Global Challenges in Focus

WIPO Re:Search

Advancing science for neglected tropical diseases, malaria and tuberculosis

Meghana Sharafudeen
Consultant, WIPO
Introduction

The 17 neglected tropical diseases (NTDs) identified by the World Health Organization (WHO) are the most common conditions impacting over a billion of the world’s poorest people in both the developed and developing world. In addition to their impact on the health of vulnerable populations, these diseases cost billions of dollars to developing economies each year – impairing physical and cognitive development, work productivity, and burdening the families of those afflicted. When combined with the emerging threat of anti-microbial resistance, NTDs, along with tuberculosis (TB) and malaria, represent a global health crisis with stark economic and global security implications.

Through its Development Agenda and under the umbrella of the United Nations Sustainable Development Goals, the World Intellectual Property Organization (WIPO) is committed to leveraging the power of intellectual property and innovative partnerships to address such global challenges. The WIPO Re:Search consortium, a partnership between WIPO and BIO Ventures for Global Health (BVGH), connects scientists around the world so they can share compound libraries, data, expertise and other resources in a collective effort to stimulate research and development (R&D) for NTDs, TB and malaria.

This edition of the Global Challenges In Focus series takes an in-depth look at some of WIPO Re:Search’s most promising scientific collaborations and their potential impacts – as described by the researchers and organizations involved.

Repurposing Heart Disease Drug Atopaxar to Target Cerebral Malaria

Eisai (Japan) + Liverpool School of Tropical Medicine (United Kingdom)
2014 – present

Malaria is an infectious disease that affects over 200 million people worldwide, with more than 50 percent of the global population at risk. Initial symptoms resemble those of a common cold – headache, fever, chills – but if not treated within the first 24 hours, the disease can lead to severe illness and even death. Of the five Plasmodium parasite species that cause malaria, P.falciparum represents the main source of infections and mortality, resulting in more than 400,000 deaths each year, primarily in sub-Saharan Africa.

Children account for more than two-thirds of malaria deaths. They are also most at risk when it comes to cerebral malaria – the most common complication of the P.falciparum infection. Cerebral malaria causes seizures and comas, and is the leading cause of P.falciparum fatalities. Of those who survive, more than 25 percent are left with lifelong neurological impairments. Although the pathology of the disease is not yet fully understood, recent studies have suggested that brain swelling is strongly linked to cerebral malaria fatalities – meaning that a medication that interferes with this activity could have a significant positive impact on patient outcomes.

After years of research, Dr. Alister Craig and his colleagues at the Liverpool School of Tropical Medicine determined that a protein called protease-activated receptor 1, or PAR-1, plays a key role in triggering the blood clotting and inflammation seen in cerebral malaria patients. In healthy persons, PAR-1 works in conjunction with activated protein C to appropriately regulate the clotting process. Dr. Craig’s team determined that in cerebral malaria cases, the P.falciparum parasite interferes with the “activation” of protein C. When the body sends a signal through the PAR-1 pathway and finds no activated protein C, a “panic” response is triggered – causing a range of reactions from vascular leakage to inflammation – that can lead to death. Thus began the search for an effective PAR-1 inhibitor which could help modulate this panic response. Dr. Craig tried reaching out to several manufacturers with similar drugs in commercial use, without success.
On the other side of the world from Dr. Craig and his team, vascular experts at leading Japanese pharmaceutical company Eisai had invested in the development of a PAR-1 inhibitor called atopaxar to treat coronary heart disease. After Phase 1 clinical trials, however, research into the compound and its derivatives was suspended in favour of other priorities. Through the Liverpool School of Tropical Medicine’s membership in WIPO Re:Search, Dr. Craig reached out to Eisai to request access to these compounds in order to screen them against *P. falciparum*. The company was happy to collaborate.

“For Eisai, this collaboration was a great opportunity to repurpose the intellectual property we had invested so much in and to find a second indication that could benefit a great number of people – especially when speaking of malaria, which affects so many around the world.”

Dr. Asada has been Eisai’s WIPO Re:Search lead since the consortium’s launch in 2011. Eisai is highly active in the neglected and infectious disease field, perhaps most famously as the supplier of free diethylcarbamazine (DEC) tablets to the World Health Organization. DEC is the first choice medication for the treatment of lymphatic filariasis, another infectious disease that affects the world’s poorest populations. Supported by the Global Health Innovative Technology (GHIT) Fund, Eisai collaborates with academia and product development partnerships on a number of other projects focused on malaria, Chagas disease and mycetoma, amongst others.

To Dr. Craig, this expertise turned out to be invaluable. The company supplied the Liverpool team with a range of derivative compounds for pre-screening. Running these compounds through an assay resulted in several positive hits, meaning the PAR-1 inhibiting properties of the compounds had now been validated through two independent screening assays. After a discussion of these results and potential next steps, Eisai shared their most advanced original compound – E5555, also known as atopaxar – with Dr. Craig’s team.

Dr. Craig has been pleasantly surprised to find that the collaboration with Eisai has delivered benefits beyond its initial scope.

“We had spent a lot of time and energy trying to get our assay to work reliably – not just for this study, but also for several other studies. Our investment in this collaboration has helped us develop what is now a fairly stable screening system that can provide reproducible results.”

Additionally, he and his team are in the process of publishing their findings related to the identification of a second, previously unknown, biological pathway that results in a slow degradation of the essential barrier function of the cells that line blood vessels. This pathway, which is not mediated by PAR-1 and is different from the “panic” response caused by a lack of activated protein C, may also have a significant role to play in cerebral malaria infection.

This is particularly exciting, notes Dr. Craig, because “essentially, what you might envisage is a combination therapy that would be a PAR-1 inhibitor and an inhibitor of this second pathway, and we have some pretty good ideas of what that inhibitor might be.” The downside, however, is that bleeding in the brain is a contraindication – a circumstance under which a drug should not be used because it may be harmful – of some commercially available PAR-1 inhibitors. “This is just the nature of PAR-1 inhibitors, and this has worried us since we started the study … Cerebral malaria already results in a lot of bleeding in the brain. So we are kind of caught: since we do not have an animal model, the first time we would be able to test the drug in a proper efficacy trial we would be testing it on very sick children with cerebral bleeds. And there is no real way to reassure ourselves of what would happen.”

Through WIPO Re:Search, Dr. Craig now hopes to consult other experts on the possible next steps. Should a potential combination therapy be taken to clinical trials, or are the risks to vulnerable patient populations simply too great?
In 2017, approximately 10 million people were infected with TB, and 1.6 million died, making it one of the world’s deadliest infectious diseases and a top ten cause of death worldwide. Usually caused by the bacterium Mycobacterium tuberculosis (mTB) and transmitted from person to person through the air, TB is both curable and preventable. However, the symptoms of an active infection may be mild for many months – including cough, fever and weight loss – which often results in a delay in seeking care and the spread of the infection to others. On top of this, the rise of antibiotic resistance and multidrug-resistant strains of TB (MDR-TB) constitutes a public health crisis and global health security threat for which novel antibiotics are urgently needed.

Dr. Christina Stallings and her team at Washington University in St. Louis focus on understanding TB pathogenesis. By identifying proteins that are essential to the survival of mTB or essential to its virulence, they hope to find inhibitors that can then become new antibiotics. “Myself as well as almost all TB researchers I know are always thinking about how we translate into therapeutics – how do we take the work we do in our laboratories and translate that into something that is good for this cause? That’s what really motivates this field,” says Dr. Stallings.

Dr. Stallings selected an enzyme her team had proven was essential to the TB bacterium and, armed with a grant from the National Institutes of Health (NIH), set out to find inhibitors against the enzyme. At that time, the Stallings Laboratory was working with the Center for World Health and Medicine (CWHM – a former WIPO Re:Search member) at St. Louis University. The CWHM contacted BVGH, which connected them to the opportunity to access Johnson & Johnson’s medicinal chemists and designed to provide starting points for new targets and therapeutics.

The resulting Jump-stARter library is a collection of 80,000 compounds curated by Johnson & Johnson’s medicinal chemists and designed to provide starting points for new targets and therapeutics.

Dr. Paul Jackson, Scientific Director at Johnson & Johnson, points out that WIPO Re:Search has been essential in promoting this opportunity within the academic sphere.

“If it wasn’t for WIPO Re:Search and BVGH we wouldn’t be where we are now. The ability the consortium has to connect people is amazing. We wanted to use the library to “jumpstart” collaborations, but it only really took off after we joined WIPO Re:Search.”

In an example of the connective power of consortia such as WIPO Re:Search, researchers at CWHM passed along the opportunity to access the library to Dr. Stallings’ team at Washington University. She recalls that since her team had just received funding, they were eager to say yes. “We needed access to good libraries, because in our experience a lot of the libraries in academic institutions are less diverse, and often have been sitting in the freezer forever. We have had some issues validating hits from these sorts of libraries. So we wanted something good. We became a member of WIPO Re:Search and applied for the Jump-StARter opportunity and got it, which was very exciting.”

Johnson & Johnson sent over the library in blinded (masked to reduce bias), ready-to-screen plates. When the initial screens identified hits, Dr. Stallings’ team sent the data to Dr. Jackson’s team, and after a phone call to discuss the results, received additional stock with which to conduct further, in-depth confirmation tests. Based on those results, they prioritized the most promising hits and coordinated to get the materials needed to make new stocks and further test the promising compounds.

There are a variety of advantages to these types of collaborations, says Dr. Stallings.
“When you can re-use compounds with a lot of high quality data available on essential factors like structures, toxicity and bioavailability, you are starting a step ahead.”

We need drugs fast; the further along drugs already are, the shorter the time to get to a new therapeutic, which is particularly relevant in TB with the threat of antibiotic resistance. Additionally, accessing the expertise from Johnson & Johnson—including their input on the chemistry, what the next steps should be, and how we should progress—that is also an invaluable resource. Paul and his team have been so responsive and enthusiastic about the project, and that has been a real pleasure.

Both sides are very interested in continuing this promising collaboration, and excited for what the future may hold. Immediate plans include potentially writing joint grant proposals so that both Washington University and Johnson & Johnson can continue to develop these hits further as a team.

Dr. Alan Cowman, Director of the Division of Infection and Immunity at the Walter and Eliza Hall Institute of Medical Research (WEHI), is one of the world’s leading malaria research scientists. He and his team focus on understanding how the \textit{P.falciparum} parasite invades human blood cells and survives, and on using this understanding to develop novel antimalarial drugs. Through WIPO Re:Search, they are involved in multiple collaborations, including one that recently received a multi-million dollar grant from the Wellcome Trust.

In 2016, Dr. Cowman reached out to WIPO Re:Search to get access to a series of compounds WEHI researchers could screen against \textit{P.falciparum} using their laboratory’s high throughput in vitro culture system. BVGH put him in touch with Dr. Jackson at Johnson & Johnson, and thus began a collaboration involving the \textit{Jump-stARter} library. The aim of the collaboration was to identify and prioritize hit compounds that are both potent against various development stages of the \textit{P.falciparum} parasite and that have negligible toxicity.

When the initial screening resulted in hits, Johnson & Johnson shared fresh compounds for confirmation testing, and helped WEHI determine whether or not the hits had been previously explored by other groups. “Once they had a series of hits that looked good, we began looking at related compounds and sent a group of those over;” says Dr. Jackson. “I feel lucky to work with someone of Dr. Cowman’s calibre. The pace of his team’s work, the quality of the data generated and their ability to replicate results—it is all very impressive.” Now the teams are in conversation with product development partnerships to move forward with further studying the promising leads, and hope to begin that lead optimization process in early 2019.

Dr. Jackson sums up his thoughts on WIPO Re:Search by reflecting on the experience as a whole. “It has been a great opportunity for Johnson & Johnson that we’re able to help move along research in neglected tropical diseases, TB, and malaria. From my personal point of view, we’re doing new and exciting science, and that is why I come into work every day.

“Working with people like Dr. Stallings at Washington University and Dr. Cowman and his group—these individuals are phenomenal scientists. And we get to collaborate on these issues that affect such a large portion of the world. I’ve been given the freedom and backing from Johnson & Johnson to really pursue this work and that too
is extremely rewarding. We would not have been able to do it without WIPO Re:Search.”

Screening Natural Product Extracts Against TB

INFECTIOUS DISEASE RESEARCH INSTITUTE (USA) + NATIONAL INSTITUTES OF HEALTH (USA) + UNIVERSITY OF BRITISH COLUMBIA (Canada)
2013 – present

In order to contribute to this important work, WIPO Re:Search connected IDRI with Dr. Barry O’Keefe, Chief, Natural Products Branch, at the NIH’s National Cancer Institute, which administers large natural products repositories and shares them with qualified researchers in the United States and around the world.

NIH sent several extracts to the Seattle team, and the initial screening of these product extracts resulted in multiple hits. Dr. Shilah Bonnett, who works with Dr. Parish, recalls the process. “We quickly screened about 8,800 crude natural extracts, and any extract that inhibited growth of mTB by 85 percent we considered a hit. And then we followed up by confirming that activity through additional tests. With those results, we went back to NIH with our list.” When the team realized they also needed to elucidate the crystal structure of the compounds in order to identify the active ingredients at play and investigate the promising hits further, they turned to WiPO Re:Search, which put them in touch with Dr. Raymond Andersen at the University of British Columbia (UBC).

Dr. Andersen has over 40 years’ experience as a natural products chemist, and his particular expertise is in solving the chemical structures of complex novel natural compounds. He sheds light on the importance of natural products research in the TB context. “Marine natural products that we collect from habitats around the world represent an almost endless source of new compounds with incredible biological and chemical diversity. These products are a vast potential source of new antibiotics, particularly in the case of TB, where the need is great.”

Dr. Andersen, who examined the data and offered his insight into potential next steps, speaks to the value of bringing disparate yet equally integral types of expertise together. “Collaborations such as these require a rich library of natural products extracts, such as the ones we have here at the University of British Columbia and that the National Cancer Institute has at the NIH. They also need biologists at the cutting edge of their field, who have bioassays and are interested in developing compounds. So working with Tanya and Barry has been a perfect fit.” Dr. O’Keefe at the NIH agrees. “Many labs do not have natural products chemists to isolate the active ingredients, and that’s where someone like Ray comes in. We send plated extracts to the Infectious Disease Research Institute, and they screen them. If they get interesting hits, we send the bulk extracts to Dr. Andersen to isolate and do the structural elucidation [identification of the chemical structure] of the active component.”

The Infectious Disease Research Institute and University of British Columbia teams initially focused on nine extracts, and are in the process of publishing data on the resulting purified natural products. Although some of these had known chemical structures, most had no previously reported anti-mTB activity. Dr. Bonnett reflects on the next steps. “We want to try to understand the key structural features driving anti-mTB activity and whether the compound has enough stamina to make it further down the pipeline – can we design analogs, improve its potency, decrease toxicity, etc. … I also want to potentially write a grant with Dr. Andersen so that we can continue this work. Natural material has such a rich, diverse set of compounds that have yet to be explored, with many pharmaceutical properties that we need to look into.”

“Our team here at the Infectious Disease Research Institute values collaborations, and I am grateful for this opportunity to

She further reflects on the value of collaborative partnerships.
pursue natural products work. Bringing in different expertise to ensure we reach a common goal – I think that’s a theme for science and it is particularly true in the TB world. It will take a global scientific community to eradicate TB.”

**Repurposing Cholesterol-Lowering Compounds to Target Schistosomiasis**

UNIVERSITY OF CALIFORNIA, SAN DIEGO (USA) + MERCK / MSD (USA) 2011 - present

**Schistosomiasis** is a chronic infectious disease that is caused by the parasitic flatworm Schistosoma and transmitted by certain freshwater snails. It is prevalent in tropical and subtropical environments, and particularly affects the poorest populations, who do not have access to safe water and adequate sanitation. More than 700 million people are at risk of infection. The debilitating symptoms and chronic nature of the disease mean that the economic impact of infection is high, especially in the most vulnerable communities.

At the Center for Discovery and Innovation in Parasitic Diseases at the University of California, San Diego (UCSD), Dr. Conor Caffrey’s team focuses on preclinical discovery and investigation of drugs and drug targets for schistosomiasis. When the team demonstrated that an enzyme called HMG-CoA reductase – a key contributor to cholesterol metabolism in the human body – is also essential for the survival of schistosomes, they set about looking for inhibitors, known as statins. In 2012, they received a grant from the NIH to screen statins against schistosomiasis. BVGH connected Dr. Caffrey with Dr. David Olsen’s team at Merck & Co., who shared a number of statins to screen against the schistome parasite. Because these statins come with a wealth of data – known target, safety studies and information on pharmacokinetics (how the body’s absorption, distribution, and metabolic mechanisms affect a drug after it has been administered) – sharing these kinds of compounds saves time and money and enables research to move forward more rapidly. The initial phenotypic screenings conducted by the Center provided a great deal of promising data. However, although the team had a general idea of the chemistries at play, the range of data available was still too broad. It became necessary to figure out which outputs and hits should be taken forward. Merck suggested a target-based approach in order to hone in on the best candidates, but this required the identification of the crystal structures of the relevant compounds.

In order to move this work forward, BVGH reached out to the Structural Genomics Consortium, a non-profit open collaborative partnership which specializes in basic research for drug discovery, including protein crystallography. The SGC became a member of WIPO Re:Search and is in the process of establishing a collaboration with Merck to facilitate the sharing of data and resources that will enable SGC to clarify the crystal structures of the statins relevant to Dr. Caffrey’s work.

In the meantime, the team at the Center for Discovery and Innovation in Parasitic Diseases hopes to publish some of the data and lessons learned thus far, to benefit the research community as a whole. “The Merck statins really helped us refine our screening approach and we learned a lot,” says Dr. Caffrey, noting that this will have long-term benefits beyond this specific collaboration.

“One of the most important aspects that organizations like WIPO bring to the table is that they increase visibility for the diseases and the research involved. This increased visibility has enabled us to access further opportunities and resources.”

BVGH is now coordinating with UCSD to gain access to additional Merck compound libraries. “One of these libraries is similar to
that which generated a drug candidate that our Center is moving forward as an Investigational New Drug at the United States Food and Drug Administration for Chagas disease, so we are excited about having access to these promising resources,” observed Dr. Caffrey. “We have now been collaborating with Merck for seven years, and that builds a level of trust that opens doors.”

Dr. Caffrey also notes how his lab’s experience hosting two WIPO Re:Search fellows from Kwame Nkrumah University in Ghana has led to new opportunities for his team. After reading about the fellowships, and particularly the efforts to translate technologies and methodologies to different laboratory settings, the National Institute for Medical Research in Lagos, Nigeria reached out to Dr. Caffrey. The two institutions are now collaborating on diagnostics for schistosomiasis. Additionally, researchers from a number of Brazilian institutions are now engaged in collaborative research with the UCSD team after having read about the WIPO Re:Search fellowship program. Finally, Dr. Caffrey, in collaboration with Johnson & Johnson (and Dr. Paul Jackson), is co-hosting the training of another WIPO Re:Search fellow from Papua New Guinea, Dr. Martha Yahimbu. Dr. Yahimbu will work on a number of projects utilizing Johnson & Johnson’s compound libraries.

Dr. Caffrey concludes, “WIPO Re:Search should consider expanding efforts to support capacity building for research in endemic countries, which is particularly relevant when discussing natural products, and to increase the visibility of the research being undertaken. It can also support promising research by harnessing the intangible value of the scientific and technical expertise industry can offer on strategies to move the best compounds forward (or remove them [from the process] quickly). WIPO also has a significant role to play in offering advice on capturing intellectual property to support the possible commercialization of novel research. This input is worth a great deal as many academic researchers, particularly those in smaller research institutions, do not have ready access to this kind of advice.”

About Us

Since 2011, WIPO Re:Search – a public-private consortium founded by the World Intellectual Property Organization (WIPO) and BIO Ventures for Global Health (BVGH) – has catalyzed research and development (R&D) for neglected tropical diseases (NTDs), tuberculosis (TB) and malaria through the sharing of intellectual property assets, including compounds, technologies, laboratory capacities, and expertise. In the last eight years, consortium membership has grown from 31 to 140, with presence in over 40 countries. Members include premier research institutions, universities, non-profit organizations, and companies from around the world. WIPO Re:Search has facilitated more than 150 collaborations between owners and users of intellectual property, supporting and advancing science on these debilitating diseases.

The WIPO Global Challenges Division is responsible for addressing innovation and IP at the nexus of interconnected global issues, with a particular focus on global health, climate change and food security. The Division’s activities, including the two multi-stakeholder platforms it administers and trilateral cooperation with the World Health Organization and World Trade Organization, aim to harness the power of innovative partnerships to generate practical solutions for the benefit of all – especially developing countries.