

also to extracellular gliding and cell invasion. Monitoring how and where these filaments emerge, elongate, and recycle will certainly require future imaging adjustments to increase signal sensitivity, speed, and resolution. Thanks to the great achievement in generating a tool that all the community was waiting for, and in conjunction with photoactivation and inactivation-based approaches, and super-resolution live-cell imaging, the mystery of the actin contribution to the lytic cycle of tachyzoites might be finally elucidated in the near future.

Periz *et al.* [7] now describe unique F-actin networks that (1) connect one daughter to the other, and presumably contribute to the rosette pattern while allowing interparasite communication, and (2) collapse while F-actin retreats to the RB before the networks reform again and expand throughout the PV. Breakdown of the network also precedes tachyzoite egress from the PV and the host cell while residual F actin can still be seen within the RB (Figure 1).

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Forum

The Future of Drug Development for Neglected Tropical Diseases: How the European Commission Can Continue to Make a Difference

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In this article, the four coordinators of neglected tropical disease (NTD) drug development projects funded under the European Commission (EC) Framework Programme 7 argue that the EC should reassess their funding strategy to cover the steps necessary to translate a lead compound into a drug candidate for testing in clinical trials, and suggest ways in which this might be achieved.

EC Funding of NTD Drug Development

The EC has consistently and substantially supported research into NTDs, starting well before the London Declaration of 2012 (<http://unitingtocombatntds.org/resource/london-declaration>), which put the control or elimination of NTDs at the forefront of global efforts to ‘chart a new

course toward health and sustainability among the world’s poorest communities to a stronger, healthier future’. However, grants for research on NTDs represented only 11% of the total funding for infectious diseases during the EC Framework Programmes (FP) 5 to 7 up to 2013, 70% going to the so-called ‘Big Three’ diseases: malaria, tuberculosis, and HIV/AIDS [1]. The development of new drugs is particularly important in order to circumvent problems with current treatments, including drug resistance, severe side-effects, or exacting dosing schedules. There is a recognized need to identify new chemical entities (NCEs) as candidate drugs in order to both improve patient care and meet targets for elimination, particularly of neglected parasitic diseases [2]. Nevertheless, only 6% of the EC infectious disease funding was dedicated to drug development.

EC FP7 Drug Discovery Projects

The EC has been notably successful in bringing together large, multinational research networks. Four such consortia, with the acronyms NMTrypI (<http://fp7-nmtrypi.eu>), KINDReD (<http://kindred-fp7.com/>), A-ParaDDisE (<http://a-paradise.cebio.org/>), and PDE4NPD (www.pde4npd.eu), involving more than 50 teams in Europe, Africa, India, South America, Australia, and the USA, were funded in the last call under FP7 related to drug development in neglected infectious diseases. The projects targeted the major chronic parasitic diseases leishmaniasis, Chagas disease, sleeping sickness, schistosomiasis, and malaria. Together, these diseases affect more than a billion people worldwide, cause hundreds of thousands of deaths, and are major contributors to the poverty trap in the countries concerned [2]. The projects were given the following objectives:

- To establish a common drug-discovery platform that should have the capacity to undertake screening of compound libraries, lead development.
- To test validated hit compounds in relevant animal models as well as

toxicology and safety testing of new drug candidates.

The four projects pursued distinct strategies for drug discovery, involving both phenotypic screening, target-based methods, and repurposing of existing approved drugs, and have all made significant progress. Based on the criteria for the selection of 'hit' and 'lead' compounds, recently defined [3], well over 100 hits have been identified of which more than 10 can so far be defined as lead compounds with promising profiles in animal studies and significant potential for further development. These numbers will grow as the projects reach term. In addition, novel drug targets have been identified and validated for each of the parasites studied, homology models and crystal structures of target enzymes have been resolved, and new chemical entities identified as potential drugs of interest both in NTDs and other pathologies.

Importantly, as suggested by the EC at the time of funding, the four consortia

have worked in close collaboration throughout the course of their projects under the umbrella of common 'Synergy' activities. These involved regular discussions, a joint symposium in 2016, common partner teams and/or external advisory board members, resource pooling, and a common data storage platform (<https://fp7h-synergy.h-its.org/>). This has enabled them to adopt a common strategy to face the challenge of ensuring that the advances made will not be lost once the current projects come to an end. Crucially, support is needed for developing hit and lead compounds from *in vivo* animal studies through preclinical testing up to and including phase I clinical trials. This involves rigorous pharmacokinetic, pharmacodynamic, and toxicity studies (Absorption, Distribution, Metabolism, Excretion, and Toxicity; ADMET) and drug production according to Good Laboratory Practice/Good Manufacturing Practice (GLP/GMP) standards (Figure 1).

No funding opportunities exist for these types of study in the current EC research programme, Horizon2020 (H2020),

which at present supports only clinical trials through the European & Developing Countries Clinical Trials Partnership (EDCTP). While NTDs have been added to the remit of the EDCTP, the support proposed in the business plan until 2024 (<http://www.edctp.org/web/app/uploads/2016/12/EDCTP-Strategic-Business-Plan-2014-2024.pdf>) is restrictive, whether for diagnostics, vaccine or drug development. Support for the latter concerns predominantly phase II to phase III clinical trials, with a focus on drug combinations, and only in sub-Saharan Africa (ruling out support for clinical trials on some important NTDs like Chagas disease). Moreover, only in the case of diseases where treatments are 'inadequate or lacking' will phase I trials be funded. This leaves a yawning 'funding gap' between hit-to-lead development and clinical trials.

Funding Initiatives for NTD Drug Development

Mechanisms do exist to fill the funding gap and take validated lead compounds through the complex and costly early-clinical phase of testing. These are mainly nonprofit initiatives funded by various sources, including, for example, the Bill & Melinda Gates foundation (<http://www.gatesfoundation.org/>), governments, and the pharmaceutical industry. Examples are the Drugs for Neglected Diseases Initiative (DNDi; <http://www.dndi.org/>), WIPO Re:search (<http://www.wipo.int/research/en/>), and the Medicines for Malaria Venture (<https://www.mmv.org/>). The DNDi has overseen the progress of fexinidazole to phase IIb/III clinical trials for the treatment of human African trypanosomiasis, to phase IIa for the treatment of Chagas disease, and to phase IIa in combination with miltefosine for the treatment of leishmaniasis, and has other leads in the pipeline for NTDs, as well as for other diseases such as paediatric HIV and hepatitis C. Nevertheless, due to the high attrition rate for candidate drugs at all stages of the development pipeline, it is advantageous to have more candidates to feed into it. This again implies

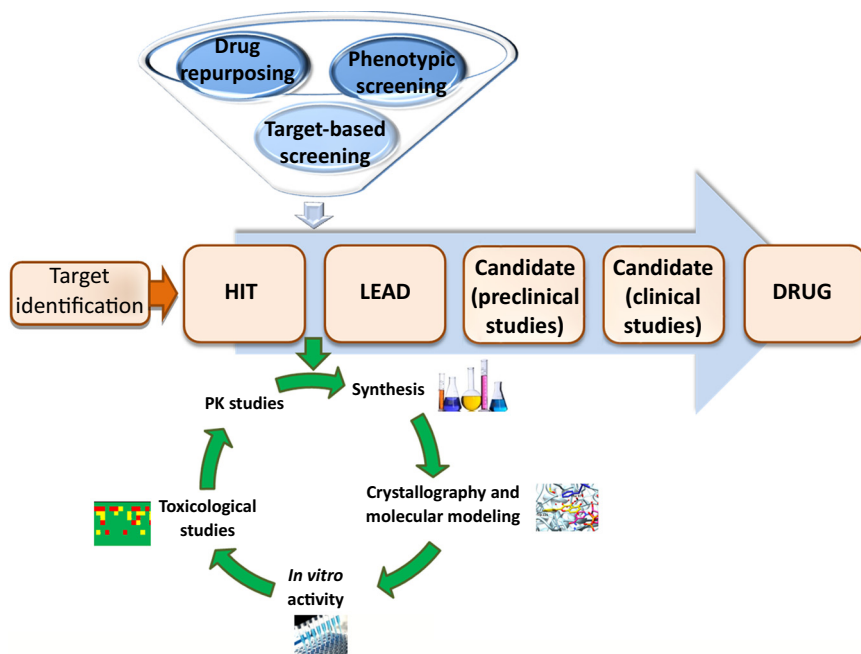


Figure 1. The Drug Discovery Pipeline.

Trends in Parasitology

appropriate funding: a pooled R&D fund has been proposed by the WHO [4] but this remains theoretical. The absence of such a large pooled funding mechanism and the fragmentation of current efforts are to be deplored [2,5].

How the EC Can Make a Difference

The considerable contribution of the EC-funded programmes to NTD research is not in question. It is also clear that emphasis has previously been placed on basic research, but that this should now shift in order to address the gaps in the pipelines for the development of drugs, vaccines, and diagnostics. The most obvious gap separates drug hit and lead development from the type of clinical trial funded by the EDCTP. The next logical step for the drug development investment strategy of the EU would be to fund a call within H2020, to build upon the synergy developed in the last FP7 call. This would enable continued interaction between academia and small and medium-sized enterprises by creating a platform to take on the task of bridging the gap between lead optimization and early-stage clinical trials (phases I–II). Lead compounds developed by the four consortia, but also from other sources (e.g., teams participating in the current EC-funded COST 1307 initiative) would feed the platform regardless of the parasitic disease targeted, overcoming the problem of fragmentation amongst groups in the field and removing replication of effort. While this should not replace funding of basic research, it would lead to an increase in the density of the different stages of preclinical testing and in the numbers of candidates entering phase I clinical trials. In this way the previous investment in NTD drug discovery would be consolidated.

While it is evident that no single funder can completely cover the whole drug development pipeline, targeted funding, as suggested here, could attract support

from other sources, including industry, foundations, and nongovernmental organizations, and collaborations between these stakeholders should be sought. Finally, the cooperation of the pharmaceutical industry, whose expertise is essential for any drug to finally reach the clinic, could be engineered through the Innovative Medicines Initiative (IMI), cofunded by the EC and industry, by adding NTD drug development to the IMI remit.

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Forum

Insights on Heme Synthesis in the Malaria Parasite

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The malaria parasite has a functional heme-biosynthetic pathway, although it can access host hemoglobin-heme. The heme pathway is dispensable for blood stages, but essential in the mosquito stages which do not acquire hemoglobin-heme. We propose that the blood stage parasites maintain a dynamic heme pool through multiple back-up mechanisms.

Heme Pathway in the Malaria Parasite

Heme-containing cytochromes are essential for the functioning of the electron transport chain (ETC) in the malaria parasite. The ETC is required to support pyrimidine biosynthesis in the blood stages, whereas in the sexual and liver stages it is also involved in ATP generation and oxidative metabolism. The malaria parasite acquires host hemoglobin in the blood stages and digests it in the food vacuole to generate amino acids. Since accumulation of free heme is toxic, it stores the excess heme derived from hemoglobin as hemozoin pigment, a biocrystallized form of heme-aggregates [1]. Interestingly, the parasite can synthesize its own heme from glycine, and the entire pathway involves three different parasite compartments: mitochondria, apicoplast, and cytosol (Figure 1A) [2]. Studies with *Plasmodium berghei*-infected mice [3] and *Plasmodium falciparum* in cultures [4] using knockout (KO) parasites generated for δ -aminolevulinic acid synthetase (ALAS) and ferrochelatase (FC), the first and last enzymes of heme-biosynthetic