Tres Cantos Open Lab: celebrating a decade of innovation in collaboration to combat endemic infectious diseases

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Tres Cantos Open Lab is a collaborative initiative that integrates teams from academia and GlaxoSmithKline to enable rapid testing of innovative therapeutic hypotheses for endemic infectious diseases. Here, we provide an overview of the key scientific achievements in its first decade.

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https://doi.org/10.1038/d41573-021-00143-2

Contrary to common assumption, the major challenges for industry–academia collaboration in drug discovery are not caused by misalignment of priorities or cultural differences. Rather, it is the practical issues of resource constraints, legal and administrative process complexity, and coordination that are the main barriers for such collaborations[1]. These factors are within the control of the scientific teams, but addressing them requires close coordination, process integration and transparent collaborative structures.

The Tres Cantos Open Lab is a collaborative initiative established by GlaxoSmithKline (GSK) in 2010 to accelerate drug discovery in endemic infectious diseases via an innovative industry–academia partnership model[2]. The Open Lab is supported by the Tres Cantos Open Lab Foundation (TCOLF), a charity governed by an independent board of experts in the field of infectious diseases that aims to advance the discovery of new treatments for infectious diseases that disproportionally affect low-income and middle-income countries.

TCOLF reviews proposals from academic researchers, with successful applicants gaining access to industrial-scale discovery platforms and technical expertise to progress their own projects. By these means, innovative, high-risk, scientific proposals lying at the boundary of fundamental and applied science, which are potentially game-changing, can be tested in months rather than years. There are two key distinguishing features of this model: co-location of scientists from both sectors in the same laboratory at the GSK Research and Development site in Tres Cantos, Madrid, and the greater sharing of intellectual property. A parallel article describes the model in more depth[3]. Here, we discuss the scientific impact of this initiative in the past decade. Further information about this impact is provided in Supplementary Box 1.

Diseases in scope

To remain at the forefront of innovative research, the Open Lab's scientific priorities are regularly reviewed. Initially, malaria, tuberculosis plus three major diseases mediated by kinetoplastids (Chagas disease, visceral leishmaniasis and human African trypanosomiasis (sleeping sickness)) were targeted. In 2013 and 2018, sleeping sickness and leishmaniasis, respectively, were deprioritized as the global development pipelines matured. In 2015, diarrhoeal diseases were added to the scope, initially focusing on shigellosis. This area evolved rapidly with pioneering projects being undertaken, such as investigations into environmental enteric dysfunction. Although current priorities remain focused on malaria and tuberculosis, the Open Lab also accepts disruptive proposals for the most pressing unmet needs for infectious diseases included in the Global Health agenda.

Contributions to drug discovery pipelines

Assay development and screening. For neglected diseases, validated screening assays may be lacking and drug targets are sparse and poorly defined. Phenotypic and target-based screening against large compound libraries is one way that industrial-level processes can accelerate drug discovery. More than 40 such projects have been completed or are ongoing in the Open Lab. Academic teams contribute in-depth knowledge regarding the biology of the pathogen, target and host, and GSK provides expertise in protein expression, purification, biochemical assay development, data analysis and scale-up to high-throughput screening platforms. These collaborations have stimulated the development of innovative platforms and physiologically relevant assays ready to be implemented in academic labs, and provided novel chemical starting points for medicinal chemistry efforts.

For example, to launch drug discovery programmes for the three kinetoplastid-mediated diseases in scope, a partnership was established to identify the quality hits needed. Supported by the Open Lab, it included Northeastern University, the University of Dundee, New York University, the Spanish National Research Council and GSK. The project had three components: technology development, including novel imaging assays; screening of 1.8 million small molecules from the GSK collection; and triage using confirmatory and orthogonal intracellular assays as well as cytotoxic and physicochemical evaluation. The resulting three chemical sets were published and made available upon request. These have so far delivered several lead compounds with opportunities for lead repositioning and a clinical candidate for visceral leishmaniasis, now supported by the Drugs for Neglected Diseases Initiative.

Further examples (highlighted in Supplementary Box 1) include industrialization of assays to identify hits against metabolically diverse sub-populations of *Mycobacterium tuberculosis* (Cornell University), as well as more unconventional approaches, such as using changes in Gram-negative bacterial shapes for phenotypic drug discovery (University of Cambridge), or exploiting the stiffness of *Plasmodium* gametocytes (French National Institute of Health and Medical Research). Host–pathogen interactions in diseases such as shigellosis have been explored using intracellular assays (University of Oxford and University of Michigan), and in vivo bioimaging platforms developed to evaluate compounds in acute and chronic stages of visceral leishmaniasis (Universidad Autónoma de Madrid). Target-based screening has been applied to proteins essential for pathogen survival, replication or transmission (for malaria) with various collaborators exploring both new and well-characterized but unexploited targets.

Medicinal chemistry. The Open Lab has also received multiple applications to access GSK medicinal chemistry platforms to investigate hits identified in academic labs. So far, 21 projects have benefited, enabling hits to be progressed, validated or discarded (see Supplementary Box 1 for a full list). New antimicrobial chemical classes have been identified across the diseases in scope. A project run in collaboration with the Institute Pasteur Korea was critical in identifying a novel clinical candidate for tuberculosis, GSK-2556286, as the best-in-class compound.

Drug repurposing. Drug repurposing is a recognized strategy to mitigate the slow pace, high cost and attrition of traditional drug discovery processes. Given the acute need for new interventions against the diseases in scope, the Open Lab has actively explored this strategy, with notable success. Repurposing opportunities now in phase IIa trials include the use of carbapenems and penicillins against shigellosis, tuberculosis and buruli ulcer.

Aligning future needs and opportunities

During the past decade, a combination of scientific breakthroughs and the development of new collaborative models has led to considerable progress in the field of endemic infectious diseases[4,5]. Consequently, in 2018 the TCOLF Governing Board conducted a review of strategic priorities and the model structure. The majority of new projects were expected to be located in three areas: the development of tools to support malaria elimination; treatment-shortening strategies for tuberculosis; and the development of non-classical anti-infectives across diseases. The board also recommended that the scope of the Open Lab be expanded to include proposals in the preclinical and post-candidate space. This presents a new opportunity for interaction between academics and GSK scientists engaged in translational medicine. This shift prompted 70 proposals or letters of interest, leading to implementation of 18 projects so far. The projects are organized into innovation clusters with complementary approaches to encourage interaction among groups and to optimize investment. For example, for tools supporting malaria elimination, a cluster of six complementary projects involving nine different institutions is concentrated on non-erythrocytic *Plasmodium* lifecycle stages (Supplementary Fig. 1). Projects include identification of essential targets for parasite liver stages, development of in vitro and in vivo models, compound screening, and hit identification and optimization. The first results from this cluster are expected by the end of 2021, with outcomes that are potentially transformative for the discovery of new chemotherapeutic and transmission-blocking antimalarial drugs.

In summary, the Open Lab has catalysed drug research and development for endemic infectious diseases that affect the world's poorest people. Academic researchers are given the opportunity to harness cutting-edge technologies to pursue high-risk and disruptive projects, while GSK scientists can benefit from a greater depth of understanding of how industrial platforms can better be aligned to the needs of the community. By putting science and the focus on patient impact first, the Open Lab model has delivered the rare win–win scenario that can be elusive in any collaboration. The flexibility to apply new technologies and respond to changing priorities will maintain the Open Lab as a valuable tool for driving the discovery of new medicines to advance global health.

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Acknowledgements
The authors thank former governing board members, principal investigators and GSK staff involved in the development of projects.

Competing interests
F.C., L.B., D.B., R.G., A.H., M.E.S. and P.M.W. are GSK employees. The other authors declare no competing interests.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1038/d41573-021-00143-2.