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Digest paper

Repurposing strategies for tropical disease drug discovery

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ABSTRACT

Neglected tropical diseases (NTDs) and other diseases of the developing world, such as malaria, attract research investments that are disproportionately low compared to their impact on human health worldwide. Therefore, pragmatic methods for launching new drug discovery programs have emerged that repurpose existing chemical matter as new drugs or new starting points for optimization. In this Digest we describe applications of different repurposing approaches for NTDs, and provide a means by which these approaches may be differentiated from each other. These include drug repurposing, target repurposing, target class repurposing, and lead repurposing.

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Neglected tropical diseases (NTDs) are defined by the World Health Organization (WHO) as ‘a diverse group of communicable diseases that prevail in tropical and subtropical conditions;’ the official WHO list of NTDs is currently comprised of 17 infectious diseases.¹ Alongside malaria, these diseases predominantly affect populations living in poverty, under poor living conditions and in close proximity with the vectors of disease-causing agents. Their effects are far-reaching and devastating: over 1 billion people in 149 countries suffer from one or more NTDs with millions of others at risk, and the economic repercussions of these diseases can be just as damaging as their health effects.¹ These diseases are ‘neglected’ primarily because there is no financial incentive to develop drugs for a patient population that cannot afford them. Consequently, noting that most drugs are developed by for-profit companies, there is little reason for these companies to invest in research and development for drugs that will not result in high financial returns.

Therefore, much of the drug discovery and hit-to-lead optimization for these diseases is performed in academic laboratories without the financial, personnel, and technical resources of a pharmaceutical company. With a view toward overcoming these limitations, a popular strategy for academic groups has been to ‘repurpose’ or re-use existing chemical matter, target knowledge, and other data from human or animal drug discovery campaigns

in order to cut down on the time and cost of advancing a program from hit to lead to clinical candidate. Indeed, a number of the drugs currently in use for treating NTDs originated from low-throughput screens or repurposing of either human or veterinary drugs (Table 1). A recent review² on approaches to drug discovery for malaria, HAT, and schistosomiasis highlights drug repurposing, drug repositioning, and drug rescue as strategies employed by NTD researchers; other terms employed in the field include ‘target repurposing’³ and ‘piggyback drug discovery.’⁴ Repurposing as a general strategy is therefore a well-established approach in the NTD drug discovery community. By systematizing the nomenclature for the many flavors of repurposing, we aim to enable the community to readily identify at the outset what type of information was available at the start of the campaign and the extent of optimization involved. A clearly defined, common vocabulary for these strategies will ease communication and collaboration in the field of NTD drug discovery.

The many terms for repurposing strategies can be grouped into four major categories, which are (a) drug repurposing, (b) target repurposing, (c) target class repurposing, and (d) lead repurposing. Each has distinct advantages and disadvantages and may be appropriate in different project situations. These four approaches are characterized by the type of chemical matter that is being repurposed, the kind of information that is typically available at the starting point of a campaign, and the type of optimization that is required. For each strategy, the characteristics, advantages, and

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Table 1
Selected drugs currently employed in the treatment of NTDs discussed in this review, according to WHO

Disease	Drug	Discovery	Limitations
Malaria	Artemisinin	Natural product, found to have anti-malarial activity in the 1980s ⁵	Emerging resistance ⁶
Human African Trypanosomiasis	Suramin	Dye derivative, found to be anti-trypanosomal in the 1920s ⁷	Treats Stage 1 only ⁸
	Pentamidine	Part of a class of compounds discovered to treat equine trypanosomiasis in the 1940s ⁷	Treats Stage 1 only ⁸
Chagas disease	Melarsoprol	Arsenicals discovered to cure infected laboratory animal models of trypanosomiasis; melarsoprol introduced in 1949 ⁷	Fatal to 3–10% of patients; emerging resistance ⁸
	Eflornithine	Originally an anti-cancer drug, in use for HAT since 1990 ⁷	Complex treatment regimen ⁸
	Benznidazole	Empirical screening, introduced in 1971 ⁹	Rare but severe side effects, emerging resistance ⁹
	Nifurtimox	Empirical screening, introduced in 1965 ⁹	GI and CNS side effects
Lymphatic filariasis	Albendazole	Originally developed to treat gut helminths in livestock, approved for use in humans in the 1980s ¹⁰	Must be used in combination with either ivermectin or diethylcarbamazine citrate ¹⁰
	Ivermectin	Found to be effective against canine hookworms and other nematodes, registered 1987 ¹¹	Long treatment regimen, unsuitable for use in areas co-endemic with <i>Loa loa</i> , emerging resistance ¹²
River blindness	Ivermectin	Discovered to be effective against <i>Onchocerca</i> in horses ¹¹	See 'Ivermectin' above

disadvantages are discussed, and case studies are provided to illustrate each one in practice.

Drug repurposing: Drug repurposing is characterized chiefly by the lack of further optimization required for the repurposed chemical matter. In this approach, FDA-approved chemical entities for an initial indication are used for a second indication without any further structural modification of the compound at hand (although dosing and formulation modifications may be required). Drug repurposing is an established strategy used not only for neglected diseases, but other diseases as well, and is also referred to as drug repositioning, drug redirecting, and drug reprofiling.¹³ In for-profit settings, repurposing avoids the risk associated with the costs of drug discovery and development, up to (and often including) Phase I clinical trials. However, it offers great advantages for neglected diseases as well. Approved chemical matter has already been profiled in terms of safety and pharmacokinetics, giving an indication of tolerated human doses and any likely side effects. As a result, both the time and cost of drug development are drastically reduced using this approach. We describe below three examples of drug repurposing in various stages of progression along the drug discovery pipeline.

Case study 1: Eflornithine as a successfully repurposed drug for sleeping sickness. Human African trypanosomiasis (HAT), also known as sleeping sickness, is caused by two subspecies of the parasite *Trypanosoma brucei* (*T.b. gambiense* and *T.b. rhodesiense*). Prevalent in 36 countries in sub-Saharan Africa, HAT progresses from the lymph to the central nervous system, causing disruptions in sleeping patterns and death if left untreated.⁸ Originally developed as a cancer therapeutic (and now utilized as topical agent for hirsutism), eflornithine (**3**, Fig. 1), also known as difluoromethylornithine or DFMO, is an inhibitor of polyamine biosynthesis that was shown by Bacchi et al. to inhibit the growth of trypanosomes by the same mechanism.¹⁴ In addition, eflornithine cured *T.b. brucei* infections in mice when given as a 1 or 2 percent solution in drinking water (defined as survival of greater than 30 days beyond that of untreated controls); the drug was also shown to be generally nontoxic.¹⁴

Although in use as a single agent for many years, eflornithine requires large doses to be effective, has a complex mode of administration and high cost per patient, and is ineffective against *T.b. rhodesiense*.¹⁵ Recently, however, some of these drawbacks have been mitigated through the use of nifurtimox–eflornithine combination therapy (NECT). By combining eflornithine with nifurtimox (a Chagas disease therapeutic), the dose of eflornithine required, the complexity of administration, and the cost of the treatment are reduced.¹⁶ Importantly, eflornithine is effective against stage 2 HAT wherein the parasite crosses the blood–brain barrier, and

NECT has become the most promising front-line treatment for second-stage *T.b. gambiense* infections.¹⁶

Case study 2: Tamoxifen as an anti-leishmanial treatment. 310 million people are at risk of infection by *Leishmania* spp., which cause leishmaniasis in several forms, including the deadly visceral leishmaniasis (VL).¹⁷ The anti-leishmanial activity of tamoxifen (**1**, Fig. 1), an approved breast cancer drug used in the treatment of estrogen receptor-positive tumors, was first reported in 2007.¹⁸ Starting with the observation made by previous groups that tamoxifen was able to induce alkalization of organelles in several cell lines,¹⁹ it was hypothesized that *Leishmania* parasites, which live in acidic vacuoles within the host cell and require low pH to survive, would be susceptible to tamoxifen via this mechanism. The drug was tested against the promastigote form of five species of *Leishmania* (including *L. amazonensis*), and against the intracellular amastigote of *L. amazonensis*, and was shown to have a cidal effect on all species with micromolar EC₅₀ values. The mechanism of action was also investigated and was shown to be independent of host estrogen receptor modulation.¹⁸

In further studies, tamoxifen was evaluated in a mouse model of leishmaniasis.²⁰ In a 15-day treatment of *L. amazonensis*-infected mice, tamoxifen reduced the parasite burden by 99% compared to untreated mice, outperforming meglumine antimonate, the standard treatment. Although a cure was not achieved (typical for leishmaniasis treatments), no toxicity was observed during or after treatment and symptoms were greatly alleviated. Tamoxifen was also shown to be effective in mouse and hamster models of *Leishmania braziliensis* and *Leishmania chagasi*, respectively, with 95–98% reduction in parasite load and 100% survival of treated animals 18 weeks post-infection.²¹

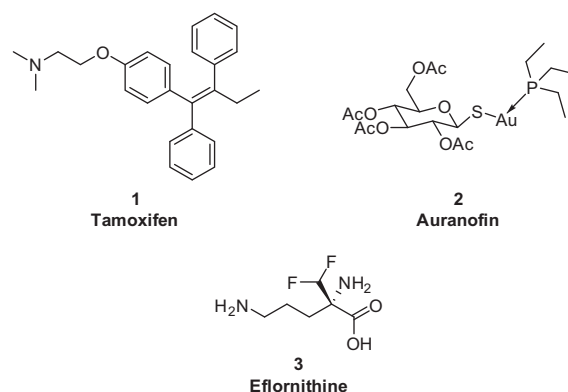


Figure 1. Drugs that have been directly repurposed for NTDs.

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