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Therapeutics for Neglected Infectious Diseases: Progress and Challenge

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Infectious diseases remain a significant cause of morbidity and mortality, among which tuberculosis (TB) and malaria are among the biggest killers and dengue is the most prevalent mosquito-borne viral pathogen in human. Other protozoan parasitic diseases, such as human African trypanosomiasis (HAT, also known as sleeping sickness), Chagas disease, and visceral leishmaniasis, contribute to over 4.4 million disability-adjusted life years (DALY).[1] The global burden of these diseases remains unacceptably high, given that they are all preventable and/or treatable. However, one has to acknowledge the tremendous progress that has been made. For example, TB and malaria mortality rates have fallen by 45 and 47%, respectively, over the past two decades. Unfortunately, the sustainability of these gains is threatened by the global spread of multidrug-resistant (MDR) TB strains and, more recently, the emergence in Southeast Asia of drug resistance to artemisinin, the last remaining effective drug for malaria treatment. New drugs are thus urgently needed.

Therapeutics development for tropical diseases has been historically neglected, but over the past decade, this trend has reversed in part due to increased research funding from philanthropic organizations, government, and industry. Pharmaceutical companies and product development partnerships have joined forces to fight tropical diseases. As a result, the past decade has seen the emergence of a pipeline of new chemical entities. Here we comment on the recent progress and challenges on the development of therapeutics for malaria, HAT, TB, and dengue.

Malaria. The apicomplexan parasites *Plasmodium falciparum* (Pf) and *Plasmodium vivax* (Pv) infect 500 million people annually, causing more than 600,000 deaths, mostly children under the age of 5, in sub-Saharan Africa. The current first-line malaria treatment includes (i) artemisinin-based combination therapy for *Pf* and (ii) primaquine and chloroquine treatment for *Pv* and *Plasmodium ovale*. The progress accomplished over the past few decades has made it an achievable goal to eliminate malaria, even in highly endemic regions. This aspiration has spurred efforts to discover and develop new malarial drugs and vaccines.

New malaria drugs are required not only to quickly treat acute phase and reduce parasitemia but also to prevent and block parasite transmission. This requires drugs to be active across the parasite life cycle. A promising pipeline of drugs with complementary profiles has recently emerged. Cipargamin (also known as KAE609 or NITD609) achieved proof-of-concept in a small trial with uncomplicated malaria patients and showed remarkably fast parasitemia clearance time.[2] Cipargamin belongs to a new class of antimalarial compounds discovered through phenotypic screening. The inhibitor potently kills *Plasmodium* asexual blood stages through inhibition of the P-type non-SERCA ATPase PfATP4.[3] Cipargamin is also active against adult gametocytes and effectively blocks malaria transmission in preclinical experiments.[4] KAF156 is another antimalarial drug candidate with a novel mechanism of action in phase II trials. KAF156 has a preclinical pharmacological profile to be effective not only as a therapeutic but also as a prophylactic drug.[4] Finally, the discovery and validation of the *Plasmodium* lipid kinase PI4K as a malaria drug target may offer the opportunity to design new drugs capable of achieving radical cure, which is challenging for *Pv* treatment.[5] This is because of the existence of dormant forms of the parasite (hypnozoites) in the liver, which cause relapse if they are not eliminated. As the global pipeline for *Pf* grows, it becomes increasingly clear that *Pv* radical cure remains a very challenging objective and that extra efforts are needed to develop the biological tools necessary for *Pv* radical cure drug discovery.

Human African Trypanosomiaisis. HAT is caused by the parasite *Trypanosoma brucei* and is lethal if left untreated. Encouragingly, WHO estimated that the annual cases of HAT have decreased by 72% since 2009. The approval of the current gold-standard treatment combining eflornithine and nifurtimox (NECT) was definitely a milestone improvement. Unfortunately, the treatment is inadequate for disease elimination, as evidenced by case numbers that have reached a baseline from which they are no longer falling. NECT administration requires an infusion, which posed complexity to administer in resource-poor settings and increased the treatment cost. Thus, WHO questioned the sustainability of NECT administration in the long term (http://www.who.int/iris/bitstream/10665/77950/1/9789241564540_eng.pdf).

Two oral drug candidates (fexinidazole and SCYX-7158) are presently in clinical development for HAT. The current HAT drug discovery aims to deliver superior compounds to eliminate the parasite in a setting of very low incidence and inaccessible foci. To support the endgame of the HAT elimination, we need a novel oral combination therapy with a shortened treatment (~3 days), low pill burden, and no safety follow-up requirement.

Tuberculosis. TB affects one-third of the world's population. About 9 million new cases and 1.1 million TB-related deaths were reported in 2013. The first line drugs Isoniazid, pyrazinamide, ethambutol, and Rifampicin were all introduced over 40 years ago. In that era, it was widely believed that these drugs might lead to TB eradication. Research efforts were scaled down in the 1970s and 1980s; such complacency indirectly contributed to the re-emergence of TB with increased prevalence of multidrug-resistant (MDR) strains. Furthermore,

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emergence of the HIV/AIDS epidemic and development of severe drug-resistant forms have created new challenges in TB management. Today, there is an urgent need to discover new TB drugs with novel mechanisms from which to develop improved combination regimens that can simplify and shorten treatment (currently 6−18 months), tackle MDR, reduce side effects, and tackle latent infection.[6] Toward this goal, of particular note have been the approvals of bedaquiline and delamanid for MDR TB, and the progression of novel regimens including many repurposed drugs (pretomanid, bedaquiline, moxifloxacin, pyrazinamide, and linezolid) into midstage clinical trials.[7]

There has been a surge in research efforts to find new antitubercular compounds. The uncovering of mechanism of action of existing TB drugs has opened up the possibility to identify new drugs acting on these targets (e.g., inhA). In addition, phenotypic screening and lead optimization have identified promising compounds with new TB drug targets. Interestingly, phenotypic screens run by different organizations have frequently identified diverse chemical series working on the same targets, many of which are membrane associated (e.g., Mmpl3, DprE1, and QrcB).[7] Looking forward, funding for discovery of new chemical entities and biomarkers to predict relapse-free cure needs to continue to ensure these advances are translated into new medicines.

Dengue. The mosquito-borne dengue virus (DENV) threatens 3 billion people, causing 390 million human infections annually, of which 96 million infections manifest symptoms.[8] DENV infection can lead to dengue fever (DF), life-threatening hemorrhagic fever (DHF), or shock syndrome (DSS). No clinically approved vaccine or therapy is currently available. Development of a vaccine has been challenging because of the four serotype nature of DENV (30−35% amino acid variation). A successful vaccine needs to simultaneously induce a long-lasting immune protection against all four serotypes; an individual with incomplete immunization may be sensitized to develop severe DHF or DSS. The most advanced vaccine (CYD-TDV) was recently shown to have good efficacy against serotypes-1, -3, and -4, but weak protection against serotype-2 virus.[9] As a complement to vaccine, antivirals should be developed for dengue. The rationale of antivirals is to reduce viremia and prevent patients from developing severe DHF and DSS. Because DENV is limited to human hosts, reducing viremia through antivirals should also block transmission between humans and mosquitos.

Because the hallmark of dengue pathogenesis is vascular leakage, current treatment is limited to fluid resuscitation (isotonic crystalloid fluids or colloid solutions) and supportive care. In the past decade, significant progress has been made in understanding the biology of DENV replication to enable modern drug discovery, including solving the atomic structures of all viral enzymes and structure proteins. Although compounds with potent in vitro and in vivo efficacies have been reported, no bona fide inhibitors specifically designed for DENV have been advanced to clinics.[10] Designing a compound that can inhibit all four serotypes is challenging due to the 30−35% sequence variation. The same challenge was encountered for hepatitis C virus (HCV) antiviral development as the seven genotypes of HCV share a similar sequence variation. HCV drug discovery has demonstrated that nucleoside inhibitors have the highest chance to fulfill this pan-genotype/serotype requirement.

Repurposing compounds previously developed for other indications has been actively pursued for dengue treatment. Ten clinical trials have been performed for such compounds, including Balapiravir (a nucleoside inhibitor), Celgosivir (a host α-glucosidase inhibitor), chloroquine (a malaria drug with antiviral and immunomodulatory activities), and prednisolone (a steroid drug). Unfortunately, none reduced viremia or improved clinical outcomes in dengue patients. The failed clinical trials have pointed out two important knowledge gaps about dengue pathogenesis: What are the authentic target cells and organs during the acute phase of infection? What molecular targets of the host pathway lead to vascular leakage in dengue patients?

Overall, great momentum has been built to develop therapeutics for tropical infectious diseases. The collaborative effort from academia, industry, and funders has transformed the preclinical and clinical pipelines. There is no room for complacency, as pathogens are constantly evolving. We humans have to continue to develop new therapeutic options to stay ahead of the game.

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Notes

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