Collaborative drug discovery for neglected diseases: Novel compounds for the treatment of Chagas disease


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Chagas disease, caused by the parasite Trypanosoma cruzi, is a major neglected parasitic disease endemic in South and Central America.

**Aim**: to discover a new oral therapy for Chagas disease non-inferior to existing treatment Benznidazole, with improved safety profile, shorter treatment time, active against the chronic form of the disease, inexpensive and easy to manufacture.

**Conclusion**

A collaborative drug discovery consortium established by Drugs for Neglected Diseases initiative (DNDi) has identified and developed two novel compound series active against intracellular protozoan parasite Trypanosoma cruzi the causative agent of Chagas disease.

Compounds suppress parasitemia to undetectable levels after once-a-day oral dosing in a mouse model of chronic T. cruzi infection. Compounds are non-cytotoxic and chemically tractable facilitating rapid optimisation of target biology and drug characteristics.

Studies continue to progress compounds to pre-clinical candidate status.

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**Novel compounds active in vivo**

In 2008, DNDi brought together Epichem (Medicinal Chemistry), Murdoch University Parasitology group (Biology) and The Centre for Drug Candidate Optimisation (DMPK) to form the Chagas Disease Drug Discovery Consortium.

The team has developed:

i) mouse models simulating acute & chronic T. cruzi infection

ii) an understanding of the PK/PD relationship required for activity

iii) identified and progressed a suite of novel, orally available molecules active in the in vivo T. cruzi models at lower doses and shorter treatment times than standard of care Benznidazole.

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**Structural diversity**

Scaffold hopping has generated further compound series orally active in the chronic T. cruzi model: 3 (IC_{50} 11nM), 4 (IC_{50} 11nM) and 5 (IC_{50} 7nM).

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**Further collaborations**

With DNDi, the Chagas Consortium has collaborated with Anacor Pharmaceuticals to profile novel benzoxaborole compounds active against T. cruzi in vitro. AN4169 (6) was active in vivo following oral treatment at 10mg/kg/day, with parasite rebound occurring after 2 rounds of immunosuppression.

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**In vivo model: Acute phase**. Female Swiss mice (n=5/group) are infected with 25,000 bloodstream forms of T. cruzi (Tulahuen strain). Infection is non-lethal, parasites can be detected in a number of organs, and parasitemia levels peak in the blood on day 11 p.i. Mice are administered test compounds once daily for 20 consecutive days, starting day 8 p.i. A reduction in blood parasitemia over the course of treatment gives an indication of compound efficacy. Parasitemia is measured by taking 3μL of blood from the tail vein, diluting 1:10 with red blood cell lysis buffer, and counting live trypomastigotes using a neubauer haemocytometer. Posaconazole and vehicle-only treated groups are included as controls. Chronic phase. Animals showing significant reduction in parasitemia are immunosuppressed by three rounds of cyclophosphamide each day of the first 5 days, with 3 days rest between cyclophosphamide treatments. Parasitemia is measured as days p.i. from the time of cyclophosphamide treatment.

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SAR investigations have identified novel pyrazole analogues 7 & 8 also active in vivo.

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References:

1. Essential medicines to treat diseases that affect the world’s poor are too expensive, no longer produced, highly toxic, or ineffective. Drugs for Neglected Diseases initiative (DNDi) is a collaborative, patients’ needs-driven, non-profit R&D organisation developing new treatments for malaria, visceral leishmaniasis, sleeping sickness, and Chagas disease.

2. Working in partnership with industry & academia DNDi has built the largest ever R&D portfolio for the kinetoplastid diseases.

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