Kinetoplastid Drug Development: strengthening the preclinical pipeline
KINDReD

Concept and Objectives

1. Challenging the global burden of trypanosomatid diseases

The trypanosomatid diseases, Leishmaniasis, Human African trypanosomiasis and Chagas disease, continue to impart a heavy toll on human health, affecting millions of people worldwide particularly in the economically poorest countries[1]. The handful of treatments available to control this enormous heath burden is limited by serious adverse effects, high costs, difficulties in administration and threatened by the continually advancing problem of drug resistance[2,3,4]. PubMed keyword search on '(*Leishmania*) or (*Trypanosoma*)' retrieves over 39 000 articles, of which a mere 17 concerned clinical trials of drugs (Phase I to IV). Of these, the 8-aminoquinoline sitamaquine represents the only new clinical candidate for the treatment of visceral leishmaniasis (VL) following the 2002 introduction of miltefosine in India. The CNS permeable drugs fexinidazole, a 2-substituted 5-nitroimidazole, and SCYX-7158, an orally available benzoxaborole, show promising efficacy with the advanced stage of HAT entered phase II clinical trials in 2012 (www.clinicaltrials.gov). Nonetheless, whilst several drug candidates are under review at the preclinical trials stage, the pipeline remains sparse. **There has been general market inertia to translate recent scientific and technological advances into the discovery of potent, safe drug candidates against the kinetoplastid protozoan parasites.**

An increasing number of European and global efforts have been set up in the public sector over recent years in an attempt to correct the bleak outlook in anti-kinetoplastid chemotherapy[5,6]. Such initiatives have focused on the identification and validation of parasite drug targets[7,8] and/or the setting up and running of high throughput physiological[9,10,11] or target based screening platforms[12]. A portfolio of promising lead compounds has been identified from physiological screens incorporating both novel drug candidates[13] and FDA approved drugs[11,14]. **The KINDReD consortium brings such promising initiatives together with key experts in industry and academia to create a unique and powerful drug discovery platform with the common objective of *advancing promising laboratory-driven discoveries into clinical utility*.**

The KINDReD consortium's infrastructure for parasite screening integrates five leading academic laboratories in Europe (Portugal, United Kingdom and Switzerland), the United States of America (California) and South America (Brazil) **with high throughput screening (HTS) facilities equally distributed between all three major kinetoplastid parasites**. Follow-up **medicinal chemistry and ADMET expertise** is spear-headed by the industrial partners and several academic members of the consortium. Intracellular amastigote screening is being employed as the most relevant for *Leishmania spp* and *Trypanosoma cruzi*. Compound libraries (focused, diversity oriented or natural) are being screened on this platform, as well as compound series devised through target screening and *in silico* approaches - led by research intensive European SMEs. High-value validated protein targets will be carefully chosen and **all available kinetoplastid parasite homologues will be screened and compared to their human homologue(s) to establish selectivity**. This is particularly important when determining *differential* ligand-binding efficiency, a key element to identify optimal starting points in fragment based drug design[15] (see below). **Promising lead compounds, such as bisnapthalimidopropyl polyamine inhibitors of tubulin deacetylase[16], will undergo optimisation for efficacy and tolerability in cell-based and then animal disease models.** Toxicological markers are being evaluated in human cell lines prior to toxicity (acute, subacute and chronic) testing in the mouse model and then larger mammals. In parallel, and in line with the US Food and Drug Administration's (FDA's) Critical Path Initiative[17], several check point controls have been built into the pipeline to flag, identify and allow early correction of potential safety or efficacy issues. These include (i) a systems biology approach to identify and validate both drug on-target and off-target

interactions (potential toxicity markers) via activity-based chemoproteomics[18] (ii) 'uptake and metabolism' as potential modulators of drug efficacy and/or resistance and (iii) the establishment of a firm set of criteria for drug efficacy and safety in kinetoplastid chemotherapies. **Our goal is to strengthen, inform and advance the current drug development pipeline in order to achieve at least one new Phase I clinical candidate for at least one trypanosomatid disease commensurate with the lifetime of the FP 7-funded project.**

References

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