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Repurposing Know-how for Drug Development: Case Studies from the Swiss Tropical and Public Health Institute

Lukas Meier*[ab], Marina Antillon[ab], Christian Burri[ab], Nakul Chitnis[ab], Yvette Endriss[ab], Jennifer Keiser[ab], Sarah Moore[abc], Pie Müller[ab], Melissa A. Penny[ab], Till S. Voss[ab], Pascal Mäser[ab], and Jürg Utzinger[ab]

Abstract: In pursuing novel therapeutic solutions, drug discovery and development rely on efficiently utilising existing knowledge and resources. Repurposing know-how, a strategy that capitalises on previously acquired information and expertise, has emerged as a powerful approach to accelerate drug discovery and development processes, often at a fraction of the costs of *de novo* developments. For 80 years, collaborating within a network of partnerships, the Swiss Tropical and Public Health Institute (Swiss TPH) has been working along a value chain from innovation to validation and application to combat poverty-related diseases. This article presents an overview of selected know-how repurposing initiatives conducted at Swiss TPH with a particular emphasis on the exploration of drug development pathways in the context of neglected tropical diseases and other infectious diseases of poverty, such as schistosomiasis, malaria and human African trypanosomiasis.

Keywords: Drug development · Drug discovery · Human African trypanosomiasis · Malaria · Neglected tropical diseases · Product development partnerships · Public-private partnerships · Repurposing know-how · Schistosomiasis · Swiss Tropical and Public Health Institute

Dr. Lukas Meier is trained in history and is the Secretary General of the R. Geigy Foundation/Swiss Tropical and Public Health Institute

PD Dr. Nakul Chitnis leads the Mathematical Epidemiology Group at the Swiss Tropical and Public Health Institute

Dr. Marina Antillon is a Project Leader in modelling and health economics at the Swiss Tropical and Public Health Institute

Yvette Endriss is the Head of the Central Laboratory at the Swiss Tropical and Public Health Institute

Prof. Dr. Christian Burri is trained in pharmacy, the Deputy Head of the Department of Medicine and the Head of the Medicines Implementation Research Unit at the Swiss Tropical and Public Health Institute

Prof. Dr. Jennifer Keiser is trained in pharmacy and heads the Helminth Drug Development Unit at the Swiss Tropical and Public Health Institute

**Correspondence:* Dr. L. Meier[ab], E-mail: lukas.meier@swisstph.ch
[a]Swiss Tropical and Public Health Institute, CH-4123 Allschwil, Switzerland; [b]University of Basel, CH-4001 Basel, Switzerland; [c]Ifakara Health Institute, Bagamoyo Branch, Bagamoyo, Tanzania

PD Dr. Sarah Moore is a medical entomologist and Group Leader in the Vector Biology Unit at the Swiss Tropical and Public Health Institute. For the past 15 years she has been based at the Bagamoyo Branch of the Ifakara Health Institute in Tanzania

PD Dr. Pie Müller is trained in biology and the Head of the Vector Biology Unit at the Swiss Tropical and Public Health Institute

Prof. Dr. Melissa A. Penny is an Assistant Professor and heads the Disease Modelling Unit at the Swiss Tropical and Public Health Institute

Prof. Dr. Till S. Voss is trained in biology and the Deputy Head of the Department of Medical Parasitology and Infection Biology and Head of the Malaria Gene Regulation Unit at the Swiss Tropical and Public Health Institute

Prof. Dr. Pascal Mäser is trained in molecular biology and the Head of the Parasite Chemotherapy Unit at the Swiss Tropical and Public Health Institute

Prof. Dr. Jürg Utzinger is trained in environmental sciences and epidemiology and is the Director of the Swiss Tropical and Public Health Institute

Introduction

Advancing drug discovery and development requires a deep understanding of the underlying biology of the target organisms and the associated disease mechanisms. Within this framework, the Swiss Tropical and Public Health Institute (Swiss TPH), an associated institute of the University of Basel, has been conducting research on novel therapeutics for neglected tropical diseases (NTDs) and other infectious diseases of poverty, including Buruli ulcer, Chagas disease, food-borne trematodiasis, human African trypanosomiasis (HAT), leishmaniasis, malaria, schistosomiasis and soil-transmitted helminth infections.[1–6] Basic, translational and implementation science are integrated as continuum in the drug discovery and development science of the institute. This integration supports a positive impact on the health and well-being of marginalized populations, living in resource-constrained settings in low- and middle-income countries (LMICs).[7,8] For example, as early as the 1980s, researchers at Swiss TPH developed culture media for the successful *in vitro* cultivation of *Trypanosoma brucei*, the pathogen that causes HAT.[9] In a similar vein, they established the life cycle of *Schistosoma mansoni*, the causative agent of intestinal schistosomiasis, in their laboratories in the 1970s that is maintained to date.[10] Both activities provided a foundation for later successes in the search for new therapies against these NTDs.

The history of Swiss TPH is full of examples of discoveries in basic research, or the establishment of platforms and technologies that originally had a different purpose than drug development but which were later used for exactly that end. To illustrate this phenomenon, we use the term 'repurposing know-how', defining know-how in the broadest sense.[11,12] While 'know-how' belongs to the realm of basic science, 'repurposing know-how' – in our current article – refers to activities in translational research whose primary aim is not only to yield scientific understanding, but also new medical interventions (*e.g.* drugs, vaccines or diagnostic tests) with a measurable impact on reducing the global burden of disease.

For successful iterative journeys from basic to translational – and indeed implementation – science, research partnerships with institutions in LMICs and the private sector, and an iterative process of laboratory and field studies and circulation of knowledge are key. As far back as 1951, Swiss TPH together with partners from the South helped establishing research and implementation organizations in Tanzania and Côte d'Ivoire, which have developed into renowned centres of excellence pursuing research and education while providing essential health system services for their respective countries.[13–15]

This article presents a selection of case studies which exemplify the transformative power of repurposing know-how in the field of drug discovery and development (Fig. 1). The first case study traces the path from the establishment of the *S. mansoni* life cycle to the search for new antischistosomal drugs and a suitable paediatric formulation. The second case study pertains to gametocytes, the sexual blood-stage forms of the malaria parasite. Researchers at Swiss TPH demonstrated the conditions under which this parasite differentiates into gametocytes. This knowledge allows the production of pure gametocyte populations with high yields, accelerating the discovery and development of new drugs and vaccines against malaria. The third case study goes back in history and traces the long search for a safe and efficacious therapy against HAT. Today, acoziborole, a single-dose treatment is under development as an efficacious and safe drug against HAT, which, some 30 years ago, was still a fatal disease. The drug sparks realistic hopes that the 'elimination of transmission' of the West African form of the disease (gambiense HAT) will be feasible in the future. The fourth case study is again devoted to malaria. It traces the path from malaria modelling at the population level to multi-scale modelling within the human body or assessing the impact of vaccines and drug development. The fifth case study has a different angle: it examines the evolution from vector biology to compound mining of new molecules for the next generation of insecticides and repellents.

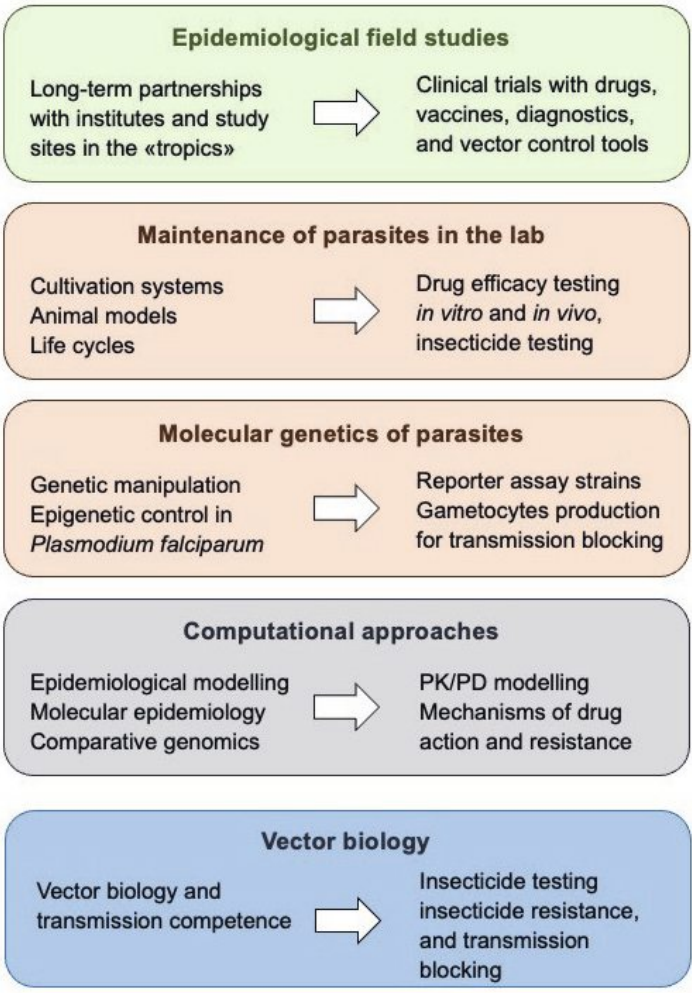

Fig. 1. Selected repurposing know-how case studies at Swiss TPH that are exemplified in this article.

Case Study I: Establishment and Maintenance of *S. mansoni* Life Cycle for Research on Diagnostics and Drug Efficacy Testing *in vivo*

A key expertise of the laboratory of Yvette Endriss at Swiss TPH is the cultivation of living pathogens and their vectors or intermediate hosts to use their complete life cycle for an array of research and development questions.[10,16] This is the case for *S. mansoni*, one of the causative agents of human schistosomiasis (Fig. 2). Schistosomiasis is caused by trematode worms, which belong to the genus *Schistosoma*, of which six species are clinically relevant in humans.[17] Two species, *S. mansoni* and *S. haematobium*, are responsible for the high prevalence and burden of the disease in the African region.[18] Apart from their definitive host (humans), *Schistosoma* species require specific freshwater snails as intermediate hosts to complete their life cycle (*e.g. Biomphalaria* snails act as an intermediate host for *S. mansoni*). The infectious forms of the parasite, called cercariae, hatch from the snails and are released into the water. Humans become infected when their skin comes into contact with contaminated freshwater.

From Research to Diagnostics

At an early stage, Swiss TPH successfully bred different strains of *Biomphalaria* spp. to establish and maintain the life cycle of *S. mansoni* in-house. In the 1970s, this life cycle was mainly used for research purposes and for serological-diagnostics, while Swiss TPH acted as the National Reference Centre for Imported Human Parasitoses in Switzerland. Immunologists at Swiss TPH studied the cellular and humoral immune responses in hamsters

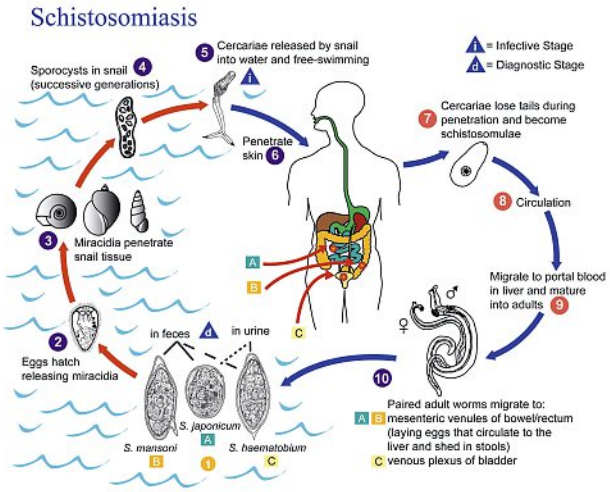

Fig. 2. Life cycle of *Schistosoma* spp. (source: Centres for Disease Control and Prevention).

to soluble egg antigens or evaluated different helminth antigens in enzyme-linked immunosorbent assays (ELISA).[19,20] These research efforts were paralleled and led the way for subsequent field studies in Tanzania,[21,22] Côte d'Ivoire[23,24] and the People's Republic of China to deepen the understanding of the epidemiology and control of schistosomiasis.[25,26]

Drug Efficacy Testing in vivo

In 1975, praziquantel, a pyrazinoisoquinoline, was introduced as a novel anthelminthic (Fig. 3). Due to its high efficacy, low toxicity and ease of administration, it has replaced other antischistosomal agents to become the treatment of choice for a wide range of both veterinary and human trematode and cestode infections, most importantly schistosomiasis.[2,27,28] However, immature schistosomes are not susceptible to praziquantel at the curative dose, and therefore, the first considerable challenge of schistosomiasis chemotherapy is the inefficacy of praziquantel at the initial phase of infection. Moreover, the concern that an overreliance on praziquantel in endemic settings would select for resistance unleashed new efforts in drug development, especially in repurposing existing drugs.[29,30]

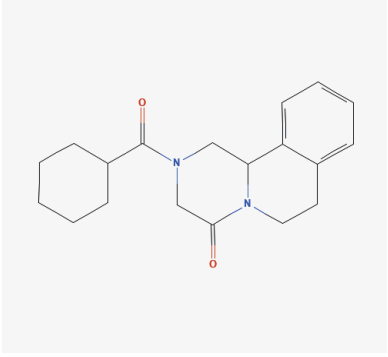

Fig. 3. Praziquantel is the treatment of choice against schistosomiasis. 2-[cyclohexyl-carbonyl]-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-a]isoquinolin-4-one is a member of the isoquinoline group.

Antischistosomal Properties of Antimalarials

As a consequence of the in-house life cycle of *S. mansoni* and long-term research partnerships in endemic settings, Jacques Chollet, Jennifer Keiser and Jürg Utzinger at Swiss TPH entered

the field of drug discovery and development for schistosomiasis during the late 1990s and early 2000s. At the onset of these activities, which, in the meantime, have become a highly productive field of scientific inquiry,[31,32] laboratory and field research at Swiss TPH focused on the antischistosomal properties of many antimalarial compounds. Artesunate and artemether, two semi-synthetic derivatives of the plant-derived peroxide artemisinin, gained particular attention. After the discovery of artemisinin as an effective antimalarial during the 1980s,[33] its antischistosomal properties were identified against the juvenile stages of *S. japonicum* in Chinese laboratories.[34] In a series of *in vivo* studies at Swiss TPH, the activities of artemether against the juvenile stages of *S. mansoni* and *S. haematobium* were confirmed in animal models.[35–37] Once this evidence was established, a series of randomised, placebo-controlled clinical trials were conducted by Swiss TPH and partners in Côte d'Ivoire to confirm the protective efficacy of repeated oral artemether against *S. mansoni* (50%) and *S. haematobium* (25%).[38,39]

A few years later, researchers at Swiss TPH investigated the antischistosomal properties of the antimalarial drug mefloquine, which is structurally related to quinine. Studies at Swiss TPH in a mouse model demonstrated a reduction in *S. mansoni* worm burden of over 90% (at a single dose of 200 mg/kg). To test the clinical relevance of this laboratory finding, a phase II clinical trial was conducted in Côte d'Ivoire, where 38 school-aged children with *S. haematobium* infection were treated with mefloquine and a combination of mefloquine plus artesunate. Cure rates of mefloquine, artesunate, mefloquine-artesunate and praziquantel (treatment of choice; used as a comparator) against *S. haematobium* at day 26 post-treatment were 21%, 25%, 61% and 88%, respectively. Both mefloquine-artesunate and praziquantel showed high egg reduction rates of over 95%.[40]

Developing a Paediatric Formulation of Praziquantel

School-aged children are at the highest risk of schistosomiasis morbidity, spurring interest in preventive chemotherapy for this age group.[41] Treatment of preschool-aged children has been unsatisfactory, and in the absence of a paediatric formulation, crushed praziquantel tablets were administered.[42] Over the past decade, Swiss TPH partnered with Merck and others from academia and the private sector to form the Paediatric Praziquantel Consortium. This consortium aimed to develop an orally dispersible tablet (ODT), to be administered as a single dose tailored to treat preschool-aged children. The new formulation based on (*R*)-praziquantel was shown to be safe and efficacious in a phase II trial in *S. mansoni*- and *S. haematobium*-infected preschool-aged children in Côte d'Ivoire and Kenya.[43]

Case Study II: From Basic Research to the Production of Pure Gametocytes for Antimalarial Drug Screening

Malaria research at Swiss TPH includes aspects along the value chain from innovation to validation and application. Swiss TPH has been conducting malaria research since its inception in 1943. But it was particularly during the 1990s when large-scale malaria research cum-action intervention programmes took shape. Reasons for the expansion of activities during this period were (i) the fundamental understanding of local transmission; (ii) the expansion of research partnerships mainly in malaria-endemic settings; and (iii) building up a coherent research portfolio as key elements for propelling evidence-based malaria elimination efforts as part of national malaria control programmes.[44]

The late 1990s and early 2000s also witnessed the emergence of new funding mechanisms, such as the Global Fund or the Bill & Melinda Gates Foundation to name a few, which, alongside large-scale roll-out of insecticide-treated nets (ITNs) and other mosquito vector control strategies, new drugs for treatment including artemisinin-based combination therapy, and chemoprevention for young children, led to a remarkable decline in malaria cases worldwide during the last two decades till 2020.[45] However, with the funding for malaria control stagnating and newly emerging challenges such as the COVID-19 pandemic and emergence and spread of insecticide and drug resistance, the successes of the past decades are at risk. In 2022, malaria still accounted for an estimated 247 million clinical cases and 619,000 deaths, mainly due to *Plasmodium falciparum* and primarily in sub-Saharan Africa in children under the age of 5 years.[46]

All these efforts did not just target prevention and treatment of the deadly disease, but were also aimed at reducing malaria transmission within the population. While reducing malaria burden and saving lives remains a strong focus, the ultimate goal is malaria elimination and eradication. Continued innovation and discovery of new drugs, vaccines and immunotherapies for malaria will be required to combat malaria. In addition to support the end goal of elimination, drugs and vaccines that block transmission from humans to mosquitoes will be required. A special target for malaria transmission blocking are the gametocytes, the precursors of the sexual gametes of the parasite. As shown in the life cycle (Fig. 4), gametocytes are the only forms of the parasite that are able to infect mosquitoes. This biological bottleneck represents an essential target for future transmission-blocking drugs and vaccines. Today, primaquine and tafenoquine are the only licensed drugs with potent activity against gametocytes, but due to potential adverse events they are of limited use.

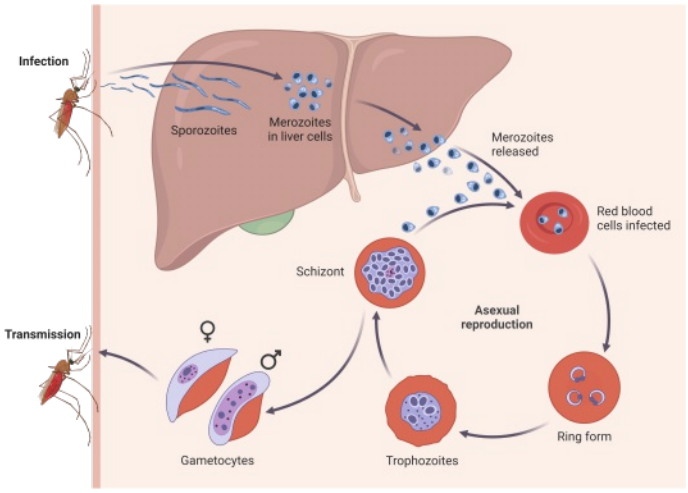

Fig. 4. People become infected with *P. falciparum* when bitten by an infested female *Anopheles* mosquito that injects sporozoites into their skin. After reaching the liver *via* the bloodstream, sporozoites multiply within hepatocytes to release thousands of merozoites into the blood circulation. These merozoites invade the red blood cells and develop through the ring and trophozoite stages into a multinucleated schizont. After complex cell formation, up to 32 merozoites egress from the infected red blood cell to find new red blood cells to replicate. Consecutive rounds of these intraerythrocytic development cycles are causing the common symptoms of the disease (Created with BioRender.com).

Epigenetic Switch and its Drivers

During each replication cycle of malaria, a small proportion (about 1–5%) of parasites receive a sexual commitment signal which makes them differentiate into the sexual form of the parasite, the gametocytes. In 2014, researchers from Till S. Voss' laboratory at Swiss TPH shed light on the molecular mechanisms behind this sexual commitment event. They showed that this process is triggered by an epigenetic switch that activates expression of the master transcription factor AP2-G.[47] Two proteins, HP1 (heterochromatin protein 1) and GDV1 (gametocyte devel-

opment 1) play a key role in this process. The former prevents the production of gametocytes by silencing expression of AP2-G, while the latter activates a molecular switch leading to AP2-G expression and subsequent gametocytogenesis.[47,48]

The transformation from the asexually reproducing and disease-causing blood stages to the transmissible sexual stages does not take place according to a fixed pathway. Researchers at Swiss TPH have helped to demonstrate that the parasite reacts to molecular signals from human blood, with the lipid lysophosphatidylcholine (LysoPC) playing a central role. This molecule helps the parasite to produce new cell membranes, and hence, to reproduce. If the concentration of LysoPC in the blood falls, which is often the case with infectious diseases, the parasites respond with increased gametocyte production. LysoPC, therefore, seems to serve as an indicator for the parasite to regulate the rate at which gametocytes are produced and thus ensuring transmission from person to mosquito.[49]

Potential for Drug Development

When research on the process of sexual commitment and differentiation of malaria parasites took off in 2014 at Swiss TPH, scientists did not necessarily think of having an impact on malaria drug discovery and development. However, thanks to the new understanding of the molecular mechanisms that trigger gametocyte differentiation, and facilitated by the development of inducible gene expression systems, it is now possible for Swiss TPH laboratories to produce *in vitro* pure gametocytes in sufficiently high numbers for high-throughput screening.[50] Moreover, through the introduction of reporter genes expressed by the gametocytes, they can be monitored based on fluorescence or bioluminescence readouts. This greatly facilitates the discovery and validation of drugs or vaccines that act specifically against this infectious stage of the parasite. This platform will now enable the search for molecules with potent activity against gametocytes and catalyse the discovery and development of transmission-blocking drugs and vaccines.

Case Study III: The Long Road towards an Effective Drug against HAT

On June 7–9, 2023, global experts in NTDs met at the 'Fifth WHO Stakeholders Meeting on Human African Trypanosomiasis Elimination'. The meeting concluded that "an outstanding reduction in the number of HAT cases was achieved, reaching the global threshold targeted for the elimination of HAT as a public health problem." However, some countries are lagging behind, and HAT remains a public health problem within their borders.

HAT is caused by the parasite *Trypanosoma brucei* and is transmitted by an infectious bite of the tsetse fly. It is a fatal disease and has resulted in the death of millions in Central and Western Africa (*T. brucei gambiense*) as well as Eastern Africa (*T. brucei rhodesiense*) and dwindling economic development. In the last decades, progress in the field of research and control of HAT has been substantial; safer and more effective drugs have made the goal of elimination more realistic than ever, which is how participants of the recent WHO meeting considered HAT, formerly a scourge, no longer a serious public health problem.

Swiss TPH has a long history of drug screening and discovery against HAT. Already in the 1940s, the Institute pioneered the maintenance of tsetse flies in its laboratory in Basel – paving the way for a fascinating research journey, connecting laboratory and field studies, setting up and managing clinical research trials in endemic settings as well as compound mining efforts. Consequently, engaging in research and building partnerships with Trypanosomiasis Research Organizations in East-Africa and later in the Democratic Republic of the Congo (DRC), has been at the heart of Swiss TPH's renowned global efforts to control NTDs. In this case study, repurposing know-how represents two different forms and models of repurposing. First, is the actual repurposing and recombination of existing drugs for a safer and more efficient therapy of HAT. Second, is similar to a global learning curve; concepts and models that were exchanged in international fora thus travelled from one research body or clinical trial site to another. This transmission of knowledge was clearly observed in the processes of setting up clinical trials according to good clinical practice (GCP) principles and international ethics standards for HAT clinical trials. GCP principles set up for the HAT trials in DRC were then also applied in other various African settings.

Laboratory and Field Itineraries: in vitro *Cultivation of Trypanosomes and East African Partners*

The rearing of tsetse flies in the laboratory shortly after Swiss TPH's beginnings in 1943 laid the foundation for the Institute's scientific inquiry of HAT[51] and other NTDs more generally. Later, in the early 1980s, Reto Brun and his team at Swiss TPH successfully achieved the long-term *in vitro* cultivation of the blood stages of trypanosomes by introducing new feeder cells and rabbit serum to the culture medium.[9] In 1986, a research group led by Leo Jenni discovered that the pathogens 'mate' in the tsetse fly, they undergo sexual recombination and produce new genotypes.[52] These laboratory findings have been accompanied by research in the field. The work on HAT – from basic science at Swiss TPH's headquarters to the epidemiology and control with partners in disease-endemic countries – is a prime example of how innovation in the laboratory and field studies are closely intertwined. As early as the 1950s, Rudolf Geigy, the founder of Swiss TPH, roamed vast plains of East Africa in order to better understand the behaviour of tsetse flies in the wild. He and his team isolated *Trypanosoma* strains and made them available to other research groups.[51]

After the colonial powers had withdrawn from Africa, local research institutions emerged to study and control HAT. This was the case in Uganda (Uganda Trypanosomiasis Research Organization, UTRO), Kenya (Trypanosomiasis Research Institute, KETRI), Nigeria (Nigerian Institute for Trypanosomiasis Research, NITR) and Côte d'Ivoire (Projet de Recherches Cliniques sur la THA).[53] Swiss TPH worked closely with these institutions. In particular, together with organisations in Uganda and Kenya, Swiss TPH was instrumental in founding the 'Eastern Africa Network for Trypanosomiasis' (EANETT), which focused on establishing surveillance-response mechanisms, the exchange between the emerging research organisations, and the training of a new generation of African scholars.

Hazardous Treatment

The 1990s witnessed not only stronger efforts in HAT drug development, but also a series of crucial clinical trials in Angola and DRC to improve the therapeutic regimen. HAT is not an easy disease to treat. For centuries, anyone who received an infectious bite by a tsetse fly had little chance of surviving. *Trypanosoma brucei* would migrate into the blood vessels and multiply rapidly. They would break through the blood-brain barrier, making their way into the nervous system and causing sleep and neurological disorders. The infection is generally fatal if left untreated. Between 1896 and 1906, an estimated 700,000 people in the Congo Basin and Uganda fell victim to a sleeping sickness epidemic. The French and British colonial governments took different approaches to contain the sporadic epidemics. While the British concentrated on vector control and environmental management, the French reached out to mass-treat the population with mobile teams, which was called 'lomidinisation' or 'pentaminisation'.[54] The drugs available were potentially harmful and none was able to cure the late stage in the central nervous system. Using trypanosomes as a model to screen molecules to treat syphilis in 1905, Paul Ehrlich discovered the first organo-arsenic compound Atoxyl. Although the name of Atoxyl meant 'non-toxic' the drug

caused severe adverse drug reactions, particularly affecting the optic nerve.[55] The experience with tryparsamide (1919) was not much more pleasant. In 1930, a French colonel doctor in Cameroon reported his intention to accelerate the therapy of his patients. To this end, he gave them double the dose of tryparsamide, which ended in disaster: two days after the treatment, all 800 patients had gone blind. This condition motivated the Swiss chemist and physician, Dr. Ernst Friedheim to explore alternative therapies. He synthesised the drug melarsoprol in 1948, which remained the standard therapy for the second stage of HAT for decades. Drug development against NTDs was non-existent in the 50 years after the Second World War. The pharmaceutical companies were too reluctant to invest in this costly and lengthy process for a disease only affecting the poorest parts of sub-Saharan Africa without a viable market.

Improved Regimen of Melarsoprol

An important step in the improvement of HAT chemotherapy was taken by researchers at Swiss TPH and their partners. At KETRI, Christian Burri studied the pharmacokinetics (PK) of melarsoprol. Based on these data and with financial support from the East Africa Section of the Swiss Agency for Development and Cooperation (SDC), Swiss TPH launched the IMPAMEL programme (IMProved Application of MELarsoprol) in civil war-torn Angola, a phase III trial that enrolled 500 individuals to shorten the treatment regimen of melarsoprol from 25–36 days to 10 days. The abridged schedule was further tested in an implementation study in over 2,000 patients with late-stage HAT at 16 centres in 7 African countries.[55] This new treatment regimen was subsequently recommended by WHO. Whereas the new regimen had major socio-economic advantages, the disappointment was that the frequency of the worst adverse drug reaction, the encephalopathic syndrome, continued to occur in 5–10% of patients treated, still resulting in death in 10–50% of those with encephalopathy.[56] Hence, it was concluded that, while IMPAMEL may not have been a breakthrough towards a new treatment against second-stage HAT, it remained a milestone in public health as it comprised the first large-scale clinical trial on this disease executed according to GCP. The trial demonstrated the feasibility of modern clinical development for NTDs even under the challenging conditions in countries of Central Africa.

PPPs and the Prospect of HAT Elimination

At the beginning of the new millennium, there was a unique momentum in drug development for HAT, other NTDs and malaria. While the prospect of eliminating HAT was still a long way off, the dimension and fatality of the disease was increasingly recognised by a wide range of actors in endemic settings and on a global scale. The 36th Ordinary Summit of the African Heads of State and Government in 2023, held in Lome, Togo, made HAT a top priority for development efforts in their countries, emphasising the importance of surveillance-and-response mechanisms in endemic areas, as well as the availability of treatment and the implementation of operational research programmes. In 2001, Aventis Pharma (now Sanofi) and WHO signed a 5-year agreement which continues to date and includes financial support for control and research programmes as well as the donation of the key antitrypanosomal drugs pentamidine, melarsoprol and eflornithine. A similar contract was signed with Bayer for suramin and later for nifurtimox. Another key step towards elimination was the establishment of the first generation of public-private partnerships (PPPs), new forms of collaboration between the pharmaceutical industry, academia and new private donors such as the Bill & Melinda Gates Foundation. In 2003, in the wake of the award of the Nobel Prize to Médecins sans Frontières (MSF), the Drugs for Neglected Disease *initiative* (DND*i*) was launched. Swiss TPH and DND*i* have been working closely together over the past 20 years. The overarching goal is to revive research and development of new drugs against NTDs. In the beginning, DND*i* focused primarily on trypanosomatid diseases (*i.e.* HAT, leishmaniasis and Chagas disease). Later, HIV, tuberculosis and hepatitis C were to be added to the portfolio. Former Swiss TPH Director, Marcel Tanner chaired the DND*i* Board from 2007 to 2017 and was key in the development of a coherent portfolio and value chain from innovation to validation and application.

Drug Repurposing and New Combination Therapies

In addition to drug repurposing, finding new drugs was an important approach of DND*i* to treat HAT. Supported by DND*i*, MSF started studies on the combination of eflornithine (Sanofi), nifurtimox (Bayer) and melarsoprol (Sanofi) in 2004. Eflornithine had originally been developed by scientists at the Merrell International Research Centre in Strasbourg in 1980 against breast cancer, it soon revealed its toxic effect against trypanosomes.[57] The logistics of eflornithine were extremely challenging since its chemistry makes it costly to synthetize, and the 56 infusions over 14 days that constituted full treatment made eflornithine too expensive for the National Sleeping Sickness programmes. Still, the drug was widely used by non-governmental organisations like MSF. Eflornithine was called the 'resurrection drug' as for the first time treatment was possible without the severe adverse drug reactions of melarsoprol, and the case fatality could be reduced by 90%. Therefore, even though the development of eflornithine against cancer was abandoned, it became a beacon of hope in the fight against sleeping sickness until the Merrell International Research Centre decided to stop its production in the course of several waves of mergers. When eflornithine was brought back to the market against hirsutism (*i.e.* excessive facial hair growth in women) under the brand name Vaniqa® (Bristol-Myers Squibb), it was integrated into the HAT support programme with Sanofi. Together with Sanofi and Bayer, DND*i* started clinical trials with the combination therapy nifurtimox-eflornithine (NECT). Based on the Congo network established through Swiss TPH and the IMPAMEL programme that had tested a short-course of melarsoprol, a multiple-centre trial, conducted in the Republic of Congo and DRC, compared NECT with standard eflornithine therapy. It showed that in combination with nifurtimox, the number of eflornithine infusions could be reduced from 56 to 14, reducing the total dose of eflornithine by half while shortening hospitalization time by one-third. While NECT is a milestone, the complexity of its application and spectrum of activity still restricts its use to the second stage of gambiense HAT. Hence, NECT did not provide much relief for the poorest of the poor living in remote villages in endemic settings without access to adequate health services. The only solution for them would be an orally administered drug.

Fexinidazole – A Leap Forward in the Treatment of HAT

In 2005, DND*i* launched a major compound mining effort to test nitroimidazoles and related compounds against trypanosomatid parasites. One out of over 800 compounds screened at Swiss TPH in the laboratory of Reto Brun and Marcel Kaiser, was fexinidazole (Fig. 5). The compound proved to be orally available and active against both *T. b. gambiense* and *T. b. rhodesiense* in animal studies, and it had a good safety profile. Fexinidazole had the advantage that it could be administered orally during a 10-day course to children as well as adults and was active against both stages of the disease.[58] Fexinidazole is actually a story of a rediscovery. The German chemist Heinz Hänel who worked as a student trainee at the then Hoechst AG (today: Sanofi-Aventis) in the 1970s already described the good effect of fexinidazole (HOE 239) against *T. brucei* at that time (personal communication). However, this finding was not further pursued. In 1980, the board of Hoechst AG decided to abandon research on NTDs and Heinz Hänel turned to other activities. It was not until an article pub-

lished together with Wolfgang Raether in 2003, in which he once again referred to fexinidazole's potential, that Bernadette Bourdin of DND*i* became aware of it.[59,60] The promising pre-clinical performance of fexinidazole led to a new agreement between Sanofi and DND*i* for further development of fexinidazole in 2009. While DND*i* was responsible for preclinical, clinical and pharmaceutical development, Sanofi ensured the industrialisation, production, registration and distribution of the drug. The crucial clinical trials were conducted at 10 sites in DRC and Central African Republic, led by African investigators and drawing extensively on the support from Swiss TPH and the Société Française et Francophone d'Éthique Médicale (SFFEM) to be in accordance with the highest international standards in ethics and GCP.[61] In 2018, fexinidazole received a positive scientific opinion from the European Medicines Agency (EMA) for treatment of gambiense HAT and was approved by the drug regulatory authority in DRC and added to the WHO Model List of Essential Medicines in 2019. The 10-day fexinidazole treatment is still quite long, and the drug is not approved for children under the age of 6 years. Moreover, a lumbar puncture is still necessary for patients with observed neurological abnormalities for potential referral to treatment with NECT if the white blood cell count in the cerebrospinal fluid is above 100 per µl. Currently, fexinidazole is also undergoing assessment against the East African form of HAT (*T. b. rhodesiense*) in the legitimate hope to eventually replace melarsoprol as the first-line treatment.

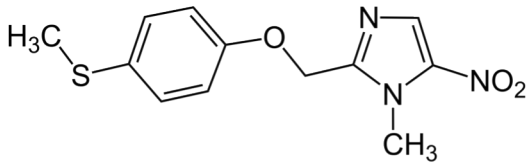

Fig. 5. Fexinidazol® (1-methyl-2-{[4-(methylthio)phenoxy]methyl}-5-nitro-1H-imidazole).

Acoziborole – A Single Oral Dose against HAT

Fexinidazole has been a huge success in treating HAT and providing optimism for the goal of elimination. However, a new oral treatment was considered necessary to further simplify treatment of both stages without the need of lumbar puncture for staging of the disease. Acoziborole (SCYX-7158), a compound from the benzoxaborole class of active substances, was included in DND*i*'s lead optimisation programme in 2007, in collaboration with Anacor, SCYNEXIS and Swiss TPH who demonstrated its efficacy.[62,63] Acoziborole has the unique advantage to be effective as a single-dose treatment against gambiense HAT. Its excellent *in vitro* activity against *T. brucei* spp., outstanding physicochemical properties and reassuring safety profile allowed for a first-in-man study in 2012.[64] Ten years later, the results of the phase II and phase III trials in adult patients led to the conclusion that acoziborole's high efficacy and favourable safety profile holds promise in the efforts to reach the WHO goal of interrupting HAT transmission by 2030. At the same time, paediatric clinical trials for children diagnosed with gambiense HAT were initiated. While fexinidazole as the first oral treatment was a true game-changer for sleeping sickness, acoziborole has the potential to become the first single-dose treatment for HAT, helping to achieve the global elimination goal.

Case Study IV: From Computational Modelling to Multi-scale Modelling for Drug Development

Malaria modelling has a long history. It was Ronald Ross who formulated a powerful model for malaria transmission in 1911, postulating the thesis of a 'critical mosquito density' below which the malaria parasite becomes extinct.[66] Translated into practice, this meant that it is not necessary to eliminate the mosquitoes but is sufficient to reduce them below a certain threshold to be able to stop malaria transmission. Ross' model and its further development by George Macdonald, who showed that killing adult mosquitoes (such as by the use of insecticides) has a stronger impact on reducing malaria than killing larval stages, formed the mathematical foundation of the Global Malaria Eradication Programme (GMEP). Ross' and Macdonald's models and other models of the 20th century necessarily made simplifications of a complex disease. The models did not account for seasonal fluctuations in malaria cases (*i.e.* rainy season and temperature), the movement of people and mosquitoes, the status of naturally acquired immunity in people, or other significant heterogeneities or infection in mosquitoes.[67] While some models included immunity, *e.g.*, as an important component in the WHO's Garki model based on data from Nigeria,[68] these models did not capture the details of parasite dynamics within humans and accurately represent the acquisition of immunity.

In 1992, Swiss TPH with partners from Tanzania, Spain and the United Kingdom evaluated the first ever malaria vaccine in Africa.[65] This commitment to malaria research required investments in the area of prediction and mathematical modelling. After the evaluation of the first malaria vaccine, a series of large-scale malaria intervention trials were initiated by Swiss TPH, including studies on the effect of iron supplementation on the course of malaria;[69] the world's first trial of intermittent preventive treatment of malaria in infants,[70] and evaluation of ITNs.[71] Broadening the tool box of new malaria prevention, prophylaxis and treatment required more sophisticated malaria models. Consequently, at the turn of the millennium, Swiss TPH experts in statistics and mathematical modelling, alongside partners, embarked on developing a new simulation model using real-world data to address the missing malaria model functionality previously highlighted. While originally purposed for estimating the potential impact and cost-effectiveness of malaria vaccines[72,73] their efforts, led by Thomas Smith and more recently by Melissa A. Penny and Nakul Chitnis, resulted in a large-scale, individual-based simulation model of malaria transmission, OpenMalaria, which is now in its 45th release.[74] The model not only examines the relationship between mosquitoes and disease, but also how vaccines, drugs and vector control interventions could reduce burden, and how their effectiveness changes with drug and insecticide resistance.

Multi-scale Modelling

The broad knowledge of modelling in malaria research and other infectious diseases of poverty also found its way into drug development a few years ago, especially in PK and pharmacodynamics (PD). From the knowledge of what happens to an active ingredient once it is in the human body and how it affects the parasite, basic models may also be developed for drug development. These models are of fundamental importance for the development of new drug therapies since they allow for assessing the impact of different regimens *in silico* at both the population and individual level, including in children, in whom malaria may result in severe disease and death.[75] By predicting concentration and toxicity profiles due to sophisticated statistical tools, Swiss TPH researchers are today able to use PK and PD models to develop rational dosing schemes by predicting concentration and toxicity profiles and to evaluate the appropriate dosing even in high-risk groups such as children. Children do not only differ from adults with regards to body weight but also in the maturation of certain enzymes, in the function and expression of receptors that determine PD, the variability in regional blood flow, organ perfusion or the permeability of cell membranes to mention just a few. Recent contributions of Swiss TPH include studies which improve the curative dosing of anthelminthic treatment efficacy,[76] antimalar-

ial drugs against *P. falciparum* such as piperaquine[77] and amodiaquine-artemisinin drug combinations.[75]

Modelling NTDs

It is within the context of mathematical modelling in malaria that Swiss TPH has built the capacity for work that has culminated in simulation models of other NTDs, including rabies, lymphatic filariasis, opisthorchiasis and HAT – an excellent example of how skills in one domain are repurposed for innovation in another. In 2021, under the leadership of Nakul Chitnis, Swiss TPH analysed the potential impact of the introduction of fexinidazole on the incidence of HAT and its potential elimination. As described earlier, the ease of administration and diagnostic process for fexinidazole is likely to improve access to care for HAT patients but may lead to reduced adherence since treatment is no longer conducted in the hospital. In response to a request by the WHO HAT team, analysis by the Swiss TPH showed that there is a small probability that reduced compliance could lead to higher incidence, and that maintaining adherence in stage I patients is crucially important. However, increases in access to care can mitigate the effects of reduced adherence.

Economics and Modelling Malaria and NTDs

Alongside mathematical modelling, economic analysis is an important component for policy recommendations[67] and for assessing and implementing new interventions against malaria and NTDs. Alongside Thomas Smith and Melissa A. Penny, Fabrizio Tediosi and, later, Katya Galactionova supported economic analysis for malaria intervention assessments that grew out of OpenMalaria models. Initially focusing on answering questions about the cost-effectiveness of new malaria vaccines by attaching costs to simulation outputs.[78.79] Swiss TPH and collaborators from three other modelling groups supported policy and funding decisions for RTS,S, the world's first malaria vaccine. Economic analysis at the Institute also moved towards costing of intervention and strategy implementation[80] and assessing malaria intervention combinations.[81]

Just like malaria modelling gave way to modelling of NTDs and COVID-19, model-based cost-effectiveness analyses of malaria gave way to collaborations on the investment cases to eliminate NTDs – specifically gambiense HAT, lymphatic filariasis and onchocerciasis. These elimination investment cases encompassed not only cost-effectiveness,[82] but pushed the envelope to grapple with questions that are relevant to elimination efforts and disease of the poor: the additional justice-based benefits of elimination,[83] savings to the poorest individuals[83] and quantifying the uncertainties in elimination and its additional benefits.[84] These studies yielded insights that are not only useful for the disease communities involved, but also to expand the analytical toolbox available to researchers of all diseases. Upcoming collaborations across the clinical, service and research arms of Swiss TPH and its network of partners pave the road to the use of these frameworks in tuberculosis and helminth infections.

Case Study V: From Vector Biology to Developing New Molecules for Insecticides and Repellents

Tsetse flies, ticks and mosquitoes: since its foundation, Swiss TPH has had specialised rearing facilities for a wide range of disease vectors in its laboratories. The control of tropical diseases required in-depth behavioural studies of the vectors. The successful attempt to bring live tsetse flies to Basel was already mentioned above.[85] During the Second World War, Rudolf Geigy and his students also devoted themselves intensively to the study of the spread of malaria in Switzerland.[86] In the '*Anopheles* station' established at Swiss TPH in July 1944, two species common to Switzerland, *Anopheles maculipennis* and *An. claviger* (= *An. bifurcatus*) and fed on malaria-infected soldiers cared for at Swiss TPH at the end of the Second World War. It was shown that 9% of the laboratory-reared *Anopheles* could be infected, rejecting the hypothesis that the disappearance of malaria in Switzerland was linked to immunity in the malaria vectors.[87] Subsequently, this work led to first transmission-blocking experiments, carried out by feeding mosquitoes with new compounds and testing their effect on malaria parasites. Entomology was an important research branch at Swiss TPH throughout the 1950s as well. Research groups experimented with human scent that might be attractive to the yellow fever mosquito, *Aedes aegypti*.[88] Others were testing repellents with which *Ae. aegypti* could be kept away.[89]

Resistance Development as a Serious Public Health Threat

With the advent of molecular biology, organismic biology at Swiss TPH was somewhat sidestepped. The study of molecular mechanisms dominated the research agenda and shifted the focus away from behavioural studies. It was only in the last 20 years that behavioural studies, and medical entomology as a whole, have regained interest. Key drivers that sparked a renewed interest were the requirement for the development of new vector control tools together with increased funding for malaria vector control.

No new insecticides were developed over decades due to the lack of investment in vector control. Therefore, due to the heavy use of a single class of insecticides (*i.e.* pyrethroids), the mosquitoes are now strongly resistant to neurotoxic insecticides throughout most malaria endemic areas, threatening the success of interventions using ITNs and indoor residual spraying that still constitute the cornerstone of malaria control today.

New Molecules for Insecticides and Repellents

Today, the specialised facilities for medical entomology at the new headquarters of Swiss TPH in Allschwil allow researchers such as Pie Müller and his team to screen new compounds at high throughput, test new concepts and study how vectors interact with those molecules and their formulations to better understand their behavioural mode of action (Fig. 6). One of the insecticides currently under study at Swiss TPH is chlorfenapyr. Chlorfenapyr is a pyrrole, a new insecticide class in public health that has been repurposed from agriculture. It is a protoxin that has an entirely different mode of action as compared to the other available insecticides that primarily act as neurotoxins. Chlorfenapyr is converted to tralopyril in mitochondria which affects the production of adenosine triphosphate, leading to cell death and eventually killing the mosquito. This mechanism substantially reduces the likelihood of cross-resistance in mosquitoes that are resistant to the currently used neurotoxins. Intriguingly, at a sub-lethal dose, chlorfenapyr-exposed mosquitoes are less likely to become infected with malaria parasites, suggesting that the molecule may have additional beneficial effects contributing to malaria transmission blocking. Consideration of the behavioural and sub-lethal effects of volatile pyrethroids on mosquitoes[90] has also led to the development of a number of highly effective long-lasting spatial repellents[91] that may provide effective protection against disease especially for vulnerable refugee and mobile populations.

The 'Golden Triangle': Swiss TPH, Ifakara Health Institute and Centre Suisse de Recherches Scientifiques en Côte d'Ivoire

Understanding the disease vectors as well as developing new repellents and insecticides, and other vector control tools, would be unthinkable without intense collaboration with research organizations in disease-endemic countries (Figs. 7 and 8). The Ifakara Health Institute (IHI) in Tanzania and the Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS) are renowned centres of entomological research in sub-Saharan Africa. In June 2021 and June 2023 IHI and CSRS, respectively, were both cer-

Fig. 6. Arm-in-cage test combined with 3D-video tracking at the laboratories of Swiss TPH in Allschwil measuring how mosquitoes interact with topical repellents. Photo credit: Joachim Pelikan, Swiss TPH.

tified in good laboratory practice (GLP) by the South African National Accreditation System (SANAS) for their expertise in testing new vector control products for industry, product development partnerships and generating data for regulatory submissions. Together with Swiss TPH and often supported by the Integrated Vector Control Consortium (IVCC) and the Bill & Melinda Gates Foundation, IHI and CSRS researchers such as Sarah Moore and her team based at IHI collaborate to test new repurposed molecules such as chlorfenapyr, clothianidin, pirimiphos-methyl and pyriproxyfen under field and operational conditions.[92–94]

Fig. 7. An IHI researcher measures the effects of interventions blocking malaria from completing its life cycle in the mosquito. Photo credit: Olivier Brandenberg, Switzerland.

Fig. 8. Experimental huts are used for the evaluation of vector control products under controlled conditions that resemble those in which mosquitoes enter a human habitation and interact with the product in normal use. Photo credit: Ifakara Health Institute, Tanzania

Conclusions

The selection of case studies collated in this article shows how different knowledge systems, once established at Swiss TPH, were later utilised or repurposed for drug and insecticide discovery and development against malaria and various NTDs. In an early phase of the Institute's history, the focus was not necessarily on new solutions for neglected populations but on establishing and maintaining entire exotic life cycles leveraged for deeper biological insights and developing new platforms and technologies. Since the new millennium, with a focus on innovation and validation, Swiss TPH has grown into a global player in the field of drug discovery and development with a particular focus on poverty-related infectious diseases. Several key factors support this success, including new forms of partnerships – PPPs and product development partnerships[95] – and long-lasting connections with African partner institutions such as IHI in Tanzania and CSRS in Côte d'Ivoire.[96] The success of research and development of new drugs and tools in recent years at Swiss TPH has led to important contributions in the fight against malaria and NTDs with the examples of HAT and schistosomiasis as cases in point. For example, HAT was for a long time a neglected scourge of Africa, periodically spreading like a shadow over the continent. The therapy was potentially dangerous for the patient, and the interest of pharmaceutical companies was non-existent for a long time. The progress from the dangerous and cumbersome melarsoprol treatment to oral therapies with fexinidazole or acoziborole is indeed remarkable, especially as it has transpired over only 25 years after half a century of little therapeutic development. Thanks to continuous control efforts, the number of new HAT cases has been reduced by 97% in the past 20 years. This is a huge success and contributes to an increased quality of life for neglected populations in sub-Saharan Africa and a better performance of entire economies. But this success also has its dangers. First, the more HAT is pushed out of the public awareness, the less financial support will become available to quickly react to disease outbreaks. History in general, and the history of HAT in particular, is full of examples of 'donor fatigue' leading to re-emerging pathogens. Second, the younger generation of physicians lacks firsthand experience with the disease. As a consequence, knowledge is becoming increasingly theoretical and, therefore, the disease is pushed further to the edge of public awareness. Drug discovery and development has no expiration date for existing diseases, but must be maintained as a continuous process, to avoid knowledge loss or a lack of candidate pipelines should resistance or evolution of pathogens render disease more severe. Drug discovery and development thus requires continued commitment to research, funding, motivation and innovation. Demonstrating commitment to new and improved drugs and being prepared for re-emergence or drug resistance, on June 30, 2023 Swiss TPH researchers together with colleagues from Novartis and the University of Glasgow have published a new class of compounds, called cynanotriazoles, that show effective inhibition in the growth of trypanosomes, raising hopes for new and improved treatments for HAT or Chagas disease.[5] While we illustrated our final points here on HAT, they apply to malaria and all NTDs.

Here, we write about the repurposing of know-how to create valuable knowledge platforms that have resulted in the translation of innovations of molecules to effective therapies and control tools against some of the most insidious diseases. In addition to the continued effort towards next-generation therapies, future ef-

forts must also aim at improving the socio-economic status of neglected populations in disease-endemic areas. Swiss TPH remains committed to the health and well-being of neglected populations, living in resource-constrained settings in LMICs, by working with African researchers who will pave the way for the future economic and social development of the communities they serve.

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