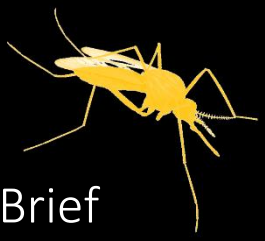

ISNTD Disease Brief

BENCHTOP TO BARRIOS

The challenge of developing new drugs for Chagas disease

The
International
Society
for
Neglected Tropical Diseases

January 2016

Benchtop to barrios: the challenge of developing new drugs for Chagas disease

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Date: January 2016

1 SUMMARY

Chagas disease is one the WHO's 17 designated neglected tropical diseases (NTDs). Its causative agent is the protozoan parasite *Trypanosoma cruzi.* This is predominantly spread by blood-sucking triatomine bugs which typically inhabit poorly-constructed rural dwellings in Latin America. Infection by the parasite leads to an acute phase, which can resemble other infections (with fever etc), and then a chronic phase which can last years or even decades. While most of those infected remain symptom-free, up to 40% will develop progressive organ damage, notably in the heart and gastrointestinal tract. Despite a major reduction in Chagas cases in the last 20-30 years – achieved largely through WHO-led efforts at vector control and reduced transmission – Chagas is still estimated to affect some 6-8m people worldwide and it remains the leading cause of cardiac morbidity and mortality in rural and poor suburban areas of Latin America as well as a growing problem in other continents (through population migration). Current therapeutic options, benznidazole and nifurtimox, were introduced 40+ years ago and, while they are very effective at eradicating the parasite in the acute phase, their impact on indeterminate and chronic disease is not fully elucidated (indeed the recently reported BENEFIT study showed that benznidazole did not significantly reduce cardiac deterioration over 5 years). Furthermore they have important drawbacks (prolonged dosing, toxicity). New, more convenient and safer treatment options are needed. Unfortunately, reinvigorated attempts to develop newer drugs have been met with disappointment in recent years with the failure of the ergosterol biosynthesis inhibitors, posaconazole (especially) and ravuconazole. These drugs had been shown to be highly potent and effective anti-parasitic agents in murine models but ultimately fell badly short in monotherapy clinical trials, both as monotherapy and (in the case of posaconazole) in combination with benznidazole. Their failure illustrates one of several key challenges to new drug development in Chagas – the lack of reliable, predictive animal models. Additional challenges are posed by the difficulty in assessing disease activity/progression and response to therapy in chronic Chagas given the lack of validated biomarkers and the protracted timescale of the disease. While the current clinical pipeline of drugs for Chagas disease is desperately thin – mainly comprised of line extensions and combinations of mainstay drugs -

we do see firm grounds for optimism in the medium-to-long term. First and foremost, the London declaration on Neglected Tropical Diseases in 2012, the WHO's publication of a roadmap with specific targets for all 17 NTDs, and the tragic Ebola outbreak of 2014 have together galvanized the pharmaceutical industry, NGOs and other global stakeholders in terms of commitment and involvement. A dozen pharmaceutical companies are now actively pursuing R&D in Chagas, albeit most are in the pre-clinical stage - screening, identifying and optimizing new leads. Second, the setbacks with the ergosterol inhibitors have led to a focus on improved disease models in support of new drug development. Together with promising work underway on biomarkers this gives increased hope that the pharmaceutical industry and other key players (DNDi etc) in collaboration will be able to develop new and improved treatment options for this insidious disease in the coming decade.

2 CHAGAS DISEASE: OVERVIEW

Chagas disease (aka American trypanosomiasis) is a vector-borne 'neglected tropical disease' that affects approximately 6-8m people worldwide. The vector is a blood-sucking insect, the triatomine (or 'kissing') bug, which tends to live in the cracks in badly-constructed dwellings and spreads the parasitic kinetoplasmid protozoan *Trypanosoma cruzi* via its faeces when it bites humans (see Figure 1 below for a more detailed backgrounder). Infection can also occur from other means (eg, via maternal transmission, consumption of faeces-contaminated food or blood transfusion from infected individuals).

Originally confined mainly to the more remote rural regions of Latin America, Chagas has spread into urban areas across 21 countries in the continent and, more recently, into other continents (eg, North America and Western Europe) as a result of population migration. Estimates vary but there are now thought to be over 300,000 Chagas cases in the US and at least 100,000 in Europe (including more than 50,000 in Spain). While Latin America still accounts for the overwhelming majority of Chagas cases, recent research has indicated that the prevalence of the disease in Latin American migrants living in Europe is high (eg, 18% of migrants from Bolivia were shown to be infected in a review and meta-analysis by Requena-Mendez et al). The latter is likely to represent a growing problem as the level of disease recognition and treatment remains very low (some 95% of cases in Europe are thought to be undiagnosed and a study by Repetto et al showed that less than 30% of diagnosed Chagas patients in Italy actually completed treatment for their condition).

An important feature of Chagas disease is that, in the majority of cases, it is relatively symptom-free or 'silent' (which almost certainly results in under-recognition and under-reporting of the disease). However, in a sizeable proportion of those chronically infected (thought to be as high as 40%), parasitic invasion of target organs and the associated immune response can over a period of years/decades result in progressive damage to the heart and/or intestinal tract: in such cases, there is significant morbidity and the disease may ultimately be life-threatening (eg, from heart failure). Thus it is vital that those infected be diagnosed (preferably in the acute phase of infection) and treated appropriately. Current therapeutic options (benznidazole and nifurtimox; discussed in detail below) can be curative in the acute phase but do possess drawbacks, notably in terms of toxicity. Whether treatment may delay/curb chronic disease is more debatable especially in the light of the recently-reported BENEFIT study which revealed that treatment over 5 years with benznidazole did not result in reduced cardiomyopathy (albeit some observers believe this was down to methodological problems with the trial itself, as discussed

later).

Improved diagnosis, surveillance and treatment and enhanced efforts at vector control (eg, insecticidal spraying) and transmission prevention (eg, blood screening) are at the heart of the WHO's strategy to tackle the disease. Nevertheless, despite the very considerable efforts to date – which have seen the number of new Chagas cases fall from 700,000 pa in 1990 to less than 50,000 - the WHO states that Chagas remains one of the biggest public health problems in Latin America, noting that some 25m people are at risk of infection and that there are still more than 7,000 deaths pa. A recent review article (Urbina et al; J Eukaryotic Microbiology 2015; 62, 149-56) was more blunt in its description of the continuing threat: '*Chagas disease … is the first cause of cardiac morbidity and mortality in poor rural and suburban areas of Latin America and the largest parasitic burden in the continent, now spreading worldwide due to international migrations'.*

Figure 1: Chagas disease overview

Cause	Chagas disease (also known as American trypanosomiasis) results from infection by the protozoan parasite *Trypanosoma cruzi* and is primarily transmitted by triatomine bugs (colloquially known as 'kissing bugs'). These blood sucking insects typically emerge at night time from their normal habitat (cracks in badly-constructed dwellings in rural areas) to bite exposed areas of the sleeping victim (typically the face). In so doing they deposit contaminated faeces or urine, which then results in the parasites passing through skin membranes to infect humans (directly via the wound or indirectly via the victim rubbing the bite area and accidentally spreading the faeces to a vulnerable membrane, eg, the eye). The disease may also be spread by other means, including maternal (congenital) transmission, organ transplantation, blood transfusion and eating contaminated food.
Clinical manifestation	Initial infection is followed by the acute phase which typically lasts around two months and is either symptom-free or has symptoms that resemble those of other diseases (eg, fever, diarrhea, rash and joint pain). A characteristic symptom is Romana's sign, a swelling of the eyelid (from inadvertent rubbing of the faeces into the eye). The chronic phase that follows the acute phase last many years during which the parasites enter various target organs. In most cases, individuals remain symptom-free despite life-long infection. However, in up to 40% of cases the parasites enter heart muscle (the primary problem affecting those chronically infected) or the muscles of the digestive tract and serious life-threatening issues can arise (heart failure, colon enlargement, neurological symptoms). Co-infection with HIV has become an increasing problem since the 1980s.
Affected regions	The vast majority of the estimated circa 7m infected people worldwide live in 21 countries in Latin America. The highest number of cases are seen in Mexico, Brazil and Argentina. Originally a rural disease, an increasing number of cases are being seen in urban areas of Latin America and indeed in other continents/countries (eg, North America, Western Europe, Japan and Australia) as a result of population migration. As noted above, most of those infected are symptom-free and unaware of their disease so that the spread to other geographies is almost certainly under-reported.
Treatment	Effective anti-parasitic treatment is available in the form of benznidazole (produced by the Argentinian company Laboratorio ELEA under the brand name 'Abarax') and the second-line therapy nifurtimox ('Lampit'; donated to the WHO by Bayer). Treatment early in acute phase can cure the disease in nearly all cases and drug therapy may be effective in halting development of the disease in the early chronic phase. Long-term chronic treatment, however, has not been shown to reduce cardiomyopathy although the clinical trial supporting this conclusion has been questioned. The WHO's primary focus (below) is on vector and transmission control, together with patient care.
Progress to date	The WHO's three-part strategy for Chagas disease involves: (1) interrupting transmission (for example by improved blood screening, insecticidal spraying of households, educating on the importance of repairing cracks in housing which harbor bugs, the use of bed-nets and improved food hygiene); (2) providing patient care (via medication and support programs); and (3) raising awareness and building effective surveillance systems . Unlike most other tropical diseases, incomplete information is available on whether these efforts have yielded progress towards the WHO's disease control and elimination targets. Indeed some areas thought to be under control have seen the persistence of disease (eg, Chaco region of Bolivia) while previously unaffected areas have seen the development of Chagas disease (eg, Amazon basin). On the other hand, effective blood screening programs are now in operation in 20 of 21 Latin American countries.
WHO target	The WHO has two targets in its Roadmap: (1) it aims to have interrupted regional transmission by blood transfusion in the Americas, Europe and Western Pacific by 2015 and (2) to interrupt household (intra-domiciliary) transmission in Latin America by 2020.

Source: WHO website, miscellaneous medical websites

3 CURRENT TREATMENT OPTIONS

The parasite that causes Chagas disease, *T. cruzi,* can be treated effectively with benznidazole and also by the second-line agent nifurtimox. Both are long-established nitroheterocyclic-based compounds (benznidazole was introduced in the 1970s and nifurtimox in the 1960s) and each is included in the WHO's List of Essential Medicines for Children. Benznidazole is currently supplied solely by the Argentinian manufacturer Laboratorio ELEA under the brand name 'Abarax' (previously it was also supplied by the Brazilian public manufacturer LAFEPE, which received the drug via a technology transfer from Roche in 2008). Nifurtimox is supplied as part of a WHO donation program by Bayer (which brands the drug 'Lampit'). Figure 2 sets out the WHO prescribing information for each agent for comparative purposes.

Both drugs can be curative in the early stages of the acute phase of infection with substantial cure rates of 65-80% noted in the literature and approaching 100% in infants treated for congenital infection. In addition to the acute phase, treatment with these agents is deemed appropriate in those with reactivated disease (eg, arising from immunosuppression) and in those in the early chronic phase of infection (when there is possible evidence that drug therapy may delay or curb disease progression). Unfortunately, the utility of benznidazole in chronic Chagas' disease was thrown into serious doubt late last year by results of the landmark 2,854-patient BENEFIT study (clinicaltrials.gov identifier NCT00123916) which failed to show that treatment with the drug for >5 years resulted in a significant reduction in cardiac morbidity and mortality (NEJM; Morillo et al; 373:1295-1306; 1 October 2015). This disappointing finding has since come under scrutiny with some observers citing methodological issues that may have compromised the findings. A recent letter in the New England Journal of Medicine, for example, suggests that the drug exposure in the study may have been sub-optimal, as evidenced by "modest" PCR sero-conversion rates (NEJM; Hamers et al; 374:188-190; 14 January 2016;). Nevertheless, the validity of long-term treatment in chronic disease is now open to debate, particularly given other known drawbacks with each of the two approved agents which we highlight below:

1. The two drugs are labelled for a long duration of treatment (60+ days) which risks compliance problems especially given toxicity issues highlighted next (we note, however, that there are no controlled studies indicating that such a treatment duration is warranted and that the DNDi is beginning a study with benznidazole examining different dosages and treatment durations).
2. Importantly, up to 40% of patients experience adverse events (eg, rash and nausea) which in turn has been shown to lead to up to 30% drop-out rates from treatment.
3. They are contra-indicated in pregnant women in the first trimester (although use is encouraged thereafter to prevent congenital transmission) and in those with renal or liver failure.
4. Nifurtimox is also specifically contra-indicated in those with neurological or psychiatric disorders (eg, convulsions or alchohol dependence).

The shortcomings of the two drugs were highlighted in the introductory comments in a 2015 New England Journal of Medicine paper (Molina et al; 370;20; 15 May 2015) which noted that '*in light of these problems, safer and more effective therapeutic options for patients with Chagas disease are clearly needed*'. It is not a simple task, however, to devise and develop new treatment options and indeed the aforementioned paper reported the failure of a promising new drug for Chagas disease, namely posaconazole. We discuss next some of the challenges which have arisen in developing the next generation of medicines for Chagas disease and then highlight the current pipeline of clinical candidates.

Figure 2: Prescribing information for benznidazole and nifurtimox

	Benznidazole	**Nifurtimox**
General	Benznidazole is a trypanocidal nitroimidazole derivative which is rapidly absorbed from the alimentary tract. Peak plasma concentrations are reached after 2-4 hours and then decay with a half-life of approximately 12 hours. Benznidazole is partly metabolized in the body and all metabolites are rapidly eliminated in the urine and stools	A synthetic trypanocidal nitrofuran compound which is efficiently absorbed from the gastrointestinal tract. It is rapidly and extensively metabolized and little is excreted in the urine. Intracellular forms of the parasite are more susceptible than extracellular forms under experimental conditions
Use	Treatment of acute American trypanosomiasis (Chagas disease). Cure rates of 80-90% have been recorded	Treatment of acute American trypanosomiasis (Chagas disease). The response is variable. Cure rates of 80-90% have been recorded but in some areas of central Brazil higher failure rates have occurred
Dosage	Adults: 5-7 mg/kg orally in two divided doses daily for 60 days. Children (up to 12 years): 10 mg/kg orally in two divided doses daily for 60 days	Adults: 8-10 mg/kg orally in three divided daily doses for 90 days. Children: 15-20 mg/kg orally in four divided daily doses for 90 days
Contra-indications & precautions	Patients with hepatic, renal or haematological insufficiency should receive the drug only under close medical supervision. The blood count, especially leukocytes, should be monitored throughout treatment and patients should be advised to abstain from alcohol. Benznidazole should not be administered during early pregnancy	Early pregnancy. Gastrointestinal irritation may be reduced if an aluminium hydroxide preparation is taken simultaneously. Alcohol should be avoided since it may increase the incidence and severity of adverse effects. Nifurtimox should not be administered to patients with a history of convulsions, psychiatric disease or alcohol dependence only under close medical supervision. Daily dosage schedules should be reduced if weight loss, neurological disturbances or other manifestations of intolerance occur
Use in pregnancy	Safe use in pregnancy has not been established and treatment should be deferred until after the first trimester. It should then be instituted immediately to avoid the risk of congenital transmission	Safety in pregnancy has not been established and treatment should be deferred until after the first trimester. It should then be instituted to avoid the risk of congenital transmission
Adverse effects	Adverse effects are frequent. Rashes may appear during the first 2 weeks of treatment. They are usually mild, but when they are severe and accompanied by fever and purpura, treatment should be definitively discontinued. Nausea may also occur during the initial phase of therapy. Paraesthesiae or symptoms of peripheral polyneuritis are dose-related effects; if they occur treatment should be discontinued immediately. More serious adverse effects include leukopenia and, rarely, agranulocytosis.	Adverse effects are frequent, dose-related and reversible. They include anorexia, nausea, vomiting, gastric pain, insomnia, headache, vertigo, excitability, myalgia, arthralgia and convulsions. Seizures may be controlled symptomatically with anticonvulsants. A peripheral polyneuritis can occur which may necessitate discontinuation of treatment

Source: WHO

4 CHALLENGES TO DEVELOPING NEW THERAPEUTICS

For many years (lasting until the 1990s), the misplaced hypothesis that the chronic phase of the disease and its resulting serious sequelae (cardiac, digestive, neurological) is autoimmune inflammation-mediated (and thus not impacted by the persistence or otherwise of *T. cruzi* parasites in the body) acted as a deterrent to the development of novel anti-infective drugs for Chagas. In short, this hypothesis deemed treatment of parasites in the chronic phase as irrelevant. This notion has been overtaken and it is now broadly accepted that the persistence of parasitic infection is, together with the associated immune (or auto-immune) response, the primary reason for the progressive organ damage and resulting morbidity and mortality. Renewed enthusiasm for developing new treatment options over the past decade or so has, however, been met by disappointment and an absence of approved new modalities (other than the introduction of paediatric-friendly formulations of benznidazole by LAFEPE/DNDi in 2011/12 and by ELEA/DNDi beginning in 2015).

One of the key challenges to developing novel Chagas disease treatments has been presented by the lack of reliable animal models. This was highlighted by the disappointing results of clinical trials in 2013 and 2014 of two ergosterol biosynthesis inhibitors, posaconazole (especially) and ravuconazole (also known as E1224). These anti-fungal agents were widely thought to represent the next potential generation of treatments for Chagas (NEJM editorial, May 2015: "*since the 1990s, ergosterol inhibitors, and specifically posaconazole, have been considered promising drugs for the treatment of T. cruzi infection*"; WHO Technical Report 975, 2012: "*among the most promising approaches are ergosterol biosynthesis inhibitors, such as posaconazole and ravuconazole*").

Animal models (as well as preclinical studies) had suggested much greater trypanocidal potency and selectivity than benznidazole, as well as activity in *T. cruzi* strains resistant to standard therapy (specifically, murine models showed cure rates with posaconazole of 90% and up to 60% respectively in the acute and chronic phases, as compared with 76% and 0% with benznidazole). In clinical trials, however, the newer agents showed significantly higher rates of treatment failure than benznidazole. In particular the CHAGASAZOL study conducted by Molina et al – noteworthy as it was the first prospective randomized open-label trial of a new Chagas treatment in decades – showed that only 10-20% of chronic Chagas patients were free of parasites 10 months after treatment with posaconazole, as measured by PCR, whereas for benznidazole the corresponding figure was an impressive 94%, supporting the latter as standard of care.

In attempting to explain the lack of reproducibility of murine models in humans, the study authors hypothesised that existing animal models perhaps more accurately reflect the early chronic stage of the disease (when the effects of ergosterol inhibitors are likely to be more pronounced) and that in late stage chronic Chagas there may be a more quiescent form of *T. cruzi* against which the ergosterol inhibitors are less effective. Other theories have been proposed which do not lay the blame on the mouse models – for example, some commentators have questioned the plasma exposure of the ergosterol inhibitors in these clinical trials (suggesting the levels were significantly below the curative levels employed in murine models) and whether there was a sub-optimal duration of treatment (should dosing have been carried on for 90 rather than 60 days?). These potential explanations are explored in a paper by Urbina ([MC1][MC2]J Eukaryot Microbiol. 2015 Jan-Feb; 62(1):149-56.) in which the author concludes that the "*results are probably related to suboptimal exposure and/or treatment duration*". Nevertheless the unexpected failure of these studies has undoubtedly undermined confidence in the

predictivity of animal disease models and prompted calls for new, alternative models. Fortunately, such newer models are in development (eg, bioluminescent imaging and high-throughput cell-based assays). Furthermore, application of one of these methodologies would have accurately predicted the failure of posaconazole according to Francisco, Kelly et al (Antimicrob Agents Chemother. 2015 Aug;59(8):4653-61). By using bioluminescent imaging, the authors noted that "*posaconazole was found to be significantly inferior to benznidazole as a treatment for both acute and chronic T. cruzi infections*" and further stated that this "*in vivo screening model for Chagas disease is predictive, reproducible and adaptable to diverse treatment schedules. It should provide greater assurance that drugs are not advanced prematurely into clinical trial*."

As a side note, it is a valid question in the light of the foregoing to ask whether the ergosterol inhibitors should necessarily be abandoned. Some commentators speculated in the immediate aftermath of the monotherapy trial failures that these drugs may find a place in combination regimens with benznidazole or nifurtimox or in treatment of drug resistant strains of *T. cruzi*. Unfortunately such a conclusion was not supported by the subsequent results of the STOP CHAGAS study (clinicaltrials.gov identifier NCT01377480; results reported July 2015) which showed that posaconazole conferred no additional benefit when added to benznidazole in patients with chronic Chagas disease (PCR response 82% for the combination vs 86% with benznidazole alone). It would appear therefore that any residual hopes of the ergosterol inhibitors playing a meaningful role in Chagas disease therapy are slim at best.

An additional challenge to developing new therapeutics for the chronic phase of Chagas is in measuring disease activity and progression, especially as the process can take place over many years. Assessing parasitemia via PCR is potentially flawed as a negative finding does not mean there are no active parasites present in the body – it may mean instead that the parasites are concentrated in internal organs (where the damage is after all being done, rather than in the circulation) and/or that the levels simply fell below the sensitivity threshold of the PCR assay employed (although we note that this methodology was relied on in the CHAGASAZOL study). In short, a negative PCR finding does not definitively indicate a parasitological cure in adult chronic patients. New validated biomarkers are clearly needed to better assess response to treatment and eventual cure rates. Recent developments hold promise in this regard and include the identification of novel markers of *T. cruzi* infection (eg, fragments of apolipoprotein A1 and human fibronectin which result from the actions of cruzipain, a protease enzyme which is involved in mammalian cell invasion, immune activation and evasion by the parasite).

5 NEW DRUG PIPELINE

A comparison of the new drug pipeline for Chagas disease with that from just 2-3 years ago is rather disheartening given the failure in monotherapy of the much-vaunted ergosterol inhibitors, posaconazole and ravuconazole. Indeed the pipeline now largely comprises line extensions and combinations of the existing 40+ year old agents, benznidazole and nifurtimox. The only NCEs in development are fexinidazole, an oral nitroimidazole drug (similar to benznidazole), which looks doubtful as a prospect given that safety and tolerability issues noticed early in its Phase II proof-of-concept trial have limited recruitment to less than 50 patients, and ravuconazole in a combination regimen with benznidazole.

An examination of www.clinicaltrials.gov is also a disappointing exercise: the only clinical studies of anti-parasitic treatments listed are a 500-patient head-to-head, placebo-controlled comparison of benznidazole and nifurtimox ('CHICAMOCHA-3'), which is due to complete in February 2017, the

fexinidazole proof-of-concept study, and two studies by Bayer in pursuit of a paediatric formulation of nifurtimox.

Clearly we are a long way from the launch of the next generation of Chagas treatments, albeit we are still learning about how best to use the existing options.

Figure 3: Chagas disease clinical pipeline

Phase	Product/compound (sponsor)	Comment
Registration	Paediatric benznidazole (DNDi/ELEA)	DNDi has sought a second LatAm-based supplier of a child-friendly formulation of the standard of care (in addition to LAFEPE in Brazil) and has partnered with Mundo Sano and ELEA in Argentina. Filing was due from 2015 onwards, beginning in Argentina.
III	Paediatric nifurtimox (Bayer)	Adaptive program to develop a formulation of Lampit that is suitable for children. 390-patient Phase III trial starts in January 2016 and estimated completion in November 2018 (note: Bayer is also looking at new dosage schemes for easier and shorter treatment as well as a more precise body weight adjusted treatment scheme)
II	Fexinidazole (DNDi/partners)	Phase II PoC trial started in July 2014 to determine whether fexinidazole administered orally at 1200mg or 1800mg/day over 2, 4 or 8 weeks is efficacious and safe vs placebo in clearing *T. cruzi* parasitemia in adults with chronic Chagas disease. After reports of safety and tolerability issues, trial recruitment was limited to 47 patients (of 140 targeted).
II	New benznidazole combinations/regimens (DNDi/Eisai)	PoC evaluation of new treatment regimens of benznidazole in monotherapy (shorter duration courses and lower dosing) or in combination with ravucazole, for the treatment of adults with chronic Chagas. Trials were due to start in 2015 to determine if the safety/tolerability issues of benznidazole can be managed by reduced doses and treatment duration.

Source: DNDi, Bayer

6 WHERE NEXT?

As we have highlighted, the current outlook is not optimistic in regards to the likelihood of new treatments for Chagas disease in the next several years, especially following the failure of the ergosterol inhibitors in monotherapy. Chagas patients will continue to be reliant on established drugs, especially benznidazole, albeit there remains considerable scope for expanding our understanding about how best to use this agent (eg, through shorter treatment durations). We do, however, see grounds for an improvement in the situation in the medium-to-long term.

First and foremost the London declaration on Neglected Tropical Diseases (NTDs) in 2012, together with the WHO's publication of a roadmap with specific annual targets for all 17 NTDs, has galvanized the pharmaceutical industry, NGOs and other global stakeholders in terms of commitment and involvement. The corollary of the tragic and unprecedented Ebola outbreak in 2014 has been heightened public and industry attention to tropical diseases and increased calls for action. We note in this regard that the IFPMA lists a dozen companies actively pursuing R&D in Chagas, mostly in the pre-clinical stage (screening, lead identification, lead optimization; Figure 4).

Figure 4: IFPMA companies active in Chagas R&D

Company	Partners	Project	Phase
AbbVie	DNDi	Compound screening, preclinical support, technical consulting	Lead identification
Astellas	DNDi, Tokyo Univ, Tokyo Int of Tech, Nagasaki Uni, KEK, AIST	Hit characterisation and SAR development	Lead identification
AstraZeneca	DNDi	Focused compound library screening at Swiss TPH, Inst. Pasteur K	Lead identification
Bayer	-	Nifurtimox paediatric	Phase IIb
Bristol-Myers Squibb	DNDi	Focused compound library screening	Lead identification
Celgene	DNDi, Antwerp Uni	Compound screening	Screening
GSK	DNDi	HTS compound library screening	Lead identification
GSK	Dundee Uni	LO project	Lead optimisation
GSK	Wellcome grant	LO project	Lead optimisation
Eisai	DNDi, GHIT	E1224	Phase II
Eisai	DNDi, GHIT	Compound screening	Lead identification
Eisai	Broad Inst,GHIT	Focused compound library screening	Lead identification
Merck Inc.	DNDi	Targeted screening and hit SAR development	Lead identification
Novartis	-	Discovery efforts	Preclinical
Sanofi	DNDi	Compound screening	Lead identification
Sanofi	DNDi	Focused compound library screening	Lead optimisation
Takeda	DNDi, GHIT	Compound screening	Lead identification
Vaccines:			
Eisai	SVI, Baylor College, Aeras, GHIT	Adjuvant to support vaccine development	Preclinical
Eisai	Fiocruz	Adjuvant to support vaccine development	Preclinical

Source: IFPMA; adjusted for discontinuation of posaconazole

Second, the setbacks with the ergosterol inhibitors have led to a focus on improved disease models in support of new drug development. Consistent with the paper referenced earlier by Kelly, Francisco et al, it was noted at the ISTND d3 R&D meeting in May 2015 that experimental bioluminescent cell assays under development would have accurately predicted the failure of the ergosterol drugs, unlike the murine models which had proven so disappointingly unreliable. Together with promising work underway on biomarkers to better assess and measure the progress of Chagas disease and response to therapy this gives increased hope that the pharmaceutical companies listed above and the other central players (DNDi etc) will be able to develop new and improved treatment options for this insidious disease in the coming decade or so. As a final reminder of the crucial need and imperative here, to use a quote cited earlier, *'Chagas disease … is the first cause of cardiac morbidity and mortality in poor rural and suburban areas of Latin America and the largest parasitic burden in the continent, now spreading worldwide due to international migrations'*.

KEY SOURCES:

Fact sheet on Chagas disease (WHO; March 2015)

'Investing to overcome the global impact of neglected tropical diseases' (WHO; February 2015)

'Prevalence of Chagas disease in Latin American migrants living in Europe: a systematic review and meta-analysis' (Requena Mendez et al; PLOS Neglected Tropical Diseases, 13 February 2015)

'Neglect of a neglected disease in Italy: the challenge of Access-to-care for Chagas disease in Bergamo area' (Repetto et al; PLOS Neglected Tropical Diseases; 25 September 2015)

'Randomised trial of posaconazole and benznidazole for chronic Chagas disease' (Molina et al; NEJM 370; 20; 15 May 2015)

'Advancing the treatment for Chagas disease' (Albajar-Vinas et al; NEJM editorial 370;20)

'Recent clinical trials for the etiological treatment of chronic Chagas disease: advances, challenges and perspectives' (Urbina; J Eukaryotic Microbiology 2015; 62, 149-165)

'Randomized trial of benznidazole for chronic Chagas' cardiomyopathy' (Morillo et al; NEJM 2015; 373:1295-1306)

'Limited Ability of Posaconazole To Cure both Acute and Chronic Trypanosoma cruzi Infections Revealed by Highly Sensitive In Vivo Imaging' (Francisco, Kelly et al; Antimicrob Agents Chemother. 2015 Aug;59(8):4653-61)

'Research priorities for Chagas disease, Human African Trypanosomiasis and Leishmaniasis' (WHO Technical Report Series, No. 975, 2012)

Neglected disease portfolio graphic pages on DNDI and BVGH websites

ISNTD d3 2015 conference presentations (May 2015; see ISNTD website)

'Pharmaceutical R&D projects to prevent and control neglected conditions' (IFPMA, 2014)

'2014 Access to Medicine Index' (Access to Medicine Index website)

ISNTD d3 2015 Research handbook (May 2015)

www.clinicaltrials.gov

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Mark Clark is a 30-year veteran analyst of the pharmaceutical industry and set up the consultancy firm BIApharma LLP in late-2015. Prior to this, he jointly headed the Deutsche Bank European pharmaceutical research team (from 2009-15). His interest in the field of tropical diseases led to his authoring the well-received report 'Tropical diseases; social responsibility, neglected market' in September 2014. Copies of this report, which was referenced by all of the leading news services (eg, WSJ, FT, Reuters), can be requested from Deutsche Bank and a link is available on the Access to Medicine Index website (www.accesstomedicineindex.org).Mark has also volunteered for Malaria No More UK.