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The importance of collaboration between industry, academics, and non-profits in tropical disease drug discovery.

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Abstract

Collaborations between academic, industrial and non-profit companies can provide sufficient impetus to propel projects that have little economic return, which is prevalent in tropical disease drug discovery. Each partner contributes a unique set of skills and technical expertise which is advantageous to the project as a whole; highly product-focused process and wide expertise dominates industry groups, strategic guidance from public-private partnerships and the academic tendency to work on high-risk projects with low financial rewards. There are numerous examples throughout the literature around these collaborative efforts to combat a variety of tropical diseases, (including leishmaniasis, Chagas disease, African sleeping sickness and malaria) from all stages of the drug discovery process, through to the advancement of new drugs into the clinic. However, there is still uncertainty from many academic institutions as to how to establish and engage in these research consortiums.

Graphical Abstract.

Introduction.

Tropical diseases, neglected and otherwise, have received significantly more attention from the drug discovery community over the last 10–15 years, perhaps more than ever before. Increasing investment by non-profit foundations (like the Bill and Melinda Gates Foundation, The Global Health Innovation Technology Fund, and the Wellcome Trust) and government funding agencies (such as the National Institutes of Health and the European Union) have attracted researchers into the high-risk field of drug discovery. This has led to increased focus in the cell biology of the pathogens that cause these diseases, and all aspects of drug discovery. Indeed, high-throughput assays, new target identification, medicinal

chemistry (and the inclusion of requisite pharmacokinetics and toxicology), and clinical trials have been enhanced.

Nonetheless, despite the disease burden, tropical diseases do not receive a level of research funding that is likely to produce new drugs at a high rate. For example, in 2013, the three kinetoplastid diseases (African sleeping sickness, Chagas disease, and leishmaniasis) were responsible for approximately 5 million disability adjusted life-years, and total research and development spending on these diseases totaled \$149 million.¹ Noting that the cost of discovering a new drug has been estimated to be between \$1.8 and \$2.87 billion.² Taking these realities into account, along with the fact that the for-profit drug industry (the primary source of new drugs) is not generally enthusiastic to invest large amounts of research resource into an unprofitable space, it is understandable that new therapeutics have not emerged.

Industrial engagement.

There are indeed companies that have made strong investments in tropical disease drug discovery. For example, the Tres Cantos, Spain facility of GlaxoSmithKline (GSK) is focused entirely on discovery of drugs for malaria, tuberculosis, Chagas disease, and leishmaniasis (both using company resources, and funding from the Tres Cantos Open Lab Foundation (TCOLF) that is used to fund visiting scientists working in tropical diseases; *vide infra*). Until recently Novartis had a research site in Singapore that was entirely devoted to tropical disease drug discovery (Novartis Institute for Tropical Diseases). This operation has been merged into the wider infectious disease work ongoing at their Emeryville, CA research site, and the tropical disease focus consists of African sleeping sickness, leishmaniasis, Chagas disease, and cryptosporidiosis. Celgene has a Global Health division focused on seven tropical diseases.

Academic contributions.

On the other hand, the academic environment is contributing substantially to tropical disease drug discovery, across the entire range of the pipeline. For example, while our laboratory has been primarily focused on hit-to-lead medicinal chemistry against protozoan parasites, others have done late-stage optimization leading to clinical trials (c.f. the DHODH program led by UT Southwestern, University of Washington, and a large consortium of academic institutions, non-profits, and drug companies).³ Institutions such as UC San Diego have established centers devoted to this work (Center for Discovery and Innovation in Parasitic Disease), with high-throughput screening capabilities and access to University-established core facilities resources that many aspects of drug discovery capabilities. The Broad Institute (Cambridge, MA) has performed multiple HTS campaigns against infectious parasites, including *Trypanosoma cruzi*⁴ and *Plasmodium falciparum*.⁵ With funding from the Wellcome Trust, among other funders, the Drug Discovery Unit (DDU) at the University of Dundee has engaged in a number of programs directed at discovery of new therapeutics for diseases caused by protozoan parasites, and recently discovered an antimalarial compound in clinical trials.⁶ The DDU recently entered into a significant collaboration with GSK, funded by the Wellcome Trust.⁷

Public-private partnerships.

Tying together these programs are established public-private partnership (PPP) organizations whose mission is devoted to tropical disease drug discovery. By way of example, Medicines for Malaria Venture (MMV) funds and coordinates multiple projects and programs to produce a substantial pipeline of antimalarial agents.⁸ The Drugs for Neglected Diseases *initiative* (DNDi) has funded and overseen compounds through all stages of discovery and development,⁹ and, besides successfully implementing improved treatments with repurposed compounds (such as the nifurtimox-eflornithine combination therapy for African sleeping sickness),¹⁰ they have also developed new chemical matter, including two compounds that have advanced to stage two and three clinical trials (acoziborole, also known as SCYX-7158,¹¹ and fexinidazole,¹² respectively). Helpfully, these organizations have established and shared targeted product profiles (TPPs) with the research community. This level of transparency helps ensure that other ongoing research programs outside of DNDi or MMV collaborations are also producing potential new therapeutics that are directed towards meeting the desired TPP.

Collaborations.

Some of the strongest work towards discovery of new drugs for tropical diseases are done in collaboration between two or more of these organizations. This can produce a fertile and productive environment by combining the highly product-focused process and wide expertise inherent in the drug industry, with the strategic guidance from PPPs and the academic tendency to work on high-risk projects with low financial rewards. Such collaborations have emerged. For example, the collaboration between two companies (Anacor and Scynexis) and DNDi, plus academic groups (Pace University and the Swiss Tropical and Public Health Institute), led to the discovery and development of acoziborole.¹³ Led by the Winzler lab at UC San Diego, a team of academic and industrial scientists (six academic institutions and GSK) plus a PPP (MMV) have combined forces to contribute to the “Malaria Accelerator,” the goal of which is to identify drug targets and mechanism of action for a collection of compounds identified in a recent, whole-cell antimalarial high-throughput screen.¹⁴

Working at the academic-industry interface.

Our laboratory’s experience in the collaborative sphere is primarily at the academic-to-industry interface; this is the subsequent focus of this Perspective.

The key question that many academics ask is “how do I best establish and engage in such research collaborations that have the best likelihood to succeed in improving treatments for tropical diseases?”

An important catalyst for establishing these relationships has been WIPO Re:Search, an initiative of the non-profit organization BioVentures for Global Health (BVGH), which manages the International Patent Pool for Neglected Diseases. Academic and industrial organizations who contribute to this patent pool make their intellectual property available for potential use against NTDs. In return, the BVGH team works to make connections between

members of the patent pool, identifying potential synergies and gap-filling opportunities. As of the date of this publication, BVGH indicates that they have enabled over 120 member organizations from 30 countries to engage in 113 collaborations. These engagements include access to compounds or compound libraries, access to drug discovery expertise, and access to resource (such as our laboratory's arrangement with AstraZeneca to obtain physicochemical and drug metabolism measurements on compounds synthesized in our lab). Note that there are no research funds changing hands in these collaborations. Nonetheless, such in-kind contributions of resource and expertise can be transformational, game-changing developments for an aspiring academic drug discovery research project.

A unique mechanism by which industry-academic collaborations can be established is through the TCOLF and GSK. Investigators outside of GSK can submit proposals to TCOLF, seeking support for projects that fall into the Foundation's and GSK's strategic priority diseases, which currently include Chagas disease, leishmaniasis, malaria, and tuberculosis. Funded projects typically cover the cost for a researcher from the academic lab to work for a period of time (months) at the GSK Tres Cantos facility, and to access GSK resources, such as compounds, infrastructure, technology, and expertise, to prosecute their project. At the end of the funded program, the external collaborator receives the data generated during the course of the program, with permission to pursue the results (data, compounds, etc) for tropical disease indications, with no strings attached. These collaborations have produced meaningful results that transform how such projects are further pursued in academic labs. One transformational aspect of this sort of arrangement is the ability to produce strong preliminary data for funding proposals that are directed towards advancing the project further along the drug discovery pipeline. Furthermore, the relationship built between the GSK scientists and academic investigators continue via informal consultation and discussion, further enriching the resulting drug discovery program pursued in the academic's lab. Our laboratory has benefitted from multiple TCOLF-funded programs, each of which produced and characterized compelling new chemical matter for further optimization against African sleeping sickness.¹⁵

Building and operating such collaborations typically requires an adjustment of mindset from both the academic and industrial sides. Academic scientists may be more attuned to operating within a fundamental, open-ended research paradigm, whereas industrial teams tend to be milestone-and-deliverables driven. Academics are typically driven by production of high-impact publications that can help support future funding proposals, whereas industrial scientists may be more focused on accomplishing TPPs than on publication. A key aspect of any such collaboration, therefore, requires appreciation and acknowledgement of the culture of both sides, and deliberate discussion and establishment of a *modus operandi* to form a compromise that meets both sides' needs.

A sense of realism is also required on the part of the academic. Though industrial drug discovery organizations are resource-rich compared to the academic environment, these resources are carefully managed, prioritized, and allocated, and may not necessarily be directed toward pursuing the questions that interest the academic. For example, in an antiparasitic optimization program, interesting cell biology observations may be made. Whereas an academic scientist may be inclined to divert some attention to focus intently on

studying and understanding the fundamental science behind these observations, the translational scientist is focused primarily on achieving the TPP. Noting that these are not necessarily mutually exclusive, the industrial resource may be more likely to be invested in pursuit of the translational endpoint rather than the fundamental understanding. Both sides of the collaboration need to understand this tension and communicate openly about it.

Another tension between the academic and industrial mindset is one of intellectual property and secrecy. This is because, typically, the reason industrial assets exist is to support operations that will lead to profitable drugs down the road. Therefore, even those assets that are to be involved in a collaboration for tropical diseases (where little profit is likely), secrecy will still be paramount. As a result, there is most often a delicate dance between data sharing (structures, properties, technologies) and protection of this information. Material transfer agreements and confidentiality agreements are often required, and require time and patience (not to mention organizational buy-in). There can be middle ground that can accelerate the process of getting to the scientific experiments. For example, if an academic group wishes to screen a set of compounds that originate in a drug company, it may be more expeditious to first test these compounds blinded to the chemical structure. Those that prove to be of interest following the screen could then have the structures disclosed.

In the same vein, the academic impulse to publish results may be met with delays. Often, agreements with industrial collaborators require company review and embargoes that delay publication; however, this is the payment that the academic should be prepared to make in order to collaborate with a commercial enterprise and to access such unique and specialized resources. However, industrial collaborators need to understand the “publish-or-perish” mentality that pervades academic research, and work to help expedite publication as much as possible.

Summary.

Industry-academic collaboration brings together research strengths and cultures of each side to provide advances in tropical disease drug discovery. Importantly, with more examples of these arrangements, there is increased understanding of how to establish them, operate them smoothly, and demonstrate success. This requires understanding of the factors that drive both sides of the collaboration, providing open communication, and setting reasonable expectations.

References.

1. G-Finder. <http://polycycures.org/gfinder.html> (accessed 28 October 2017).
- 2 (a). DiMasi JA; Grabowski HG; Hansen RW, Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ* 2016, 47, 20–33; [PubMed: 26928437] (b) Paul SM; Mytelka DS; Dunwiddie CT; Persinger CC; Munos BH; Lindborg SR; Schacht AL, How to improve R&D productivity: the pharmaceutical industry’s grand challenge. *Nat Rev Drug Discov* 2010, 9 (3), 203–14. [PubMed: 20168317]
3. Phillips MA; Lotharius J; Marsh K; White J; Dayan A; White KL; Njoroge JW; El Mazouni F; Lao Y; Kokkonda S; Tomchick DR; Deng X; Laird T; Bhatia SN; March S; Ng CL; Fidock DA; Wittlin S; Lafuente-Monasterio M; Benito FJ; Alonso LM; Martinez MS; Jimenez-Diaz MB; Bazaga SF; Angulo-Barturen I; Haselden JN; Louttit J; Cui Y; Sridhar A; Zeeman AM; Kocken C; Sauerwein R; Dechering K; Avery VM; Duffy S; Delves M; Sinden R; Ruecker A; Wickham KS; Rochford R; Gahagen J; Iyer L; Riccio E; Mirsalis J; Bathhurst I; Rueckle T; Ding X; Campo B; Leroy D; Rogers MJ; Rathod PK; Burrows JN; Charman SA, A long-duration dihydroorotate dehydrogenase

inhibitor (DSM265) for prevention and treatment of malaria. *Science translational medicine* 2015, 7 (296), 296ra111.

4. Germain AR; Carmody LC; Dockendorff C; Galan-Rodriguez C; Rodriguez A; Johnston S; Bittker JA; MacPherson L; Dandapani S; Palmer M; Schreiber SL; Munoz B, Identification of small-molecule inhibitors of *Trypanosoma cruzi* replication. *Bioorg. Med. Chem. Lett* 2011, 21 (Copyright (C) 2014 American Chemical Society (ACS). All Rights Reserved.), 7197–7200. [PubMed: 22018462]
- 5 (a). Heidebrecht RW Jr.; Mulrooney C; Austin CP; Barker RH Jr.; Beaudoin JA; Cheng KC; Comer E; Dandapani S; Dick J; Duvall JR; Ekland EH; Fidock DA; Fitzgerald ME; Foley M; Guha R; Hinkson P; Kramer M; Lukens AK; Masi D; Marcaurette LA; Su XZ; Thomas CJ; Weiwer M; Wiegand RC; Wirth D; Xia M; Yuan J; Zhao J; Palmer M; Munoz B; Schreiber S, Diversity-Oriented Synthesis Yields a Novel Lead for the Treatment of Malaria. *ACS Med Chem Lett* 2012, 3 (2), 112–117; [PubMed: 22328964] (b) Kato N; Comer E; Sakata-Kato T; Sharma A; Sharma M; Maetani M; Bastien J; Brancucci NM; Bittker JA; Corey V; Clarke D; Derbyshire ER; Dornan GL; Duffy S; Eckley S; Itoe MA; Koolen KM; Lewis TA; Lui PS; Lukens AK; Lund E; March S; Meibalan E; Meier BC; McPhail JA; Mitasev B; Moss EL; Sayes M; Van Gessel Y; Wawer MJ; Yoshinaga T; Zeeman AM; Avery VM; Bhatia SN; Burke JE; Catteruccia F; Clardy JC; Clemons PA; Decherer KJ; Duvall JR; Foley MA; Gusovsky F; Kocken CH; Marti M; Morningstar ML; Munoz B; Neafsey DE; Sharma A; Winzeler EA; Wirth DF; Scherer CA; Schreiber SL, Diversity-oriented synthesis yields novel multistage antimalarial inhibitors. *Nature* 2016, 538 (7625), 344–349. [PubMed: 27602946]
6. Baragana B; Hallyburton I; Lee MCS; Norcross NR; Grimaldi R; Otto TD; Proto WR; Blagborough AM; Meister S; Wirjanata G; Ruecker A; Upton LM; Abraham TS; Almeida MJ; Pradhan A; Porzelle A; Martinez MS; Bolscher JM; Woodland A; Norval S; Zuccotto F; Thomas J; Simeons F; Stojanovski L; Osuna-Cabello M; Brock PM; Churcher TS; Sala KA; Zakutansky SE; Jimenez-Diaz MB; Sanz LM; Riley J; Basak R; Campbell M; Avery VM; Sauerwein RW; Decherer KJ; Noviyanti R; Campo B; Frearson JA; Angulo-Barturen I; Ferrer-Bazaga S; Gamo FJ; Wyatt PG; Leroy D; Siegl P; Delves MJ; Kyle DE; Wittlin S; Marfurt J; Price RN; Sinden RE; Winzeler EA; Charman SA; Bebrevska L; Gray DW; Campbell S; Fairlamb AH; Willis PA; Rayner JC; Fidock DA; Read KD; Gilbert IH, A novel multiple-stage antimalarial agent that inhibits protein synthesis. *Nature* 2015, 522 (7556), 315–320. [PubMed: 26085270]
7. Wellcome Trust backs Dundee and GSK in quest to find new drugs for neglected disease. <http://www.drugdiscovery.dundee.ac.uk/about-us/news/wellcome-trust-backs-dundee-and-gsk-quest-find-new-drugs-neglected-diseases> (accessed 28 October 2017).
8. MMV-supported projects. <https://www.mmv.org/research-development/mmv-supported-projects> (accessed 31 October 2017).
9. DNDi Portfolio June 2017 <https://www.dndi.org/diseases-projects/portfolio/> (accessed 31 October 2017).
10. Priotto G; Kasparian S; Mutombo W; Ngouama D; Ghorashian S; Arnold U; Ghabri S; Baudin E; Buard V; Kazadi-Kyanza S; Ilunga M; Mutangala W; Pohlig G; Schmid C; Karunakara U; Torreele E; Kande V, Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei* gambiense trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet* (London, England) 2009, 374 (9683), 56–64.
11. Pivotal Clinical Trial to Begin for First Oral Drug Candidate Specifically Developed for Sleeping Sickness. <https://www.dndi.org/2015/media-centre/press-releases/pr-scyx-7158/> (accessed 28 October 2017).
12. Fexinidazole (HAT). <https://www.dndi.org/diseases-projects/portfolio/fexinidazole/> (accessed 28 October 2017).
13. Jacobs RT; Nare B; Wring SA; Orr MD; Chen D; Sligar JM; Jenks MX; Noe RA; Bowling TS; Mercer LT; Rewerts C; Gaukel E; Owens J; Parham R; Randolph R; Beaudet B; Bacchi CJ; Yarlott N; Plattner JJ; Freund Y; Ding C; Akama T; Zhang YK; Brun R; Kaiser M; Scandale I; Don R, SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 human African trypanosomiasis. *PLoS neglected tropical diseases* 2011, 5 (6), e1151. [PubMed: 21738803]
14. Gamo F-J; Sanz LM; Vidal J; de Cozar C; Alvarez E; Lavandera J-L; Vanderwall DE; Green DVS; Kumar V; Hasan S; Brown JR; Peishoff CE; Cardon LR; Garcia-Bustos JF, Thousands of chemical

starting points for antimalarial lead identification. *Nature* 2010, 465 (7296), 305–310. [PubMed: 20485427]

- 15 (a). Amata E; Xi H; Colmenarejo G; Gonzalez-Diaz R; Cordon-Obras C; Berlanga M; Manzano P; Erath J; Roncal NE; Lee PJ; Leed SE; Rodriguez A; Sciotti RJ; Navarro M; Pollastri MP, Identification of “Preferred” Human Kinase Inhibitors for Sleeping Sickness Lead Discovery. Are Some Kinases Better than Others for Inhibitor Repurposing? *ACS Infect Dis* 2016, 2 (3), 180–186; [PubMed: 26998514] (b)Diaz R; Luengo-Arratta SA; Seixas JD; Amata E; Devine W; Cordon-Obras C; Rojas-Barros DI; Jimenez E; Ortega F; Crouch S; Colmenarejo G; Fiandor JM; Martin JJ; Berlanga M; Gonzalez S; Manzano P; Navarro M; Pollastri MP, Identification and characterization of hundreds of potent and selective inhibitors of *Trypanosoma brucei* growth from a kinase-targeted library screening campaign. *PLoS Negl. Trop. Dis* 2014, 8 (10), e3253; [PubMed: 25340575] (c)Seixas JD; Luengo-Arratta SA; Diaz R; Saldivia M; Rojas-Barros DI; Manzano P; Gonzalez S; Berlanga M; Smith TK; Navarro M; Pollastri MP, Establishment of a structure-activity relationship of the 1H-imidazo[4,5-c]quinoline-based kinase inhibitor NVP-BEZ235 as a lead for African sleeping sickness. *J Med Chem* 2014.