accelerating R&D for 
neglected diseases 
through global collaborations

WIPO Re:Search Partnership Stories  
2012-2013
Recognizing the need for more progress in NTD research and product development, the World Intellectual Property Organization (WIPO) joined ranks with BIO Ventures for Global Health (BVGH), and several leading pharmaceutical companies to form WIPO Re:Search. The consortium’s objective is to establish partnerships that facilitate sharing of IP assets to advance the discovery and development of new drugs, vaccines, and diagnostics for NTDs, malaria, and tuberculosis.

WIPO is the United Nations agency dedicated to the use of intellectual property (IP) (patents, copyright, trademarks, designs, etc.) as a means of stimulating innovation and creativity. The Organization’s mission is to promote innovation and creativity for the economic, social, and cultural development of all countries through a balanced and effective international intellectual property system, in cooperation with its 186 member states and other relevant international organizations.

WIPO’s Global Challenges program focuses on unlocking the potential of innovation to address some of the world’s toughest challenges, in particular, climate change, public health, and food security. The WIPO Re:Search platform demonstrates the Organization’s commitment to exploring, initiating, and developing platforms and goal-oriented partnerships to address these challenges. As the Secretariat of WIPO Re:Search, WIPO plays a key role in managing and overseeing the success of this endeavor. Freely sharing information is important and beneficial, but simply listing available compounds and IP assets is not enough to ensure that productive collaborations emerge from the consortium. BVGH plays a pivotal role in proactively identifying and facilitating collaborations as the Partnership Hub administrator of WIPO Re:Search.

BVGH was established in 2004 by the Biotechnology Industry Organization (BIO) to engage BIO member organizations in global health initiatives. Today, BVGH continues to work closely with BIO and many other organizations to develop programs, influence policies, create partnerships, and engage private industry to improve health worldwide. BVGH leverages its broad network to engage industry leaders in global health initiatives and to facilitate increased sharing of expertise and knowledge by pharmaceutical and biotechnology companies.

The founding pharmaceutical company Members – Alnylam, AstraZeneca, Eisai, GlaxoSmithKline, MSD, Novartis, Pfizer, and Sanofi – support the consortium and have contributed a wide variety of IP assets to the online WIPO Re:Search database managed by WIPO. The database is freely searchable and available for public viewing. It contains approximately 200 entries detailing member contributions including compounds, compound libraries, screening data, hit-to-lead series, marketed products, enabling technologies, patent estates, diagnostic tools, vaccine technologies, and other services and resources for use by consortium members.

Founding pharmaceutical company members have also shared their expertise in product development, including formulation development, protein purification approaches, and computational drug metabolism and pharmacokinetic predictions. This dissemination of knowledge has already benefited scientists in academic institutions and is helping them to advance their research and product development efforts. The breadth and value of these contributions speaks to the commitment of the founding companies, and the consortium as a whole, to develop products for diseases of poverty.
Advances in science, medicine, and technology have enabled high-income countries to dramatically reduce the burden of infectious diseases and even eliminate some diseases from their populations. Many developing countries, however, still struggle with high rates of preventable sickness and death.

A key challenge has been a lack of market-driven research and development to create products for preventing, diagnosing, and treating a subgroup of infectious diseases that are common in developing nations—especially the least developed countries. This subgroup consists of neglected tropical diseases (NTDs), malaria, and tuberculosis (TB).

Neglected tropical diseases, malaria, and TB impact nearly 2 billion people worldwide. This group of diseases primarily affects low-income and politically marginalized populations in rural and urban areas within the world’s developing and least developed countries. These populations often have little influence on administrative and governmental decisions that affect their health and sometimes seem to have no one who can advocate effectively for their interests.

Many of these diseases are transmitted by insect bites or by worms residing in the soil. Children and adults typically become infected with disease-causing parasites, viruses, or bacteria simply by engaging in normal daily activities, such as playing outside, collecting water, doing laundry, or planting crops.

The World Health Organization (WHO) designated the following as NTDs:

- Buruli Ulcer (*Mycobacterium ulcerans* infection)
- Chagas disease
- Dengue/Severe dengue
- Dracunculiasis (guinea-worm disease)
- Echinococcosis
- Foodborne trematodiases
- Human African trypanosomiasis (“Sleeping sickness”)
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Onchocerciasis (River blindness)
- Rabies
- Schistosomiasis
- Soil transmitted helminthiases
- Taeniasis/Cysticercosis
- Trachoma
- Yaws (Endemic treponematoses)

These diseases have an enormous impact on individuals, families, and communities. Many can lead to severe disfigurement and disability, as well as death.

The diseases aggravate poverty and reduce productivity by impairing children’s intellectual development, stunting growth, reducing school enrollment, and limiting the ability of infected individuals to work. Neglected tropical diseases constitute a serious barrier to socioeconomic development and improvement in the quality of life in the world’s poorest countries.
At first glance, there would not seem to be a connection between medications originally developed in the 1970s to treat high levels of so-called ‘bad cholesterol’ (LDL) and a blood-borne parasitic disease infecting millions of people living in the developing world. Schistosomiasis, caused by infection with the *Schistosoma* bloodfluke, is the second most socioeconomically devastating disease in the world with more than 200 million people suffering in 75 countries. Transmission of the parasite occurs via freshwater snails, the environmental reservoir of *Schistosoma mansoni*, hence, the historical name for schistosomiasis: “snail fever.”

Schistosomes and humans both express an enzyme called 3-hydroxy-3-methyl-glutaryl-CoA reductase or HMG-CoA reductase. In humans, the enzyme catalyzes the rate-limiting step in a pathway producing cholesterol and related molecules. As a result, drug companies invested considerable sums researching methods to inhibit HMG-CoA reductase, thereby lowering LDL cholesterol levels. Collectively, the class of HMG-CoA reductase inhibitors that emerged is known as “statins.” Statins have been one of the most prescribed medications in the developed world and have proven benefits in improving outcomes for patients.

In contrast to the human enzyme, the schistosome HMG-CoA reductase is required for egg production and, indeed, is essential for survival of the parasite in culture and in an animal model of infection. Importantly from a drug discovery perspective, there are differences in structure between the human and parasite HMG-CoA reductase protein that might be exploitable for developing parasite-specific drugs.

Since 2001, the Center for Discovery and Innovation in Parasitic Diseases (CDIPD; www.cdidp.org) at the University of California in San Francisco (UCSF) has been dedicated to the discovery and development of drugs to treat various ‘neglected’ tropical diseases, including schistosomiasis. Through the auspices of BIO Ventures for Global Health (BVGH) and the WIPO Re:Search consortium, Dr. Conor Caffrey, a senior scientist at the CDIPD, was placed in contact with Dr. David Olsen, partnering leader for infectious diseases at MSD, to discuss access to MSD’s investigational statin-compound collection. These initial contacts were followed up after Dr. Jim McKerrow, director of the CDIPD, met with BVGH to learn more about WIPO Re:Search and the collaborations that could be facilitated. It soon became clear that there was a strong interest by all parties to commit to this project.

MSD’s statin research and development efforts have yielded

*Known as Merck in the US and Canada.*
libraries of compounds with drug-like properties. These compounds will be screened against the parasite using a novel whole-organism screening platform developed by Conor and colleagues at UCSF to identify compounds with potent anti-schistosomal properties. “This is exactly the kind of opportunity our screening system is designed for,” Conor states. “We are delighted to have MSD’s collaboration as an outstanding example of the pharmaceutical industry partners the CDIPD has worked with in the search for drugs to treat tropical infectious diseases. In this case, leveraging MSD’s knowledge and expertise in the statin field will accelerate our schistosomiasis research.”

“Schistosome HMG-CoA reductase provides a promising target for the treatment of schistosomiasis infection. By using compound libraries originally created to inhibit the human HMG-CoA enzyme by developers of statin drugs, we are able to accelerate the identification of novel lead structures and significantly advance our therapeutic program. Partnerships such as this one with MSD can help us to achieve our goals in identifying promising new hits for neglected diseases,” adds Jim.

“Working with the UCSF scientists was not only enjoyable but highly educational. We look forward with great anticipation as the data roll out from the screening”
- Anja Heckeroth, MSD

At MSD, we understand the importance of assisting neglected tropical disease research. One of the founding WIPO Re:Search members, MSD committed resources to enable researchers like Jim and Conor to accelerate their drug discovery efforts. Proactively, MSD designed a form detailing a series of questions designed to provide internal decision-makers with the information needed to efficiently assess a request for compound(s) or resource sharing. This “Asset Request Form” streamlined UCSF’s request to gain statin compounds from MSD’s extensive chemical repository.

“At MSD, we understand the importance of assisting neglected tropical disease research,” says David Olsen. “Unfortunately, we can’t do everything. The one-page Asset Request Form allows us to quickly understand the science and the specific resources that are being sought for each request. This standardizes the process that allows us to make informed strategic investment decisions in a timely manner. The request for statin analogs by Dr. Caffrey is an excellent example of where we can contribute a unique asset with the potential to provide a much-needed therapy for this devastating disease.” MSD and UCSF signed a confidentiality agreement. Over the next few months, a research plan was jointly developed, focusing on the goals of screening MSD’s statins against S. mansoni at UCSF. “As an Animal Health helminths subject matter expert, I have found it a terrific experience to be able to apply my expertise to this human health project. Working with the UCSF scientists was not only enjoyable but highly educational. We look forward with great anticipation as the data roll out from the screening,” says Dr. Anja Heckeroth, Intervet/MSD Animal Health. In January 2013, a package from MSD arrived. The boxes contained screening plates with a series of statin compounds – the starting point for what is sure to be a mutually beneficial collaboration with the potential to improve treatment options for patients suffering from schistosomiasis while positively impacting drug discovery for neglected diseases in general. As a footnote to this story, Conor applied for and was awarded a two-year R21 grant from the National Institutes of Health (NIH) to investigate statins as anti-schistosomals. Adding to Conor’s proposal was a letter of support from MSD to the screening collaboration.
Dr. Dennis Liotta, Professor and Director, Emory Institute for Drug Development is an internationally recognized scientist and biotechnology leader working within Emory University’s Department of Chemistry in Atlanta, Georgia.

Dennis and his colleagues developed an antiviral drug called Emtriva™, which is now used by more than 90% of all HIV-positive patients in the United States. His research partially focuses on pathogenic viruses, including the flavivirus that causes dengue fever. Emory University was one of the first academic centers to join the WIPO Re:Search consortium. Roopa and Jennifer met with Emory University faculty, including Dennis, to present WIPO Re:Search and the Partnership Hub. During this initial conversation, Dennis expressed interest in connecting with an expert in dengue biology. A chemist by training, Dennis believed the RNA-dependent RNA polymerase inhibitors he had developed had promise as new therapies against dengue fever.

“Our meeting with BVGH proved valuable because it enabled us to easily connect with experts in dengue biology that could help us test our compounds,” says Dennis. Within weeks, BVGH met with scientific administrators and program officers at the National Institutes of Health (NIH), including Dr. Cristina Cassetti, Program Officer for Acute Viral Diseases. She explained that the NIH, more specifically the National Institute of Allergy and Infectious Diseases (NIAID), could help support Dennis’s drug discovery efforts. A teleconference was arranged to connect Cristina and Dennis so they could discuss the dengue project and how Dennis could gain access to in-kind support from NIAID. One critical aspect of the support offered by NIAID was its ability to perform in vitro antiviral screens against the four dengue virus serotypes. Following the discussion, the NIAID and Emory signed a ‘non-clinical evaluation’ agreement that would allow NIAID-funded contractors to test the compounds in vitro for efficacy against dengue viruses.

These compounds were also screened against Rift Valley fever virus, which, while primarily infecting livestock, has the capacity to infect humans. Data from these tests will help guide research efforts in Dennis’ lab to design more effective inhibitors. Some of the compounds looked promising against Rift Valley fever virus and Dennis is now considering how to collaborate to develop them further.
**Dengue fever**

Dengue fever (DF) is a viral disease transmitted by infected mosquitoes. DF causes severe, flu-like symptoms with high fever and extreme muscle and joint pain. Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are less common but more severe forms of the disease. DHF/DSS initially present with very similar symptoms to DF. The diseases then progress to a stage where the blood vessels become permeable, or “leaky,” causing a breakdown of the circulatory system, fluid loss, and possibly death.

Dengue is common in tropical and sub-tropical countries of Southeast Asia, the Pacific, and the Americas, and is also found in Africa and the Eastern Mediterranean. In 2002, a record high of 69 countries reported dengue cases. The World Health Organization (WHO) estimated that 2.5 billion people—over 40% of the world’s population—are at risk of dengue infection. Approximately 50-100 million infections (1 million confirmed) occur each year resulting in 500,000 hospitalizations and 20,000 deaths.

The economic burden of dengue in India alone is estimated to be US $29.3 million. Based on a study of eight endemic countries, the estimated total economic burden of dengue is approximately US $587 million annually. However, known underreporting of dengue infection could increase this estimate to nearly US$1.8 billion.

Dengue is transmitted through the bite of the female *Aedes* mosquito, usually *A. aegypti*, but occasionally by other species such as *A. albopictus*. A mosquito becomes infected with the dengue virus upon taking a blood meal from an infected person. The virus replicates in the mosquito and is transmitted to the next human host when the mosquito takes another blood meal. Dengue is unusual among the arthropod-borne viruses; it does not require an animal reservoir, and is instead maintained through human-mosquito-human transmission.

There are currently no drugs or vaccines approved for the treatment of dengue. Treatment instead focuses on palliative care to manage fever and prevent dehydration, especially for patients with severe dengue. There are numerous diagnostic assays available for dengue based on a wide range of technologies:

- Virus isolation
- Serological testing (including IgM antibody capture ELISA, IgG ELISA, neutralization assays, and lateral flow device for NS1-specific antibodies)
- Nucleic acid amplification (RT-PCR, real time RT-PCR, and nucleic acid-sequence based amplification assays)
- Antigen detection (NS1 antigen detected by antigen capture ELISA)

The gold standard for dengue diagnosis is viral isolation as this allows for the most specific characterization of the dengue virus. However, advanced laboratory facilities are required for this technique, limiting its application in the developing world.

*Source: Global Health Primer (www.globalhealthprimer.org)*

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**Distribution of countries or areas at risk of dengue transmission, worldwide, 2001**

*Source: World Health Organization*
Tuberculosis (TB) is not a new disease. Modern genetic analysis suggests that humans infected with *Mycobacterium tuberculosis*, the causative agent of TB, may have migrated from Africa more than 50,000 years ago. As populations grew and distributed themselves across the world, TB came along for the ride.

Existing tuberculosis treatments are decades old and are primarily restricted to the developed world. Eighty-five percent of the world’s people battling TB live in Asia and Africa, with many having limited access to life-saving medication.

iThemba Pharmaceuticals, a company based in South Africa, is working on a special class of compounds, known as isocitrate lyase inhibitors, to target TB. Isocitrate lyase is an enzyme found in microorganisms, including *M. tuberculosis* and various other pathogens, and serves as an essential step in a critical metabolic process.

In order for the *M. tuberculosis* bacterium to thrive, it needs isocitrate lyase. iThemba’s compounds under investigation inhibit the ability of isocitrate lyase to function properly.

Scientists at iThemba had characterized a library of novel isocitrate lyase inhibitors that demonstrated activity against *M. tuberculosis* during in vitro testing. In order to move into the next phase of discovery, their team needed access to computational chemistry capabilities.

Sorting through thousands of compounds to select a lead candidate capable of becoming a clinical drug requires extensive testing, which can take years to complete. One approach to accelerate compound selection is to use predictive computer models. These computer models are used primarily by large pharmaceutical companies to increase the likelihood of success for products in their early clinical pipelines.

During an introductory phone call with BVGH, the iThemba scientists summarized their work on TB and inquired about gaining access to computational chemistry support. BVGH approached AstraZeneca, who had already expressed its willingness to provide WIPO Re:Search members with access to internal computational and predictive chemistry resources. AstraZeneca’s research center in Bangalore, India focuses almost exclusively on TB and malaria research and development. Their scientists are highly skilled in the precise type of computational support iThemba needed.

A conversation was facilitated between AstraZeneca scientists and iThemba researchers. Within a couple of months, a Confidentiality Agreement had been signed between the two organizations, allowing the isocitrate lyase inhibitor...
Bytes Against Bugs: Using Computers to Battle Ancient Infections

It’s no secret that the cost of developing a successful drug is very high, both financially and in terms of resources. Selection of lead compounds is a critical step in drug discovery, as it provides the raw materials for preclinical studies and eventually, clinical development.

The use of sophisticated computer modeling software to analyze lead compounds for “druggable” characteristics is a relatively new approach known as cheminformatics. This process provides scientists with a much better understanding of complex chemical structures and potential interactions with target molecules.

Analysis of compound libraries prior to large scale in vivo testing may pinpoint specific lead compounds—or compound attributes—that are most likely to demonstrate desirable traits such as solubility, advantageous biodistribution, lower toxicity, and improved interaction with molecular targets.

Ideally, using computers to predict druggability will accelerate drug development, especially for scientists working with complex natural product libraries.

The availability of whole parasite genome sequences and cheminformatics could prove to be a powerful weapon against neglected tropical diseases.
The University of Washington (UW) sprawls across several dozen acres of scenic real estate in Seattle, Washington. Long an academic powerhouse of scientific research, UW is home to scientists who are committed to discovering new, promising drugs to treat malaria.

While attending a conference, Jennifer spoke with Dr. Wesley Van Voorhis, Professor of Medicine and Head of the UW Allergy and Infectious Disease Division. The nascent WIPO Re:Search consortium was growing and the two discussed UW becoming a member. “Having the University of Washington’s Department of Medicine as a South Lake Union neighbor makes it particularly convenient for BVGH to explore various partnership ideas and proposals with faculty. Not only is its infectious diseases group (or Division) among the top in the world, UW is also known for its bioengineering and chemistry strengths. Each of these groups represents critical components necessary for product discovery and development. Most importantly, there is important and innovative R&D ongoing for diseases of poverty,” says Jennifer.

Shortly thereafter, UW officially joined WIPO Re:Search as a Provider and User Member. The Partnership Hub wasted no time identifying synergies between UW scientists’ research and those of other WIPO Re:Search members. One such research project was Wes’s examination of a promising anti-malarial compound referred to as compound 1294.

Known as a bumped kinase inhibitor, compound 1294 blocks malaria transmission. Malaria is transmitted to a human by the bite of an infected mosquito. Soon after invading the human host, the malaria parasite multiplies in the liver, enters the bloodstream, and then infects a red blood cell. The cycle is completed when an uninfected mosquito bites an infected human, taking in the malaria parasite along with its bloodmeal.

In contrast to other anti-malarial drugs like artemisinin — which kills the parasite during the blood-stage of its lifecycle — 1294 blocks transmission by preventing the parasite from advancing through its early lifecycle stages within its mosquito host. This inhibition prevents the parasite from maturing into a form that readily replicates in the mosquito vector. By inhibiting the ability of the parasite to advance through its lifecycle stages and replicate within mosquitoes, compound 1294 prevents the parasite’s transmission to an uninfected human. Combining this unique mechanism with other drugs that target different stages of the parasite’s lifecycle could prove very powerful.

BVGH successfully connected UW researchers led by Wes with experts working in GlaxoSmithKline’s (GSK) Malaria Discovery Performance Unit (DPU) in Tres Cantos, Spain. It was agreed that Wes’s team would send their 1294 compound to the Tres Cantos lab to be re-profiled through a battery of tests performed by GSK researchers. Over the next few weeks, as calls were held to arrange the compound’s transfer, both groups discussed previous screens performed by the UW scientists on the GSK Tres Cantos Anti-Malarial Set (TCAMS). These screens had been com-
missioned by another WIPO Re:Search member, Medicines for Malaria Ventures (MMV). MMV provided financial support and guidance to UW on the discovery of protein kinases targeted by the TCAMS anti-malarials discovered by GSK and MMV continues to work with and support Wes’s team. The TCAMS, developed as a component of GSK’s research at its Tres Cantos facility, is a dataset that contains structures and screening results for 13,500 compounds that inhibit the blood-stage of malaria. These data were obtained by screening approximately 2 million GSK compounds against Plasmodium falciparum, the causative agent of the most severe form of malaria, as well as a multi-drug-resistant strain of the parasite.

“GSK is committed to developing new products for diseases that disproportionately burden individuals in the developing world – and the TCAMS is a product of that commitment. The original screen that generated the TCAMS was performed through a partnership between GSK and the Medicines for Malaria Venture. GSK is devoted to maintaining its open, collaborative approach to malaria drug discovery by offering unrestricted access to the dataset and compounds.

Through the TCAMS and other GSK initiatives, GSK hopes to stimulate more neglected diseases drug discovery and partnerships that will fill the pipeline for diseases of poverty and ultimately eliminate these diseases,” says Nicholas Cammack, Senior Vice President, Diseases of the Developing World, GSK. Previous work completed by Wes’s group identified 800 compounds in the TCAMS that appeared to target specific enzymes, called protein kinases, within the malaria parasite. Inhibitors of these kinases were predicted to result in a reduction in transmission. Since these compounds already displayed potency against the blood-stage parasite, the additional promise as transmission blocking agents added a great deal of value to these compounds.

“The TCAMS was a perfect place for us to begin our screens for multi-kinase inhibitors. Compounds that inhibit both the blood-stage and transmission stage of the parasite may cure patients as well as decrease the vector’s overall parasite load, resulting in the development of effective treatments for malaria that are useful in malaria elimination campaigns,” says Wes.

In a great example of true partnership and openness, both teams have agreed to make publicly available the output of the screen as a result of combining the significant resources within GSK and UW to identify new promising anti-malarial drug scaffolds.

“We were pleased to see how quickly these two agreements came together. What started out as a simple agreement for GSK to examine our lead compound turned into a broader collaboration. It allows GSK to prioritize further examination of the 20,000 compound TCAMS set to get compounds of added value in malaria control. This collaboration demonstrates GSK’s commitment to developing partnerships to share its resources and capabilities to accelerate the development of new drug candidates for malaria,” says Wes.

“We were pleased to see how quickly these two agreements came together. What started out as a simple agreement for GSK to examine our lead compound turned into a broader collaboration” - Wes Van Voorhis, UW
During a meeting with Dr. James McKerrow, Professor of Pathology and Director of the Center for Discovery and Innovation in Parasitic Diseases (CDIPD) at the University of California, San Francisco (UCSF), BVGH learned about Jim’s interest in accessing compounds to screen against two parasites.

The parasites belong to the Trypanosomatidae family: *Trypanosoma cruzi*, the causative agent of Chagas disease, and *Leishmania*, the causative agent of leishmaniasis. Although related, Chagas disease occurs predominantly in Central and South America, whereas visceral leishmaniasis is highly endemic in India and East Africa. Chronic *T. cruzi* infection can cause heart complications and visceral leishmaniasis can be fatal if treatment isn’t initiated in time.

One of Jim’s colleagues — Dr. Larissa Podust, Assistant Adjunct Professor, UCSF School of Medicine — was examining sterol 14α-demethylase (CYP51) inhibitors and other antifungals as potential treatments for these diseases. CYP51 is crucial for sterol biosynthesis in *T. cruzi*. In a mouse model of acute infection, analyses demonstrated that treatment with a CYP51 inhibitor caused the parasite’s cell membrane to break down, resulting in the death of the clinically relevant tissue-stage parasites. Azole-forms of CYP51 inhibitors are used to treat fungal infections in humans, and some of these compounds have proven to be effective against Chagas disease in animal models and human clinical trials. However, issues of potential drug resistance in *T. cruzi*, kidney and liver side effects, and high production costs mar the prospective utility of these azole drugs. Larissa is investigating other azole and non-azole drugs, searching for compounds with a better safety profile that are equally or more effective.

BVGH facilitated a conversation between Jim and AstraZeneca to discuss the potential of gaining access to a set of AstraZeneca’s drug-like compounds for Larissa to screen against Chagas disease and leishmaniasis. Larissa shared the structures of the compounds that she had shown to inhibit the CYP51 of *T. cruzi* with scientists at AstraZeneca.

A Material Transfer Agreement was put in place allowing AstraZeneca to provide Larissa with 905 compounds with similar
What is a kinetoplast?

A kinetoplast is a unique type of circular DNA found only within the mitochondria of Kinetoplastida protozoa. *Trypanosoma spp.*, which cause Chagas disease, nagana, and sleeping sickness, and *Leishmania spp.*, which are responsible for leishmaniasis, are examples of kinetoplastids.

The kinetoplast DNA exists in a series of interconnected loops of two sizes, namely mini- and maxi-circles. Electron microscopy suggests that each kinetoplast contains a dozen maxicircles and several thousand minicircles. Researchers are still exploring the gene products and functions of the kinetoplast DNA. Recent evidence suggests that the mini-circles produce guide RNA (gRNA) that is necessary to decode the “encrypted” maxi-circles. Some experts have compared this concatenated kinetoplast DNA network to sheets of medieval chainmail armor.
During the Council on Health Research and Development (COHRED) conference in Cape Town, South Africa, Jennifer met Dr. Ellis Owusu-Dabo, Scientific Director of the Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR), Kumasi, Ghana, where they discussed WIPO Re:Search. That introduction has since blossomed into several collaborations for KCCR, including one involving researchers from Stanford, and the Kwame Nkrumah University of Science and Technology (KNUST) in Kumasi, Ghana.

KCCR is a joint venture between the Ministry of Health of the Republic of Ghana, KNUST, and the Bernhard-Nocht Institute for Tropical Medicine (BNITM) in Hamburg, Germany. The venture provides Ghanaian researchers access to world-class instrumentation, laboratory space, and other resources.

KCCR is located on the campus of KNUST and is one of the two biosafety level-3 laboratories in the country. The combination of experienced parasitologists and access to rural field sites makes KCCR and KNUST ideal partners to collaborate with during NTD product development.

Through faculty at Stanford, BVGH was introduced to Johan Guillaume, an MD student who was working to develop a diagnostic for soil-transmitted helminths as a SPARK project, in collaboration with Josh Lichtman, a PhD candidate. After learning more about the project and the need for stool samples containing helminths, BVGH reached out to Ellis at KCCR and arranged a teleconference between the potential partners. During the conversation, they discussed gaining access to stool samples from populations infected with single or multiple species of soil-transmitted helminths.

There are four main genera of soil-transmitted helminths that infect humans: *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and the hookworms (*Ancylostoma duodenale* and *Necator americanus*). Helminth eggs are transmitted through contact with or ingestion of feces-contaminated soil. The resulting infection can lead to debilitating weakness, malnutrition, stunted childhood development, reduced adult productivity, and even mortality.

According to a report published by the WHO in 2010, these parasites infect more than one billion people worldwide, including populations from huge swaths of central and southern Africa. In that same report, the WHO suggested that effective deworming would increase adult income by nearly 40%.

“Soil-transmitted helminths are an interesting group of parasites. Unlike several other neglected tropical diseases that lack effective therapeutics, soil-transmitted helminths can be quite successfully...
treated through mass drug administration campaigns. However, to ensure that there is complete coverage across all geographic locations, a simple, fast diagnostic tool is needed,” says Ellis. Currently, widespread prophylactic treatments for school-age children rely on light microscopy-based examination of stool samples. This low-sensitivity, low-throughput method is used to determine whether or not a particular village requires treatment with anti-helminthic drugs, typically an annual dose of albendazole. The treatment program is considered successful if the overall number of eggs available for re-transmission is reduced. An accurate estimate of infected individuals is therefore key to interrupting the transmission cycle. An accurate point-of-care (POC) diagnostic is required not only to test the effectiveness of mass drug administration campaigns but, in elimination settings, to test for infection prior to initiating treatment. Access to clinical samples from the targeted population, in this case stool samples from areas where soil-transmitted helminth infections are endemic, is critical to ensuring the accuracy and utility of a POC diagnostic.

“Students in the SPARK program are developing a novel, easy-to-use diagnostic platform. We can test this diagnostic using purified helminth antigens, but this doesn’t adequately represent the test’s effectiveness in the clinic. We need to test stool samples from patients with known helminth infections in order to verify that there aren’t other factors within the stool that will block the helminth antigen or otherwise prevent the proper interaction with the diagnostic’s components. Collaborating with KCCR or another African research institution to acquire stool samples is critical to our further development of the diagnostic,” says Johan.

Currently, the researchers at Stanford are still awaiting stool samples infected with helminths. Due to successful eradication programs in Ghana, KCCR was not successful in securing the needed samples. The Stanford researchers are leveraging BVGH connections through WIPO Re:Search to gain access to samples. An introduction to a parasitologist at the University of Lagos in Lagos, Nigeria has been made and looks promising. Helminth infections are still endemic in many regions of Nigeria so the hope is samples will be accessed through this new collaboration.

Soil-transmitted helminthiasis

Hookworm is a parasitic roundworm of the small intestine that is transmitted through contaminated soil. When hookworm eggs are passed in human feces, they are shed into the surrounding environment, where the eggs hatch and penetrate through the skin of exposed individuals.

Although most patients are asymptomatic, heavy worm burdens lead to anemia, diarrhea, abdominal pain, weight loss, and loss of appetite. Hookworm is found throughout the tropics and subtropics.

It is estimated that 600-700 million people are infected worldwide, resulting in the loss of approximately 1.1-22.1 million disability-adjusted life years (DALYs) annually and 65,000 lives annually.
Research institutions in African countries offer local scientists an opportunity to be a part of the global movement to develop effective and affordable products for neglected tropical diseases – diseases that these researchers and their communities are intimately more familiar with than developed world researchers.

They personally see the devastating results these diseases can have in their communities and often have suffered from them individually. Yet, while these diseases cause the greatest burden within these regions, African institutions frequently lack experienced staff and resources to facilitate moving a new discovery through preclinical and clinical development and manufacturing to commercialization.

To address this gap in research and development, IP Australia, a branch of the Australian government, provided funds to WIPO to financially support sabbatical arrangements for African researchers at international pharmaceutical and academic institutions. Through the WIPO Re:Search consortium, BVGH identified African scientists who could benefit from further training and matched them with international organizations that could provide that training and experience.

BVGH learned that Novartis had an interest in building relationships with researchers from African countries and institutions. BVGH presented the sabbatical program to Novartis and they quickly responded with interest in hosting one or more researchers from African academic institutions at its Basel, Switzerland headquarters. BVGH went to work to identify senior African researchers who were interested in spending three months with Novartis in Switzerland.

Two scientists were selected: Dr. Fidelis Cho-Ngwa, Associate Professor of Biochemistry, University of Buea, Cameroon, and Dr. Wellington Oyibo, Associate Professor, College of Medicine, University of Lagos, Nigeria, who have backgrounds complementary to programs at Novartis. Fidelis and Wellington were enthusiastic about gaining a broad experience at a large pharmaceutical company. Novartis organized telephone interviews with each candidate to ensure alignment of expectations.

Following the interviews and review of submitted written proposals, the administrative planning got underway for visas, travel plans, housing, and local temporary healthcare. Finally everything was in place, thanks to some creativity and personal dedication, and Wellington and Fidelis traveled to Basel to begin their...
“Building relationships and sharing our capabilities with researchers in Africa is core to our values and desires to develop new products to treat infectious diseases” - Petra Keil, Novartis

Fidelis, whose research focuses on discovering natural products that may be developed into drugs for onchocerciasis, also known as river blindness, and phenotypic drug screens relevant to curing the disease, worked alongside Novartis scientists to gain experience with small molecule isolation and characterization, as well as a number of cutting-edge analytical methods, and quality control/assurance in drug manufacturing. His goal is to apply his industry training to his own efforts to develop onchocerciasis drugs. “I see this as an opportunity not only to gain invaluable experience and knowledge from a world-class company like Novartis, but to develop relationships and collaborations that I can leverage to advance my research upon my return to Cameroon,” says Fidelis.

During his visit, Wellington, who focuses on research targeting malaria, gained broad pharmaceutical industry experience, including product pipeline development processes and management, as well as insights into clinical trial conduct, and the governance of knowledge and intellectual property. He plans to translate the skills learned to his development of malaria diagnostics. While in Basel, Wellington presented his research on malaria biomarkers to Novartis scientists. “The chance to participate in a sabbatical with Novartis was an amazing opportunity – one which I will utilize to gain skills and knowledge to fill the gaps in product development at my home institution. I am also excited by the opportunity to transfer my new skills to my students at the University of Lagos,” says Wellington.

The sabbatical opportunity has been a fruitful experience for all. Both Fidelis and Wellington have built relationships with Novartis scientists that will continue long after their return home. Plans to collaborate beyond the sabbatical are already being explored and planned. “We are extremely happy that we had the opportunity to host both Wellington and Fidelis. They have been wonderful colleagues to our team here in Basel, and we have enjoyed learning from their perspectives and insights. Building relationships and sharing our capabilities with researchers in Africa is core to our values and desires to develop new products to treat infectious diseases,” says Petra Keil, Head, Global Public Policy at Novartis.

“I see this as an opportunity not only to gain invaluable experience and knowledge from a world-class company like Novartis, but to develop relationships and collaborations that I can leverage to advance my research upon my return”  
- Fidelis Cho-Ngwa, University of Buea, Cameroon
Researchers at the University of Dundee in Scotland are advancing their discovery of new drugs to treat NTDs with the help of the WIPO Re:Search consortium and one of the world’s largest pharmaceutical companies, AstraZeneca.

At the Consortium’s launch, AstraZeneca contributed its entire patent estate, including advanced preclinical compounds, to the online IP database maintained by the World Intellectual Property Organization (WIPO). BVGH profiled kinase inhibitors, including AstraZeneca’s glycogen synthase kinase-3 (GSK-3) beta inhibitor, in the Partnership Hub monthly newsletter and then began the search for a researcher who was likely to be interested in these compounds. “AstraZeneca believes that there is potential for repurposing our advanced preclinical compounds for neglected tropical diseases, and that those compounds demonstrating drug-like properties will accelerate researchers’ progress. We want to share compounds from diverse classes with researchers so they have tool compounds to investigate different pathways in parasites,” says Kevin Pritchard, Science Policy Enablement Lead, AstraZeneca.

Publications from the University of Dundee hinted at a possible interest in screening GSK-3 beta inhibitors. At a Keystone Conference, Roopa met with Dr. Paul Wyatt, Professor of Drug Discovery and Head of the Drug Discovery Unit at the University of Dundee and spoke with him about the GSK-3 beta inhibitors in the WIPO Re:Search database. Paul subsequently requested access to a library of related GSK-3 beta inhibitors to screen for selectivity to parasite targets. BVGH approached AstraZeneca with Paul’s request and facilitated communication between the two. Within months, AstraZeneca and the University of Dundee signed a Material Transfer Agreement enabling the sharing of compounds.

Drug repurposing is becoming more popular among infectious disease researchers for very good reasons. Pharmaceutical companies spend considerable resources developing and characterizing potential drugs to fill their development pipeline. Data from these studies include pharmacokinetics, safety/toxicity, metabolic profiling, and formulation data — studies that are expensive to complete and often financially out of reach for academic laboratories. Access to this information, as well as to the actual compounds, can significantly accelerate drug discovery. Moreover, pharmaceutical companies typically discontinue projects based on insufficient activity against a human disease, which is opportune for infectious disease researchers seeking to re-apply such compounds to parasitic targets.

In this project, scientists at Dundee will be testing a group of GSK-3 inhibitors, originally developed by AstraZeneca as a potential treatment of Alzheimer’s disease. Dundee will evaluate these com-
pounds against the parasites responsible for Chagas disease, leishmaniasis, and human African trypanosomiasis (HAT). GSK-3 kinases are implicated in multiple intracellular signaling pathways, including cell growth, migration, and immune responses. While the compounds in question may not have shown adequate potency in Alzheimer’s disease models, they may be highly effective against these parasitic diseases.

These compounds, having been developed for Alzheimer’s disease, already possess the ability to penetrate the blood-brain barrier, an essential requirement for drugs treating Stage II HAT.

“Partnering and gaining access to compounds is key to the success of our Drug Discovery Unit at Dundee,” Paul says. “Through WIPO Re:Search, BVGH has been instrumental in helping us to access various new compounds to evaluate.”

Chagas disease, leishmaniasis, and HAT are caused by parasites known as kinetoplastids. These single-celled organisms are characterized by a unique granule, the kinetoplast, found at the base of the parasites’ flagellum, or “tail.”

*Trypanosoma cruzi* parasites are transmitted by an insect vector — triatomine or “kissing” bugs — prevalent throughout Central and South America. Leishmaniasis, caused by several parasite species, is spread by the bite of an infected sandfly that is found throughout the world, most notably in Southeast Asia, Africa, and the Middle East. Trypanosomiasis, both human and livestock forms, is caused by *Trypanosoma brucei* sub-species and can only be transmitted by infected tsetse flies. These insects are found primarily in sub-Saharan Africa within the vegetated areas along rivers and streams.

Together, the parasites responsible for these three diseases infect more than 10 million people annually in Africa and South America. In addition to the significant morbidity and mortality associated with active trypanosomal infection, the economic burden to populations battling these diseases is immense.

The United Nations Food and Agriculture Organization (FAO) estimated that approximately US $1.5 billion in agriculture losses on the African continent were due to livestock and human trypanosomiasis. A successful treatment for Chagas disease, leishmaniasis, and HAT would alleviate a disease burden equivalent to 4.1 million DALYs (disability-adjusted life years). The need for new, safe, and effective drugs to combat these diseases is undeniable. Thanks to WIPO Re:Search, the work of BVGH, and the willingness of pharmaceutical companies, such as AstraZeneca, to share valuable IP, University of Dundee scientists now have a new collection of compounds to test that may potentially lead to a faster drug development path.

“A successful treatment for Chagas disease, leishmaniasis, and human African trypanosomiasis (HAT) would alleviate a disease burden equivalent to 4.1 million DALYs

“Partnering and gaining access to compounds is key to the success of our Drug Discovery Unit at Dundee”

- Paul Wyatt, Univ. of Dundee
At an American Society of Tropical Medicine and Hygiene (ASTMH) conference, Jennifer and Roopa met with Drs. Frederick Duncanson, Senior Director and Infectious Diseases Clinical Lead, and Michael Everson, Associate Director-Clinical Research, of Eisai.

Fred and Mike described some of the challenges Eisai was having with an anti-fungal compound it had developed. The compound was highly protein-bound and had bioavailability and solubility limitations. They were interested in obtaining the opinion of other scientists who had experience with this type of compound to see if they might have recommendations or advice to share.

The University of Kansas (KU) was a relatively new member of WIPO Re:Search and had considerable expertise in drug formulation development and problem solving.

An introduction was made by BVGH and the parties entered into a Confidential Disclosure Agreement to move discussions forward. Eisai provided extensive information regarding the various approaches it had tried to Dr. Michael Baltezor, Director, Biotechnology Innovation & Optimization Center, University of Kansas.

Michael determined that Eisai had covered every approach that his lab would have taken. The Eisai scientists were pleased to hear they had already considered the approaches Michael would have recommended and expressed appreciation for a second opinion from KU's formulation experts.

The compound was highly protein-bound and had bioavailability and solubility limitations.

Eisai provided extensive information regarding the various approaches it had tried to Dr. Michael Baltezor, Director, Biotechnology Innovation & Optimization Center, University of Kansas.
The WIPO Re:Search consortium includes pharmaceutical companies, academic and nonprofit research institutions, product development partnerships, and government organization.

Members join WIPO Re:Search as Providers of IP, know-how, and expertise; as Users of these resources; or as Supporters of the consortium. In some cases, members enroll in multiple categories. Through WIPO Re:Search, qualified researchers gain access to the following types of resources:

- Compounds
- Compound libraries
- Unpublished scientific results
- Regulatory data and dossiers
- Screening technologies and capabilities
- Platform technologies
- Expertise and know-how
- Patents and patent rights

When joining the consortium, members agree to abide by the following WIPO Re:Search Guiding Principles:

- Providers of IP will offer royalty-free licenses for products made available to least developed countries.
- Users of IP shared through WIPO Re:Search may retain ownership of new IP but are encouraged to make their inventions available to other consortium members.
- License agreements are individually negotiated between member organizations in accordance with the consortium’s guiding principles.

The work of WIPO Re:Search centers around three main areas of activity:

- A global database: Hosted by WIPO, this is a publicly accessible, comprehensive database of IP assets—including compounds, enabling technologies, know-how, and other information.
- Supporting services: Led by WIPO, these services include general licensing support from WIPO and technical advice provided by WIPO and the World Health Organization (WHO).
- Partnership Hub: BVGH facilitates connections and partnerships between members

For more information about WIPO Re:Search, please visit www.wipo.int/research.
Jennifer and Roopa presented WIPO Re:Search to researchers at the invitation of the Consortium’s new Member, McGill University, in Montreal, Canada. At this presentation, they met Dr. Joseph Dent, Associate Professor of Biology, Centre for Host-Parasite Interactions, at McGill University.

Joe uses Caenorhabditis elegans as a model organism to screen potential anti-helminth compounds. Compounds identified through this screening process could be used to treat worm infections, such as roundworm, hookworm, and whipworm, as well as onchocerciasis and lymphatic filariasis. These diseases are endemic in African countries and result in the stunting of growth and development of children.

Joe shared with BVGH that he had mutant strains of C. elegans resistant to known anti-helminthic drugs. Compounds that inhibit all of these drug-resistant C. elegans strains may have novel targets or mechanisms of action and thus could potentially work on drug-resistant helminths.

BVGH knew that the Drugs for Neglected Diseases initiative (DNDi) had collaborated with AstraZeneca to screen AstraZeneca’s compounds against the worms causing onchocerciasis, or river blindness, using DNDi’s phenotypic assay. DNDi identified five AstraZeneca compounds that appeared promising against the adult parasites of two species of Onchocerca worms. AstraZeneca and DNDi wanted to know whether these compounds had a different mechanism of action compared to currently available drugs. Joe’s C. elegans mutants appeared to be an interesting system to address this question. BVGH connected scientists at AstraZeneca with Joe to explore a possible collaboration leveraging the work already completed by DNDi.

“C. elegans has been used for decades in a wide range of scientific fields and thus it is not only extremely well-characterized, but scientists have developed significant expertise in its handling and with the assays and reagents that work best with the worm. This is in contrast to many pathogenic helminths that are not as easy to work with and are difficult to maintain in a laboratory. Because C. elegans is so easy to maintain in a laboratory, scientists can perform drug screens – including high-throughput screens – much faster than on its pathogenic cousins,” says Joe.

A Material Transfer Agreement (MTA) was put in place between AstraZeneca and McGill. Joe then began by screening the five compounds against a drug-susceptible strain of C. elegans. While this particular collaboration didn’t produce promising results that would lead to a new drug, it did lead to a broader collaboration between McGill and AstraZeneca. Joe and AstraZeneca are moving forward to develop a new collaboration to screen different compounds against C. elegans and observe if any of these inhibit the helminth.
An MTA is in place that will allow McGill to screen 10,000 AstraZeneca compounds against his *C. elegans* wild-type strain to identify potential inhibitors. These data will be included as supporting information in Joe’s application for the Wellcome Trust’s Seeding Drug Discovery grant. This funding opportunity was brought to the attention of Joe and AstraZeneca by BVGH through their BVGH Funders Database program. If funding is secured, it will allow Joe’s *C. elegans* to be screened against AstraZeneca’s entire compound collection at its High-Throughput Screening facility in the UK.

“This is exactly the type of collaboration our infectious disease division at AstraZeneca is interested in pursuing, and WIPO Re:Search is presenting these opportunities,” says Manos Perros, Global Head of Infection Innovative Medicines and Site Head, Boston R&D, AstraZeneca. “We’re pleased to be collaborating with McGill and look forward to a long-term partnership.”

“Joe has provided us with an exciting opportunity to utilize our state-of-the-art High Throughput Screening facility to screen against a different model organism. Combining a model organism for pathogenic helminths that is capable of being used in high-throughput screens with AstraZeneca’s facility and capabilities and its collection of 1.8 million drug-like and lead-like compounds has the potential to yield some amazing results. We are pleased to be collaborating with Joe on this project,” says Kirsty Rich, HTS Team Leader, AstraZeneca. With the dedication of Joe and scientists at AstraZeneca, *C. elegans* is on its way to helping rid the world of pathogenic worms.

“Combining a model organism for pathogenic helminths that is capable of being used in high-throughput screens with AstraZeneca’s facility and capabilities and its collection of 1.8 million drug-like and lead-like compounds has the potential to yield some amazing results”
- Kirsty Rich, AstraZeneca
Diarrheal disease, which is responsible for the deaths of approximately 760,000 children annually, is the second highest cause of death in children under the age of five.

Acute secretory diarrhea (ASD) is common in developing nations and caused by pathogens such as *Vibrio cholerae*, enterotoxigenic *E. coli*, and rotavirus. Oral rehydration therapy (ORT) substantially reduces mortality from ASD, but there is still a need for anti-secretory therapies to combine with ORT.

The human neutral endopeptidase (NEP) is a promising anti-secretory target. The NEP inhibitor racecadotril is used to treat ASD in Europe and several developing countries, but it has drawbacks. It needs to be taken three times a day to be effective and that makes compliance difficult in areas where resources are limited.

The Center for World Health and Medicine (CWHM) at Saint Louis University is focused on discovering treatments for diseases of poverty, including new therapies to treat diarrheal disease. In collaboration with PATH, CWHM established a rat diarrheal model suitable for testing anti-diarrheal compounds.

CWHM contacted BVGH with the hope of identifying WIPO Re:Search members that would share clinical-stage NEP inhibitors to test in its rat model. The goal is to find a compound, superior to racecadotril, that could be repurposed as an anti-diarrheal agent.

BVGH reached out to two founding members of WIPO Re:Search, Sanofi and Pfizer, to explore gaining access to compounds the companies previously had in development for different indications. Sanofi agreed to share Ilepatri and MDL-100240 and Pfizer agreed to share Candoxatril and Candoxatrilat.

In CWHM’s rat diarrheal model, racecadotril inhibits castor oil-induced diarrhea by approximately 70%. This is the benchmark CWHM set to test other compounds against. CWHM will compare the activity of the supplied NEP inhibitors against racecadotril. If a compound exhibits greater efficacy, CWHM scientists will determine the compound’s pharmacokinetic-pharmacodynamic relationship in the castor oil-induced rat diarrheal system.

“Access to these compounds through WIPO Re:Search and the efforts of BVGH has been an important component of allowing us to more quickly advance our research on diarrheal diseases”
- Peter Ruminski, CWHM
“These partnerships with large pharmaceutical companies are extremely important to a number of our programs and WIPO Re:Search has been a big help” - Peter Ruminski, CWHM

Sanofi and Pfizer signed separate Material Transfer Agreements with CWHM and shared the requested compounds. CWHM has begun testing these compounds and initial screening has shown promise.

“Access to these compounds through WIPO Re:Search and the efforts of BVGH has been an important component of allowing us to more quickly advance our research on diarrheal diseases,” says Dr. Peter Ruminski, Executive Director, Center for World Health and Medicine, Saint Louis University. “These partnerships with large pharmaceutical companies are extremely important to a number of our programs and WIPO Re:Search has been a big help.” If the hopes for these compounds are realized, developing nations could gain a more effective tool for their fight against diarrheal disease.

Old drugs, new tricks: drug repurposing for NTDs

The gap between a preclinical lead candidate and a successful clinical compound is often referred to as the “valley of death” in drug development circles. The vast majority of compounds that show promise in preclinical and animal studies never receive market approval. Understandably, the bar is set very high for drug approval: safety/tolerability profile, efficacy, dosing, and product stability must all meet or exceed stringent standards.

For neglected tropical disease researchers, the chasm between lead identification and clinical investigation is even wider. One strategy to de-risk clinical development on new drugs to treat NTDs is the concept of drug “re-purposing” or “re-positioning”. Existing, approved drugs are screening for activity against pathogenic parasites.

The presumption follows that if one of these molecules demonstrate anti-parasitic activity, the regulatory hurdles will be fewer and better defined. For example, if a marketed oncology treatment is found to be more effective than existing anti-malarials, the developers will have access to years of toxicity, safety, pharmacokinetic, and product testing data.

Logically, this concept seems very straightforward. However, in practice, difficulties could arise. Recognizing the value of drug repurposing, the National Institute of Health (NIH) recently launched the “Discovering New Therapeutic Uses for Existing Molecules” initiative within the National Center for Advancing Translational Sciences (NCATS). This initiative will provide up to US $20 million to fund several cooperative research agreements between large pharmaceutical companies and nonprofit researchers.

To date, the pharmaceutical company partners—AbbVie, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical R&D, Pfizer, and Sanofi—have agreed to provide 58 compounds for this initiative. To further streamline the collaborations, NCATS has prepared boilerplate (template) agreements that delineate intellectual property rights and data sharing arrangements that might otherwise bog down the timeline in lengthy negotiations.

For more information on the NCAT’s drug repurposing initiative, please visit: http://1.usa.gov/KsK4Md
One-third of the world’s population is believed to be infected with *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis (TB). TB infections resulted in more than 1.4 million deaths in 2011, mostly in the developing world. Drug resistance is increasing and treatments focused on new targets are desperately needed.

One such class of targets, known as methionine aminopeptidases (MetAPs) has received attention as a potential drug target for tuberculosis.

MetAPs perform many critical functions, including tissue repair, protein synthesis, and protein degradation. In humans, the role of MetAP enzymes in generating new blood vessels makes them especially interesting as potential cancer and rheumatoid arthritis treatments.

In bacteria, including *M. tuberculosis*, the MetAP enzymes help to process proteins by clipping off the beginning amino acid, methionine. When researchers stop expression or ‘knock out’ the gene encoding MetAP type 1 (MetAP-1) enzymes in bacteria, the bacteria do not survive.

For Executive Director Dr. Peter Ruminski and his colleagues at the Center for World Health & Medicine (CWHM) in Saint Louis, Missouri, the MetAP enzymes showed promise in the fight against *M. tuberculosis*. Established in 2010 as a not-for-profit research center, the CWHM is dedicated to discovering and developing treatments for diseases that disproportionately affect the world’s poor and underserved populations, including neglected tropical diseases, TB, and malaria. Staffed by chemists, biologists, and pharmacologists, the CWHM team is experienced in transitioning drug candidates from the laboratory bench to the clinic.

Setbacks are not uncommon in science, especially when working with the intractable TB bacteria, which is notoriously difficult to treat thanks to a dense, waxy coating on its cell surface using a series of unique compounds. Dr. David Barros Aguirre, Director of Drug Discovery, TB Discovery Performance Unit (DPU), and Dr. Monica Cacho-Izquierdo, a researcher at GSK’s Tres Cantos Medicines Development Campus outside Madrid, Spain, had tested a series of inhibitors specific to the MetAP-1 enzyme present in TB bacteria.

Their initial efforts were met with disappointing results. Setbacks are not uncommon in science, especially when working with the intractable TB bacteria, which is notoriously difficult to treat thanks to a dense, waxy coating on its cell surface.

After joining the WIPO Re:Search consortium, CWHM contacted BVGH, stating its interest in accessing MetAP-1 inhibitors to test in a TB model. BVGH arranged a series of conversations between CWHM and GlaxoSmithKline (GSK).

GSK is one of the founding Members of the WIPO Re:Search consortium. One of GSK’s research programs focused on the inhibition of MetAP enzymes using a series of unique compounds. Dr. David Barros Aguirre, Director of Drug Discovery, TB Discovery Performance Unit (DPU), and Dr. Monica Cacho-Izquierdo, a researcher at GSK’s Tres Cantos Medicines Development Campus outside Madrid, Spain, had tested a series of inhibitors specific to the MetAP-1 enzyme present in TB bacteria.
what is MDR/XDR tuberculosis?

Multidrug-resistant TB (MDR-TB) is caused by organisms that are resistant to the most effective anti-TB drugs (isoniazid and rifampicin). XDR-TB, an abbreviation for extensively drug-resistant TB, is a form of TB which is resistant to at least four of the core anti-TB drugs, including second-line anti-TB drugs.

MDR-TB and XDR-TB both take substantially longer to treat than ordinary (drug-susceptible) TB, often requiring the use of second-line anti-TB drugs, which are more expensive and have more side-effects than the first-line products used for drug-susceptible TB.

XDR-TB is rare, however 77 countries worldwide had reported at least one case by the end of 2011. Information from countries with reliable data suggests that about nine percent of all MDR-TB cases worldwide are actually XDR-TB.

WHO estimates that there are about 650,000 MDR-TB cases in the world at any one time.

Only a small proportion of these cases are detected and treated appropriately given that many low and lower middle-income countries still lack sufficient diagnostic capacity to detect MDR/XDR-TB.

Source: Global Health Primer (www.globalhealthprimer.org)
At the University of Dundee in Scotland, Professor Ian Gilbert studies malaria and performs screens to identify compounds that inhibit malaria parasite activity.

Results of his screens against a chemogenomic library assembled by the Drug Discovery Unit at Dundee suggested that two compound classes might have anti-malarial activity.

When Jennifer and Roopa spoke with Ian to learn about his research and collaboration interests, he shared his desire to obtain other inhibitors in the same compound classes to screen against these potential drug targets in the malaria parasite.

BVGH searched through WIPO Re:Search pharmaceutical member pipelines and discovered that Eisai had an approved inhibitor in one of the compound classes that had been developed.

They contacted Eisai to learn if the company would be willing to share some selection of such proprietary inhibitors, in support of Ian’s malaria research. Dr. Makoto Asada, Director, Special Associate to Chief Innovation Officer, expressed Eisai’s willingness to support the request.

He also shared with BVGH that Eisai had inhibitors for the second class of compounds that could be made available to support Dundee’s research as well. These compounds were shared with Dundee.

Thanks to the WIPO Re:Search consortium and Eisai’s support, these proprietary compounds can be evaluated as potential anti-malarials.

Thanks to the WIPO Re:Search consortium and Eisai’s support, these proprietary compounds can be evaluated as potential anti-malarials.
Malaria: a global challenge

Malaria is a parasitic disease that is transmitted by infected mosquitoes. The non-specific nature of the symptoms of uncomplicated malaria, including fever, chills, sweating, body aches, nausea, headache, vomiting, and diarrhea, make clinical diagnosis challenging.

In contrast, severe disease rapidly leads to anemia, dehydration, respiratory distress, seizures, and coma. Although severe malaria is easier to identify clinically, the symptoms are difficult to manage in resource poor settings, contributing to a high mortality rate in these patients. When left untreated, uncomplicated malaria can rapidly progress to severe disease, especially in young children.

Malaria is widespread in the tropical and subtropical regions of Africa, Asia, and Central and South America. In 2013, 97 countries experienced ongoing malaria transmission, and the estimated at risk-population in high burden countries was close to 1.2 billion.

Human malaria is caused by protozoan parasites of the *Plasmodium* genus. There are five species of *Plasmodium* known to affect humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. The classical periodic fevers and severe anemia associated with malaria are the result of lysis of infected red blood cells caused by the replication of the parasite in its blood-stage.

Malaria affected over 207 million people and resulted in more than 627,000 deaths in 2012. Approximately 90% of all malaria deaths occur in sub-Saharan Africa, primarily in children under the age of five. In high transmission regions of Africa, malaria accounts for up to 40% of all health expenditures and 30-50% of all hospital admissions.

The impact of malaria goes beyond health. In Africa, malaria has been estimated to result in more than US$12 billion in lost annual gross domestic profit. It is estimated that in high transmission areas, malaria can decrease GDP by up to 1.3% per year.

Sources: Global Health Primer (www.globalhealthprimer.org), World Health Organization

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Countries with malaria transmission, WHO 2011.
The University of California, San Francisco (UCSF), joined the WIPO Re:Search consortium as one of its early Members. Access to pharmaceutical companies’ compound libraries was of vital importance for many Members, including Dr. James McKerrow, Professor of Pathology at UCSF School of Medicine and Director of the Center for Discovery and Innovation in Parasitic Diseases (CDIPD), Dr. Conor Caffrey, Associate Research Scientist at UCSF’s Department of Pathology, and Professor Phil Rosenthal, UCSF School of Medicine. Each year, thousands of compounds are tested by pharmaceutical companies, with a significant portion of these molecules undergoing pharmacokinetic and safety studies. The data associated with these compounds is invaluable for researchers like Jim, Conor, and Phil, allowing them to more rapidly select promising molecules to move into advanced studies.

“The discovery of drugs for infectious diseases requires significant time spent screening hundreds to thousands of different compounds to identify a few lead candidates. Pharmaceutical companies’ compound collections represent a treasure trove of potential drugs, and gaining access to their libraries that target specific pathways allows us to screen for selectivity against specific parasite targets. Access to key company data and information such as pharmacokinetic and safety data will help us move forward quickly with drug development once we identify promising compounds,” says Jim.

During his initial meeting with BVGH, Jim mentioned his interest in a group of compounds known as cysteine protease inhibitors. These inhibitors target a family of enzymes that are nearly ubiquitous in plants and animals. Cysteine proteases are molecule scissors, clipping the bonds between amino acids in a huge range of proteins. For each type of protein to be hydrolyzed, there is a different cysteine protease. Inhibitors of two such varieties – known as cathepsin K and cathepsin B – are highly active in collagen and fibrous tissue, respectively, and have been developed by pharmaceutical companies as treatments for osteoporosis and cancer.

The McKerrow lab, like many other drug discovery groups, hoped that re-purposing compounds that were not sufficiently potent in pharmaceutical companies’ screens might lead to a new weapon against parasitic diseases. Lack of significant effect against human molecular targets could translate into higher effectiveness or selectivity against the parasite target. “Compared with bacteria and viruses, at the cellular and molecular level, parasites are very similar to humans and other mammals. This presents a real challenge when developing drugs that inhibit parasitic enzymes – the drug has to affect the parasite enzyme, but leave the human counterpart relatively unscathed. Using drugs that didn’t demonstrate sufficient activity against the human protein allows us to examine the compounds’ efficacy against the parasite, while knowing that the compound will have a higher chance of clearing later in vivo toxicity studies,” says Jim. BVGH facilitated discussions between Jim and researchers from AstraZeneca to explore sharing a series of cathepsin inhibitors. The compound library under consideration contained cathepsin K inhibitors that had previously been in development at AstraZeneca for osteoporosis. The teams moved forward to put an agreement in place to enable the sharing of compounds with UCSF.

Every AstraZeneca compound shared with the McKerrow lab was tested against a series of parasites, including Trypanosoma brucei, Schistosoma mansoni, Trypanosoma cruzi, and Plasmodium falciparum the causative agents of human African trypanosomiasis, schistosomiasis, Chagas disease, and malaria, respectively. Taken together,
these organisms annually infect more than 250 million people worldwide and significantly delay, impede, or prevent economic development in endemic regions. Current treatments, if they exist, are moderately effective but often cause severe side effects, leading to low compliance and increasing drug resistance.

Dr. Conor Caffrey has spent years characterizing molecules that could treat neglected tropical diseases, especially hookworm and schistosomiasis. Recent work by Conor and Dr. Jon Vermeire of Yale University (now at UCSF collaborating with Conor) demonstrated potent anti-hookworm activity of a cysteine protease inhibitor, suggesting that the compounds AstraZeneca shared with the McKerrow lab would be of interest to Conor. After reading the publication, Roopa Ramamoorthi reached out to Conor to see if he would be interested in gaining access to AstraZeneca’s compounds.

“My group focuses on utilizing high-content, high-throughput methods to screen compounds for activity against tropical parasitic diseases. We recently discovered that a cysteine protease inhibitor, originally developed to treat Chagas disease, had a significant effect on hookworms – so we were excited by BVGH’s proposal to test a new set of cysteine protease inhibitors to potentially identify an even more potent hookworm therapy,” says Conor. The initial agreement between UCSF and AstraZeneca was subsequently amended to include screens against hookworms. Results from the compound screening efforts at UCSF were showing very interesting results. Tests against *T. cruzi* and malaria were particularly promising. “I’m encouraged by the results of the cathepsin inhibitor screens against malaria and am really pleased to have access to these new compounds through WIPO Re:Search. My laboratory has studied cathepsin inhibitors as potential anti-malarials for some time now and I would be thrilled to see these compounds progress into the clinic,” says Phil Rosenthal, Professor in Residence, UCSF School of Medicine.

If lead candidates are selected from the AstraZeneca libraries for further development, the UCSF labs will have a head-start, thanks to the reams of data collected by AstraZeneca during their past development efforts. “While these compounds failed to have an acceptable level of activity against osteoporosis, their application towards diseases of poverty gives us a genuine opportunity to put the significant investments AstraZeneca had spent during discovery and initial development to good use,” says Dr. Manos Perros, Head of Infection and Site Head, Boston R&D, Innovative Medicines and Early Development AstraZeneca. Months of work remain for the researchers at UCSF to fully characterize and evaluate the compounds against several parasites. With early promising leads against Chagas disease and malaria, Jim’s lab will be taking steps toward preclinical testing in animal models and further compound development. This important research continues thanks to the generosity of companies like AstraZeneca and the dedication of researchers in the McKerrow, Rosenthal, and Caffrey labs.

“Their application towards diseases of poverty gives us a genuine opportunity to put the significant investments AstraZeneca had spent during discovery and initial development to good use” - Manos Perros, AstraZeneca
In support of WIPO Re:Search’s mission to engage academic and nonprofit organizations in developing world countries, Roopa traveled to India to recruit research institutions to the Consortium. During her trip, she met with Dr. Chandrima Shaha, Director of the National Institute of Immunology (NII) in New Delhi. Their discussions were fruitful, and NII swiftly joined WIPO Re:Search as a User and Provider.

Mike Strange, Head of Operations, Tres Cantos Medicines Development Campus, had shared with BVGH GSK’s interest in initiating collaborations with developing world researchers through GSK’s Open Lab. “GSK is committed to sharing our capabilities and experience with scientists across the globe to help them advance their neglected disease research projects”, says Mike. The Tres Cantos Medicines Development Campus (TCMDC) in Spain is GSK’s facility dedicated to discovering and developing medicines for diseases of the developing world. GSK’s Open-Lab provides external scientists with an opportunity to perform their research on state-of-the-art equipment with the support of GSK scientists’ experience and expertise across drug discovery and development.

“Using GSK’s kinase inhibitors, we could examine the molecular and phenotypic results of inhibiting malaria signaling pathways”
- Pushkar Sharma, NII

Roopa followed up with Chandrima to see if NII researchers would be interested in speaking with GSK to learn more about its Open-Labs program. Chandrima suggested BVGH connect with infectious disease faculty at NII, specifically with Dr. Pushkar Sharma. Roopa connected Pushkar with Dr. Lluis Ballell, Director of External Opportunities, and Dr. Elena Fernandez Alvaro, Senior Scientist within the TCMDC at GSK.

Pushkar described his research and his interests in using kinase inhibitors to dissect and understand signaling pathways in malarial parasites. “Many of the kinases we are interested in are essential to the malaria parasite, and thus we cannot create viable knock-out mutants. To circumvent this problem, we can use kinase inhibitors at varying concentrations to produce phenotypes that mimic, to a lesser degree, a complete knock-out. Using GSK’s kinase inhibitors, we could examine the molecular and phenotypic results of inhibiting malaria signaling pathways,” says Pushkar.

Another GSK scientist, Dr. David Drewry, Director, Department of Chemical Biology based at GSK’s facility in North Carolina, was brought into the discussion. David had been actively involved in assembling GSK’s kinase set (PKIS – published kinase inhibitor set).

“Kinases are chemically tractable drug targets. For this reason, GSK compiled a set of over 360 small-molecule kinase inhibitors to share with academic labs to facilitate and stimulate kinase research. The molecules in the set span over 20 different chemotypes. The set, which includes information relating to the inhibitors’ activity against over 200 different kinases, would be an ideal starting point for Pushkar,” says David. Following discussions between Pushkar and the GSK team, a Material Transfer Agreement between GSK and NII was signed, enabling Pushkar to obtain a set of kinase inhibitors, some of them being compounds which are active against the malaria parasite (belonging to the Tres Cantos AntiMalarial Set, TCAMS). Using these inhibitors, Pushkar will be able to examine the essential malaria kinases’ mechanisms of action. Understanding how a parasite functions brings scientists one step closer to a solution to this devastating disease.

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Pfizer is in the early stages of discussion with 60 Degrees Pharmaceuticals (60P), based in Washington DC, and has shared information that will support 60P’s efforts to develop a drug for dengue fever. Access to this information will enable 60P to more efficiently advance their research and development program in this area.
Compounds that appear to inhibit a pathogen in early testing may not work when they come into contact with humans. To identify which promising research candidates are most likely to succeed in a patient, scientists can resort to computer models and predictive software.

Dr. Michael Pollastri, Associate Professor of Chemistry & Chemical Biology at Northeastern University in Boston is working to develop drugs to treat neglected tropical diseases. Mike has designed over 1,000 compounds that could inhibit human African trypanosomiasis (HAT), a neglected parasitic disease also known as sleeping sickness. HAT is caused by protozoan parasites belonging to the genus *Trypanosoma*. The small, single-celled organisms called trypanosomes are transmitted through the bites of tsetse flies. Sleeping sickness is endemic in 36 African countries, including some of the world’s least developed countries, and more than 70 million people in Africa are at risk of being infected.

The promise of Mike’s compounds was encouraging but it was unclear whether these compounds would be capable of reaching the various regions of the body where the HAT parasites reside, specifically the brain. BVGH connected Mike with AstraZeneca, which has a blood-brain barrier computer prediction model. AstraZeneca swiftly agreed to collaborate with Mike to run his compounds through their unique computational prediction software.

This collaboration has also enabled Mike to better understand critical drug properties including: absorption, distribution, metabolism, and excretion (ADME). The partnership between Mike and the scientists at AstraZeneca has proved fruitful for him. With AstraZeneca’s valuable computational predictions, Mike now has some of the answers he was looking for and is advancing his research program to find a new drug to treat HAT.

Unlike *E. coli*, which has a doubling time of approximately 20 minutes, *M. ulcerans* is extremely slow-growing — it requires nearly five days to double. This slow reproduction cycle lengthens the time required to identify lead candidates and ultimately extends the drug discovery process. Funding and support for Buruli ulcer drug development is minimal and scarce. Thus it makes sense to link Buruli ulcer with TB drug development programs to leverage TB knowledge and data and accelerate the development of new treatments.

The team of Professor Gerd Pluschke, Head of the Medical Parasitology and Infection Biology Department at the Swiss Tropical and Public Health Institute, has developed a low-to-medium throughput screening method to identify compounds that inhibit *M. ulcerans*. BVGH spoke with him and learned of his interest in gaining access to anti-TB compounds in development that he could screen against *M. ulcerans*.

BVGH followed up to connect Gerd with scientists at AstraZeneca to discuss synergies and access to TB compounds. An agreement was signed between the parties enabling AstraZeneca to provide Gerd with 100 carefully selected compounds. One of the compounds is already in clinical trials and has shown promise against *M. tuberculosis*. This repurposing of a drug in development for one mycobacterial disease for another is a great example of the potential impact of WIPO Re:Search partnerships.

There are ten FDA-approved drugs currently available to treat TB, but only one, rifampicin, has been shown to be highly active against Buruli ulcer. Buruli ulcer is caused by *Mycobacterium ulcerans*, a cousin to *Mycobacterium tuberculosis* and *Mycobacterium leprae*, the causative agents of TB and leprosy respectively. This family relationship suggests that at least some *M. tuberculosis* compounds may work against *M. ulcerans*.

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Phosphodiesterases (PDEs) are important regulators of cell signal transduction, and inhibitors of PDEs have been developed to treat various diseases such as erectile dysfunction and chronic obstructive pulmonary disease (COPD). Professor Michael Pollastri from Northeastern University and Dr. Robert Campbell from the Marine Biological Laboratory read reports that when two PDEs in Trypanosoma brucei, the causative agent of human African trypanosomiasis (HAT), were knocked down, the parasites died. This suggested that repurposed PDE inhibitors might be potent anti-trypanosome drugs, and the research team tested this hypothesis by screening existing human PDE inhibitors. However, when the team examined the inhibitors’ structure-activity relationships (SAR) against the parasite enzymes — the relationship between a compound’s structure and its biological activity — it was difficult to discern a trend or pattern in structural changes that corresponded with increased inhibition. Without this essential information, the compound optimization process was slowed significantly.

Mike contacted BVGH requesting help in identifying chemists who had specifically worked on PDE inhibitors. BVGH knew that a PDE inhibitor had been contributed by Eisai to the WIPO Re:Search database. BVGH reached out to Eisai and shared background information about the trypanosome PDE project and the challenges it faced. Discussions followed between Mike, Bob, and two Eisai scientists with expertise in the field, Dr. Yasutaka Takase, Director, Chemical Biology, and Dr. Tadashi Nagakura, Pharmacologist. The trypanosome PDE team received valuable advice and insights, including suggestions for future approaches and experiments.

Through the combined knowledge and interests of scientists on opposite ends of the globe, the PDE inhibitor project can continue to advance.

In response to a request from LSTM researchers working on malaria, AstraZeneca shared a set of diverse preclinical and clinical-stage compounds under a Material Transfer Agreement. These compounds, which were originally developed for a range of non-communicable diseases – including diabetes, depression, cancer, and gastrointestinal disorders – were screened by LSTM scientists against Plasmodium falciparum, the most deadly species of the malaria parasite.

These screens have already produced promising results and a potential new drug candidate for malaria treatment. AstraZeneca and LSTM are broadening this partnership to include additional support from AstraZeneca scientists for studies of the promising candidate discovered and more compounds will be shared with LSTM for further screening.

Dr. Philippe Gros, a professor in the department of Biochemistry and Vice-Dean of Life Sciences at McGill University, studies cerebral malaria. Cerebral malaria is characterized by severe inflammation in the brain, and it is this inflammation that makes the disease invariably lethal. Philippe studies anti-inflammatory compounds that may help to prevent inflammation-associated brain damage. The JAK-3 kinase is a key enzyme in an important inflammation-signaling pathway. By inhibiting JAK-3, Philippe hopes to inhibit cerebral inflammation. Soon after McGill joined WIPO Re:Search, BVGH paid a visit to present WIPO Re:Search to researchers working on...
The immune system is incredible — it protects the human body against viral, bacterial, fungal, and protozoal invaders, and rarely forgets a microbe it has encountered. Yet even the complexities of the immune system have been matched by pathogens' immune-modulating molecules. TB is one such infection that circumvents our bodies' defense against foreign invaders. Dr. Jyothi Rengarajan, a faculty member at Emory University, suspected that a TB membrane-bound protein might be an important factor in TB's modulation of the immune response, and thus an ideal target for anti-TB drugs.

To study the activity of this protein in more detail and screen compounds against it, Jyothi needed to purify the protein. However, due to aggregation and misfolding, the membrane-bound protein was proving difficult to purify. Jyothi turned to BVGH to identify a WIPO Re:Search member with protein purification expertise. BVGH introduced Jyothi to Dr. Jacqueline Fine, Director, Outlicensing and Global Health Strategic Partnerships at Merck, Sharp & Dohme (MSD). After signing a Confidential Disclosure Agreement, Jackie connected Jyothi to MSD's experts in membrane-associated protein purification techniques. Scientists at MSD shared their experience and ideas with Jyothi to help her plan next steps in advancing her research on the protein.

Dr. Nir Qvit is a postdoctoral researcher in Prof. Daria Mochly-Rosen’s laboratory at Stanford University. He develops drugs to treat cutaneous leishmaniasis. In particular, Nir developed a set of peptides that target Leishmania’s LACK protein. The LACK protein is a scaffold protein — one which potentially regulates multiple signaling pathways — that is necessary for Leishmania viability and infectivity. Nir presented his work testing these peptides against cutaneous leishmaniasis at an American Society for Tropical Medicine and Hygiene annual meeting. Afterwards, Roopa met with Nir to learn more about his work and how WIPO Re:Search might be able to help accelerate his research. Nir shared his desire to develop his peptides into a topical drug that could be applied directly to the skin lesions caused by Leishmania. To achieve this goal, he knew he would need the assistance of drug formulation experts.

Roopa contacted Dr. Kevin Pritchard, Science Enablement Lead at AstraZeneca, who agreed to introduce Nir to Dr. William Lambert, Fellow, Drug Delivery and Device Development, at AstraZeneca’s MedImmune Division. Bill had significant experience and expertise formulating peptides and was able to provide Nir with advice on methods to test skin diffusion and penetration and peptide stability in a leishmaniasis-induced skin lesion. He also shared his experience with vehicles and delivery methods that would work best with the peptides.

By combining the innovation, experience, and expertise of these two researchers, the world is one step closer to a cutaneous leishmaniasis therapy.
BIO Ventures for Global Health (BVGH) is a non-profit organization whose mission is to build partnerships with the biopharmaceutical sector to accelerate the development of new drugs, vaccines, and diagnostics to address the unmet medical needs of the developing world.

For more information on BVGH, please visit: www.bvgh.org

WIPO Re:Search is a worldwide consortium whose primary objective is to catalyze research and development of needed vaccines, diagnostic technologies, and drugs by sharing intellectual property, know-how, technologies, expertise, and related resources. To learn more about WIPO Re:Search, please visit www.wipo.int/research

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Alnylam has contributed more than 1,500 issued and pending patents, and all “fundamental” RNAi technology to scientists researching neglected tropical diseases. (NTDs)

As a partner in the WIPO Re:Search initiative, AstraZeneca has made all published patents and patent applications available for license, including royalty-free licenses, for NTD R&D in any country. In addition, AstraZeneca offers access to its high-throughput screening technologies, compound collection, and laboratories around the world.

As a global pharmaceutical company addressing unmet medical needs, Eisai is committed to making contributions to better healthcare for patients and their families around the world through its business activities.

GlaxoSmithKline (GSK) supports activities to tackle NTDs through donations of medicines and financial and practical support. Its global health programs focus on malaria, lymphatic filariasis, and intestinal worms, in partnership with governments, NGOs, and other organizations, to maximize the benefits to communities.

MSD’s investments in global NTD partnerships and programs have yielded great progress in recent years, and promise important advances in the near future. MSD continues to work in partnership with others to build on its portfolio of current programs and leverage its planned future investments to address the most critical needs in the fight against NTDs.

Novartis fosters collaboration and works to contribute drugs and vaccines for neglected diseases through drug discovery and vaccine research, contributing to new therapeutic targets, and researching basic molecular mechanisms of disease through its global research institutions.

Pfizer has a long history of contributions to research aimed at controlling or eliminating diseases that disproportionately impact poor patients in the developing world. It is currently working to address malaria in pregnancy, the most common and yet preventable cause of maternal and perinatal morbidity and mortality in sub-Saharan Africa.

Of the 17 NTDs listed by the WHO, the Sanofi group is present in the fight against eight: dengue, rabies, yaws, lymphatic filariasis, human African trypanosomiasis, leishmaniasis, Chagas disease, and Buruli ulcer.

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