Special Report
Special Focus Issue: Schistosomiasis

Future Medicinal Chemistry

Repurposing pharma assets: an accelerated mechanism for strengthening the schistosomiasis drug development pipeline

Roopa Ramamoorthi[1], Katy M Graef[1] & Jennifer Dent*,[1]
[1]BIO Ventures for Global Health, 401 Terry Avenue North, Seattle, WA 98109, USA
*Author for correspondence:
Tel.: +1 206 732 2131
jdent@bvgh.org

Schistosomiasis, one of 17 diseases deemed to be neglected by the World Health Organization, has received little attention from the biopharmaceutical industry. Due to this, only a handful of drugs have been developed to treat schistosomiasis, with only one, praziquantel, used in most endemic regions. Growing concern over resistance coupled with praziquantel's incomplete efficacy across all stages of the *Schistosoma* platyhelminth life cycle highlights the urgent need for new drugs. The WIPO Re:Search consortium is a platform whereupon biopharmaceutical company compounds are being repurposed to efficiently and cost-effectively develop new drugs for neglected diseases such as schistosomiasis. This article summarizes recent clinical-stage efforts to identify new antischistosomals and highlights biopharmaceutical company compounds with potential for repurposing to treat schistosomiasis.

Schistosomiasis (also known as snail fever or bilharzia) is a disease caused by parasitic flatworms of the genus *Schistosoma*, predominantly *Schistosoma mansoni, S. haematobium* and *S. japonicum*. The disease has exacted a toll on individuals living in tropical and subtropical regions for millennia [1]. Today schistosomiasis continues to affect millions of people worldwide [2], resulting in pain, diarrhea, weakness and hepatosplenomegaly, as well as anemia and stunting in children. *S. haematobium* infection is additionally associated with bladder carcinomas [3] and increased susceptibility to HIV infection [4–6]. No vaccine for schistosomiasis exists and the short-term prospect for a vaccine is poor. Only two vaccines have undergone clinical trials in the past decade [7], with a third trial recently filed [8]. Schistosomiasis control measures thus rely predominantly on the World Health Organization recommended antischistosomal drug, praziquantel.

Praziquantel is the gold standard for treatment of schistosomiasis and is routinely administered via mass drug administrations in hyperendemic regions [9]. The producer and manufacturer of praziquantel, Merck KGaA, has committed to donating, by 2016, 250 million tablets annually for these mass drug administrations until the disease is eliminated from Africa [10]. Praziquantel has robust efficacy against adult schistosomes [11], yet it also has a number of limitations. These limitations include minimal activity against the juvenile helminths and the pathology-inducing *Schistosoma* eggs [12,13] and its contraindication in pediatric patients. The Pediatric Praziquantel Consortium, a public–private partnership established in 2012, is reformulating praziquantel for use in young children [14]. However, reduced praziquantel susceptibility in field isolates and successful induction of resistance in *S. mansoni* and *S. japonicum* in laboratory settings highlights the need for the expedient development of alternative antischistosomals with novel molecular targets [15]. In addition to the requirement of a novel molecular target, a new antischistosomal should ideally be active against both mature and immature forms (including eggs) of the helminth, require a short treatment course, be stable under tropical

FUTURE SCIENCE part of fsg

conditions and be active against all relevant species of *Schistosoma* [16].

Drug repurposing for schistosomiasis

Seven registered clinical trials studying alternative schistosomiasis drug candidates have been completed in the past decade (Table 1). Four of the five trials with published results obtained moderate efficacy (cure rates of 21–75%) against at least one *Schistosoma* species [17–20]. Interestingly, six of the seven trials investigated the antischistosomal activity of a drug originally developed for a different neglected disease; mefloquine, lumefantrine, artesunate, sulfamethoxypyrazine and pyrimethamine are antimalarials, whereas albendazole is an anthelmintic used to treat soil-transmitted helminthiases and filarial diseases [21]. These clinical trials are part of a growing global trend of repurposing old drugs toward new indications.

Because repurposing (or repositioning) eliminates the risk, cost and time associated with *de novo* product development, it has been a consistently used means of developing drugs for neglected diseases. For example, a recent analysis revealed that of the 29 drugs developed and approved during 2000–2011 for a neglected disease, only four were new chemical entities [32]. The remaining 25 were new formulations of old drugs, fixed-dose combinations or old drugs approved for new indications. Given the lengthy time required to develop a drug [33,34], the high failure rate of clinical trial-stage drugs, the paucity of schistosomiasis drugs in clinical development, the potential for praziquantel resistance and the toll schistosomiasis continues to exact annually, repositioning drugs for schistosomiasis is an ideal approach.

In contrast to broad phenotypic screens of large-scale compound libraries, which are largely target-agnostic, drug repurposing is usually a narrower approach that relies on the identification of a druggable target or prior scientific evidence. The aforementioned clinical trials (Table 1, rows 1–4 and 6) were undertaken due to data from antimalarial clinical trials that noted test subjects' ancillary cure of schistosomiasis [35,36]. Prior *in vitro* and *in vivo* screens that assessed antimalarial drugs against adult and juvenile schistosomes also indicated the drugs' efficacies alone and in combination with praziquantel [37–40]. These laboratory studies overwhelmingly demonstrated the activities of antimalarial drugs against the juvenile (artemether) or both juvenile and adult (mefloquine) schistosomes – an ideal effect of a schistosomiasis therapy [31].

Drug repurposing for schistosomiasis is not limited to antimalarials and other drugs approved for the treatment of other neglected tropical diseases (NTDs). Drugs and lead candidates in development to treat noncommunicable diseases are also of relevance. Numerous druggable targets have been identified in schistosomes [41] including HMG-CoA reductase (SmHMGR) [42], a voltage-gated calcium channel ($SmCa_v\beta_{var}$) [43], a histone deacetylase (HDAC) (SmHDAC8) [44] and protein kinase B/Akt (SmAkt) [45]. The human homologs of these proteins are the targets of drugs for cardiovascular disease [46], hypertension [47] or cancer (HDAC and Akt) [48,49], respectively. A review of the 20 companies listed in the *2014 Access to Medicine Index* [50] revealed that these companies alone have 7 HMG-CoA reductase inhibitors, 15 calcium ion channel blockers, 5 HDAC inhibitors and 8 Akt protein kinase inhibitors on the market or in development (Table 2). All of these products could theoretically be repurposed to treat schistosomiasis.

Key terms

Drug repurposing: Practice of applying a compound originally developed for one indication to an alternate indication.

HMG-CoA reductase: Rate-limiting enzyme in the metabolic pathway responsible for cholesterol synthesis. Inhibition of the enzyme through the use of statins reduces serum cholesterol concentrations, which lowers the risk for cardiovascular disease

World Intellectual Property Organization: United Nations agency established to promote the use of an international intellectual property platform to stimulate innovation and creativity.

WIPO Re:Search

Drug development is an iterative process that results in the production of large sets of target class-specific inhibitors, in addition to the final, marketed product. These sets contain compounds that interact with a human target molecule to varying degrees and thus may include compounds that are more selective toward the homologous target of another species, such as *Schistosoma* spp., than toward the human target. An open-source approach that facilitates neglected disease researchers' access to these sets is imperative if these compounds are to be screened and repurposed as antischistosomal drugs.

In 2011, the World Intellectual Property Organization (WIPO, Switzerland), BIO Ventures for Global Health (BVGH) (WA, USA), and eight leading biopharmaceutical companies (Alnylam [MA, USA], AstraZeneca [UK], Eisai [Japan], GlaxoSmithKline [UK], MSD [NJ, USA; [53]], Novartis [Switzerland], Pfizer [NY, USA], and Sanofi [France]) established

Table 1. Schistosomiasis drug clinical trials performed within the past decade.

Drug(s) examined (dose)	Year initiated	Trial Phase	Indications, test subjects	Trial results (day post-treatment measured [dpt])	Trial ID	Ref.
Co-Arinate FDC® (artesunate [100 mg] + sulfamethoxypyrazine [250 mg] + pyrimethamine [12.5 mg]) once daily × 3 days	2009	III	*S. mansoni*, school-aged children	Cure rates (28 dpt):	NCT01054651 [22]	[23]
Praziquantel (40 mg/kg) once				Co-Arinate FDC®: 14% Praziquantel: 65%		
Co-Arinate FDC® (artesunate [100 mg] + sulfamethoxypyrazine [250 mg] + pyrimethamine [12.5mg]) thrice in 1 day	2007	II/III[†]	*S. haematobium*, school-aged children	Cure rates (28 dpt):	NCT00510159 [24]	[17]
Praziquantel (40 mg/kg) once				Co-Arinate FDC®: 43.9%/81.4%[‡] Praziquantel: 53%/97.7%[‡]		
Mefloquine (15 mg/kg) once daily × 2 days[§]	2010	II	*S. haematobium*, pregnant women	Cure rates (70 dpt):	NCT01132248 [25]	[18]
Sulfadoxine (500 mg) + pyrimethamine (25 mg) thrice in 1 day				Mefloquine: 47% Sulfadoxine + pyrimethamine: 7%		
Mefloquine (25 mg/kg) + praziquantel (40 mg/kg) once	2011	III	*S. haematobium*, school-aged children	Cure rates (78 dpt)[NS]:	ISRCTN00393859 [26]	[19]
Mefloquine–artesunate (mefloquine [250 mg] + artesunate [100 mg]) once daily × 3 days + praziquantel (40 mg/kg) once				Mefloquine + praziquantel: 21%		
Praziquantel (40 mg/kg) once				Mefloquine–artesunate + praziquantel: 33% Praziquantel: 19%		

[†]Phase II for Co-Arinate FDC®, Phase III for praziquantel.
[‡]Corrected cure rate based on the absence of viable *Schistosoma* eggs detected in urine.
[§]Doses administered one month apart.
Clinical trials evaluating drugs for the treatment of schistosomiasis that were performed within the past 10 years (2004–2014) were identified using ClinicalTrials.gov and the International Clinical Trials Registry Platform [30]. Regimens excluded from the table include trials evaluating the use of supplements, treatments for schistosomiasis symptoms, effect of drugs on schistosomiasis co-infections or alternative praziquantel dosing regimens. Unless otherwise noted, cure rate was defined as the percentage of study participants with no *Schistosoma* eggs found in urine (*S. haematobium*) or stool (*S. mansoni*). The goals of the above clinical trials were to assess the efficacy of the experimental drug/drug combinations against schistosomes, and in the cases of the first three trials (rows 1–3), the efficacy of the experimental drug/drug combination against a reference drug (praziquantel [rows 1 and 2] or sulfadoxine + pyrimethamine [row 3]). In comparison to *in vitro* and *in vivo* data, the cure rates of the experimental drugs were unexpectedly low. The antimalarial drugs under examination in these trials were administered at the standard regimen given to treat malaria and thus the studies' authors noted that further analyses of the therapeutic dose range and regimen may be warranted. Additional optimization of these drugs is limited by the lack of a definitive understanding of the drugs' target(s) and mechanisms of action against the adult and juvenile schistosomes [31]. Furthermore, given the substantial threat of the emergence of drug-resistant *Plasmodium* strains, the use of antimalarial drugs for the treatment of schistosomiasis should be considered with caution, especially in schistosomiasis and malaria co-endemic regions.
FDC: Fixed-dose combination; NP: Results not published; NS: Cure rates not statistically significant.

Table 1. Schistosomiasis drug clinical trials performed within the past decade (cont.).

Drug(s) examined (dose)	Year initiated	Trial Phase	Indications, test subjects	Trial results (day post-treatment measured [dpt])	Trial ID	Ref.
Mirazid® (myrrh) (600 mg) daily × 6 days Praziquantel (40 mg/kg) once	2011	III	*S. mansoni; S. haematobium*, adolescent and young adults	NP	NCT01529710 [27]	
Mefloquine (25 mg/kg) once Artesunate (4 mg/kg) once daily × 3 days Mefloquine–artesunate (mefloquine [250 mg] + artesunate [100 mg]) once daily × 3 days Praziquantel (40 mg/kg)	2008	III	*S. mansoni; S. haematobium*, school-aged children	Cure rates (*S. haematobium*/*S. mansoni*) (26 dpt): Mefloquine: 21/37.5% Artesunate: 25/33% Mefloquine–artesunate: 61/75% Praziquantel: 88/83.3%	ISRCTN06498763 [28]	[20]
Artemether–lumefantrine (artemether [20 mg] + lumefantrine [120 mg]) twice daily × 3 days + albendazole (400 mg) once Artemether–lumefantrine (artemether [20 mg] + lumefantrine [120 mg]) twice Daily × 3 days + albendazole (400 mg) once + praziquantel (40 mg/kg) once Albendazole (400 mg) + praziquantel (40 mg/kg) once	2010	IV	*S. mansoni; S. haematobium*, school-aged children	NP	NCT01459146 [29]	

†Phase II for Co-Arinate FDC®, Phase III for praziquantel.
‡Corrected cure rate based on the absence of viable *Schistosoma* eggs detected in urine.
§Doses administered one month apart.
Clinical trials evaluating drugs for the treatment of schistosomiasis that were performed within the past 10 years (2004–2014) were identified using ClinicalTrials.gov and the International Clinical Trials Registry Platform [30]. Regimens excluded from the table include trials evaluating the use of supplements, treatments for schistosomiasis symptoms, effect of drugs on schistosomiasis co-infections or alternative praziquantel dosing regimens. Unless otherwise noted, cure rate was defined as the percentage of study participants with no *Schistosoma* eggs found in urine (*S. haematobium*) or stool (*S. mansoni*). The goals of the above clinical trials were to assess the efficacy of the experimental drug/drug combinations against schistosomes, and in the cases of the first three trials (rows 1–3), the efficacy of the experimental drug/drug combination against a reference drug (praziquantel [rows 1 and 2] or sulfadoxine + pyrimethamine [row 3]). In comparison to *in vitro* and *in vivo* data, the cure rates of the experimental drugs were unexpectedly low. The antimalarial drugs under examination in these trials were administered at the standard regimen given to treat malaria and thus the studies' authors noted that further analyses of the therapeutic dose range and regimen may be warranted. Additional optimization of these drugs is limited by the lack of a definitive understanding of the drugs' target(s) and mechanisms of action against the adult and juvenile schistosomes [31]. Furthermore, given the substantial threat of the emergence of drug-resistant *Plasmodium* strains, the use of antimalarial drugs for the treatment of schistosomiasis should be considered with caution, especially in schistosomiasis and malaria co-endemic regions.
FDC: Fixed-dose combination; NP: Results not published; NS: Cure rates not statistically significant.

Table 2. Representative inhibitor classes with antischistosome activity.

Schistosoma targets and non-neglected indications of representative inhibitor classes				
	HMG-CoA reductase Inhibitor	**Ca^{2+} ion channel blocker**	**HDAC inhibitor**	**Akt protein kinase inhibitor**
Schistosoma target	SmHMGR [42,51]	$SmCa_v\beta_{var}$ [43]	SmHDAC8 [44,52]	SmAkt [45]
Inhibitor class non-neglected disease indication	Cardiovascular disease [46]	Hypertension [47]	Cancer† [48]	Cancer†[49]
Biopharmaceutical companies' assets from representative inhibitor classes				
Company name	**HMG-CoA reductase Inhibitor**	**Ca^{2+} ion channel blocker**	**HDAC inhibitor**	**Akt protein kinase inhibitor**
AbbVie	ADVICOR®	CARDIZEM® LA TARKA®	Depakote®	–
Astellas	–	–	ISTODAX®	–
AstraZeneca	CRESTOR®	PLENDIL®	–	AZD5363[II]
Bayer	–	ADALAT® CC	–	Allosteric Akt1/2 inhibitor[I]
Boehringer Ingelheim	–	TWYNSTA®	–	–
Bristol-Myers Squibb	Pravachol®	–	–	–
Daiichi Sankyo		Rezaltas®	–	–
		AZOR®		
Eisai	–	–	–	–
Eli Lilly	–	–	–	LY2780301[I]
Gilead	–	–	–	–
GlaxoSmithKline	–	Lacipil™	–	2110183[I], [II‡]
				2141795[I]
Johnson & Johnson	–	–	Quisinostat[II]	–
Merck KGaA	–	–	–	MSC 2363318A[I]
MSD	Zocor®	–	ZOLINZA®	MK-2206[II]
	Mevacor®			
Novartis	Lescol®	Amturnide®	LBH589[III]	–
Novo Nordisk	–	–	–	–
Pfizer	LIPITOR®	CADUET®	–	–
		NEURONTIN®		
		CALAN®		
		LYRICA®		
		PROCARDIA®		

†It is important to mention that while approved for the treatment of cancer, these and other cancer chemotherapies may not have a safety profile that would be acceptable for use in the treatment of infectious diseases and/or of certain populations (children, pregnant/nursing women).
‡Phase I for multiple myeloma and Phase II for ovarian cancer.
Links to products' prescribing information and other references are located in Supplementary Table 1.
Four representative examples of druggable *Schistosoma* targets and their respective inhibitor classes were selected. Inhibition of these targets affected adult schistosome egg-laying (Akt kinase), disrupted pairing (Akt kinase and HDAC), and/or resulted in a reduction in juvenile (Akt kinase, HDAC, HMG-CoA) and/or adult (HMG-CoA) schistosome viability. Prior publications have demonstrated that HMG-CoA reductase Inhibitors, calcium ion channel blockers, HDAC inhibitors and Akt protein kinase inhibitors specifically inhibit their in-class *Schistosoma* target [42–45], thus suggesting that other inhibitors within these classes would display similar target-specific activity, rather than off-target effects. The marketed and clinical-stage products, within these classes, of the 20 companies captured in the *2014 Access to Medicine Index* [50] were reviewed for their potential to be repurposed for schistosomiasis. All products, unless otherwise noted ([I]Phase I, [II]Phase II, [III]Phase III), are commercially available. Please note that this list is not meant to be an exhaustive presentation of all schistosome drug targets and their inhibitor classes.

Table 2. Representative inhibitor classes with antischistosome activity (cont.)

Biopharmaceutical companies' assets from representative inhibitor classes				
Company name	**HMG-CoA reductase Inhibitor**	**Ca^{2+} ion channel blocker**	**HDAC inhibitor**	**Akt protein kinase inhibitor**
Roche	–	–	–	RG7440[II]
Sanofi	–	Renedil®	–	–
Takeda	–	–	–	–

[†]It is important to mention that while approved for the treatment of cancer, these and other cancer chemotherapies may not have a safety profile that would be acceptable for use in the treatment of infectious diseases and/or of certain populations (children, pregnant/nursing women).
[‡]Phase I for multiple myeloma and Phase II for ovarian cancer.
Links to products' prescribing information and other references are located in Supplementary Table 1.
Four representative examples of druggable *Schistosoma* targets and their respective inhibitor classes were selected. Inhibition of these targets affected adult schistosome egg-laying (Akt kinase), disrupted pairing (Akt kinase and HDAC), and/or resulted in a reduction in juvenile (Akt kinase, HDAC, HMG-CoA) and/or adult (HMG-CoA) schistosome viability. Prior publications have demonstrated that HMG-CoA reductase Inhibitors, calcium ion channel blockers, HDAC inhibitors and Akt protein kinase inhibitors specifically inhibit their in-class *Schistosoma* target [42–45], thus suggesting that other inhibitors within these classes would display similar target-specific activity, rather than off-target effects. The marketed and clinical-stage products, within these classes, of the 20 companies captured in the *2014 Access to Medicine Index* [50] were reviewed for their potential to be repurposed for schistosomiasis. All products, unless otherwise noted ([I]Phase I, [II]Phase II, [III]Phase III), are commercially available. Please note that this list is not meant to be an exhaustive presentation of all schistosome drug targets and their inhibitor classes.

WIPO Re:Search – a consortium committed to the research and development of new drugs, vaccines and diagnostics for NTDs, malaria and tuberculosis. Members include for-profit, academic, nonprofit and government research organizations from across the globe [54]. The Consortium was established as a platform through which participating biopharmaceutical companies could contribute their intellectual property (IP) assets, including compounds/compound libraries, know-how, data and expertise, to neglected disease scientists through collaborative research opportunities. Through such collaborations disease experts can screen company compounds against neglected disease targets they have identified through *in vitro* and *in vivo* assays they have developed; collaborate around the development of a new vaccine based on an immunogenic antigen they discovered; contribute their novel platform technologies, disease biomarkers or clinical samples to the development of a rapid, point-of-care diagnostic and partner with other researchers with complementary expertise to study underlying mechanisms of disease.

Key term

WIPO Re:Search: Consortium established to catalyze the discovery and development of drugs, vaccines and diagnostics for neglected tropical diseases, malaria and tuberculosis. The World Intellectual Property Organization (WIPO) is the Consortium's Secretariat and BIO Ventures for Global Health (BVGH) leads partnership development and alliance management. Members include more than 90 for-profit, nonprofit, academic and government research institutions committed to the development of products to treat and eliminate these burdensome diseases. Within the 3 years since WIPO Re:Search was launched, more than 80 collaborative agreements have been facilitated and established between Members. Agreements include sharing of intellectual property assets, such as compounds and compound libraries, and the transfer of knowledge, know-how, and experience between scientists and organizations..

These collaborative research efforts are established and managed by BVGH. As the Partnership Hub Administrator of WIPO Re:Search, BVGH proactively examines researchers' projects and proposes novel opportunities for collaboration. Researchers are also encouraged to review the WIPO Re:Search Database – an online database of IP assets that Members are willing to share – and request access to these assets through BVGH. In the Consortium's first three years, 86 partnerships have been formed, including seven involving schistosomiasis drug discovery [55–58]. The contribution and use of Consortium Members' IP assets and the products developed from their use are governed by the WIPO Re:Search Guiding Principles. These principles are in place to support accessibility and affordability of any products developed through WIPO Re:Search [59].

By connecting biopharmaceutical companies with neglected disease researchers, WIPO Re:Search is reducing the barrier of access to pharmaceutical company compounds for repurposing. For example, HMG-CoA reductase activity is essential to *S. mansoni* egg production and parasite survival *in vitro* and *in vivo* [60]. HMG-CoA reductase inhibitors (statins) are a commercially successful group of drugs developed to reduce elevated cholesterol levels in patients, including those suffering from hypercholesterolemia, and reduce the risk of cardiovascular disease [46]. Previous screens by Caffrey *et al.* demonstrated that commercially available statins were potent inhibitors of both immature and adult schistosomes *in vitro* [42,51]. To determine whether analogs of marketed statin drugs might prove to be even more potent against schistosomes, BVGH connected Dr Conor Caffrey from the University of California, San Francisco,

with MSD, the makers of one of the successfully marketed statin drugs. After initial communications, a confidential disclosure agreement between University of California, San Francisco, and MSD was signed and in-depth discussions commenced. A collaborative study agreement was subsequently finalized and MSD shared a carefully selected set of statin analogs. Dr Caffrey and his team are screening these compounds against *S. mansoni*. MSD's scientists have remained in close contact, aiding Dr Caffrey in the interpretation of the screening results. In the event that a lead compound is identified, MSD has offered to conduct similarity searches and supply analogs to advance structure activity relationship analyses. The access to compounds with a known target, prior toxicity and pharmacokinetics data, and drug-like properties will likely facilitate downstream optimization efforts by Dr Caffrey and his colleagues.

Conclusion

Repurposing drugs is an important means of identifying new treatments for a variety of ailments. Drug repurposing not only reduces the cost of developing a new drug, but it also has the propensity to significantly accelerate development. Fast-tracking development of drugs for NTDs, including schistosomiasis, where there is little investment by industry, is critically important. As demonstrated in this article, drug repurposing efforts can begin with compounds at various stages of development – from screening analogs of a commercial product to performing clinical trials of a currently marketed drug. Repurposing is not limited to drugs developed for a similar indication. As eukaryotes, parasites such as *Schistosoma* often rely on enzymes and signaling pathways homologous to those found in humans. Leveraging these potential similarities is a cornerstone of successful drug repurposing.

As Table 2 demonstrates, 80% of the largest biopharmaceutical companies have developed an inhibitor that targets the human homologue of one of four validated *Schistosoma* drug targets. A more in-depth study of inhibitors of the human homologues of all validated *Schistosoma* drug targets would likely reveal that each of these top companies has compounds that could potentially be repurposed to treat schistosomiasis. WIPO Re:Search was established to bolster drug repurposing for NTDs by eliminating the barrier of access to these pharmaceutical company compounds. Researchers such as those at the University of California, San Francisco are leveraging this platform to advance and accelerate the discovery and development of products, including drugs, for neglected tropical diseases, malaria, and tuberculosis. While this article and collaboration example focuses on schistosomiasis, pharmaceutical companies have a wealth of compounds that could be repurposed for any number of diseases of poverty. WIPO Re:Search provides the opportunity to leverage these.

Future perspective: strengthening the drug pipeline

Drug repurposing is of particular importance to the development of drugs for diseases that disproportionately affect the world's poorest populations. Given the current economic atmosphere and stagnating funding for biomedical research, drug repurposing may be the best way to reduce the burden caused by NTDs. WIPO Re:Search is enabling access to valuable biopharmaceutical assets and know-how and spurring new product development for a variety of neglected indications. The WIPO Re:Search consortium is expected to strengthen drug development pipelines for NTDs and accelerate the development of much-needed treatments for several of the world's greatest unmet medical needs.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/full/10.4155/FMC.15.26

Acknowledgements

The authors thank C Caffrey and MSD for their review and helpful suggestions. A background review of the current antischistosomal drug landscape was performed with the assistance of R Sriram, U Sheth and N Penumetcha (BVGH).

Financial & competing interests disclosure

J Dent, R Ramamoorthi and KM Graef are employees of BVGH. BVGH receives WIPO Re:Search sponsorship funding from Alnylam, Eisai, GlaxoSmithKline, MSD, Merck KGaA, Novartis, Pfizer, and Sanofi. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- New drugs are desperately needed to treat schistosomiasis.
- WIPO Re:Search accelerates discovery and development of products for neglected tropical diseases, malaria, and tuberculosis through collaborations around biopharmaceutical company assets.
- Repurposing of biopharmaceutical company compounds offers a potentially expedient and cost-effective mechanism to develop new schistosomiasis drugs.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Anastasiou E, Lorentz KO, Stein GJ, Mitchell PD. Prehistoric schistosomiasis parasite found in the Middle East. *Lancet Infect. Dis.* 14(7), 553–554 (2014).

2 World Health Organization. Schistosomiasis Fact sheet No. 115. www.who.int/mediacentre

3 Mostafa MH, Sheweita SA, O'Connor PJ. Relationship between schistosomiasis and bladder cancer. *Clin. Microbiol. Rev.* 12(1), 97–111 (1999).

4 Feldmeier H, Krantz I, Poggensee G. Female genital schistosomiasis as a risk-factor for the transmission of HIV. *Int. J. STD AIDS* 5(5), 368–372 (1994).

5 Kjetland EF, Ndhlovu PD, Gomo E *et al.* Association between genital schistosomiasis and HIV in rural Zimbabwean women. *AIDS* 20(4), 593–600 (2006).

6 Mbabazi PS, Andan O, Fitzgerald DW, Chitsulo L, Engels D, Downs JA. Examining the relationship between urogenital schistosomiasis and HIV infection. *PLoS Negl. Trop. Dis.* 5(12), e1396 (2011).

7 Colley DG, Secor WE. Immunology of human schistosomiasis. *Parasite Immunol.* 36(8), 347–357 (2014).

8 ClinicalTrials Database: NCT02337855. https://clinicaltrials.gov/ct2/show/NCT02337855

9 World Health Organization. Preventative Chemotherapy in Human Helminthiasis. Geneva. http://whqlibdoc.who.int

10 Merck KGaA. Corporate Social Responsibility Report 2012 – Philanthropy and product donations. Darmstadt. http://reports.merckgroup.com

11 Chai JY. Praziquantel treatment in trematode and cestode infections: an update. *Infect. Chemother.* 45(1), 32–43 (2013).

12 Pica-Mattoccia L, Cioli D. Sex- and stage-related sensitivity of *Schistosoma mansoni* to *in vivo* and *in vitro* praziquantel treatment. *Int. J. Parasitol.* 34(4), 527–533 (2004).

13 Botros S, Pica-Mattoccia L, William S, El-Lakkani N, Cioli D. Effect of praziquantel on the immature stages of *Schistosoma haematobium*. *Int. J. Parasitol.* 35(13), 1453–1457 (2005).

14 TI Pharma. Pediatric Praziquantel Consortium awarded US $1.86 million GHIT grant. www.tipharma.com

15 Wang W, Wang L, Liang YS. Susceptibility or resistance of praziquantel in human schistosomiasis: a review. *Parasitol. Res.* 111(5), 1871–1877 (2012).

16 Nwaka S, Hudson A. Innovative lead discovery strategies for tropical diseases. *Nat. Rev. Drug Discov.* 5(11), 941–955 (2006).

•• **Target product profiles for several neglected tropical diseases (NTDs).**

17 Sissoko MS, Dabo A, Traore H *et al.* Efficacy of artesunate + sulfamethoxypyrazine/pyrimethamine versus praziquantel in the treatment of *Schistosoma haematobium* in children. *PLoS ONE* 4(10), e6732 (2009).

18 Basra A, Mombo-Ngoma G, Melser MC *et al.* Efficacy of mefloquine intermittent preventive treatment in pregnancy against *Schistosoma haematobium* infection in Gabon: a nested randomized controlled assessor-blinded clinical trial. *Clin. Infect. Dis.* 56(6), e68–e75 (2013).

19 Keiser J, Silue KD, Adiossan LK *et al.* Praziquantel, mefloquine-praziquantel, and mefloquine-artesunate-praziquantel against *Schistosoma haematobium*: a randomized, exploratory, open-label trial. *PLoS Negl. Trop. Dis.* 8(7), e2975 (2014).

20 Keiser J, N'Guessan NA, Adoubryn KD *et al.* Efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, and praziquantel against *Schistosoma haematobium*: randomized, exploratory open-label trial. *Clin. Infect. Dis.* 50(9), 1205–1213 (2010).

21 World Health Organization. WHO Model List of Essential Medicines – 18th List. Geneva. http://apps.who.int

22 ClinicalTrials Database: NCT01054651 https://clinicaltrials.gov/ct2/show/NCT01054651

23 Obonyo CO, Muok EM, Mwinzi PN, Efficacy of artesunate with sulfalene plus pyrimethamine versus praziquantel for treatment of Schistosoma mansoni in Kenyan children: an open-label randomised controlled trial. *Lancet Infect Dis* 10(9), 603–611 (2010).

24 ClinicalTrials Database: NCT00510159 https://clinicaltrials.gov/ct2/show/NCT00510159

25 ClinicalTrials Database: NCT01132248 https://clinicaltrials.gov/ct2/show/NCT01132248

26 ISRCTN registry. Praziquantel, praziquantel plus mefloquine and praziquantel plus mefloquine-artesunate in the treatment of schistosomiasis. http://www.isrctn.com/ISRCTN00393859

27 ClinicalTrials Database: NCT01529710 https://clinicaltrials.gov/ct2/show/NCT01529710

28 ISRCTN registry. Mefloquine and artesunate against schistosomiasis. www.isrctn.com/ISRCTN06498763

29 ClinicalTrials Database: NCT01459146 https://clinicaltrials.gov/ct2/show/NCT01459146

30 World Health Organization. International Clinical Trials Registry Platform (ICTRP) Search Portal. (2014). http://apps.who.int/trialsearch/Default.aspx

31 Keiser J, Utzinger J. Antimalarials in the treatment of schistosomiasis. *Curr. Pharm. Des.* 18(24), 3531–3538 (2012).

•• **Summarizes and analyzes the use of anti-malarials against schistosomes.**

32 Pedrique B, Strub-Wourgaft N, Some C *et al.* The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment. *Lancet Glob. Health* 1(6), e371–e379 (2013).

33 Dickson M, Gagnon JP. The cost of new drug discovery and development. *Discov. Med.* 4, 172 (2004).

34 Pharmaceutical Research and Manufacturers of America® (PhRMA). Clinical trials: the phases of drug testing and approval. www.phrma.org/innovation

35 Adam I, Elhardello OA, Elhadi MO, Abdalla E, Elmardi KA, Jansen FH. The antischistosomal efficacies of artesunate-sulfamethoxypyrazine-pyrimethamine and artemether-lumefantrine administered as treatment for uncomplicated, *Plasmodium falciparum* malaria. *Ann. Trop. Med. Parasitol.* 102(1), 39–44 (2008).

36 Boulanger D, Dieng Y, Cisse B *et al.* Antischistosomal efficacy of artesunate combination therapies administered as curative treatments for malaria attacks. *Trans. R. Soc. Trop. Med. Hyg.* 101(2), 113–116 (2007).

37 Xiao SH, Catto BA. *In vitro* and *in vivo* studies of the effect of artemether on *Schistosoma mansoni*. *Antimicrob. Agents Chemother.* 33(9), 1557–1562 (1989).

38 Keiser J, Chollet J, Xiao SH *et al.* Mefloquine – an aminoalcohol with promising antischistosomal properties in mice. *PLoS Negl. Trop. Dis.* 3(1), e350 (2009).

39 Utzinger J, Chollet J, You J, Mei J, Tanner M, Xiao S. Effect of combined treatment with praziquantel and artemether on *Schistosoma japonicum* and *Schistosoma mansoni* in experimentally infected animals. *Acta Trop.* 80(1), 9–18 (2001).

40 Keiser J, Manneck T, Vargas M. Interactions of mefloquine with praziquantel in the *Schistosoma mansoni* mouse model and *in vitro*. *J. Antimicrob. Chemother.* 66(8), 1791–1797 (2011).

41 Special Program for Research and Training in Tropical Diseases (TDR). The TDR Targets Database, v5. http://tdrtargets.org

42 Rojo-Arreola L, Long T, Asarnow D, Suzuki BM, Singh R, Caffrey CR. Chemical and genetic validation of the statin drug target to treat the helminth disease, schistosomiasis. *PLoS ONE* 9(1), e87594 (2014).

•• **Presents screens of statins against schistosomes.**

43 Salvador-Recatala V, Greenberg RM. Calcium channels of schistosomes: unresolved questions and unexpected answers. *Wiley Interdiscip. Rev. Membr. Transp. Signal.* 1(1), 85–93 (2012).

44 Cabezas-Cruz A, Lancelot J, Caby S, Oliveira G, Pierce RJ. Epigenetic control of gene function in schistosomes: a source of therapeutic targets? *Front. Genet.* 5, 317 (2014).

45 Morel M, Vanderstraete M, Cailliau K, Lescuyer A, Lancelot J, Dissous C. Compound library screening identified Akt/PKB kinase pathway inhibitors as potential key molecules for the development of new chemotherapeutics against schistosomiasis. *Int. J. Parasitol. Drugs Drug Resist.* 4(3), 256–266 (2014).

46 Tobert JA. Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors. *Nat. Rev. Drug Discov.* 2(7), 517–526 (2003).

• **Review of statins and their use.**

47 Ghamami N, Chiang SH, Dormuth C, Wright JM. Time course for blood pressure lowering of dihydropyridine calcium channel blockers. *Cochrane Database Syst. Rev.* 8, CD010052 (2014).

48 Atadja PW. HDAC inhibitors and cancer therapy. *Prog. Drug Res.* 67, 175–195 (2011).

49 Garcia-Echeverria C, Sellers WR. Drug discovery approaches targeting the PI3K/Akt pathway in cancer. *Oncogene* 27(41), 5511–5526 (2008).

50 Access to Medicine Index Foundation. Access to Medicine Index 2014. Haarlem. (2014). www.accesstomedicineindex.org

51 Abdulla MH, Ruelas DS, Wolff B *et al.* Drug discovery for schistosomiasis: hit and lead compounds identified in a library of known drugs by medium-throughput phenotypic screening. *PLoS Negl. Trop. Dis.* 3(7), e478 (2009).

52 Marek M, Kannan S, Hauser AT*et al.* Structural basis for the inhibition of histone deacetylase 8 (HDAC8), a key epigenetic player in the blood fluke *Schistosoma mansoni*. *PLoS Pathog.* 9(9), e1003645 (2013).

53 Merck Sharp & Dohme Corp. www.merck.com/index.html

54 BIO Ventures for Global Health. Current Programs: WIPO Re:Search. (2015). www.bvgh.org/Current-Programs/WIPO-ReSearch.aspx

55 Dent J, Ramamoorthi R, Graef K, Nelson LM, Wichard JC. WIPO Re:Search: a consortium catalyzing research and product development for neglected tropical diseases. *Pharm. Pat. Anal.* 2(5), 591–596 (2013).

•• **Describes in detail WIPO Re:Search and WIPO Re:Search agreements**

56 Ramamoorthi R, Graef KM, Dent J. WIPO Re:Search: accelerating anthelmintic development through cross-sector partnerships. *Int. J. Parasitol. Drugs Drug Resist.* 4(3), 220–225 (2014).

57 BIO Ventures for Global Health. WIPO Re:Search partnership stories (2012–2013). Seattle. (2014).

58 World Intellectual Property Organization. WIPO Re:Search (2015). www.wipo.int/research/en/

59 World Intellectual Property Organization. WIPO Re:Search Guiding Principles. www.wipo.int

60 Chen GZ, Foster L, Bennett JL. Antischistosomal action of mevinolin: evidence that 3-hydroxy-methylglutaryl-coenzyme a reductase activity in *Schistosoma mansoni* is vital for parasite survival. *Naunyn-Schmiedebergs Arch. Pharmacol.* 342(4), 477–482 (1990).