a private biopharmaceutical company located in Palo Alto, California. The company was founded in 2002 and is developing novel small-molecule therapeutics derived from its boron chemistry platform to treat infectious and inflammatory diseases. The most advanced is AN2690, a novel topical antifungal for the treatment of toenail onychomycosis, a fungal infection of the nail and nail bed. The company has entered into a worldwide license, development, and commercialization agreement with Schering-Plough for the development and commercialization of AN2690 for all indications including the treatment of onychomycosis. In addition, the company is developing systemic antiviral and antibacterial therapeutics under a research and development agreement with GlaxoSmithKline.

**Scynexis, Inc.,** is a private spin-off biotech created by a team of researchers from Aventis CropScience. The company is headquartered in the United States with more than 100 employees located in North Carolina. Scynexis leverages its scientific expertise by helping global clients discover and develop new drugs, including using its proprietary platforms, Kinase inhibitor Technology (KIT), HEOS Software Suite, and MEDCHEM-FACTORY. The company also uses its proprietary technologies to develop its own pipeline which includes a lead product candidate for hepatitis C.

**The Haskins Laboratory at Pace University** is a department in the Dyson School of Arts and Sciences at Pace University, Downtown Campus in New York. Previously a privately endowed nonprofit research laboratory, it was assimilated into Pace in 1970. The microbiology group specialized in biochemistry and nutritional requirements of free-living and parasitic protozoa. Dr. Cyrus Bacchi has been a member of the laboratory since 1964 and was director from 1977 to 2006. Dr. Nigel Yarlett — a twenty-year veteran — became director in 2006. For many years Drs. Bacchi and Yarlett worked with a variety of free-living and parasitic protozoa including African trypanosomes, trichomonads, Cryptosporidium, and Microsporidia. The group has had WHO funding for 30 years and NIH funding from 1976 to 2009. Both Dr. Yarlett (Chemistry) and Dr. Bacchi (Biology) are professors in the School of Arts and Sciences.
pies will all need support and incentives provided by
the industrialized world.

**Project Overview**

The Geneva-based nonprofit foundation **Drugs for
Neglected Diseases initiative (DNDi)** in April 2006
engaged the contract research organization **Scynexis,
Inc.,** to form a drug discovery program to find effec-
tive and less toxic treatments for HAT. This is part
of DNDi’s R&d portfolio for HAT, which spans from
early stage compound screening to late stage clinical
trials to develop new treatments in and for disease-
endemic countries. Scynexis works with DNDi on a
fee-for-service basis, offering DNDi a reduced rate
below its regular fee structure. This project accounts
for approximately 10% of Scynexis revenues.

Through its separate agreement with DNDi signed
in late 2007, the biotechnology company **Anacor
Pharmaceuticals, Inc.,** participates in the HAT
collaboration. The company has contributed intel-
lectual property and know-how related to its boron
chemistry platform that has enabled the discovery
of a lead compound series in DNDi’s HAT program.
Anacor is partially funded by DNDi for expenses and
FTEs dedicated to this project. Much of the animal
model testing is done by the **Haskins Laboratory at
Pace University** and to a lesser extent by the **Swiss
Tropical Institute,** both of whom have state-of-the-art
capabilities in HAT animal models and are funded by
DNDi for their contributions.

The collaborators, linked by individual bilateral agree-
ments with DNDi, are now working closely to identify
a compound that meets the efficacy and safety criteria
required to advance it into preclinical toxicology
studies that would enable phase 1 clinical trials.

The target date for achieving the goal of delivering a
compound for phase 1 clinical trials is 2012.

**Progress to Date**

Since its inception in 2003, DNDi has been continu-
ally screening compounds obtained from a variety of
pharmaceutical companies, biotechnology companies,
and others for activity against HAT. By April 2008,
the program had two chemical series progressing to
lead optimization. One of these series, originated at
Anacor and optimized at Scynexis, has moved from
an initial screening and evaluation phase to a point
where the lead compounds have demonstrated effi-
cacy in a stage 2 HAT mouse model. The project
leader at Scynexis, Dr. Robert Jacobs, expressed his
hope that one of the compounds showing efficacy in
mouse models will progress to preclinical status soon.
The rapid progress of this project is underscored
by the fact that today the partners have promising
compounds that appear to be orally available and effi-
cacious in both stages of the disease. DNDi’s Director
of Research and Development Shing Chang states,
“We have made progress that exceeded our expecta-
tions. We already have compounds that display effi-
cacy in animal models. We are very, very pleased.”

**Partnership Roles and Responsibilities**

**Scynexis** supports the partnership in developing early
leads into clinical candidates, a process that requires
a deep knowledge of medicinal chemistry, parasite
biology, pharmacokinetics, and other disciplines.
Under its agreement with DNDi, Scynexis provides
the partnership with medicinal chemistry, in vitro
screening, and pharmacokinetic profiling of potential
drug candidates. A team of sixteen Scynexis scientists
including chemists and biologists, led by Dr. Robert
Jacobs, is dedicated to the HAT program.

**Pace University’s Haskins Laboratory** has one of
the leading in vivo models for HAT and provides the
animal research capacity required for this effort. The
laboratory receives compounds directly from Scynexis
and enters them into acute (1 month) or CNS (>6
month) efficacy testing in various models of HAT. Dr.
Bakela Nare of Scynexis and Dr. Cyrus Bacchi of the
Haskins Laboratory communicate frequently via phone
and e-mail. Dr. Nare conducts all of the in vitro prelim-
Once a candidate molecule progresses past preclinical testing into human clinical trials, DNDi will be responsible for managing and financing these trials as well as for registration of the drug.

**Project Timeline and Evolution**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
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<tbody>
<tr>
<td>2003</td>
<td>DNDi founded.</td>
</tr>
<tr>
<td>2005</td>
<td>Anacor begins working in global health, exploring the efficacy of its compounds against parasitic diseases impacting the developing world; Scynexis hires employees and independently begins screening proprietary compound library for activity against HAT.</td>
</tr>
<tr>
<td>Late 2005</td>
<td>Scynexis approaches DNDi with an offer of free access to its compound library.</td>
</tr>
<tr>
<td>April 2006</td>
<td>DNDi and Scynexis sign agreement allowing DNDi free access to Scynexis’s library.</td>
</tr>
<tr>
<td>January 2007</td>
<td>DNDi approaches the Bill &amp; Melinda Gates Foundation for funding for the HAT drug discovery program.</td>
</tr>
<tr>
<td>May 2007</td>
<td>Anacor meets with DNDi to review data collected in collaboration with UCSF on those compounds active against HAT.</td>
</tr>
<tr>
<td>Late 2007</td>
<td>DNDi is awarded $27 million in funding from the Bill &amp; Melinda Gates Foundation. DNDi and Scynexis established a multyear broader lead optimization agreement.</td>
</tr>
<tr>
<td>Late 2007</td>
<td>DNDi and Anacor formalize an agreement for IP and research collaboration.</td>
</tr>
<tr>
<td>March 2008</td>
<td><strong>In vitro</strong> screening shows promising activity, and the project rapidly advances to lead series. Lead optimization provides several promising compounds that are tested in acute and long-term CNS mouse models at the Haskins Laboratory at Pace University.</td>
</tr>
<tr>
<td>April 2008</td>
<td>Promising in vivo efficacy in the 180-day mouse CNS model is achieved and lead optimization efforts are focused on achieving preclinical candidates with suitable pharmacokinetic and safety profiles.</td>
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</table>

Scynexis and DNDi partner to create a HAT drug discovery program: Scynexis management has a strong desire to apply the company’s expertise in discovery of anti-parasitic drugs. In late 2005, Scynexis recruited a parasitologist with expertise in HAT and leishmaniasis to screen Scynexis’ proprietary compound library. Scynexis donated any hits to DNDi for neglected disease uses. Following this initial screening, discussions continued between DNDi and Scynexis to develop a lead optimization program to take to the Bill & Melinda Gates Foundation for...
(1) DNDi obtains compounds from a variety of sources and funds Scynexis to test DNDi’s and Anacor’s compounds for activity against HAT.

(2) Scynexis synthesizes compounds and grants DNDi the IP rights for these under this agreement.

(3) DNDi funds Anacor to provide strategic input on its boron-based product platform and consulting on product development.

(4) Scynexis tests Anacor’s boron-containing compounds for activity against HAT.

(5) Scynexis conducts in vitro testing, and passes promising compounds onto the Haskins Laboratory at Pace University for animal model testing.

(6) DNDi funds research at the Haskins Laboratory at Pace University, including its animal model testing.

(7) Anacor assigns royalty-free licensing to DNDi for the neglected disease uses of any products with activity against HAT.

KEY
- PDP
- Academic
- Industry
- Product Testing
- Staff
- Funding
- IP
funding. In 2005, Scynexis approached DNDi and worked to convince it that the company’s fee-for-service model has the potential to deliver results more quickly than the less-expensive partnerships with academic institutions on which DNDi had traditionally relied. DNDi had been searching for a single organization that could provide comprehensive expertise in lead optimization and drug development and entered into a collaboration agreement. In January 2007, DNDi approached the Bill & Melinda Gates Foundation and by the fall had secured $17 million in funding for a new full-fledged HAT drug discovery program that would leverage its existing platform to collect hits and screen compounds from pharmaceutical companies, academic institutions, and biotechnology firms for potential activity against HAT. DNDi’s collaboration with Scynexis was a key driver of excitement at the Bill & Melinda Gates Foundation about the project: “Scynexis is a very high performing medicinal chemistry/biotech/contractor with interest by the leadership in tropical parasitic disease drug discovery. The collaborative relationship between Scynexis and DNDi, along with the renewed leadership on the DNDi board were two factors beyond the content of the proposal per se that made it an exciting project.”

**Overview of Contractual Agreements**

Each partner has a contractual agreement with DNDi. DNDi essentially sub-contracts research work out to Scynexis, Pace, and Swiss Tropical Institute. Any IP rights related to Anacor compounds provided to Scynexis for screening as well as any new compounds developed by Scynexis during work with Anacor’s compounds are owned solely by Anacor, which provides royalty-free licensing to DNDi for the humanitarian use of any products with activity against HAT. Relationships between all parties are maintained by the direct agreements between DNDi and each partner. Anacor does not have direct contracts with any of the subcontracted research organizations. The diagram on the previous page described the nature of the agreements between all the parties involved.

**Strategic Value Realized**

**Scynexis Perspective**

**Financial profit:** From a commercial perspective, Scynexis is able to work on this project within its existing fee-for-service business model. While Scynexis offers a discounted rate to DNDi for work related to global health, it also maintains a profit margin on this work. This is a key factor in making global health drug discovery a sustainable proposition for Scynexis, a venture capital funded company.

**Longer-term projects:** Another benefit is that working in global health can yield longer-term relationships. With the majority of Scynexis clients, it is difficult to secure project agreements that are longer than six to twelve months, given that many companies operate on budgets that must be renegotiated annually. This collaboration in global health, funded by DNDi, has funding cycles longer than one year. Current funding which was announced in December 2008 runs all the way through March of 2012.

**Attracting, retaining, and motivating talent:**
Scynexis CEO Yves Ribeill states that working in global health “has an enormous motivational impact on our staff,” and specifically that “It helps us with recruitment and retention of talented scientists.”
Expansion of proprietary compound libraries: The fact that Anacor maintains the IP rights for all the chemistry work Scynexis is doing on the boron-containing compounds has large potential benefits to Anacor. Anacor receives samples of compounds prepared by Scynexis as well as the knowledge of the chemistry of these new compounds, and Anacor retains the IP rights to all of these for applications outside of neglected disease. Anacor gains further validation of its compounds and expands its compound library.

Technology validation and new opportunities: Anacor’s Head of Research Jacob Plattner states that the HAT program benefits Anacor’s other programs, in that it enables Anacor to expand its technology into new areas. Anything learned about Anacor’s boron-chemistry program through one program has benefits in other programs. This work is also helping to further validate its technology platform, by demonstrating its ability to generate clinical candidates with various applications.

DNDi Perspective
Access to compounds and medicinal chemistry expertise: DNDi is a product development partnership with research portfolios in HAT, Chagas disease, and visceral leishmaniasis. The focus of DNDi’s HAT partnership with Scynexis is lead optimization to generate drug candidates. As explained by Dr. Rob Don, senior project manager at DNDi “the process of taking a molecule, which kills the parasite, and changing different parts of it so that it can satisfy all of the ADME-tox parameters necessary for it to be an effective drug, all the while maintaining the ability to kill the parasite...It involves an iterative process of changing and testing until the molecule becomes a drug candidate or researchers realize that it is simply not possible to incorporate all the necessary features into that class of compounds.” The partnership with Anacor and others enables DNDi to “piggyback off research already conducted in universities and at pharmaceutical companies by requesting access to compounds that have already shown some biological activity.”
Technology benefits: Anacor has provided DNDi with know-how in terms of medicinal chemistry and biology. The company has worked on a specific type of boron-based chemistry since its inception and has made this knowledge available to DNDi. DNDi has been impressed by Anacor’s willingness to do so, given that their experience has been that private companies are often reluctant to share proprietary internal knowledge or compound libraries.

Results: DNDi secures faster advancement of compounds using Scynexis’ medicinal chemistry, parasitology, and informatics platform expertise. As DNDi’s June 2008 newsletter explains, “The process of drug discovery and development has been likened to that of building a jet airliner. No single partner has all of the skills, and the final product must be safe for millions of people — partnerships are essential. DNDi has had to build effective partnerships between scientists from a number of different disciplines to adequately address all the skills necessary for lead optimization.” This partnership is a good example of just such an effort to bring all relevant skills to the table.

Ownership of IP: Because Scynexis is funded as a “fee-for-service” contractor and makes no claim to any intellectual property generated during the lead optimization program, and Anacor has donated rights for developing world applications, “DNDi remains free to manage the intellectual property in a manner the organization deems to be most appropriate in order to guarantee access by those suffering from neglected diseases.”

Pace University Perspective

Funding: Dr. Bacchi explains that one of the key advantages to working on this project is that Pace is receiving funding to continue doing work that is of great interest to him and his team. As he explains, “When in early 2007 I received a call from Scynexis stating that they were interested in having me screen some compounds that they were developing, I was very interested. We were at that point looking for funding. Today, we are starting our second full year of work with DNDi. This was incredibly useful as I had done similar work in the past with WHO and NIH, but grant funding had run out and WHO really has few funds for direct drug development today. DNDi has come in and filled an enormous gap in the area of actual drug development for parasitic diseases — and their investment in us is several times the amount of funding I was receiving at that time."

Visibility: Dr. Bacchi notes: “In our extended studies this year, we hope to examine the mechanism of action of the oxaboroles which are proving to be highly active trypanocides and potential clinical candidates for HAT. After so many years in which drug development for HAT was shifted to a low priority by funding agencies, it is exciting for Haskins Laboratory to again be in the mainstream of drug development.”

Overcoming Key Challenges

Structuring the project to be financially viable: As noted, Scynexis engages in this partnership via a fee-for-service model in which it offers discounted rates to DNDi but is able to maintain a profit margin on its work in global health. The ability to work in global health profitably has been important to Scynexis’ engagement in such a partnership. Anacor engages in the partnership in order to realize the strategic benefits discussed above, provided that it maintains its responsibility to shareholders and is funded by DNDi for FTEs and costs. Pace University is also funded by DNDi for the screening work they provide the project. DNDi plays the indispensable role with public and private donors of making the case for its HAT programs to attract funding to support these collective efforts.

Crafting intellectual property agreements: Partners claim that the formation of the partnerships themselves has been relatively straightforward and without major challenges. IP agreements related to this collaboration have been without issues, given that HAT is a disease for which there is no commercial market. At the same time, each partner who brings intellectual property to the table wants to preserve its

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exclusivity in fields outside global health by ensuring that contributed IP rights are limited to a specific field (HAT) and a specific territory (the developing world). DNDi retains all IP rights generated by Scynexis under their agreements. Anacor provides DNDi with a nonexclusive royalty-free licensing of the IP rights for neglected disease applications in endemic countries and retains their developed-world IP rights. The only challenge elaborated by partners related to IP was in regard to Anacor’s contract with DNDi, which covers work on HAT, Chagas disease, and visceral leishmaniasis — though HAT is the early focus of the work. Because Chagas is a disease for which a small but viable market exists, Anacor desired to retain the value of any treatments developed in countries where patients are able to pay for the product. This had to be worked into the agreement with DNDi, which was done “relatively easily” according to partners.

**Sharing information among geographically disparate scientists:** Scynexis hosts a proprietary IT platform known as HEOS®, a Web-based drug research information management platform that supports collaboration among scientists in different locations. HEOS facilitates the exchange of data, pictures, chemical structures, pharmacokinetic profiles, and other scientific knowledge between Scynexis staff and their partners. This has provided a valuable tool to the collaborating teams.

**Delivering results:** There is the clear recognition that the drug delivered must be safe and efficacious, and there is a tremendous sense of urgency by the project teams as well. In a drug discovery program, according to Dr. Robert Jacobs of Scynexis, “projects can move at glacial paces and momentum can be insufficient to support a neglected disease program.” This is an issue which highlights the need to focus on the critical path required to reach a decision point as quickly as possible. As Dr. Rob Don of DNDi explains, to produce a drug candidate as efficiently as possible, it is very important that all players are focused on the lead optimization program and not distracted by other research efforts. Therefore, DNDi manages its HAT programs according to three clear rules, outlined in its June 2008 newsletter: “1) Once a lead is introduced into a lead optimization program, it enters a critical path which promises development through to patient access unless the compound series fails because structural liabilities prevent optimization as a drug candidate. 2) Sufficient resources are allocated to guarantee the rapid turnaround of data necessary to support the medicinal chemistry effort. 3) An active program of identifying new leads is managed separately from the lead optimization program to ensure a constant supply of new leads.” DNDi’s partnership with Scynexis is based on such a structure which allows DNDi to identify new leads while Scynexis and Pace work to screen and optimize the leading compound series contributed by Anacor.
CASE STUDY 5

Vertex Pharmaceuticals — Tuberculosis Drug Discovery by a Global TB Research Network

Disease Overview
Tuberculosis (TB)—a bacterial infection caused by Mycobacterium tuberculosis—is one of the most serious global threats to public health. One-third of the global population—two billion people—is infected. In otherwise healthy individuals, most infections remain latent and are asymptomatic. About 10% of those infected with TB will develop disease. Among all TB carriers, active TB disease is much more prevalent in immunocompromised populations, such as those groups co-infected with HIV/AIDS.

TB is a leading cause of death in the developing world. The World Health Organization (WHO) estimates that there are nine million new cases of TB and two million deaths as a result of the disease each year. TB is the leading killer of HIV-positive patients. Eighty percent of the global TB burden is borne by only twenty-two countries; one-third of those infected live in India and China. A recent increase in TB deaths stems from a variety of factors including widespread HIV infection, overburdened health systems, and drug resistance, as well as war and increasing poverty (which reduce treatment compliance). The WHO has declared TB a global public health emergency.

Current TB therapies are delivered as combinations of multiple antibiotics over six to nine months and require more than 100 doses of pills. Serious problems of efficacy and toxicity, compounded by the long course of treatment, result in low levels of patient compliance. Intermittent compliance can generate resistant bacteria — a factor contributing to the alarming rise of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). The four generic drugs constituting the current TB treatment regimen — isoniazid, rifampin, ethambutol, and pyrazinamide — were approved between 1952 and 1963 and can cross-react negatively with antiretrovirals. There is an urgent need for new drugs that act rapidly to shorten the course of treatment, are safe when co-administered with antiretrovirals, can kill MDR-TB and XDR-TB, and are better tolerated than existing treatments.

Market Overview
The global market for first-line TB treatments has been estimated by the Global Alliance for TB Drug Development to be $315 million, based on annual TB incidence data, treatment notification rates, and the average cost per patient for existing treatment regimens.1 If the two billion infected individuals were to be adequately treated and able to pay, the value of the market would be many times greater. In the near term, the size of the market may increase as private-pay

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Partner Profiles

**Vertex Pharmaceuticals** is a global biotechnology company committed to the discovery and development of breakthrough small molecule drugs for serious diseases. The company’s strategy is to commercialize its products both independently and in collaboration with major pharmaceutical companies. Vertex’s portfolio is centered on infectious diseases, inflammation, autoimmune diseases, cancer, pain, and cystic fibrosis. Vertex co-discovered the HIV protease inhibitor Lexiva in collaboration with GlaxoSmithKline. Vertex is leading the development of the hepatitis C virus (HCV) protease inhibitor telaprevir (VX-950), which is currently in phase 3 clinical development. In addition, it is focused on the development of VX-770 and VX-809, two novel drug candidates targeting cystic fibrosis; second-generation HCV protease inhibitors and novel HCV polymerase inhibitors; and VX-509, a novel Janus kinase 3, or JAK3, inhibitor that targets immune-mediated inflammatory diseases, or IMID.

**Children’s Hospital Boston** is a 396-bed comprehensive center for pediatric health care. As one of the largest pediatric medical centers in the United States, it offers a complete range of health care services for children from birth through twenty-one years of age. The hospital is also home to the world’s largest research enterprise based at a pediatric medical center. Its research community is composed of more than 600 scientists, including eight members of the National Academy of Sciences, eleven members of the Institute of Medicine, and twelve members of the Howard Hughes Medical Institute.

**The Veterans Administration Medical Center** is a State University of New York (SUNY) affiliated teaching and tertiary-care facility located at the geographic center of upstate New York. The center provides health care services to more than 40,000 veteran men and women who reside in the thirteen-county area of central New York.

**University of Iowa** was established in 1847 and is a world-renowned research and teaching university with more than 30,500 students located on a 1,900-acre campus in Iowa City in southeastern Iowa. The university has eleven colleges: the College of Liberal Arts and Sciences, the Henry B. Tippie College of Business, the Roy J. and Lucille A. Carver College of Medicine, and the Colleges of Education, Engineering, Law, Nursing, Pharmacy, Dentistry and Public Health.

**ChemPartner** is a R&D contract research company based in Shanghai, China, that provides customized services to international pharmaceutical, biotech, agrochemical, and chemical companies. It currently has a team of more than 1,500 scientists who provide such services as discovery chemistry, library generation, analytical chemistry, medicinal chemistry, process chemistry, natural product chemistry, computational chemistry, assay development, pharmacology, biomarker studies, drug metabolism/pharmacokinetic (DMPK) studies, and drug design services.

**The Institute of Medicinal Biotechnology** (IMB) is based at the Chinese Academy of Medical Sciences in Beijing. The IMB was founded in 1958 under the original name of the Institute of Antibiotics, where the first penicillin was made in China. Since then, the IMB has become the primary institute in China for drugs against infectious diseases as well as other major human diseases. The name of the institute was changed to the Institute of Medicinal Biotechnology in 1986, as the research area was largely extended and has several national drug R&D platforms and key laboratories. Together with the education section (PhD/MS programs) and institute-owned pharmaceutical/biotech firms, the IMB represents a comprehensive drug discovery base for research, teaching, and translational medicine.
The program is fully funded by Vertex with the exception of the IMB, which matches Vertex’s funding of its activities by contributing substantial numbers of its own personnel (full-time equivalents, or FTEs) to the alliance. The program’s goal is to develop new drugs that can reduce the duration of TB treatment to a matter of a few weeks or less. The company is moving on two scientific tracks, targeting both the pathogen and its host. A number of strengths define Vertex’s tuberculosis program. First, multiple new targets have been prioritized for investigation. Vertex uses the latest scientific data to validate the targets as important in persistence and drug resistance and thus suggest the potential of downstream therapeutic synergy. Second, Vertex’s approach also relies on robust medicinal chemistry, which will be supported by advanced structure-based and biological drug design methods throughout the lead optimization phases. Third, novel host cell infectious assays are being developed to better reflect the natural human niche of Mycobacterium tuberculosis (Mtb). Finally, Vertex is emphasizing very early evaluation of new compounds in combination with existing and developmental therapeutics to gain early information on synergistic potential.

One of the first areas of research is the protein kinases (Pksns) from Mtb, where chemical inhibition of these kinases may be useful for treatment of tuberculosis. Since Vertex has extensive expertise in the development of kinase inhibitors for therapeutic use and one of the richest kinase inhibitor collections in the world, it already had assets in place for this project, including enzymatic assays against a panel of mammalian kinases and a team of scientists with extensive experience in the chemistry and structural biology of Ser/Thr protein kinase inhibition. Vertex is now identifying new drug targets, developing new high throughput screens for new and validated existing drug targets, and acquiring tools to shorten the screening and development timelines.
**Progress to Date**

Dr. Peter Mueller, Vertex’s CSO and executive vice president of global research and development, states, “Using its own resources, Vertex has built and governs a worldwide network of scientists working on TB currently fluctuating between at least fifty and sixty FTEs, targeting about thirty-five in China and India, and also integrating biosafety labs with in vitro capabilities, animal models, and human clinical experience. The size of the program is substantial and about twice the size of a typical pharmaceutical industry lead optimization project.”

The program is moving from the “hit” phase to the lead optimization phase. Thus far, the project has completed multiple screens for different TB targets. The furthest advanced are protein kinase inhibitors. Vertex and its partners are evaluating compounds in animal models with the goal of developing an oral formulation of protein kinase inhibitors with promising in vivo activity. Vertex is currently setting up activities to mine other targets and creating the infrastructure to do so.

Apart from scientific milestones, Mueller says that the main achievement of the program has been identification of strategic partners that believe in the mission of the program and its approach. These partners have a deep understanding of TB disease process and pathology and know where the gaps in TB drug discovery and development lie. He says, “We’re going to have to be prepared to give up the possibility of an ‘easy fix’ — we can’t achieve our goals with clinical trials on known compounds. We need to be prepared to execute purpose-driven research and dig deeper.” Vertex’s strategic partners share their approach of mining multiple targets at once and conducting robust chemistry using structural biology approaches and advanced technologies. Mueller says, “We’re in the early stages of setting up the tools to look at these problems in a new manner. Having the right pieces assembled to mine the possibilities in an integrated fashion is what we are now focused on.”

**Partnership Roles and Responsibilities**

Vertex created, funds, and manages the Global TB Research Network partly by building on its expertise in kinase inhibition. Vertex is conducting research focused on TB kinases involved in Mtb survival. In addition, Vertex is separately conducting research aimed at targeting host cells that harbor latent TB. These efforts focus on potentially reinstalling immunological defense mechanisms to destroy latent TB. Some eight FTEs internally at Vertex have been devoted to this project, although Vertex states that without engaging support from major financial partners this level of effort cannot be maintained much longer.

Vertex’s Cambridge site also develops and executes high throughput screens against specific targets, provides gene cloning, protein expression, crystallography and structure-based drug design support, biomarker and target validation, and project management. Dr. Tiansheng Wang and Peter Jones guide the chemistry and DMPK project teams, respectively, at Shanghai ChemPartner, while Dr. Steven Jones leads the pharmacology effort. Activities at Vertex’s Iowa site are led by Dr. Ute Müh, who also heads the Pkn lead optimization project. The Vertex Iowa team has access to a biosafety level 3 (BSL3) laboratory, develops Mtb recombinant and reporter strains of Mtb, and performs a variety of biological support assays. The lead biology scientist for the project is Dr. Brian Hanzelka. Vertex’s San Diego site handles compound shipping and receiving, compound (chemical) properties analysis, and compound archiving. Vertex’s Oxford, UK site provides scientific support and feedback regarding lead optimization. The overall global balance of resources maintains maximal flexibility to optimize connection of local talents with project need and opportunity.
Children’s Hospital Boston has expertise in protein kinase research, kinase substrate identification and in mapping signal transduction pathways for TB. The TB team at Children’s Hospital Boston has a BSL3 laboratory, which is essential for experiments that involve virulent Mtb bacteria. Researchers there are working to understand how TB interacts with its host environment and how it reacts to changes in that environment. The goal of the work conducted at Children’s Hospital is to identify a large number of phosphorylated proteins and phosphorylation sites, to identify substrate motifs, and to examine in vitro phosphorylation and in vitro substrates to identify which proteins they are targeting. Two scientists work on this project full time, in addition to oversight provided by Dr. Robert Husson.

The University of Iowa is funded by Vertex to examine TB infections located within human macrophages. The university also has a BSL3 laboratory to perform studies with virulent Mtb. One of the goals of this collaboration is to develop a high throughput screen to identify new compounds that would destroy Mtb in the human host cell. The collaboration will then focus on the design and use of secondary assays to confirm and characterize the mechanisms of action of inhibitory compounds, such as determining direct inhibition of Mtb viability, inhibition of a specific host-cell mechanism required for the intracellular survival of Mtb, or inhibition of the host-cell’s viability in a way that indirectly affects the survival of Mtb. This collaboration provides core strength in better understanding the cell biology of Mtb in its natural environment. Currently there is one FTE, with additional FTE support provided by the Vertex team in Iowa. The project is led by Dr. Lee-Ann Allen, a molecular cell biologist adept in the in vitro recapitulation of the subtle in vivo niche behavior of human macrophages, the cells most prone to harboring Mtb bacilli.

The VA Medical Center provides the partnership-essential expertise in animal models and understanding of Mtb/host interactions. The VA Medical Center also has a BSL3 laboratory. Vertex sends compounds to the VA Medical Center to determine how effective the compounds work against the organism are in vivo. In addition, the VA Medical Center is helping to analyze gene regulation and pharmacokinetic/pharmacodynamics (PK/PD) parameters, and making the evaluation of compounds more efficient by shortening the time lines of compound evaluation in vivo. Two FTEs work on this project full time, in addition to oversight provided by project leader Dr. Michael Cynamon.

ChemPartner is executing the majority of the synthetic medicinal chemistry work for the project and working to finding leads that show activity against TB. In addition, ChemPartner has recently taken on protein expression, screening against Mtb enzymes and mammalian host enzymes, as well as screening against nonvirulent Mtb and other bacteria. ChemPartner provides in vitro and in vivo studies to profile compound metabolism and PK, to more effectively tie together two key drivers of lead optimization. As many as eighteen FTEs from ChemPartner have been contracted to work on this project at any one time, depending on fluctuating project requirements.

The Institute of Medicinal Biotechnology (IMB), part of the Chinese Academy of Medical Sciences, has extensive experience working with TB strains that circulate in China. It is closely linked to institutes with some of the country’s best-developed TB surveillance and treatment programs. The IMB is working to mine a large natural product library for several new and validated Mtb drug targets. More than twenty-five FTEs from the IMB are dedicated to target-based and Mtb compound screening and lead optimization, combined with key biology and assay development.
than build all the required pieces internally, we look to the people around the world who have complementary expertise.” Vertex aimed from the beginning to extend the network to partners in endemic countries. Thomson notes that actively engaging stakeholders in other countries is critical, because “to do things right you need to be able to piece together disparate pieces from across the world. All the right pieces and most interesting assets don’t occur in one place. You need to diversify from where you’re sampling certain pieces of the whole medical problem or you won’t solve it.” This philosophy encouraged Vertex to take a networked approach to TB drug discovery.

Vertex develops a virtual network with key domestic and international partners: After extensive research of the TB landscape and key players, Vertex began reaching out to strategic partners who share Vertex’s passion for TB drug discovery. In April 2007 Vertex engaged one of its earliest partners, Dr. Robert Husson from Children’s Hospital Boston, who has expertise in protein kinases and access to a BSL3 laboratory. Soon after, Vertex contracted ChemPartner, a CRO based in China, to conduct chemistry and compound screening for the program. As explained by Dr. Christopher Locher: “India and China account for about one-third of the TB cases in the world. These scientists experience TB firsthand, and they are actually quite efficient and specialized in TB research. We wanted to work with them and have an integrated program in a geographical region that is affected by TB.” By early 2008, both Dr. Lee-Ann Allen at the University of Iowa and Dr. Michael Cynamon of the VA Medical Center began conducting research for the partnership; both centers have access to a BSL3 laboratory, which is required to work with Mtb. Most recently, the IMB in China has joined the partnership, aiming to provide up to twenty-five FTEs to expand the program into a full-scale, multiple-target drug discovery effort later this year.

**Vertex identifies TB as an area of focus:** Vertex began working internally on TB drug discovery in March 2007, beginning with initial compound screening and focusing on protein kinases for lead optimization. Vertex believes that existing efforts in TB drug discovery and development are not sufficient to address the formidable obstacles to treating TB. MDR-TB and XDR-TB are an emerging threat with the potential to spread beyond the developing world. Dr. John Thomson, vice president of strategic research alliances at Vertex, notes, “We have a perilously thin veil of defense should XDR-TB start proliferating more or — heaven forbid — genetically change to become more virulent. We believe a more integrated approach to TB drug discovery is necessary — one that mines new ideas, new biological mechanisms, and new targets in an integrated and synergistic manner. To do this, you need essentially to be able to dig deeper than most research does at the moment.”

**Vertex focuses on a virtually networked model:** After Vertex began TB research internally, it focused on assembling a network of strategic partners who would provide critical expertise and resources required for an integrated drug discovery and development program. As Amit Sachdev, senior vice president of corporate affairs and public policy at Vertex explains, “A really interesting aspect of our approach is that we bring to the table a particular expertise but recognize that we do not bring an entire discovery chain.
Strategic Value Realized

**Vertex perspective**

**Fit with mission:** Vertex is engaged in TB not because of the commercial opportunity that it presents, but rather, as Thomson explains, “because we believe in neglected diseases and ending world health problems. TB is a poster child of that mission, but any unmet medical needs are interesting to us. Our mission is driven more by medical needs than unqualified commercialization, and the magnitude of the TB problem is incredibly important to us.” He adds, “We see in TB the possibility of making a difference, which stems from an ability to identify gaps or shortcomings in what others are doing and having some ideas — technological advances or new approaches — that are novel and can yield substantial progress. We believe that for TB we can bring something new to the field.” This philosophy is echoed across the company. Vertex aims to bring new solutions to diseases where others are pessimistic that a new therapeutic is possible. Employees point to Vertex’s effort in cystic fibrosis, Huntington’s disease, and multiple sclerosis. Christopher Locher summarizes Vertex’s motivation as follows: “To be a great company we want to do great things; we want to commit to diseases that present huge unmet medical needs, and we see TB as one of those diseases.”

**Learning how to operate in emerging markets:** As Thomson explains, the networked model Vertex has pursued “allows Vertex to have a more intimate knowledge and connection with different emerging business landscapes and economies.” In particular, by working with local partners in India and China, Vertex is able to develop knowledge of the hospital system and medical infrastructure in these countries, to understand different patient segments and their health-seeking behaviors, to become familiar with local clinical practices, and to establish favorable government connections. Peter Mueller notes that such connections benefit future efforts to bring drugs to market in these countries because it “gives you a better starting position for distribution and builds local support for your brand.” Locher adds, “We see that pharmaceutical compa-

**Increased familiarity with contract research organizations:** Thomson points out that working with local partners in emerging markets also provides a “basic tactical economic advantage” — the opportunity to outsource commodity science and chemistry work to trusted and capable CROs overseas, which can complete such work at a far lower cost than in the developed world. This is “an attractive possibility that adds great tactility” to the way in which Vertex can approach scientific problems.

**Increased learning through networking:** Vertex believes that its networked approach is the most efficient model to approach this drug discovery program. Vertex gains the benefit of the knowledge and infrastructure of its partners, and does not incur the cost of hiring in-house TB experts or building a BSL3 laboratory to work on this problem. Sachdev explains, “We get to work with a small team of researchers in a space that otherwise wouldn’t be in our business plan, and we are gaining knowledge on the research side that may well be applicable to a future discovery.” Mueller notes that this program “exposes our internal scientists to the brightest minds in particular research areas, which helps our scientists to excel. It fosters acceptance of different solutions and openness to diversity of opinions.”

**Commercial value:** While Vertex does not currently anticipate commercial gain related to this program, and while commercial motives are not the driving factor behind Vertex’s efforts in TB research, it’s possible that the program will ultimately generate a commercially viable molecule and that Vertex would take the product forward. Employees at Vertex note that if that were to be the case, it is also possible that the product would be eligible for a priority review voucher (PRV) from the U.S. Food and Drug
Tangible results: Dr. Robert Husson explains one of the benefits of engaging in this project with Vertex: “The vast majority of people doing basic research have a hope that what they are doing will ultimately yield practical value. We recognize there are a lot of limitations for an academic institution beyond the initial screening process. For us, it is very satisfying to be working in an area where we see the direct potential for our work to be translated directly into drug development.” He adds, “Vertex is interested because it fits into a specific area of their expertise — kinase biology and kinase inhibition. The translation into chemical inhibitors and drug development is a long process that would happen on their side, but they seem quite serious about it. My sense is that this isn’t just a public relations effort for them, but rather that they are trying to come up with drug candidates.”

Source of funding: With the exception of the substantial in-kind contributions of the IMB in Beijing, the integrated Mtb drug discovery research studies of the global network described herein is fully funded by Vertex. This project provided funding for these laboratories at a time when funding was unsure. This funding enables scientists at these laboratories to work on important projects in which they are scientifically interested.

Learning opportunities: Dr. Michael Cynamon of the VA Medical Center in Syracuse admits that there are not “a whole lot of people locally with whom I can collaborate who have my scientific interests. This project provides me with the ability to collaborate with others who are interested and actively involved. That is very positive, both professionally and personally.” In addition, Dr. Cynamon stresses that the interactions between his laboratory and Vertex are far more collaborative than past interactions with other companies that have funded projects. He notes that “a number of different people at Vertex have been involved and made decisions about what studies we do and how we approach them. They have provided significant input into the project — it doesn’t feel like a contractual relationship.”
**Overcoming Key Challenges**

**Funding:** The project’s major challenge is to secure external funding to replace or supplement Vertex’s internal funds. As the program advances from discovery to lead optimization and on to proof of concept, costs will increase significantly. Vertex does not feel it is in a position to continue spending the current level of company resources on a program that has little potential for commercial return, and it will be forced to begin downsizing the program soon unless one or more committed financial partners are identified very soon. While Vertex could have sought outside funding for the program at its inception from governments, the Bill & Melinda Gates Foundation, or product development partnerships (PDPs), it chose instead to commit company resources to build credibility and “help bootstrap a model we believe in.” Yet, narrow margins and the need to focus on its commercial opportunities have led Joshua Boger, founder and recently retired CEO of Vertex, to state, “The very large majority of direct costs have to come from the philanthropic side if we are going to pull it off. We are willing to show our enthusiasm for the problem by putting together a program and putting our capital at risk for a limited time to show we are really serious, but the model doesn’t work unless the philanthropic side steps up to the plate… It doesn’t work if we shoulder both the opportunity costs and the at-risk financial costs.” Vertex notes that the majority of philanthropic funding for TB research has been devoted to drug development programs, which has left little for brand-new discovery programs. This challenge creates uncertainty as to the sustainability of Vertex’s efforts in TB.

**Identifying partners:** Selecting the right partners for this program is a challenge for Vertex. John Thomson explains, “This is a very difficult model to pull off. We need to work with people that really know the strengths and weaknesses of their own organizations, understand how the drug discovery and development process looks from start to finish, and put tremendous energy into connecting all the pieces.” The issue of locating the optimal strategic partners is compounded when looking for partners overseas in emerging markets, where there are cultural differences to be overcome. To surmount this challenge, Thomson notes, “We groomed our relationships in a more gradual, tactical manner overseas before we launched this. We were working with our hub collaborator, IMB, for two or three years on an HCV genotyping project before we really launched into TB. It was important to get to know one another and understand the way each of us makes decisions, and how we execute those decisions.” While Vertex seeks out centers of excellence with complementary sets of expertise — “people that have interest in targeting the host itself and have an open mind for innovative therapies” — it is whether “someone’s heart is in it” that determines the success of the alliance. Christopher Locher notes, “People are engaged and committed to the program if they are emotionally invested in the disease. The level of commitment that we have from our partners determines our success.”

**Maintaining a virtual network:** Maintaining and nurturing partner relationships can present a significant logistical challenge. Thomson explains that “highly networked by definition means highly fragmented. These highly networked models require a lot of energy, commitment, and savvy to integrate them sufficiently.” He further states that too many organizations leave the network suboptimally managed and, as a result, approach problems in a piecemeal fashion. Mueller describes Vertex’s approach to mitigating this challenge: “We must engage heavily in ‘matrix management’ on a day-to-day basis. We maintain in-house capabilities to talk scientifically and politically with partners on a constant basis, and we work hard to nurture those relationships across continents. This requires committed effort and lots of energy, which is often underestimated.” Locher explains that he has regular weekly or biweekly meetings with many partners, depending on the requirements of the project, and is in constant communication to ensure that “the project is on track and that expectations are managed.”
**Disease Overview**

Japanese encephalitis (JE) is a viral disease transmitted by mosquitoes, causing potentially fatal inflammation of the brain (encephalitis). Most JE infections are mild (fever and headache) or lack apparent symptoms. Approximately 1 in 200 infections results in severe disease characterized by rapid onset of high fever, headache, neck stiffness, disorientation, coma, seizures, spastic paralysis, and death. In these cases, JE affects the brain or the membranes around the brain (meninges). Of those who survive severe JE, 30% suffer lasting damage to the central nervous system.

JE is the leading cause of viral encephalitis and neurological infection in Asia, where it is endemic. The disease is severely unreported; 50,000 new cases are recorded annually that result in 15,000 deaths and a 75% JE-related disability rate. Over three billion people live in areas endemic for JE, and large outbreaks of JE in India and Nepal have highlighted the continuing expansion of the geographic range of the disease in recent years.

The JE virus belongs to the family Flaviviridae. The viruses responsible for dengue fever, yellow fever, and West Nile disease are also flaviviruses. Mosquitoes belonging to the Culex tritaeniorhynchus and Culex vishnui groups, which breed in flooded rice fields, transmit JE. The virus circulates in birds and pigs, and tends to spill over into human populations only when Culex populations increase dramatically over a short period of time, as Culex mosquitoes prefer to feed on animals.

**Market Overview**

Although JE strikes some 50,000 individuals each year, millions more are at risk. The disease is endemic throughout Asia, from the islands of the Western Pacific in the east to the Pakistani border in the west, and from Korea in the north to Papua New Guinea in the south. Since vaccines are indicated for any susceptible people in endemic areas, there is in fact a sizeable market for JE prevention, particularly in private markets in countries where patients are increasingly willing and able to purchase healthcare. Additionally, there is a viable travel and military market for the disease.

**Project Overview**

Acambis (previously known as OraVax and now a subsidiary of Sanofi Pasteur) is developing an investigational vaccine against JE, using Acambis’ proprietary ChimeriVax™ technology. Known previously as ChimeriVax™-JE and now as IMOJEV™, this investigational vaccine candidate is being developed to provide a convenient, affordable, single-dose vaccine to travelers and those living in endemic regions.

This vaccine is a live, attenuated, injectable vaccine, and as a single-dose vaccine it offers significant benefits in terms of compliance and reduced health care infrastructure costs. It is also well-suited to travelers because it provides rapid-onset, durable immunity.
Progress to Date

IMOJEV™ (formerly known as ChimeriVax™-JE) has shown a positive safety and efficacy profile following pivotal phase 3 trials. In October 2006, Acambis announced positive results from a pivotal phase 3 safety trial, and in March 2007, data were released from the phase 3 efficacy trial, which found that IMOJEV™ met and exceeded its primary immunogenicity endpoint.

In February 2007, Acambis established a partnership with Sanofi Pasteur for the development and commercialization of IMOJEV™ worldwide. In September 2008, Sanofi Pasteur acquired Acambis and is currently conducting pediatric trials with this vaccine in the endemic region.

Project Timeline and Evolution

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1996</td>
<td>Acambis (then OraVax) constructs a vaccine candidate against JE.</td>
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<td>1997</td>
<td>Board approval secured to continue developing the JE vaccine.</td>
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<tr>
<td>2000</td>
<td>Dengue fever vaccine candidate licensed to Sanofi Pasteur (then Sanofi-Mérieux-Connaught) and funding secured for proof-of-concept development of JE vaccine.</td>
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<td>2002</td>
<td>Clinical JE program launched at Acambis, positive phase 1 and 2 trials conducted.</td>
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<tr>
<td>2005</td>
<td>Acambis enters into a memorandum of understanding with the World Health Organization, initiates plans for clinical development in Thailand and India, and launches phase 3 trials in the United States and Australia.</td>
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<tr>
<td>October 2006</td>
<td>Positive results from pivotal phase 3 of JE vaccine safety trial announced.</td>
</tr>
<tr>
<td>February 2007</td>
<td>JE program partnered with Sanofi Pasteur for worldwide development and commercialization, excluding India and the United States.</td>
</tr>
<tr>
<td>March 2007</td>
<td>Acambis extends the licensing agreement with Sanofi Pasteur to include India and the Indian subcontinent; positive data released from phase 3 efficacy trial.</td>
</tr>
<tr>
<td>September 2008</td>
<td>Acambis acquired by Sanofi Pasteur.</td>
</tr>
<tr>
<td>2009</td>
<td>Pediatric trials in endemic Asian market are ongoing.</td>
</tr>
<tr>
<td>2010-2011</td>
<td>Registration and product launch in endemic regions anticipated.</td>
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</table>

Acambis explores the applications of its ChimeriVax™ technology: Acambis licensed its yellow fever 17D live vector ChimeriVax™-technology from St. Louis University. The company was operating on the belief that this technology platform would lend itself to multiple flaviviruses and was therefore likely to have relevance for developing a vaccine against JE, dengue, West Nile, and tick-borne encephalitis. Acambis began with two vaccine development projects, against both JE and dengue fever. In 1996, a vaccine candidate for JE was constructed. Board approval to continue developing the JE vaccine candidate was secured in early 1997, and within two years Acambis had generated a good amount of data in animals, including monkeys, and it was clear that it had a viable vaccine candidate for JE. Former Chief Scientific Officer Thomas Monath explains that even at this early stage with limited funding, Acambis chose to continue the JE program because “we believed in the market.”

Acambis partners its dengue fever program with Sanofi Pasteur and receives early funding for JE proof of concept: In 2000, Acambis acknowledged that due to lack of financing, it would be unable to take the dengue fever program forward on its own. Acambis then approached Sanofi Pasteur (then Sanofi-Mérieux-Connaught) and presented preclinical data on its dengue and JE vaccine candidates to the head of research and development. The high level of interest from Sanofi Pasteur was immediately apparent — and at the end of this initial meeting a term sheet to begin negotiations was signed. This resulted in a licensing deal for the dengue vaccine candidate. As part of this licensing deal, Sanofi Pasteur provided Acambis with research and development (R&D) funding to develop dengue vaccine candidates through phase 1 and 2 clinical trials, at which point Sanofi Pasteur would take on responsibility for further clinical development. Sanofi Pasteur also provided Acambis with funding for the proof-of-concept development of the JE vaccine candidate through phase 1 and 2 clinical trials. Sanofi Pasteur, with a strong presence in Asia and a long-term distribution relationship for another JE vaccine, JE-Vax (produced by BIKEN in Japan), was familiar with the market for JE vaccines. Funding for these programs...
also included development and scale up of a manufacturing method. Acambis held the Investigational New Drug (IND) applications for ChimeriVax-JE and ChimeriVax-dengue. A steering committee composed of staff from Acambis and Sanofi Pasteur met quarterly for more than seven years during the development of JE and dengue vaccines.

**Acambis places early emphasis equally on the travel market and endemic markets:** Both the JE and dengue programs had a strong advocate in Monath. From its inception, the JE program had a global health perspective but was also a developed-world travelers market opportunity. Early in the program, Acambis approached the WHO to obtain its support. They entered into a memorandum of understanding (MoU) stating that if Acambis were to commercialize the JE vaccine in Asia, a fair price would be negotiated to meet public market needs. The clinical trials initially focused on travelers markets in the United States and Australia. Following phase 1 and phase 2 clinical trials in 2002, phase 3 trials began in both countries. Even prior to the completion of phase 1 and phase 2 trials, however, Acambis attempted to initiate a clinical study in Thailand with the assistance of WHO. Later, as phase 3 trials were getting underway in the United States and Australia, Acambis initiated clinical development of the JE vaccine in India, first in adults and then in children.

**Acambis prioritizes endemic markets over the travel market:** Acambis always intended to license the vaccine in Australia for travelers and in India for the endemic market. It had to decide whether to license in the United States as well. Acambis management met with the U.S. Food and Drug Administration and learned that the clinical trial requirements were far greater than those they had negotiated with Thailand, India, and Australia. The company also realized that the U.S. and European markets might not be as valuable as originally thought (in the United States only about 100,000 doses of JE Vax were delivered annually, yielding a market of approximately $25 million). A smaller market and higher cost of licensure in the United States led to the decision to consider a strategy to develop the vaccine for the rest of the world first, and to pursue the travelers and military market as a secondary target. It became apparent that JE was increasingly recognized as a major public health priority in China and India, where epidemics had recently affected large populations. Hence, Acambis’ focus shifted to endemic markets in Southeast Asia, where it anticipated a significant public and private market. According to Monath, “While the travel market was the original driver of our efforts, that gradually shifted, particularly as we understood the opportunity in the private markets in Asia.”

Acambis placed particular emphasis on the endemic market in India. Acambis management met with the Ministry of Health in India and entered into an MoU with the Indian government about the development of the vaccine. It also received the support of the National Institute of Virology in India, based on a dossier submitted to its advisory committee. After conducting such significant groundwork in India, Acambis partnered with Bharat Biotech International Limited (Bharat Biotech), an Indian vaccine company, to conduct sales and marketing of the vaccine in the Indian subcontinent. Under this agreement, Acambis was to provide Bharat Biotech with bulk vaccine, and Bharat Biotech was to execute the “fill and finish” of the vaccine, produce the final product, and assist with clinical trials and the regulatory process in India.

**Acambis partners JE program with Sanofi Pasteur:**
Following the agreement with Bharat Biotech in February 2007, Acambis granted Sanofi Pasteur marketing, distribution, and certain manufacturing rights to the JE vaccine for other parts of Asia. Under this agreement, Acambis agreed to supply bulk IMOJEV™ vaccine to Sanofi Pasteur from its Canton, Massachusetts, facility and Sanofi Pasteur acquired the right to sell and market the product for public and private markets in Asia, excluding India and the Indian subcontinent. In March 2008, Acambis and Bharat Biotech mutually agreed to terminate their agreement, and Acambis extended the vaccine...
Partner Profiles

**Acambis** was formerly an independent, publicly held vaccine company developing novel vaccines that address significant unmet medical needs or substantially improve upon current standards of care. In September 2008, Acambis was acquired by Sanofi Pasteur, the vaccines division of the Sanofi-aventis Group. Acambis and Sanofi Pasteur have enjoyed a long and successful relationship for more than ten years and, prior to the acquisition, had partnership agreements relating to three of Acambis’ key vaccine development programs based on Acambis’ proprietary ChimeriVax™ technology platform against Japanese encephalitis, dengue, and West Nile. Acambis’ pipeline also included an early-stage program targeting potentially significant markets in the fields of C. difficile, influenza, and genital herpes. Acambis’ product portfolio includes a licensed smallpox vaccine, ACAM2000®, for which it has a contract with the U.S. government.

**Sanofi Pasteur** is the leading player in the vaccines industry, with net sales of €2,861 million (approximately $4,055 million) in 2008 and with leading vaccines in five areas: pediatric combination vaccines; influenza vaccines; adult and adolescent booster vaccines; meningitis vaccines; and travel, endemic and measles, mumps and rubella vaccines. It provided more than 1.6 billion doses of vaccine in 2008, making it possible to immunize more than 500 million people across the globe. Sanofi-aventis, its parent company, discovers, develops and distributes therapeutic solutions to improve the lives of everyone. Sanofi-aventis is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY).

licensing agreement with Sanofi Pasteur to include India and the Indian subcontinent. As part of this licensing deal, Acambis received from Sanofi Pasteur an upfront payment and was promised a milestone payment on licensure of the vaccine in India and royalties on sales in these territories. As Bharat Biotech had made a significant contribution towards the development of the new JE vaccine, Acambis agreed to compensate Bharat Biotech for its work — but the net financial effect of extending its agreement with Sanofi Pasteur was deemed to be positive for Acambis. As Former Chief Executive Officer of Acambis Ian Garland said, “This extended agreement will enable both Acambis and Sanofi Pasteur to benefit from a more coordinated approach in the JE endemic region.” The negotiation of this partnership was relatively straightforward following the dissolution of the agreement with Bharat Biotech. Indeed, while they acknowledge that the cultures of biotechnology companies and big pharmaceutical companies are very different, former Acambis management states that the partnership between Acambis and Sanofi Pasteur was not a difficult partnership because the companies had been working together a long time with the dengue program.

**Acambis is acquired by Sanofi Pasteur:** In September 2008, Sanofi Pasteur acquired Acambis. Sanofi Pasteur, now the owner of Acambis, is now conducting pediatric trials with this vaccine in the endemic region.

**Strategic Value Realized**

**Acambis Perspective**

**Commercial value:** Engaging in global health was an outcome of a shift in Acambis’ core commercial strategy as it understood the very real commercial opportunity in endemic markets. Monath explains that because Acambis believed its product was such an improvement over existing products, and because the cost of goods was low enough that they could afford to bring it into both public and private markets in Thailand and India and still turn a profit, the JE vaccine had significant commercial value to Acambis.
“We believed that this was a viable business model. We were ahead of the game in the sense that at the time we started thinking about this in the late 1990s, there was a much vaguer recognition that this could be an interesting business model.” Sanofi Pasteur’s original partnership with Acambis and ultimate acquisition of Acambis and continued efforts to develop the vaccine are a testament to the very real market that exists for JE vaccines in endemic countries, particularly in private markets.

**Building credibility:** Clement Lewin states that “the main value Acambis gained from working in global health was that this product helped the company to prove a novel technology platform.” In particular, this product helped demonstrate to investors that Acambis’ technology platform has value and that it can successfully deliver a product. Lewin believes that this manner of engaging in global health — developing a global health product for endemic populations to build credibility for a young company — can serve as a model for other companies: “small companies need to look at these opportunities carefully and bring in people that can advise them about these opportunities. I think there are lots of interesting, smaller sorts of projects that can be done by small biotech companies in global health... There are strategic alliances possible that wouldn’t be possible with more traditional products. My prediction is that we’re right at the beginning of the global health work by biotechnology companies.”

**Publicity and access to global health stakeholders:** Acambis worked closely with the WHO during the development of its JE vaccine. Monath explains: “I saw the need to partner with WHO early on and we entered into an MoU with WHO stating that if we did commercialize the vaccine in Asia we would negotiate a fair price to meet public market needs.” This yielded great support from the WHO, and as the WHO organized several regional meetings bringing together public health experts on JE, Monath took note of that fact that WHO was “promoting our vaccine, which was a single-dose, lifetime immunity vaccine ideally suited for public market needs. We got a lot of good promotion and publicity that way.” WHO support was critical to enabling Acambis access to key players in target markets. Monath explains, “When we started talking to the Thai Ministry of Health and setting up trials there, the WHO folks were strongly supportive.”

**Staff motivation:** Monath explains how he used working in global health as a motivational tool: “It helped people to feel good about it at the company. All people that develop vaccines and drugs are in large measure focused on the fact that they are going to save lives. I think it was important.” Monath’s comments echo the comments of others that the potential for impact on poor populations in the developing world was a serious motivator.

**Overcoming Key Challenges**

**Enabling visibility of the technology:** One major hurdle Acambis faced was getting visibility of its JE vaccine technology to the numerous potential beneficiaries and other stakeholders. Monath explains, “One big challenge was getting the technology known to the scientific community and getting buy-in from our company, the investors, and the board that a disease that occurs in remote areas of the world far away from where we were located was a commercial opportunity.” To overcome these challenges, Acambis focused on leveraging WHO, scientific meetings, publication in scientific journals, and public-sector partnerships such as PATH (previously Program for Appropriate Technology in Health) to inform key stakeholders. Monath says that, additionally, Acambis launched clinical development programs in endemic countries as quickly as possible to increase the visibility of the technology. In addition, the ChimeriVax technology was further validated by a deal with Intervet for a veterinary indication, which resulted in a licensed vaccine for horses against West Nile.
Clinical trials: Conducting clinical trials in countries endemic for JE was a formidable technical challenge, as each country had its own regulatory requirements and ethical committees. There were fewer experienced research organizations on the scene that could help with trial logistics, and for a small company, there were operational difficulties that had to be managed from afar.

Partnering the program: Early in the development of Acambis’ JE vaccine, the biggest challenge was funding for the program. Acambis secured early proof-of-concept funding from Sanofi Pasteur, but a meaningful strategic partnership did not occur until Acambis had already developed the vaccine through pivotal phase 3 trials, and even then the partnership with Sanofi Pasteur was a sales and marketing agreement, rather than a deal to fund licensure of the product. Monath notes that this was also the case for Intercell and its partnership with Novartis to develop its JE vaccine, which did not occur until during phase 3 trials. Monath says, “JE at that time was not yet a disease area ripe for a meaningful strategic deal.” At the end of the day, Acambis developed the product on its own until phase 3 trials, driven by a belief in the commercial market opportunity that JE presents. Finally, Acambis looked for partners. Initial partnering efforts focused on PATH, but PATH ultimately decided to support a competing technology — the SA14142 Chengdu vaccine for JE. Lewin explains, “After PATH fell through, a regional partnering strategy was adopted. It was felt that it would provide access to endemic markets while allowing us to hold onto as much value as possible, particularly the travel market, though managing regional partners is challenging in its own right.” However, the regional deal with Bharat Biotech in India was dissolved in favor of a broader distribution agreement with Sanofi Pasteur, and Acambis’ ultimate acquisition by Sanofi Pasteur underscores Monath’s comment that “today, things are changing and people are seeing the opportunity differently in niche global health products like this one.”

Regulatory challenges: The Acambis JE vaccine was an innovative technology that had not yet been reviewed in the United States or Europe by established regulatory bodies. According to Monath, for this reason, “everywhere we faced challenging regulatory issues for clinical development and licensure.” To address this challenge, Acambis began building a package of information and supporting research related to various scientific issues that needed to be addressed during the regulatory processes. “We had to address issues such as the potential for spread by mosquito and tick vectors, vaccine virus shedding into the environment, the potential for genetic recombination, and other factors. Each country had committees that were established to deal with genetically modified organisms. That was a big challenge but we came through pretty successfully.” In addition, in the countries in which Sanofi Pasteur now intends to license the product, the regulatory structures are not always fully developed. As a result, these countries seek validation of their review process and may be hesitant to approve a product that has not been previously reviewed in the United States or other developed world country. To support these countries, Sanofi Pasteur plans to submit the vaccine for approval in Thailand and Australia simultaneously, which may allow the countries to benefit from each other’s experience during the review process. Sanofi has also worked with the WHO prequalification team to request their support of endemic countries as they complete regulatory reviews.
Tiered pricing: Sanofi Pasteur has three products in development that will be distributed in the developing world without first pursuing developed world markets. These products are focused on rabies, dengue fever, and JE. Typically, Sanofi Pasteur’s margins in the developed world would enable extremely low pricing in the developing world — maximizing access to the vaccine by the poorest patients who are most in need. The fact that the JE vaccine will be distributed primarily in the developing world poses challenges for Sanofi Pasteur in executing this tiered pricing strategy. Because there will be a limited lucrative developed world market to offset low-margin prices, concerns about access to the vaccine must be balanced by commercial concerns.

Financing: JE has been identified by the Global Alliance for Vaccines and Immunization (GAVI) as a future investment priority, but in the near-term, no significant financing of JE vaccines will be undertaken by the organization. This creates a concern for Sanofi Pasteur with regard to financing for public-sector purchase of the vaccine. It remains to be seen whether endemic country governments will be willing or able to purchase large volumes of the IMOJEV™ vaccine for their populations.

1 GAVI is a global health partnership representing stakeholders in immunization from both private and public sectors: developing world and donor governments, private-sector philanthropists such as the Bill & Melinda Gates Foundation, the financial community, developed and developing country vaccine manufacturers, research and technical institutes, civil society organizations and multilateral organizations like the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF) and the World Bank. See http://www.gavi alliance.org/about/in_partnership/index.php.
**ANNEX: INDIVIDUALS CONSULTED**

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<thead>
<tr>
<th>NAME</th>
<th>TITLE</th>
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<tbody>
<tr>
<td>Rashmi H. Barbhaiya, PhD</td>
<td>CEO and Managing Director</td>
<td>Advinus Therapeutics Pvt Ltd</td>
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<tr>
<td>Annmarie Emmet Leadman</td>
<td>Director of Communications</td>
<td>Aeras Global TB Vaccine Foundation</td>
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<tr>
<td>Peg Willingham</td>
<td>Senior Director, External Affairs</td>
<td>Aeras Global TB Vaccine Foundation</td>
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<tr>
<td>Rita Khanna, PhD, JD</td>
<td>General Counsel</td>
<td>Aeras Global TB Vaccine Foundation</td>
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<tr>
<td>David P. Perry, MBA</td>
<td>President and CEO</td>
<td>Anacor Pharmaceuticals</td>
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<tr>
<td>Jacob Plattner, PhD</td>
<td>Senior Vice President, Research</td>
<td>Anacor Pharmaceuticals</td>
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<tr>
<td>Roger Wiegand, PhD</td>
<td>Associate Director, Infectious Disease Initiative</td>
<td>Broad Institute</td>
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<tr>
<td>Robert N. Husson, MD</td>
<td>Division of Infectious Diseases</td>
<td>Children’s Hospital Boston</td>
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<tr>
<td>Denis Martin, PhD</td>
<td>Senior Project Manager</td>
<td>Drugs for Neglected Diseases initiative</td>
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<tr>
<td>Shing Chang, PhD</td>
<td>Director of Research and Development</td>
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<tr>
<td>Tom von Geldern</td>
<td>Pharmaceutical Consultant</td>
<td>Embedded Consulting</td>
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<tr>
<td>Jay G. Reilly, JD</td>
<td>Vice President, Legal-Corporate</td>
<td>Emergent BioSolutions Inc</td>
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<td>José Ochoa</td>
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<td>James A. Geraghty</td>
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<td>Jeffrey D. Klinger, MPH, PhD</td>
<td>Vice President, Humanitarian Assistance for Neglected</td>
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<td>Lori Gorski</td>
<td>Associate Director, Corporate Communications</td>
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<td>Thomas P. Monath, MD</td>
<td>Partner</td>
<td>Kleiner Perkins Caufield &amp; Byers</td>
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<td>Simon L. Croft, PhD</td>
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<td>Lita Nelsen</td>
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<td>Timothy N.C. Wells, PhD ScD</td>
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<td>Clement Lewin, PhD, MBA</td>
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<td>Jacqui Shea, PhD</td>
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<td>Cyrus J Bacchi, PhD</td>
<td>Former Director, Haskins Laboratory and Department of</td>
<td>Pace University</td>
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<td>Helen McShane, PhD</td>
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<td>Media Officer</td>
<td>The Wellcome Trust</td>
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<tr>
<td>Nicholas Dunster, PhD</td>
<td>Senior Business Analyst</td>
<td>The Wellcome Trust</td>
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<tr>
<td>Richard Seabrook, PhD, MBA</td>
<td>Head of Business Development in Technology Transfer</td>
<td>The Wellcome Trust</td>
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<tr>
<td>Ted Bianco, PhD, FIBiol</td>
<td>Director of Technology Transfer</td>
<td>The Wellcome Trust</td>
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<tr>
<td>Christopher P. Locher, PhD</td>
<td>Director, Alliance Management</td>
<td>Vertex Pharmaceuticals</td>
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<tr>
<td>Peter Mueller, PhD</td>
<td>Chief Scientific Officer and Executive Vice President, Global Research and Development</td>
<td>Vertex Pharmaceuticals</td>
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