LINK TO ORIGINAL ARTICLE

Open Lab as a source of hits and leads against tuberculosis, malaria and kinetoplastid diseases

Lluís Ballell, Mike Strange, Nicholas Cammack, Alan H. Fairlamb and Leszek Borysiewicz

In their recent paper (Hit and lead criteria for drug discovery for infectious diseases of the developing world. *Nat. Rev. Drug Discov.* **14**, 751–758 (2015))[1], Katsuno *et al.* present a set of useful guiding criteria on what constitutes a hit or a lead to initiate a drug discovery programme against tuberculosis (TB), malaria or kinetoplastid infections. But what will be the origin of future small-molecule starting points? What mechanisms are currently in place to ensure that the early-stage pipeline for diseases of the developing world remains healthy? Taking stock from epidemiological realities in areas such as microbial infections, a sustainable research and development (R&D) effort to address the continuous threat of drug resistance will be required. This effort will need to go beyond the earlier phase of 'standardized' phenotypic screening, in which hit molecules were identified and progressed by virtue of their anti-proliferative activity against parasites and bacteria. This potential gap is further compounded by the slow but steady shift of focus and funding from preclinical to clinical research as the current pipeline matures and the naturally high attrition rates affecting drug discovery continue unabated. For this phase, new community-wide R&D models based on continuous and open innovation will be required to re-invigorate hit- and lead-identification activities.

The Tres Cantos Medicines Development Campus (TCMDC) was established with the aim of contributing to the GlaxoSmithKline (GSK) vision of open-source drug discovery for diseases of the developing world. The first step in GSK's open-innovation strategy involved the public release of proprietary data generated during various drug-screening campaigns, exemplified in the Tres Cantos antimalarial, antitubercular and anti-kinetoplastid compound collections and data sets[2–5]. The objective of releasing this information through a number of freely accessible databases was to provide small molecules as starting points for synthetic drug lead generation by the wider scientific community. As a result, GSK compound sets have been shared with over 300 academic laboratories worldwide. In two instances, derivatives of compounds present in the publicly available data sets progressed to become clinical candidates for the treatment of malaria[6,7]. Albeit a crucial first step to initiate collaborative research, it was envisaged that the release of proprietary screening data would not be sufficient to facilitate the creation of a virtual community of scientists working on a sustainable pipeline for diseases of the developing world, and questions remained about how best to articulate, coordinate and financially sustain such a community. These concerns underpinned the creation of the Tres Cantos Open Lab Foundation (TCOLF).

TCOLF: open innovation in action

In order for the open-innovation agenda to become a palpable reality, high-level concepts such as openness and flexible intellectual property (IP) needed to be followed by the implementation of a pragmatic and viable model. Consequently, the TCOLF was established in 2010 as a UK-registered charity independent from GSK. The aim of the foundation is to fund external projects that are aligned with criteria including: independence of the projects from its main funder, GSK; the potential for embracing the World Intellectual Property Organization (WIPO) Re:Search guiding principles to ensure knowledge sharing and accessibility of medicines to the least-developed countries; and the need to actively collaborate with the Tres Cantos site for direct testing of new, often risky, therapeutic hypotheses. Through this scheme, external researchers gain access not only to the data set and compound samples, but also to the facilities, equipment and expertise available in Tres Cantos, under favourable funding and IP terms. During the past 5 years, more than 300 different projects have been evaluated, of which 50 have been funded and implemented in GSK's Tres Cantos facilities. The TCOLF's activities are starting to bear fruit in terms of publications, validation or disaccreditation of therapeutic targets or strategies and, most importantly, advanced preclinical lead molecules (FIG. 1). Additionally, these projects have contributed towards generating US$60 million in follow-up grants for the foundation's partners. Beyond this, the TCOLF is helping to dissolve the boundaries between industry and academia. The collocation of staff in Tres Cantos and the integration of the 60 independent Open Lab fellows in GSK drug discovery teams have enabled an unprecedented degree of scientific exchange, as exemplified by the numerous grants and follow-up activities triggered by the TCOLF programmes. At this stage, the transfer of assets to other agencies or partners is facilitated by a clear IP operational framework, in which GSK and partners commit to making all generated IP that is related to developing countries and diseases of the developing world available through the WIPO Re:Search principles. This clear framework of operation has enabled the transfer of two successful lead optimization programmes to the Wellcome Trust and to the Bill & Melinda Gates Foundation TB Drug Accelerator (TBDA) programme.

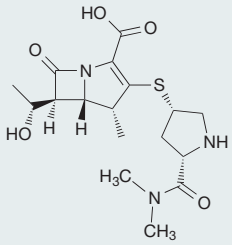
Community platforms

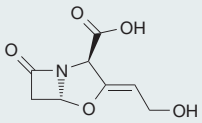
It has been proposed that the introduction of the 'open source' philosophy into drug discovery processes could have a similar effect on the pharmaceutical industry as it did for the software-development sector. However, although these two sectors are similar in some respects, several important differences need to be highlighted. In contrast to software development, drug discovery requires expensive equipment and resources with fully integrated expertise from diverse disciplines. To address this, GSK has partnered with the Medicines for Malaria Venture (MMV), the Bill & Melinda Gates Foundation and the TCOLF to first establish standardized drug discovery platforms and later grant access to these platforms to third-party researchers. These platforms (for example, transmission blocking, translational pharmacology and chemical proteomics) have not only facilitated MMV's virtual R&D agenda but also underpinned many other target-validation and preclinical candidate-selection processes led by academic and industrial partners[8,9] (see Supplementary information S1 (figure)). Data generated through these platforms are quickly shared with the scientific community and act as a catalyst to identify novel opportunities to nurture the early-stage pipelines of TCOLF and our partners.

One size does not fit all

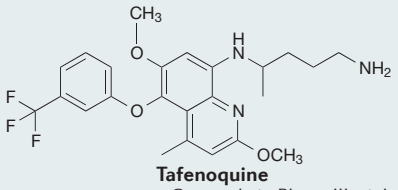
Beyond TCOLF, GSK has participated in other collaborations with fit-for-purpose models, depending on the partner type,

a **Clinically validated compounds**



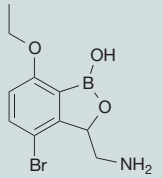


Meropenem plus clavulanate
- Validated in Phase IIa TB EBA

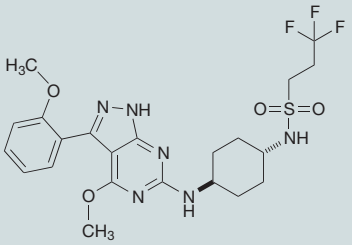


Tafenoquine
- Currently in Phase III trials
- *P. vivax* radical cure

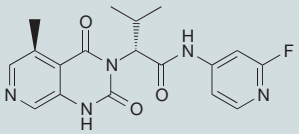
b **Advanced compounds active *in vivo***



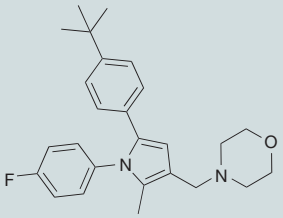
- MIC *M. tuberculosis* = 0.16 μM
- With Anacor Pharmaceuticals



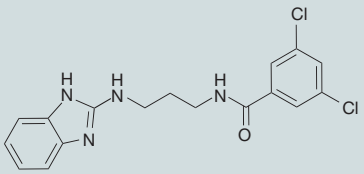
- Intramacrophage *L. donovani* IC_{50} = 0.31 μM
- With DDU



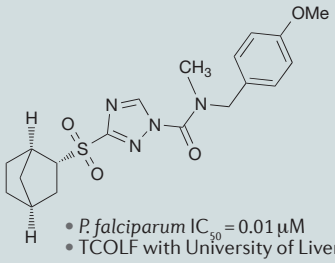
- *P. falciparum* IC_{50} = 0.03 μM
- With MMV



- MIC *M. tuberculosis* = 0.12 μM
- TCOLF with University of Rome

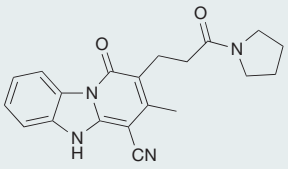


- *P. falciparum* IC_{50} = 0.094 μM
- TCOLF with University of Helsinki

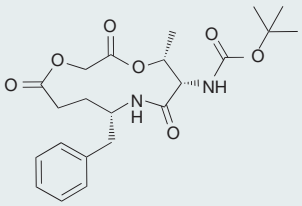


- *P. falciparum* IC_{50} = 0.01 μM
- TCOLF with University of Liverpool

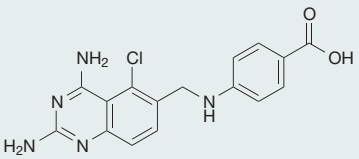
c **Early leads with no reported *in vivo* activity**



- MIC against non-replicating *M. tuberculosis* = 0.16 μM
- TCOLF with Cornell University



- MIC *M. tuberculosis* = 4 μM
- TCOLF with MLU



- MIC against intracellular *M. tuberculosis* = 0.03 μM
- TCOLF with CIDR Seattle

d

Malaria	Kinetoplastids	Tuberculosis
HTS efforts		
• Harvard School of Public Health (USA): DHODH mutant HTS screening • Imperial College London (UK): CDPKs (screening of TCAMS) • MRC/Leicester (UK): PfCLK screening • INSERM (France): gametocyte deformability • CIDR (USA): NMT screening	• Durham University (UK): IPC synthase screening • New York University (USA): *Trypanosoma cruzi* screening • Swiss Tropical Institute (Switzerland): drug-induced differentiation of trypanosomes • McGill University (Canada): targeting the trypanosome editosome • University of Glasgow (UK): PDE HTS	• CIDR (USA): DHFR screening • Omnia Molecular (Spain): tRNA synthetase screening • Cornell University (USA): non-replication screening • Florida International University (USA): topoisomerase I HTS • University of Minnesota (USA): BirA screening • Harvard Medical School (USA): Clp protease HTS • Cornell University (USA): conditional TB mutant HTS • Cornell University (USA): β-lactam hyper-susceptibility screening • University of British Columbia (Canada): macrophage HTS • University of British Columbia (Canada): synergistic combinations of rifampicin and cephalosporins
New platforms and tools for drug discovery		
• Upstate Medical University (USA): liver-stage *in vivo* model • Mahidol University (Thailand): artemisin resistance • Consorcio de Investigación Cientifica Caucaseco (Colombia): *P. vivax* screening	• London School of Hygiene and Tropical Medicine (UK): rates of kill in *Leishmania* spp. and *T. cruzi* • CEU San Pablo University and the University of Glasgow (Spain and UK): *in vivo* metabolomic markers	• Cornell University (USA): metabolomic intracellular accumulation

◀ Figure 1 | **Overview of ongoing efforts to target malaria, kinetoplastid infection and tuberculosis.** The current Tres Cantos Open Lab Foundation (TCOLF) portfolio for tuberculosis (TB; caused by *Mycobacterium tuberculosis*), malaria (*Plasmodium vivax* or *P. falciparum*) and kinetoplastid infection (including *Leishmania donovani*), including the structures of some of the most advanced lead molecules — namely, those that have been clinically validated (part **a**) or advanced *in vivo* (part **b**), or early leads with no as-yet reported *in vivo* activity (part **c**). Ongoing screening efforts and new drug discovery platforms and tools are listed in part **d**. BirA, biotin protein ligase; CDPK, calcium-dependent protein kinases; CEU, Centro de Estudios Universitarios; CIDR, Center for Infectious Disease Research; DDU, University of Dundee Drug Discovery Unit; DHFR, dihydrofolate reductase; DHODH, dihydroorotate dehydrogenase; EBA, early bactericidal activity; HTS, high-throughput screening; IC_{50}, half-maximal inhibitory concentration; INSERM, Institut National de la Santé et de la Recherche Médicale; IPC, inositol phosphorylceramide; MIC, minimum inhibitory concentration; MLU, Martin Luther University of Halle-Wittenberg; MMV, Medicines for Malaria Venture; MRC, Medical Research Council; NMT: *N*-myristoyltransferase; PDE, phosphodiesterase; PfCLK: *P. falciparum* cyclin-dependent kinase-like kinase; TCAMS, Tres Cantos antimalarial set.

objective and level of knowledge available. These types of initiatives have mainly focused on specific asset-driven projects or seeding exercises to promote the generation of new hits and leads. These agreements embody very different approaches to collaboration, reflecting a well-known dichotomy in business and international relations — that is, bilateralism versus multilateralism. In the first instance, asset-focused partnerships with MMV, the Dundee Drug Discovery Unit or Anacor Pharmaceuticals resulted in the selection of advanced lead molecules that are currently undergoing the later stages of preclinical testing (FIG. 1). In contrast with this approach, GSK has also led multilateral collaborations, such as the European ORCHID (Open Collaborative Model for Tuberculosis Lead Optimization) consortium, to address the shortage of validated drug targets and assets in clinical development for TB chemotherapy. This multi-partner effort resulted in the identification and validation of a number of druggable TB targets[10] and a positive Phase IIa study with meropenem plus clavulanate that demonstrated the efficacy of β-lactams as antitubercular agents. In this instance, the multilateral nature of the collaboration and the wider partner connections it entailed — for example, with the European Development Clinical Trials Partnership — were crucial to quickly translate preclinical research into a Phase II trial in only 5 years. These two examples, although diametrically opposed in terms of their underlying collaborative philosophy, can be effective options once the overarching objectives of the collaborative work are taken into consideration.

In summary, GSK's open-innovation agenda to diseases of the developing world is starting to bear fruit in terms of hits, leads, candidates and clinical assets. This strategy, which is based on the principles of openness, risk sharing and flexibility, shows how new models for drug discovery are possible. Although we acknowledge that the external pressures and market realities in other therapy areas might be different, we hope that some of the principles outlined here are applicable elsewhere.

Lluís Ballell, Mike Strange and Nicholas Cammack are at the Department of Diseases of the Developing World, GlaxoSmithKline, Parque Tecnológico de Madrid, Calle de Severo Ochoa, 2, 28760 Tres Cantos, Madrid, Spain.

Alan H. Fairlamb is at the Division of Biological Chemistry and Drug Discovery, College of Life Sciences, University of Dundee, Dundee DD1 5EH, UK.

Leszek Borysiewicz is at the Department of Medicine, University of Cambridge, Cambridge CB2 0SP, UK.

Correspondence to L.Ba.
lluis.p.ballell@gsk.com

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Competing interests statement
The authors declare competing interests: see Web version for details.

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