
Drugs for Neglected Diseases Iniciative
&
Universidade Federal de Ouro Preto, Brazil
DNDi
Drugs for Neglected Diseases initiative
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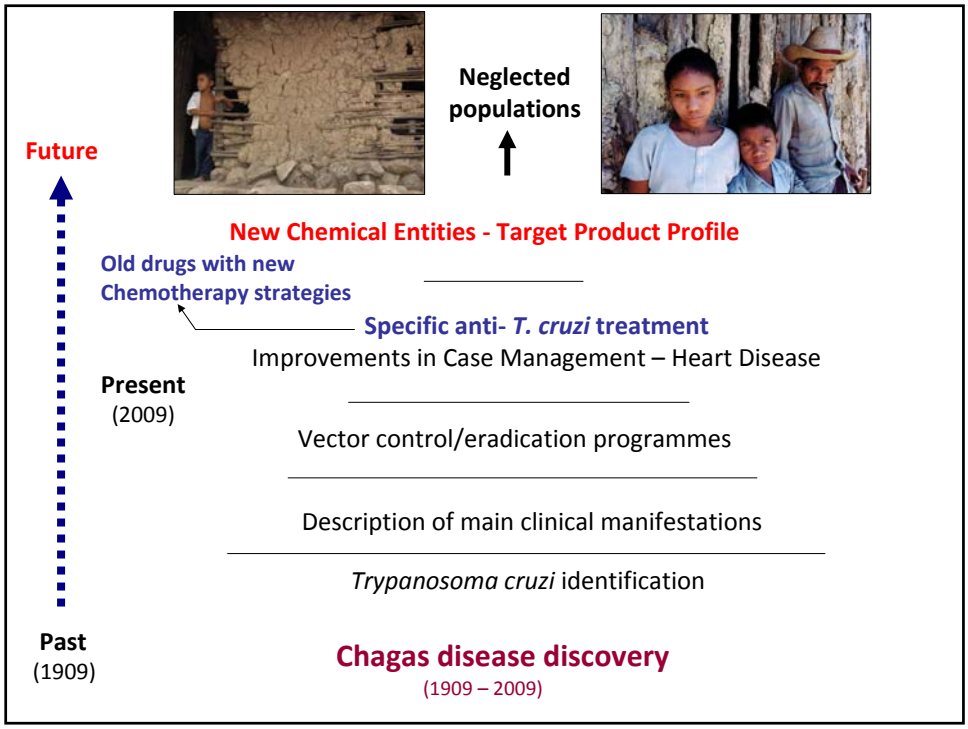
Combination of Benznidazole and Nifurtimox plus
Posaconazole enhances activity against Trypanosoma cruzi
in experimental Chagas disease
Maria Terezinha Bahia, André Talvani, Shing Chang, Isabela Ribeiro


Neglected populations
Future
New Chemical Entities - Target Product Profile
Old drugs with new Chemotherapy strategies
Specific anti- T. cruzi treatment
Improvements in Case Management – Heart Disease
Present (2009)
Vector control/eradication programmes
Description of main clinical manifestations
Trypanosoma cruzi identification
Past (1909)
Chagas disease discovery
(1909 – 2009)

Evaluating combination treatment…

Combination with registered compounds (Benznidazole/Nifurtimox)

Aims: (i) improvement of efficacy
(ii) improvement of safety and tolerability
(iii) reduction of the dose and duration of the therapeutic regimen
(iv) Potential impact on resistance development to each individual compounds from the combinations

Starting point:

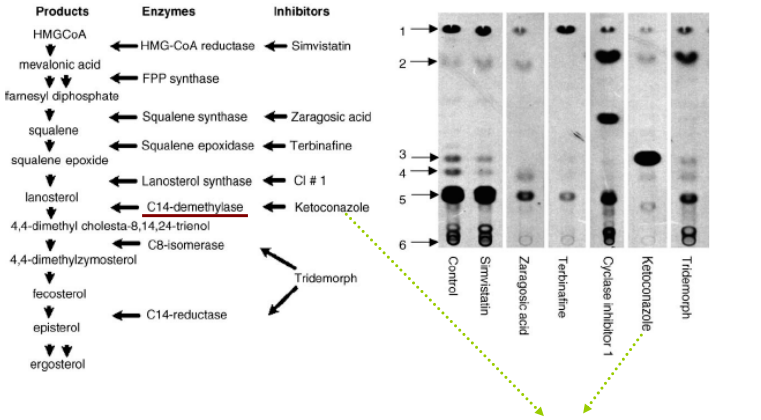
Evaluation of combination therapy Nifurtimox/Benznidazole
+
Azole compounds
« Reduction in time, costs and risks »

Current available drugs

- Benznidazole and Nifurtimox: nitroheterocyclic drugs
- Parasiticidal activity: conversion of reactive intermediates within the parasite that generate superoxide, which causes oxidative damage to components of the parasite
- Compounds activated within the parasite, probably by a Type 1 Mitochondrial Nitroreductase enzyme

Wilkinson et al. PNAS 2008; 105:5022-7
Paulino et al. Mini Rev Med Chem. 2005

Trypanosoma cruzi
Ergosterol Biosynthesis Pathway



Azole class of compounds: Posaconazole, Ravuconazole

E.G. Hankins et al. / Molecular & Biochemical Parasitology 144 (2005) 68–75

Combination of nitroheterocyclic compounds Benznidazole and Nifurtimox plus Posaconazole

Swiss mice inoculated with 5.0 x 10^3 blood trypomastigotes of T. cruzi Y strain

Treatment initiated 4 days post-infection with confirmed parasitaemia

7 consecutive days with each single drug by gavage

(n=6) Y strain — Therapeutic dose

(n=6) Y strain — Half of the therapeutic dose

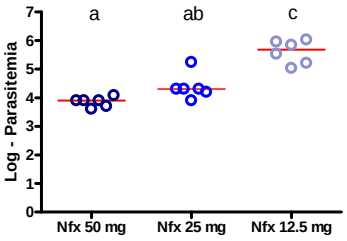
(n=6) Y strain — One forth of the therapeutic dose

Mice infected with Y strain of *Trypanosoma cruzi* treated with different doses of Benznidazole, Nifurtimox and Posaconazole

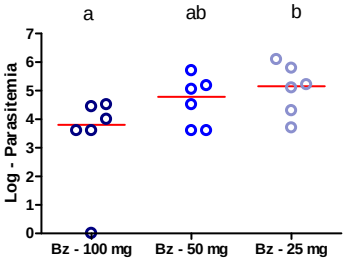
Dose	*Parasitemia suppression (dose±SD)*	*Parasitemia reactivation (day)*	*Parasitemia peak x 10^3 **
Benznidazole			
100mg	1.33±0.52	5	10.0 (17th)
50 mg	1.83±0.75	1	84.6 (16th)
25 mg	ND	-	246.6 (8th)
Nifurtimox			
50 mg	1.0±0.0	5	8.3 (16th)
25 mg	ND	-	30.6 (8th)
12.5 mg	ND	-	396.6 (8th)
Posaconazole			
Ps 20 mg	1.33±0..51	12	11.3 (24th)
Ps 10 mg	1.5±0.54	11	49.3 (25th)
Ps 5.0 mg	1.17±0.41	11	318.6 (26th)
No treated control group			
Control	-	-	900.6 (8th)

Maximum parasitemia levels of the Y strain infected mice treated with different doses of Benznidazole, Nifurtimox and Posaconazole

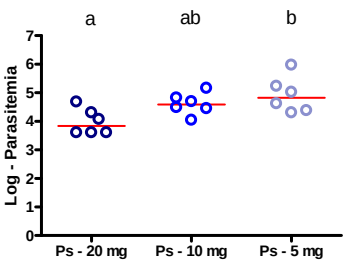
Nifurtimox



Benznidazole

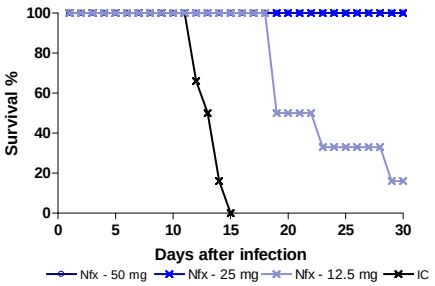


Posaconazole

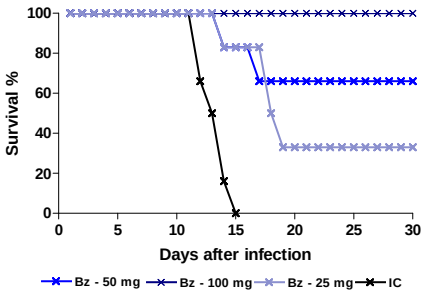


Survival rates of the Y strain infected mice treated with different doses of Benznidazole, Nifurtimox and Posaconazole

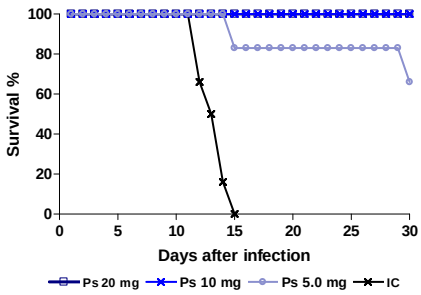
Nifurtimox



Benznidazole



Posaconazole



Drug Combination experiments

Drug combinations:

Benznidazole (Bz) plus Posaconazole (Ps)

25 and 50 mg/kg.day of Bz
+
5 and 10 mg mg/kg/day of Ps

Nifurtimox (Nfx) plus Posaconazole (Ps)

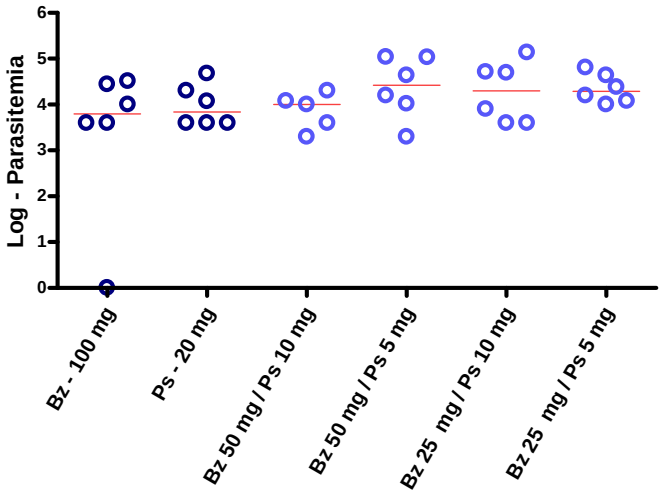
12.5 and 25 mg/kg.day of Nfx
+
5 and 10 mg mg/kg.day of Ps

Benznidazole plus Posaconazole treatment

Treatment scheme (n=6)	Parasitemia suppression (dose±SD)	Parasitemia reactivation (day)	Parasitemia peak	Survival rate (%)
Bz/Ps (50/10mg)	1.4±0.55	10	21.600 (22nd)	100%
Bz/Ps (50/5mg)	1.33±0.52	10	60.000 (22nd)	100%
Bz/Ps (25/10mg)	1.67±0.52	10	40.166 (26th)	100%
Bz/Ps (25/5mg)	1.16±0.41	7	11.133 (27th)	100%
Bz 100mg	1.33±0.52	5	10.000 (17th)	100%
Ps 20 mg	1.33±0..51	12	11.333 (24th)	100%

Benznidazole plus Posaconazole treatment

Parasitaemia



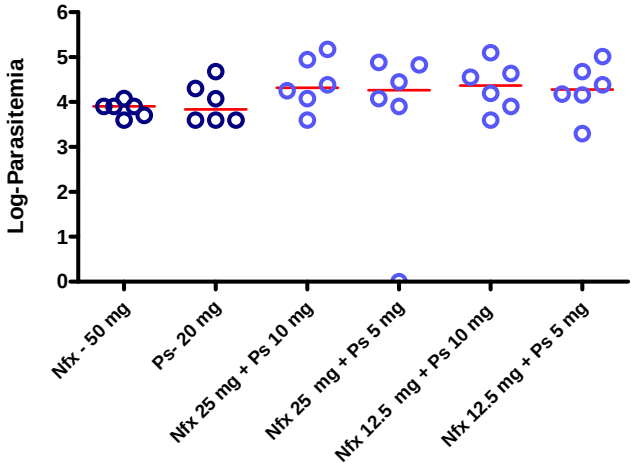
Maximum parasitemia – log parasite/0.1 mL of blood

Nifurtimox plus Posaconazole treatment

Treatment scheme (n=6)	Parasitemia suppression (dose±SD)	Parasitemia reactivation (day)	Parasitemia peak	Survival rate (%)
Nfx /Ps (25/10mg)	1.5±0.55	11	63.333 (27th)	100%
Nfx /Ps (25/5mg)	1.33±0.52	11	27.333 (27th)	100%
Nfx /Ps (12.5/10mg)	1.0±0.0	10	68.666 (27th)	84%
Nfx /Ps (12.5/5mg)	1.16±0.41	9	68.666 (27th)	100%
Ps 20 mg	1.33±0.51	12	11.333 (24th)	100%
Nfx 50 mg	1.0±0.0	5	8.333 (16th)	100%

Nifurtimox plus Posaconazole treatment

Parasitaemia



Maximum parasitemia – log parasite/0.1 mL of blood

Drug combination experiments

Conclusions and future directions

✓The combination of Ps and Bz or Nfx was significantly more efficacious against *T. cruzi* than the same dose of each drugs alone.

✓Need for confirmation of findings in experimental models with prolonged exposure and immunosuppression for assessment of cure

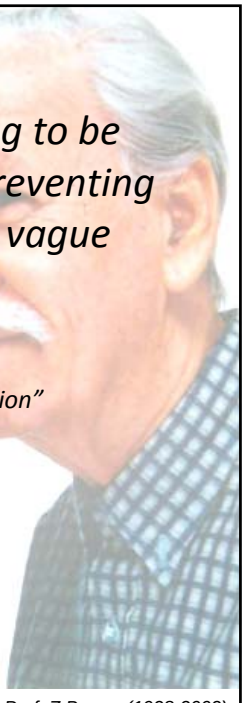
✓ Alternative combination regimens for Chagas disease should be further investigated

"A one-shot inexpensive, nontoxic drug to be used in individual cases as well as for preventing Chagas disease transmission is still a vague dream."

Brener Z: Chemotherapy of Trypanosoma cruzi infection"

Advances in Pharmacology and Chemotherapy,

13: 2-40, 1975.



Prof. Z Brener (1928-2002)


UFOP
Universidade Federal de Ouro Preto
DNDi
Drugs for Neglected Diseases initiative
Collaborators:
Post-graduated students: Isabel Mayer
Livia Figueiredo
Ivo Caldas
Sergio Caldas
DNDi: F. Alves
B. Bourdin
R. Don
E. Torreele
Graduated students: Andre Gravel
Alvaro Neto
Tassiane Martins
Technicians: Vivian Figueiredo
Hidelmagna Silva
Maira Azevedo