Until recently, the primary focus for disease control has been interruption of transmission by vector control programmes and screening of blood donors. Major initiatives began in the Southern Cone countries in 1991 and 1992. Most central and southern American countries joined the initiative over the following decade. Despite these advances in reducing the incidence of T. cruzi infection, the burden of Chagas heart disease is expected to continue in the future since virtually all of the burden of Chagas heart disease comes from individuals already infected who progress from the indeterminate phase to the chronic phase.

Unfortunately, these drugs are limited to treatment of acute and chronic infection in children, with conflicting evidence for treatment of chronic indeterminate disease in adults and no available evidence to support their use as therapy for symptomatic chronic disease. Even in children, who are known to better tolerate treatment with these compounds than adults, cure rates can be low. No new anti-T. cruzi drugs are in the clinical development pipeline and only one class of drugs, the antifungal triazoles, have demonstrated potential for therapeutic switching to the treatment of Chagas disease.

The Chagas disease-specific portfolio is a balance of objectives. In the short-
### DISCOVERY

#### CHAGAS LEAD OPTIMISATION CONSORTIUM

- **Target disease:** Chagas disease
- **Partners:** Centre for Drug Candidate Optimisation (CDCO), Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto, Brazil
- **DNDi project manager and coordinator:** Robert Don, Ivan Scandale
- **Project start:** July 2008

In 2008, a lead optimisation consortium was set up by DNDi to engage in a critical, iterative process that helps to optimise the efficacy of a lead compound while minimizing its toxicity. This consortium includes institutions in Australia (Monash and Murdoch Universities and Epichem) and Brazil (Universidade Federal de Ouro Preto) and consists of a group of analytical and medicinal chemists, pharmacologists and parasitologists with rapid turnaround facilities or compound assessment. A full lead optimisation team has been now been put in place to assure the speed of the highly iterative process. Intod 2009, five classes of compounds identified in DNDi screening programmes were further assessed in hit-to-lead studies. Work is ongoing to select a single series for lead optimisation by the end of the year.

### CLINICAL

#### AZOLES

- **Partners:** Federal University of Ouro Preto, Brazil; and companies who will provide compounds of interest
- **DNDi project managers and coordinator:** Robert Don, Isabela Ribeiro, Bethania Blum
- **Project start:** 2007

A new generation of antifungal triazoles including posaconazole, voriconazole and ravuconazole show considerable promise as anttrypanosomal agents. The marketed antifungal drug posaconazole (Noxafil®, Schering-Plough), has previously been shown to induce parasitological cure in mice with acute and chronic infections, including benzimidazole-resistant strains. DNDi has been in discussion and negotiation with Schering-Plough since 2006. Two other triazole derivatives, ravuconazole (Eisai) and TAK-187 (Takeda) have shown encouraging in vitro and in vivo...
PAEDIATRIC BENZNIDAZOLE

Meeting an acute patient need...

By developing and making available the only paediatric formulation for Chagas disease.

• Stage: Clinical
• Partners: Pharmaceutical Laboratory of Pernambuco State (LAFEPE), Brazil; Centro Nacional de Diagnostico e Investigacion de Endemo-epidemias (CeNDIE), Ministry of Health, Argentina; University of Liverpool, UK
• DNDi project manager and coordinator: Isabela Ribeiro, Bethania Blum
• Project start: June 2008

Since the 1990s, there is consensus for early diagnosis and treatment of children and adolescents in the early indeterminate (chronic) phase of Chagas disease. Young children remain an important target population for treatment despite decreasing vectorial transmission, because congenital infection may remain an important mode of transmission for at least another generation.

This is not reflected in the current treatment options as current drugs are formulated as tablets for adults, not adapted to children weights. Tablet fractionation and extemporaneous formulations are needed to treat most children: these procedures increase the likelihood of improper dosages and raises safety concerns, particularly in the very young and malnourished, reduced efficacy (due to the addition of diluents) and stability concerns.

Benznidazole, one of only two products registered for Chagas disease, can be highly efficacious in children yet no paediatric formulation exists. A number of approaches have been examined to best meet the need of developing a new paediatric formulation which is affordable, age-adapted, and easy to comply with.

With the goal to develop an adapted, dispersible tablet of benznidazole, DNDi and LAFEPE signed a development deal in July 2008. Since then, the project team has been engaged in pre-formulation and analytical development activities. Using current benznidazole dose recommendations, dosing practices, and patient age and weight profiles from 10 centers which treat children with T. cruzi infections as a guide, the team has determined the most appropriate paediatric tablet formulation, strength and associated dosing regimen. Work is progressing, with batch production and stability testing planned for later in 2009.

Chagas disease leaves a memorable impression in the areas where the disease is endemic.
Chagas Disease

AMERICAN TRYpanosOMIASIS – Chagas Disease

100 million people at risk

WHAT IS THE IMPACT OF CHAGAS DISEASE?
Approximately 8 million cases (1)
14,000 deaths per year (2)
667,000 DALYs (2) (3)

Chronic Chagas disease results in significant disability with great social and economic impact including unemployment and decreased earning ability. In Brazil alone, losses of over US$ 1.3 billion in wages and industrial productivity were due to Chagas disease (4).

HOW IS CHAGAS DISEASE TRANSMITTED?
Caused by the kinetoplastid protozoan parasite Trypanosoma cruzi, Chagas disease is primarily transmitted by large, blood-sucking reduviid insects widely known as “the kissing bugs” in endemic countries. Other ways of transmission are blood transfusion, organ transplantation, as well as congenital and oral transmissions.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?
Current treatments can cure infected patients, but highest efficacy is seen early in infection.

– Benznidazole, nifurtimox to treat acute & early indeterminate disease:
  - Long treatment period (30-60 days)
  - Dose-dependent toxicity
  - High rate of patient non-compliance
  - No paediatric strengths

No treatment for chronic disease with target organ involvement.

WHAT ARE THE PRIORITY PATIENT TREATMENT NEEDS?
– A paediatric strength which is affordable, age-adapted, safe, and efficacious would cure patients early on in the disease.
– A new drug for chronic disease that is safe, efficacious, and adapted to the field, and ideally would work in both stages of the disease.

WHERE DOES CHAGAS DISEASE OCCUR?
Endemic in 21 countries across Latin America, Chagas disease kills more people in the region each year than any other parasite-born disease, including malaria.

Patient numbers are growing in non-endemic, developed countries, due to increased population movements.

WHAT ARE THE SYMPTOMS/PRESENTATIONS?
The disease has two clinical phases:

– acute (in which 2-8% of children die)
  - often asymptomatic, or unrecognized due to the non-specific symptoms such as fever, malaise, generalized lymphadenopathy, and hepatosplenomegaly - which spontaneously resolve in four to six weeks.

– chronic disease has two phases:
  - chronic asymptomatic “indeterminate” disease, during which patients can transmit the parasite to others while showing no signs of the disease, may last decades after the infection.
  - chronic symptomatic disease develops in 10% to 30% of infected patients and most often involves the heart or gastrointestinal tract depending on geographical location or parasite strain.

Chagas disease is a leading cause of infectious heart disease (cardiomyopathy) worldwide.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?
Short term: better use of existing treatments through new formulations
  – Paediatric strength of benznidazole: first treatment designed specifically for children

Medium term: development of new treatments through therapeutic switching and combination therapy
  – Azoles: clinical assessment of well-known compounds already in development against fungal infections

Long term: new drugs, and improved clinical research capacity in Chagas disease.
  – Nitroimidazoles: a well-known class of anti-infective compounds
  – New drugs developed from promising compounds identified in discovery activities (such as GSK library of pyridones and cysteine protease inhibitors) and progressed through Chagas lead optimisation consortium.
  – A multi-country, multi-partner Chagas clinical research platform in preparation

By 2014, DNDi aims to deliver from its Chagas-specific portfolio:
  – 1 new paediatric strength available
  – 1 new drug registered
  – A robust pipeline

(3) DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.