REVIEW ARTICLE

Open innovation to bolster research and development for neglected and emerging infectious diseases

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Abstract: Infections remain a significant cause of disease, disability, and death in developing countries. Unfortunately, many of these infections, including centuries-old neglected diseases such as malaria and newly emerging and re-emerging diseases such as Ebola virus disease (EVD), have limited products available to prevent, diagnose, and treat them. One barrier that hinders the development of these products is neglected and emerging disease experts' limited access to the biopharmaceutical industry's small molecules, technologies, and know-how. Conversely, the biopharmaceutical industry's lack of attention to and expertise in these diseases impedes the development of much-needed products. Organisations are addressing these challenges by developing platforms through which disease experts can access industry's knowledge and assets. Strategic partnerships are applying a synergistic approach to leverage respective strengths of academia and industry. The following article describes two open innovation platforms, the Pool for Open Innovation against Neglected Tropical Diseases (POINT) and WIPO Re:Search, and two strategic, cross-sector collaborative efforts to develop therapeutics for EVD.

Keywords: neglected tropical diseases, Ebola virus disease, global health, POINT, WIPO Re:Search

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1. Open Partnerships for Neglected Diseases

In 2010, the World Health Organization (WHO) highlighted 17 bacterial, parasitic, and viral tropical diseases it deemed to be ''neglected'' (Table 1). These diseases disproportionately affect the poor; cause significant morbidity and mortality; and lack safe, effective, and affordable drugs, vaccines, and diagnostics. Combined, more than a billion individuals are infected with one or more of these pathogens[1]. Neglected tropical diseases (NTDs) are not only a serious health concern, but also represent a significant economic burden on individuals and communities living in poverty. The diseases hinder childhood development, limit school attendance, and prevent a substantial section of the adult population from supporting their countries' economies[2]. For example, it was estimated that dengue virus infections in the Americas directly and indirectly cost over $2 billion annually[3]. NTDs are endemic to over 140 countries worldwide. However, the majority of infections occur in low- and middle-income countries (LMICs) located in Africa, Asia, and Latin America[4]. As such, the economic effects of these diseases compound the financial challenges faced by developing markets and stifle their economic advancements.

Global NTD programs currently focus on innovative and intensified disease management; provision of safe water, sanitation, and hygiene practices; vector control; veterinary health services; and for those

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Table 1. List of the 17 neglected tropical diseases defined by the World Health Organization.

Parasitic diseases	Bacterial diseases	Viral diseases
Chagas disease	Buruli ulcer	Dengue fever
Cysticercosis/Taeniasis	Leprosy	Rabies
Dracunculiasis	Trachoma	
Echinococcosis	Yaws	
Foodborne trematodiases		
Human African trypanosomiasis		
Leishmaniasis		
Lymphatic filariasis		
Onchocerciasis		
Schistosomiasis		
Soil-transmitted helminthiases		

diseases with available therapeutics, mass drug administration (MDA) programs[4]. In 2012, over 800 million people received preventive chemotherapy through MDA programs, and between 2012 and 2013, pharmaceutical companies donated over one billion treatments for NTD MDA efforts. Through these combined efforts, the incidence of several NTDs has dramatically declined. The incidence of human African trypanosomiasis declined from 20,499 to 6,314 between 2003 and 2013[5] and annual new Buruli ulcer cases dropped from 5,148 to 2,627 between 2008 and 2013[6]. Dracunculiasis cases decreased from 63,718 to 1,797 between 2001 and 2010[7], and with only 148 cases reported in 2013, this disease is nearing eradication[4].

Despite the pharmaceutical industry's impressive drug donation schemes, companies have historically paid little attention to NTDs and other diseases that predominantly affect the poor. This is primarily due to the perceived inability to secure a return on the large investment in research and development (R&D) that is needed to bring a medicinal product to the market. As a result, there is a significant deficit in modern, safe, and effective products for most of the 17 NTDs. Furthermore, while pharmaceutical companies have the assets and expertise needed to systematically discover and develop medicinal products, they lack the intricate and in-depth knowledge of the pathogens' biologies and mechanisms of disease that NTD researchers have—knowledge that is essential to develop treatments for these diseases.

Many pharmaceutical companies and academic institutions have begun answering the plea for NTD innovation by developing novel mechanisms and programs that remove the barrier of access to the assets, knowledge, and expertise of each sector. The Pool for Open Innovation against Neglected Tropical Diseases (POINT) is one example of such a program. Established in 2009 by GlaxoSmithKline (GSK), POINT was created to allow universities and government research institutes to access GSK small molecules, patents, and know-how on favourable terms to bolster and accelerate their neglected disease therapeutic development. During the development of POINT, GSK engaged the non-profit BIO Ventures for Global Health (BVGH) to manage the program that included over 2,300 patents at its launch.

The idea of an open innovation platform dedicated to accelerating product development for diseases of poverty quickly drew interest from the biopharmaceutical industry. The demonstration that intellectual property (IP) rights can stimulate rather than hinder innovation for neglected diseases appealed to a wider group of pharmaceutical companies. The World Intellectual Property Organization (WIPO) and its Global Challenges division, which focuses on unlocking the potential of IP to address the world's toughest challenges in the areas of climate change, public health, and food security, also expressed interest in exploring a new and broader model to exhibit this open access concept. WIPO, BVGH, and eight biopharmaceutical companies (Alnylam, AstraZeneca, Eisai, GSK, MSD [known as Merck & Co., Inc. in the US and Canada], Novartis, Pfizer, and Sanofi) were motivated to increase the biopharmaceutical industry's participation in global health, leverage on WIPO's platform and infrastructure, build on the ideas and momentum created by POINT, and expand the scope of the pool to include diagnostics and vaccines. The common commitment and interests led to the establishment of the WIPO Re:Search consortium. The goal of WIPO Re:Search is to accelerate the development of new drugs, vaccines, and diagnostics for NTDs, malaria, and tuberculosis by connecting the biopharmaceutical industry's IP assets and resources to qualified academic and non-profit neglected disease researchers through collaborative research agreements.

Since its launch in 2011, over 90 for-profit, academic, non-profit, and government research organisations from 26 countries have joined WIPO Re:Search. Institutions join the Consortium as "User", "Provider", and/or "Supporter" Members. Provider Members—most notably the Founding Pharmaceutical Members—are those organisations that have declared a willing-

ness to share their IP assets with other Members. User Members subsequently utilise these contributed assets to accelerate their neglected disease R&D activities. Supporter Members join to demonstrate their approval of the WIPO Re:Search mission and its innovative and open access to IP.

Drawing on POINT's access and affordability principles, the Consortium and its activities are governed by the WIPO Re:Search Guiding Principles. These Principles require any products developed through a WIPO Re:Search collaboration to be sold royalty-free to individuals living in the 49 Least Developed Countries. WIPO Re:Search Members agree to consider access and affordability of products for all other developing countries, including those that do not qualify as "least developed", and for regions where populations cannot afford treatments. Furthermore, to bolster continued neglected disease R&D, the Guiding Principles require Members to provide products resulting from their collaborations, on a royalty-free basis, to other researchers seeking to use these products to advance their own NTD, malaria, and tuberculosis R&D. These principles ensure that the products stemming from a WIPO Re:Search collaboration is accessible to individuals who need them most[8].

As the Partnership Hub Administrator of WIPO Re:Search, BVGH is responsible for facilitating partnerships between Member researchers. Since 2011, BVGH has facilitated over 80 research agreements. The majority of these agreements involve Members sharing compounds and compound libraries with one another. For example, MSD has shared a targeted set of compounds with researchers from Walter and Eliza Hall Institute of Medical Research to screen against *Plasmodium falciparum* and *P. vivax*, the causative agents of malaria. Researchers from University of British Columbia agreed to give a selection of compounds with activity against *Mycobacterium tuberculosis* to researchers at the Swiss Tropical and Public Health Institute to screen the compounds against *M. ulcerans*, the bacterium that causes Buruli ulcer. In addition, other Members have agreed to share confidential data and expertise. GSK provided researchers from the Center for World Health & Medicine with information and data from its screens of methionine aminopeptidase 1 (MetAp-1) inhibitors against *M. tuberculosis*[9]. The National Institutes of Health has agreed to provide researchers from the Institut Pasteur de Tunis (IP Tunis) with expertise and support to improve the thermostability and the freeze-drying cycle of a rabies vaccine developed at IP Tunis. Technologies have also been shared or co-developed through WIPO Re:Search. PATH, an international non-profit organisation based in Seattle, shared its non-instrumented nucleic acid amplification (NINA) heater with the Centre Pasteur du Cameroun who will incorporate this new technology into novel point-of-care diagnostic test systems for malaria.

In each of these and others WIPO Re:Search collaborations, assets, assistance, and expertise were shared freely and without financial expectations or obligations. Furthermore, all WIPO Re:Search collaborations were entered into voluntarily and were directed by the Guiding Principles and by mutually agreed-upon roles and responsibilities. On average, it can take up to 15 years to bring a medicinal product to the market[10], so WIPO Re:Search has not yet delivered new products for neglected diseases. However, given that Member researchers are already seeing their product discovery projects advance due to access to industry assets[11], it is not overly optimistic to predict that the WIPO Re:Search consortium's goals of developing important new products for NTDs will be realised in the years to come.

2. Open Partnerships for Emerging Diseases

Not all collaborative research efforts for diseases of poverty are led by large consortia or coalitions. Disease-targeted efforts to share assets and expertise between small groups of organisations are also advancing product development. The 17 NTDs are not the only focus of open and collaborative efforts. The covered Ebola virus disease (EVD) epidemic in West Africa is the largest since the virus had been discovered in 1976; more than 26,000 individuals have been infected, of which over 11,000 have died[12]. The swiftness of this epidemic's spread highlighted the dangers of not having effective products to prevent, diagnose, or treat infectious diseases, no matter how seemingly obscure or distant they are. The 2014–2015 West African EVD epidemic reignited global interest and propelled numerous collaborative efforts focused on quickly moving any promising EVD product into clinical trials. For example, in April 2014, no vaccine for EVD was in clinical trials. Yet a year later, six different EVD vaccines were being tested on humans, half of which involved multiple parties from multiple sectors (Figure 1).

Unlike the causative agents of malaria, tuberculosis, and NTDs, live Ebola viruses must be handled in

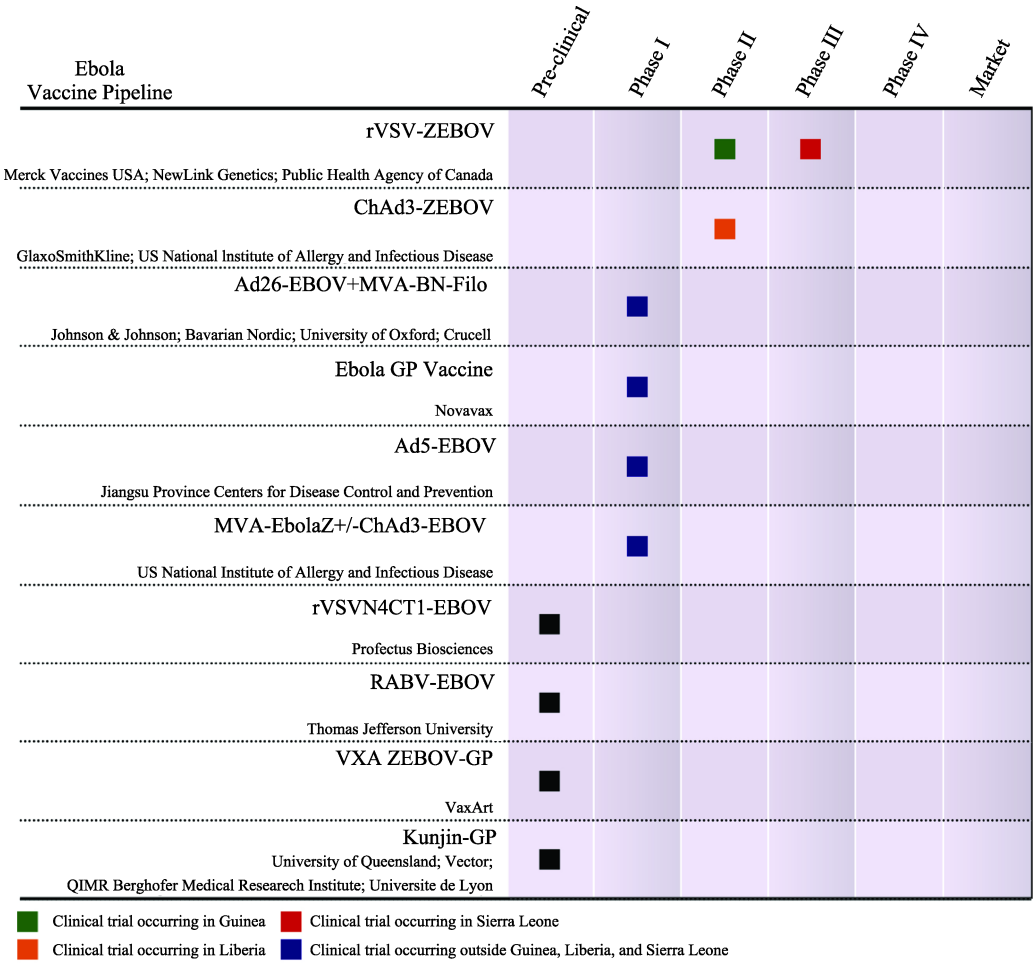

Figure 1. Ebola virus disease vaccine development pipeline. The vaccine developer(s), stage of development, and location of clinical trial(s) are shown. Information was obtained from the International Clinical Trials Registry Platform (ICTRP) Search Portal[13] and from Clinicaltrials.gov[14]. Phase I/II trials are listed as Phase II; Phase II/III trials are listed as Phase III.

high-containment (BSL4) facilities by experienced virologists. Given the rarity of BSL4 facilities and the specialised training required to handle the deadly virus, product developers must collaborate with high-containment facilities and research experts if their promising products are to be properly assessed and further developed. Kineta, Inc., a biotechnology company in Seattle, USA, has developed a portfolio of broadly-acting antiviral drugs that activate the innate immune system, leading to the inhibition of several viruses—influenza A and B viruses, West Nile virus, dengue virus, human coronaviruses, and respiratory syncytial virus—*in vitro* and *in vivo*. In order to demonstrate similar efficacy against Ebola viruses, Kineta has been collaborating with virologists from the University of Texas Medical Branch and the Galveston National Laboratory—one of only four BSL4 facilities in the USA. This synergistic approach is leveraging the respective strengths and assets of each partner to quickly drive the development of Kineta's program forward.

It is not only research entities that recognise the value of open, collaborative research. Funding agencies have begun incorporating requirements for cross-sector and transnational partnerships into their funding schemes. The Wellcome Trust recently funded a multi-partner initiative to develop broad-spectrum, fully human, therapeutic monoclonal antibodies against Ebola viruses. This initiative, co-managed by BVGH, is leveraging on the human memory B-cell interrogation platform developed by Theraclone Sciences, Inc., and the expertise of an array of R&D leaders as both project team members and advisors. The consortium is also engaging researchers in the affected West African countries to secure access to convalescent EVD patients, from which the monoclonal antibodies will be derived.

While the West African EVD epidemic is winding down, these two collaborations highlight the necessity of increased communication and collaboration across national borders, funding organisations, and R&D sectors to form product development partnerships for deadly, emerging infectious diseases.

3. Conclusion

Given today's current climate of shrinking R&D budgets and increasing demand for quality healthcare in developing countries, sharing assets, know-how, and data is an efficient and cost-effective means of bolstering development of products for diseases that primarily affect the world's poorest. Society has already embraced the concept of open access and repurposing products in other fields. Online databases such as Wikipedia share the global combined knowledge on topics ranging from history to popular culture. Society has adopted "upcycling" in an effort to minimise its carbon footprint through the reuse of gently used consumer goods. Through global consortia such as WIPO Re:Search and other strategic partnerships, neglected and emerging infectious disease researchers are leveraging and applying the biopharmaceutical industry's expertise and assets to the development of drugs, vaccines, and diagnostics for diseases of poverty. Biopharmaceutical company compounds that were dismissed due to insufficient activity against one indication are being applied to other, more neglected diseases. Data are being shared to inform neglected disease researchers' plans and direct their R&D activities away from the unnecessary repetition of negative experiments. Through these and other activities, and increased support for open access from all sectors, neglected infectious disease R&D will continue to expand and prosper.

Conflict of Interest and Funding

Jennifer Dent, Katy M. Graef, and Paddy Shivanand are employees of BIO Ventures for Global Health (BVGH). BVGH receives WIPO Re:Search sponsorship funding from Alnylam, Eisai, GlaxoSmithKline, MSD, Merck KGaA, Novartis, Pfizer, and Sanofi, and membership support from Kineta. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. MSD, GSK, and Kineta reviewed and approved the text written by BVGH for this publication.

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