

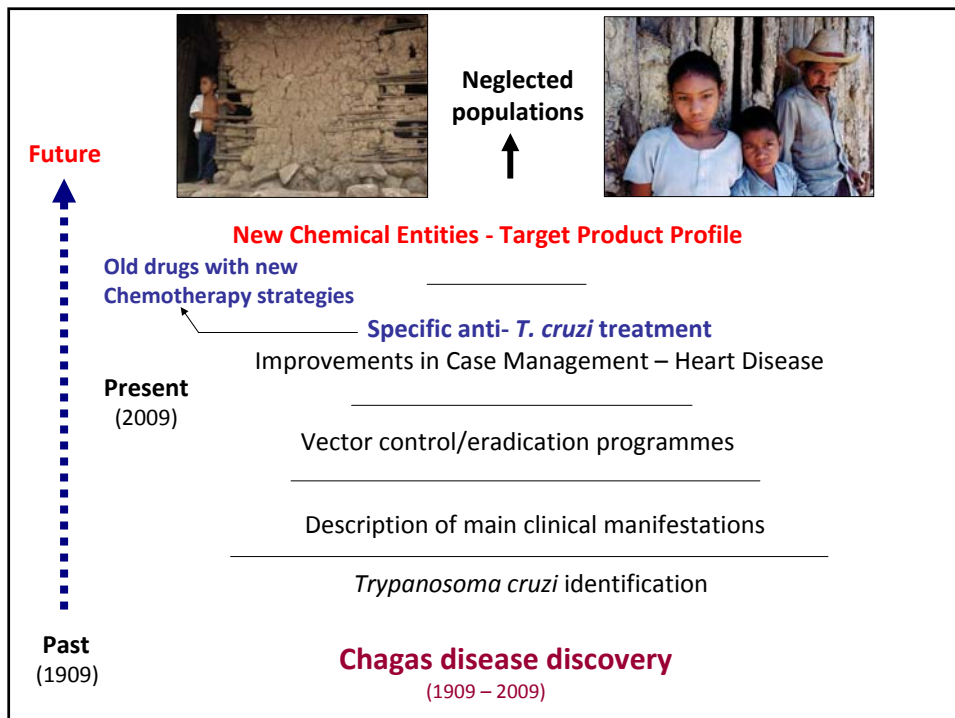
 **UFOP**
Universidade Federal de Ouro Preto

Drugs for Neglected Diseases Initiative
&
Universidade Federal de Ouro Preto, Brazil

 **DNDi**
Drugs for Neglected Diseases Initiative

Combination of Benznidazole and Nifurtimox plus Posaconazole enhances activity against *Trypanosoma cruzi* in experimental Chagas disease

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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

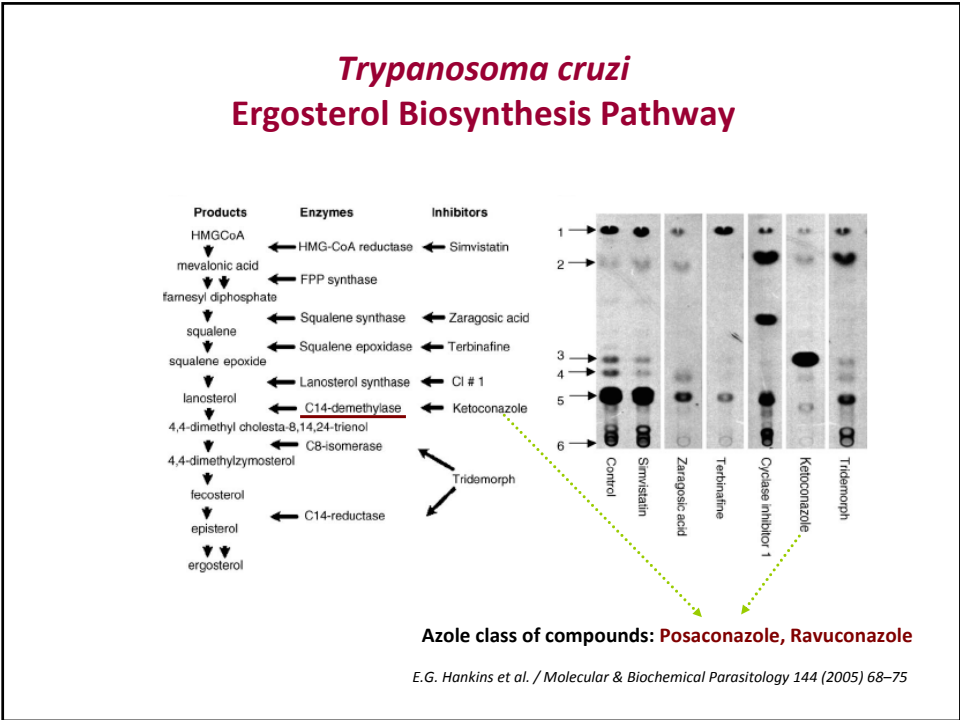
Starting point:

**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






Combination of nitroheterocyclic compounds Benznidazole and Nifurtimox plus Posaconazole

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

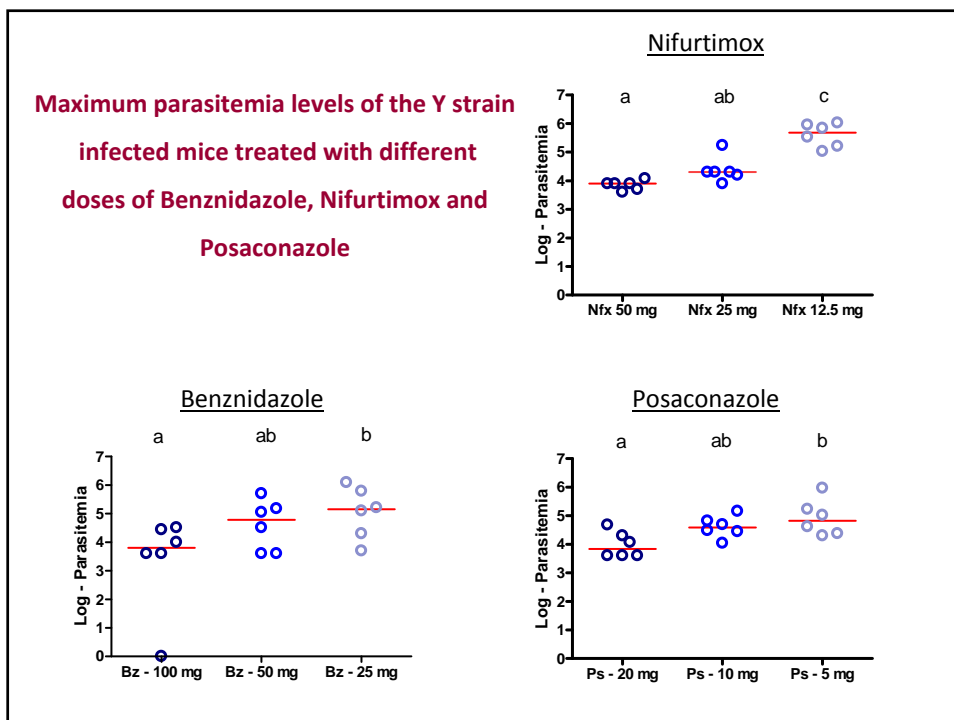
Treatment initiated 4 days post-infection with confirmed parasitaemia

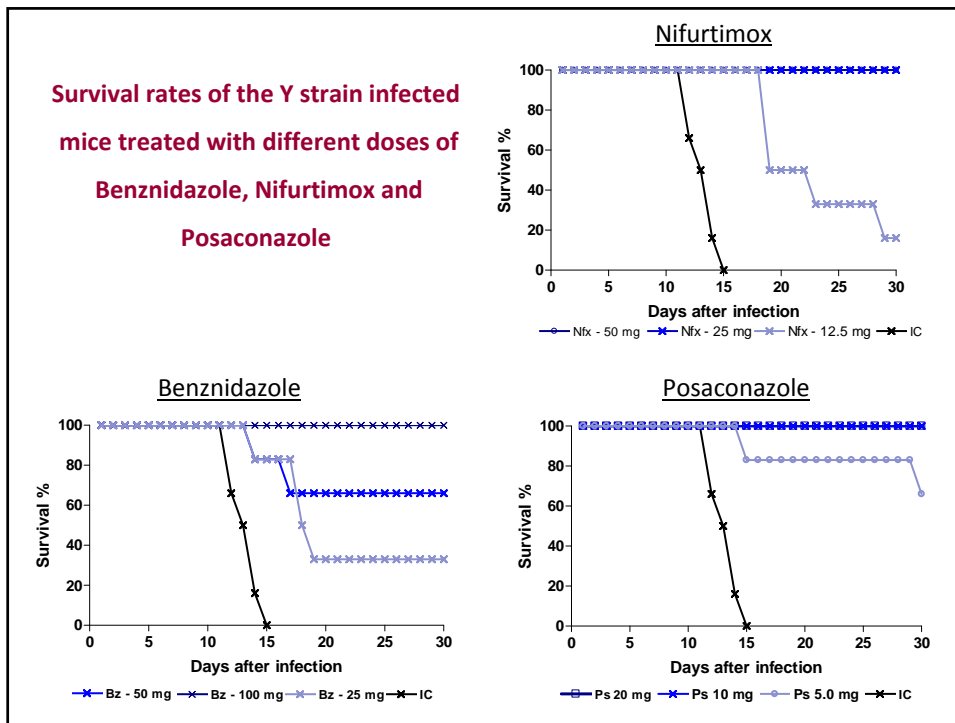
7 consecutive days with each single drug by gavage

 (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 (17 th)
50 mg	1.83±0.75	1	84.6 (16 th)
25 mg	ND	-	246.6 (8 th)
Nifurtimox			
50 mg	1.0±0.0	5	8.3 (16 th)
25 mg	ND	-	30.6 (8 th)
12.5 mg	ND	-	396.6 (8 th)
Posaconazole			
Ps 20 mg	1.33±0.51	12	11.3 (24 th)
Ps 10 mg	1.5±0.54	11	49.3 (25 th)
Ps 5.0 mg	1.17±0.41	11	318.6 (26 th)
No treated control group			
Control	-	-	900.6 (8 th)





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)

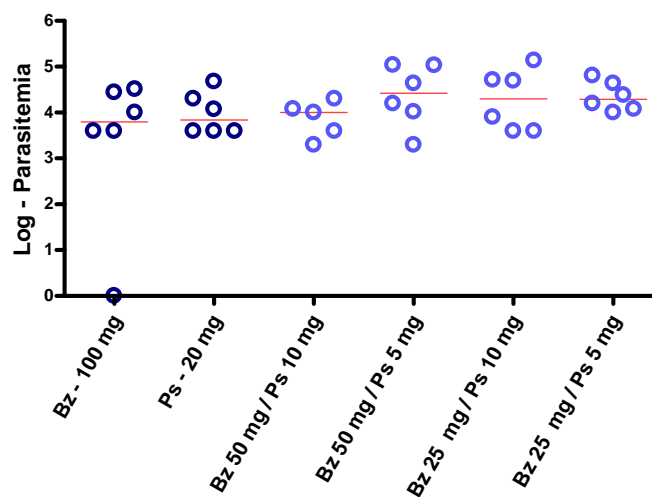
12.5 and 25 mg/kg.day of Nfx
+
5 and 10 mg mg/kg.day of Ps

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 (22 nd)	100%
Bz/Ps (50/5mg)	1.33±0.52	10	60.000 (22 nd)	100%
Bz/Ps (25/10mg)	1.67±0.52	10	40.166 (26 th)	100%
Bz/Ps (25/5mg)	1.16±0.41	7	11.133 (27 th)	100%
Bz 100mg	1.33±0.52	5	10.000 (17 th)	100%
Ps 20 mg	1.33±0.51	12	11.333 (24 th)	100%

Benznidazole plus Posaconazole treatment

Parasitaemia



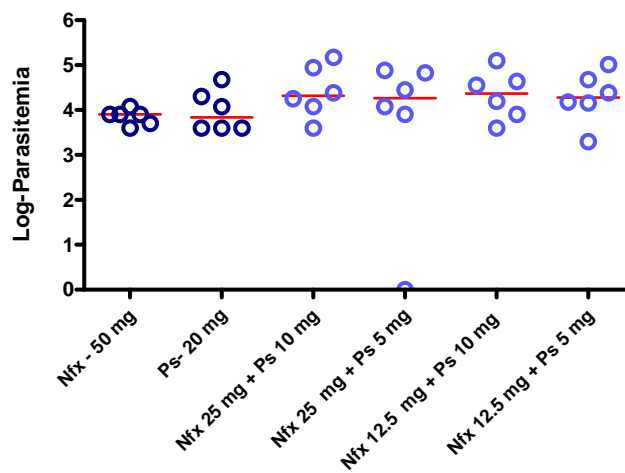
Maximum parasitemia – log parasite/0.1 mL of blood

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 (27 th)	100%
Nfx /Ps (25/5mg)	1.33±0.52	11	27.333 (27 th)	100%
Nfx /Ps (12.5/10mg)	1.0±0.0	10	68.666 (27 th)	84%
Nfx /Ps (12.5/5mg)	1.16±0.41	9	68.666 (27 th)	100%
Ps 20 mg	1.33±0.51	12	11.333 (24 th)	100%
Nfx 50 mg	1.0±0.0	5	8.333 (16 th)	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 drug 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)



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