Review of recent preclinical information and pharmacokinetic-pharmacodynamic data in Chagas disease

Isabela Ribeiro

DNDi
Drugs for Neglected Diseases *initiative*

Chagas Disease Clinical Trials - 2008

- Two randomised clinical trial of BZN in adults
  - TRAENA (started in 03/1999 – 12/2012)
  - BENEFIT (11/2004 – ongoing)
- Decades with no new clinical trials for new treatment options in Chagas disease
- R&D and access stalled by existing knowledge gaps
  - Relevance of animal models
  - Limited data on:
    - the importance of different parasite strains to human disease
    - coexistence of infection
    - mechanisms of resistance
  - PK/PD in Chagas largely unknown
  - No consensus on reference treatment
  - Lack of early test of cure
  - Limited sensitivity of PCR test

Consensus 2008

- Azoles class of compounds represented the drug class with highest potential for treatment of Chagas disease
- Existing treatments for Chagas disease were more effective against *T. cruzi* infections in acute stage than in chronic stage
- Indications that children responded to Chagas disease treatment better than adults – better efficacy and safety profile

Ergosterol biosynthesis and drug development for Chagas disease

Julio A Urbina

Instituto Venezolano de Investigaciones Científicas, Apartado 21827, 1020 Caracas, Venezuela

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1998, p. 1771–1777
0066-4804/98/$04.00+0

Cure of Short- and Long-Term Experimental Chagas' Disease Using D0870

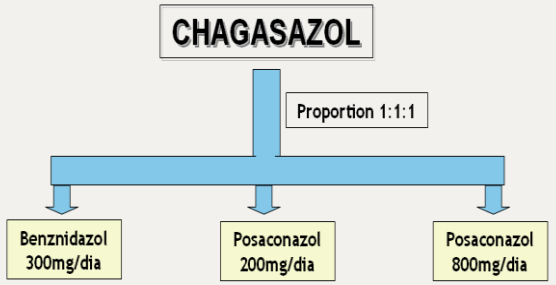
Julio A. Urbina,* Gilberto Payares, Judith Molina, Cristina Sanoja, Andreína Liendo, Keyla Lazardi, Marta M. Piras, Romano Piras, Norma Perez, Patrick Wincker, John F. Ryley

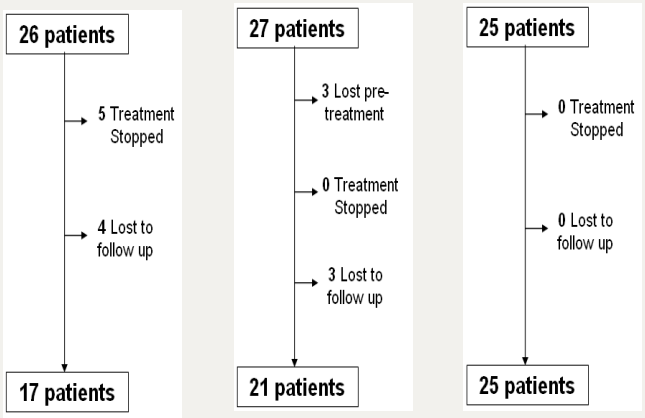
Chagas' disease, a protozoan infection by the kinetoplastid *Trypanosoma cruzi*, constitutes a major public health problem in Latin America. With the use of mouse models of both short- and long-term forms of the disease, the efficacy of D0870, a bis-triazole derivative, was tested. D0870 was able to prevent death and induced parasitological cure in 70 to 90 percent of animals, in both the short- and long-term disease. In contrast, currently used drugs such as nifurtimox or ketoconazole prolonged survival but did not induce significant curing effects. D0870 may be useful in the treatment of human long-term Chagas' disease, a condition that is currently incurable.

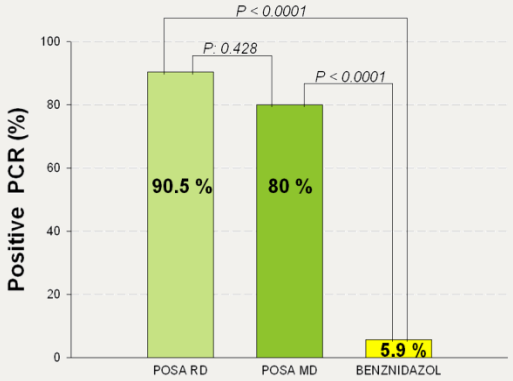
Antiproliferative Effects and Mechanism of A 56592 against *Trypanosoma* (*Schizotrypan* In Vitro and In Vivo Studies

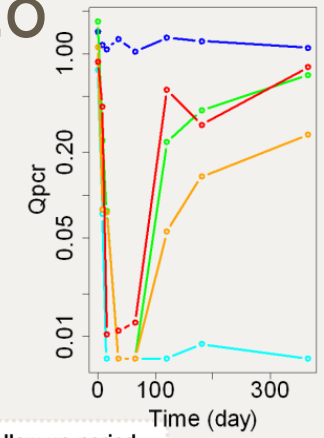
JULIO A. URBINA,[1]* GILBERTO PAYARES,[2] LELLYS M. CONTRERAS,[1] ANDREÍNA LIENDO,[1] CRISTINA SANOJA,[2] JUDITH MOLINA,[2] MARTA PIRAS,[3] ROMANO PIRAS,[3] NORMA PEREZ,[1,4] PATRICK WINCKER,[4] AND DAVID LOEBENBERG[5]

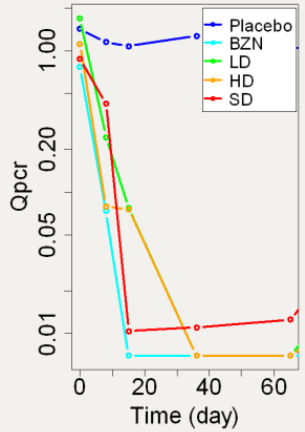
Results Adult Clinical Trials NCT0116967 and NCT01489228

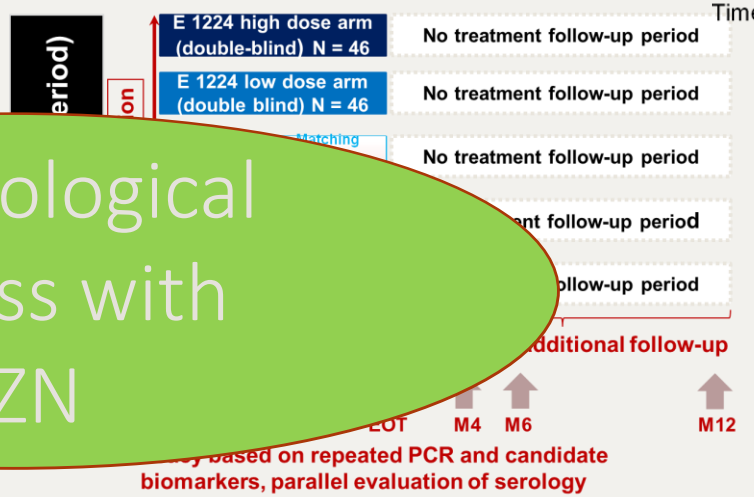












Parasitological Success with BZN

Sustained clearance At 12 months	No	n (%)	**(N=47)** 43 (91.5)	**(N=48)** 44 (91.7)	**(N=46)** 41 (89.1)	**(N=45)** 32 (71.1)	**(N=45)** 8 (19.0)	**(N=231)** **168 (72.7)**
	Yes	n (%)	4 (8.5)	4 (8.3)	5 (10.9)	13 (28.9)	37 (81.0)	**63 (27.3)**

Findings of Adult Clinical Trials

- Highlighted Major Translational Challenges
  - Need to translate research data to assays compatible with Drug Discovery & Development process
  - Better translation in vitro/in vivo models and the clinic
  - Address the right questions in our models
  - Better understanding of PK/PD relationships
- Importance of generating clinical trial data with standardised methodologies

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ANTIPARASITIC AGENTS

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9 December 2013

Accepted
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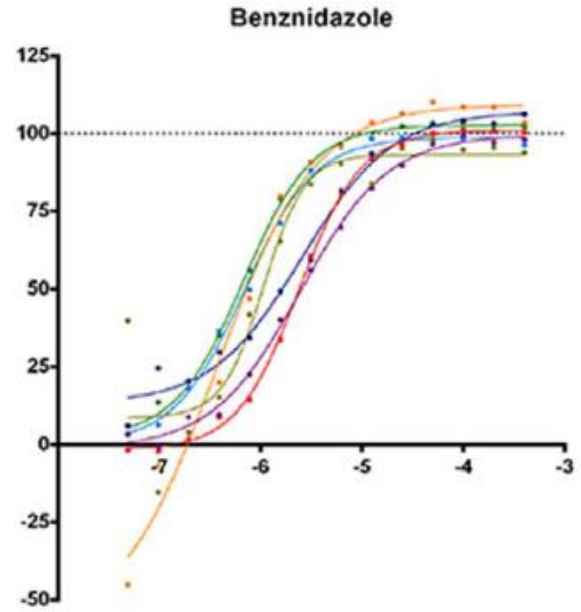
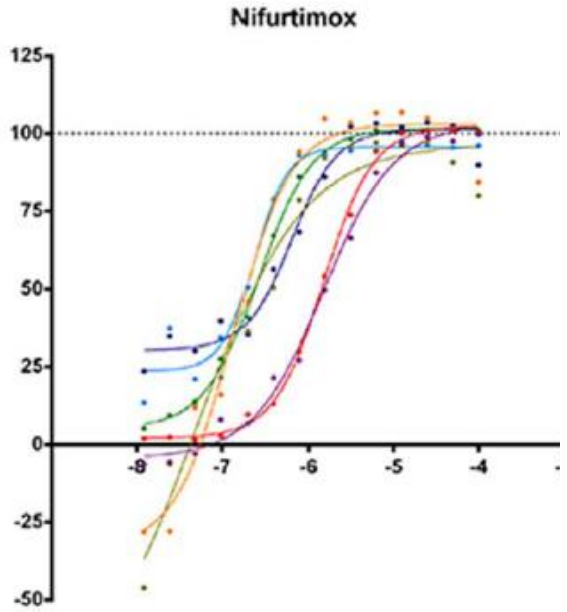
Nitroderivatives showed Potent In Vitro Activity across all T. cruzi DTUs

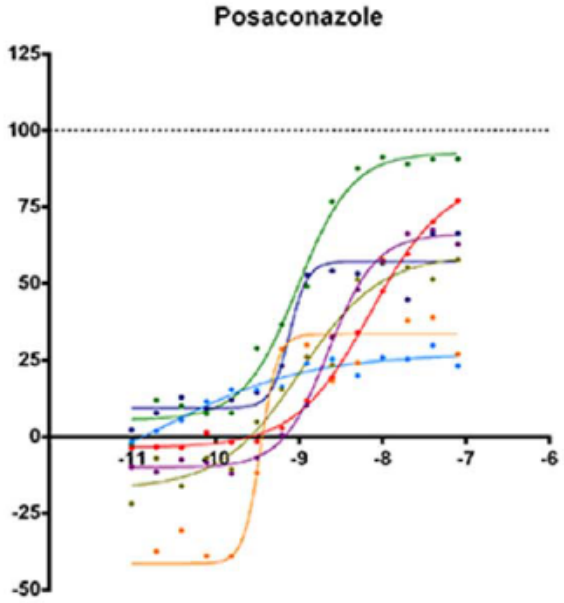
- >90% maximum activity
- Panel of different strains Dm28c (DTU I, Y (DTU II), ARMA13 cl1 (DTU III), ERA cl2 (DTU IV), 92-80 cl2 (DTU V), CL Brener (DTU VI), and Tulahuen (DTU VI)

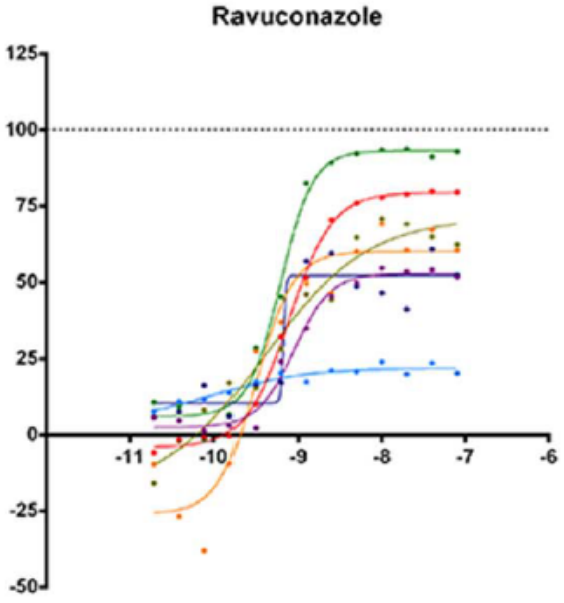
Azoles variable pattern

- <<50% maximum activity for some of the tested strains/lineages
- Considerable dispersion









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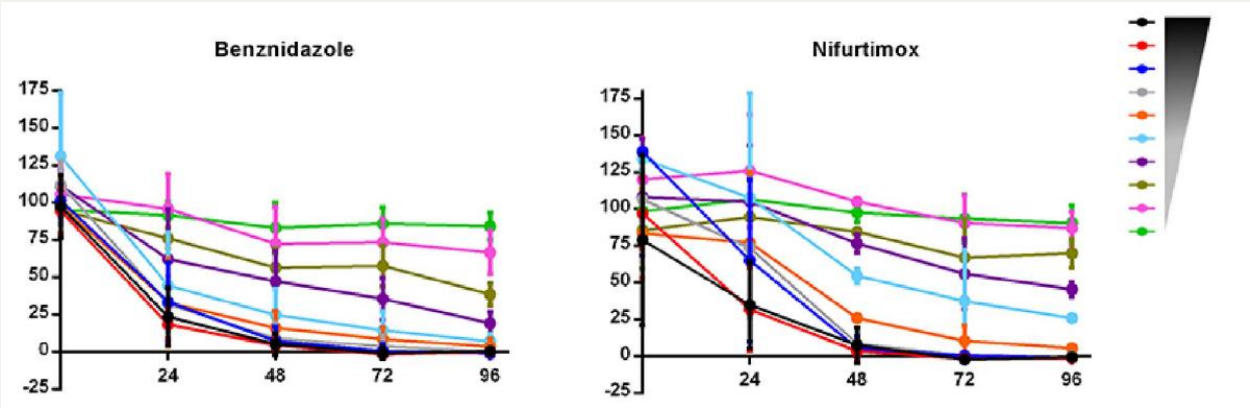

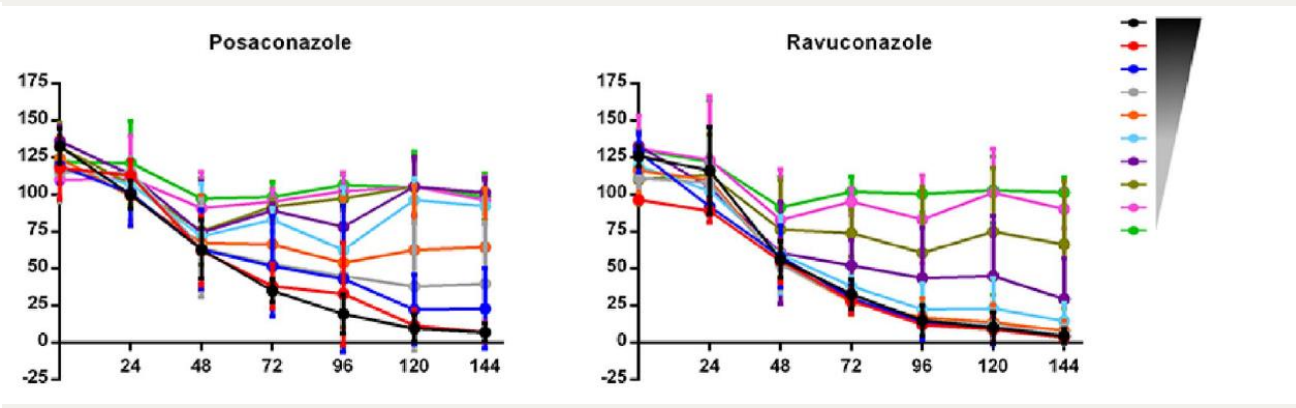

International Journal for Parasitology: Drugs and Drug Resistance 6 (2016) 165–170

Contents lists available at ScienceDirect

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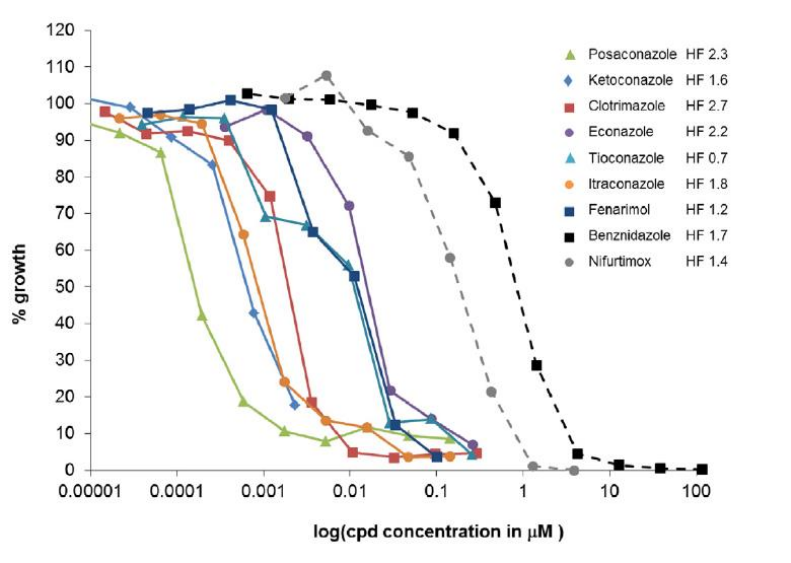
Monica Cal [a, b], Jean-Robert Ioset [c], Matthia A. Fügi [a, b], Pascal Mäser [a, b], Marcel Kaiser [a, b, *]

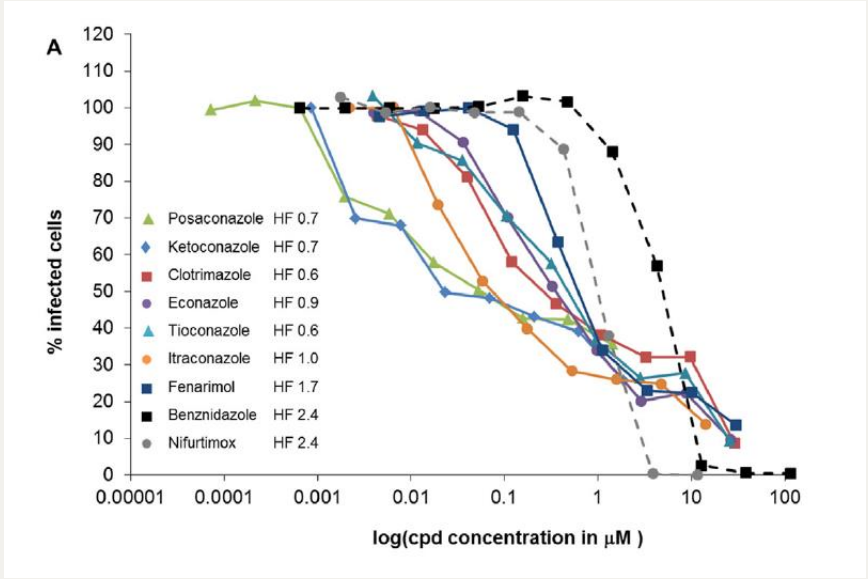
[a] Swiss Tropical and Public Health Institute, CH-4051, Basel, Switzerland
[b] University of Basel, CH-4003, Basel, Switzerland
[c] Drugs for Neglected Diseases Initiative, CH-1202, Geneva, Switzerland

In vitro evaluation of cidal activity

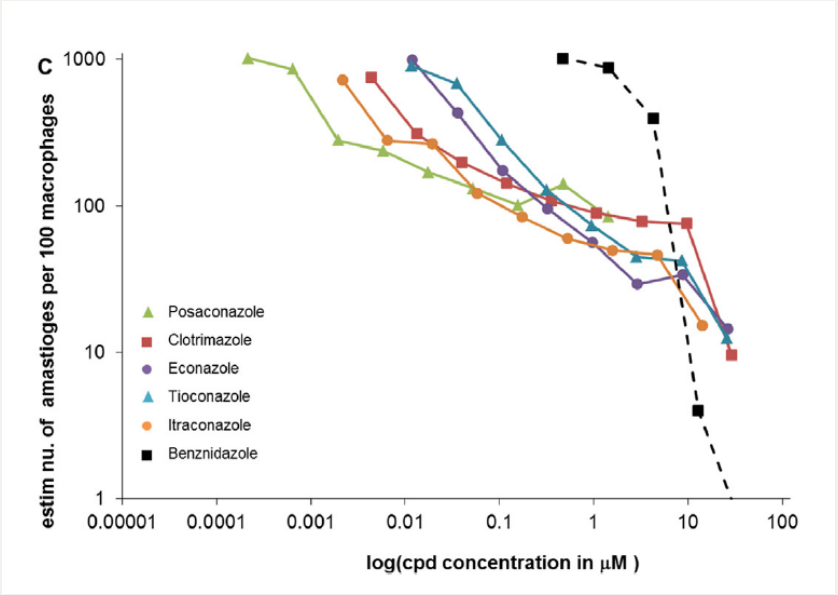
- Mouse peritoneal macrophage system – long term testing and washout experiments
- Giemsa readout : >> sensitive and accurate
- Nitros response versus Azoles
  - Azoles –
    - flat dose response curve
    - Inability to kill all parasites in 96h
  - Nitros
    - 100% clearance in infected cells
    - BZN 40uM <1 parasite/100 macrophage



In vitro sensitivity after 96 hours of exposure – B-galactosidase method



In vitro sensitivity after 96 hours of exposure – Giemsa



Estimated number of amastigotes/100 macrophages after 96 hours of exposure

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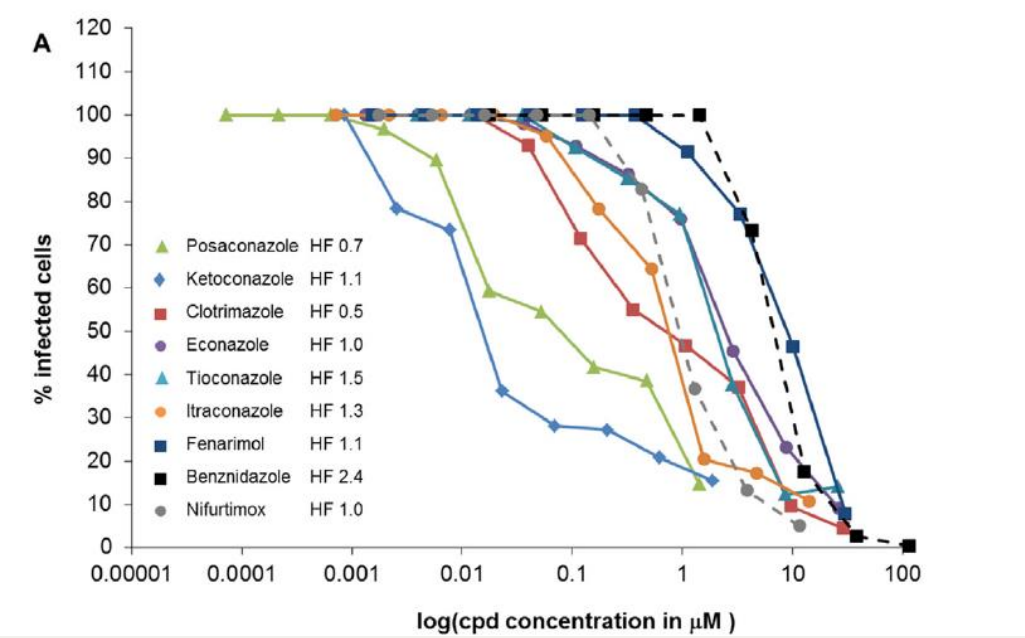
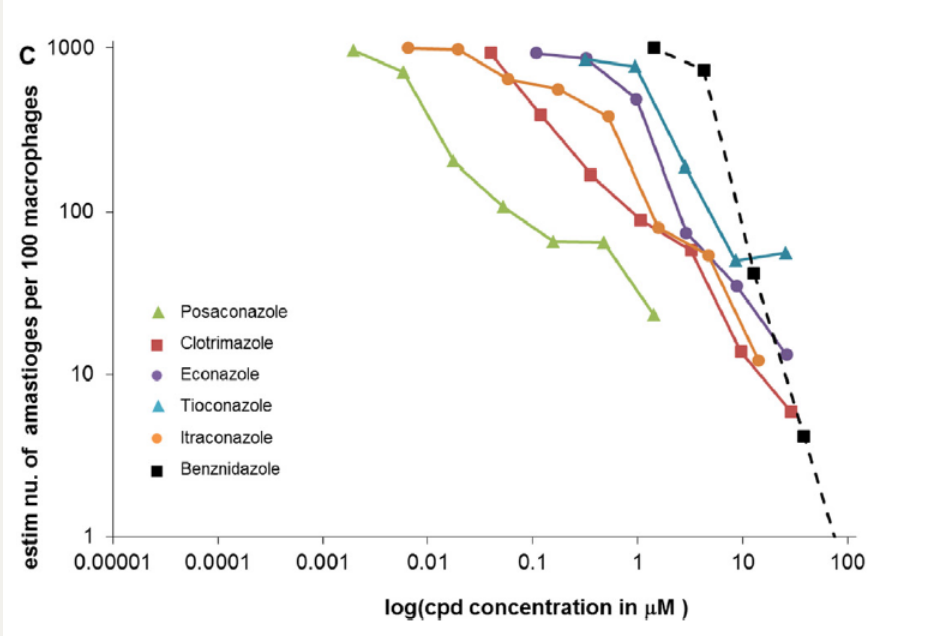
In vitro evaluation of cidal activity

- Washout experiments
- Nitros response versus Azoles
  - Azoles –
    - Shift >200% in IC50
    - Viable amastigotes
  - Nitros
    - No significant change



Drug sensitivity % infected cells after 96h washout and 168 hours recovery



Estimated number of amastigotes/100 macrophages after 96h washout and 168 hours recovery

9

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Received: 04 August 2016
Accepted: 28 September 2016
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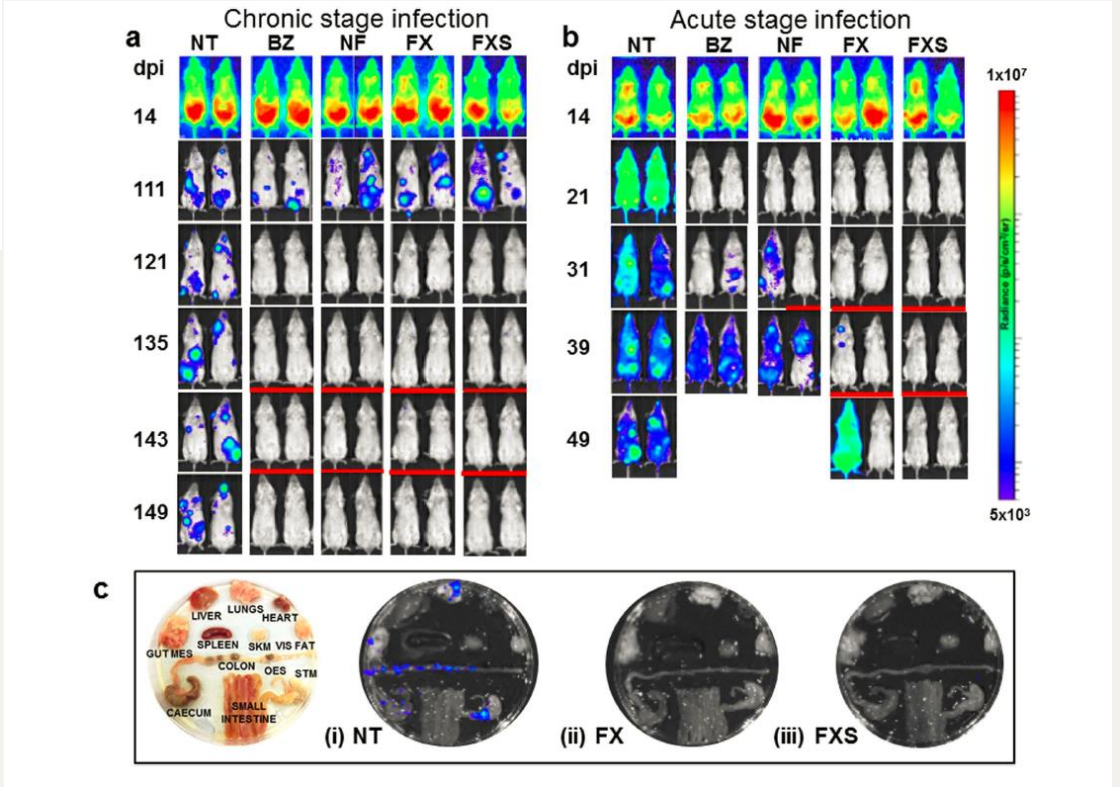
Cl Brener model – evaluation of nifurtimox, benznidazole, fexinidazole and fexinidazole sulphone



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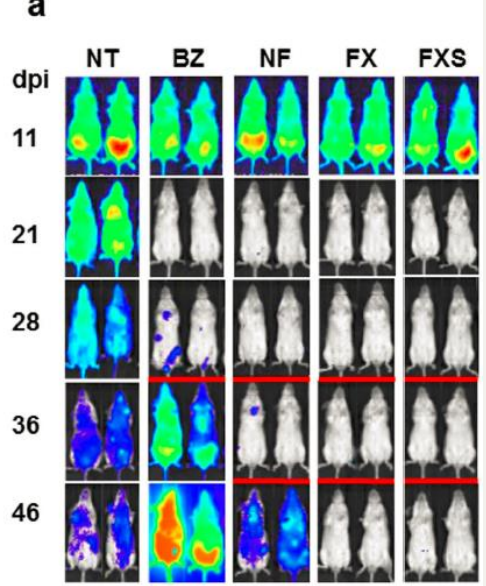
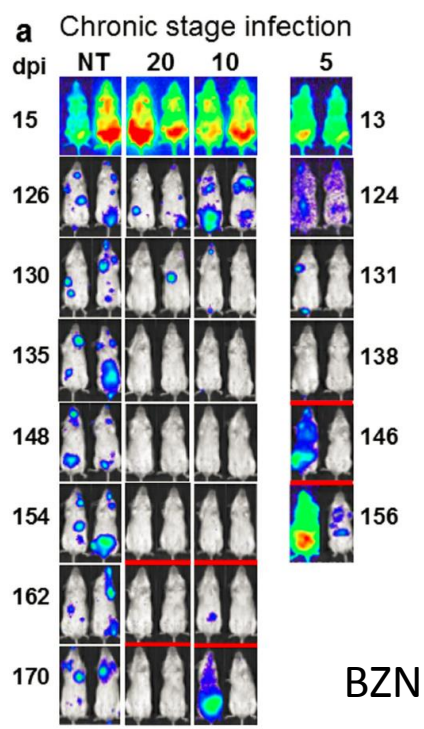
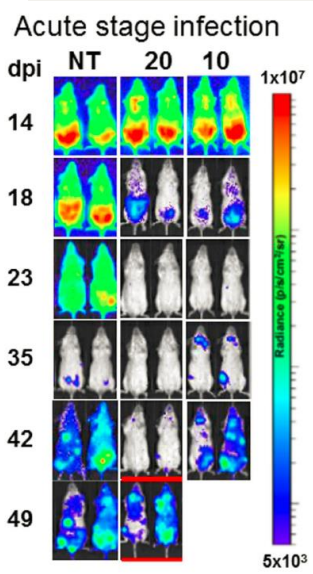
Cure rates – Dose and duration dependent

T. cruzi CL Brener strain			Chronic Infection Cure Rate			Acute Infection Cure Rate		
			Treatment length			Treatment length		
Drug	Mouse strain	Dose (mg kg^{-1})	5 days	10 days	20 days	5 days	10 days	20 days
BZ	BALB/c	10 qd	—	0% (0/6)	17% (1/6)	—	0% (0/6)	0% (0/6)
	BALB/c	30 qd	0% (0/6)	67% (4/6)	100% (6/6)	—	0% (0/6)	33% (2/6)
	BALB/c	100 qd	100% (11/11)*	100%(15/15)*	100%(11/11)*	0% (0/30)	0% (0/6)	93%(14/15)
	BALB/c	50 bid	—	100% (6/6)	—	0% (0/6)	—	—
NF	BALB/c	30 qd	33% (2/6)	83% (5/6)	—	—	—	—
	BALB/c	100 qd	90% (9/10)	—	—	0% (0/6)	17 (1/6)	—
	BALB/c	50 bid	—	—	—	17% (1/6)	—	—
FX	BALB/c	30 qd	50% (3/6)	100% (6/6)	—	—	—	—
	BALB/c	100 qd	100% (8/8)	—	—	67% (4/6)	100 (6/6)	—
	BALB/c	50 bid	—	—	—	100% (6/6)	—	—
FXS	BALB/c	30 qd	17% (1/6)	100% (6/6)	—	0% (0/6)	—	—
	BALB/c	50 qd	100% (6/6)	—	—	0% (0/6)	—	—
	BALB/c	100 qd	100% (7/7)	—	—	100%(15/15)	—	—
	BALB/c	50 bid	—	—	—	83% (5/6)	—	—
T. cruzi JR strain								
BZ	BALB/c	100 qd	—	—	—	0% (0/6)	—	—
	C3H	100 qd	60% (3/5)	—	—	0% (0/5)	—	—
FXS	BALB/c	100 qd	—	—	—	80% (4/5)	—	—
	C3H	100 qd	100% (5/5)	—	—	80% (4/5)	—	—



5 days treatment





BZN 30 mg/kg

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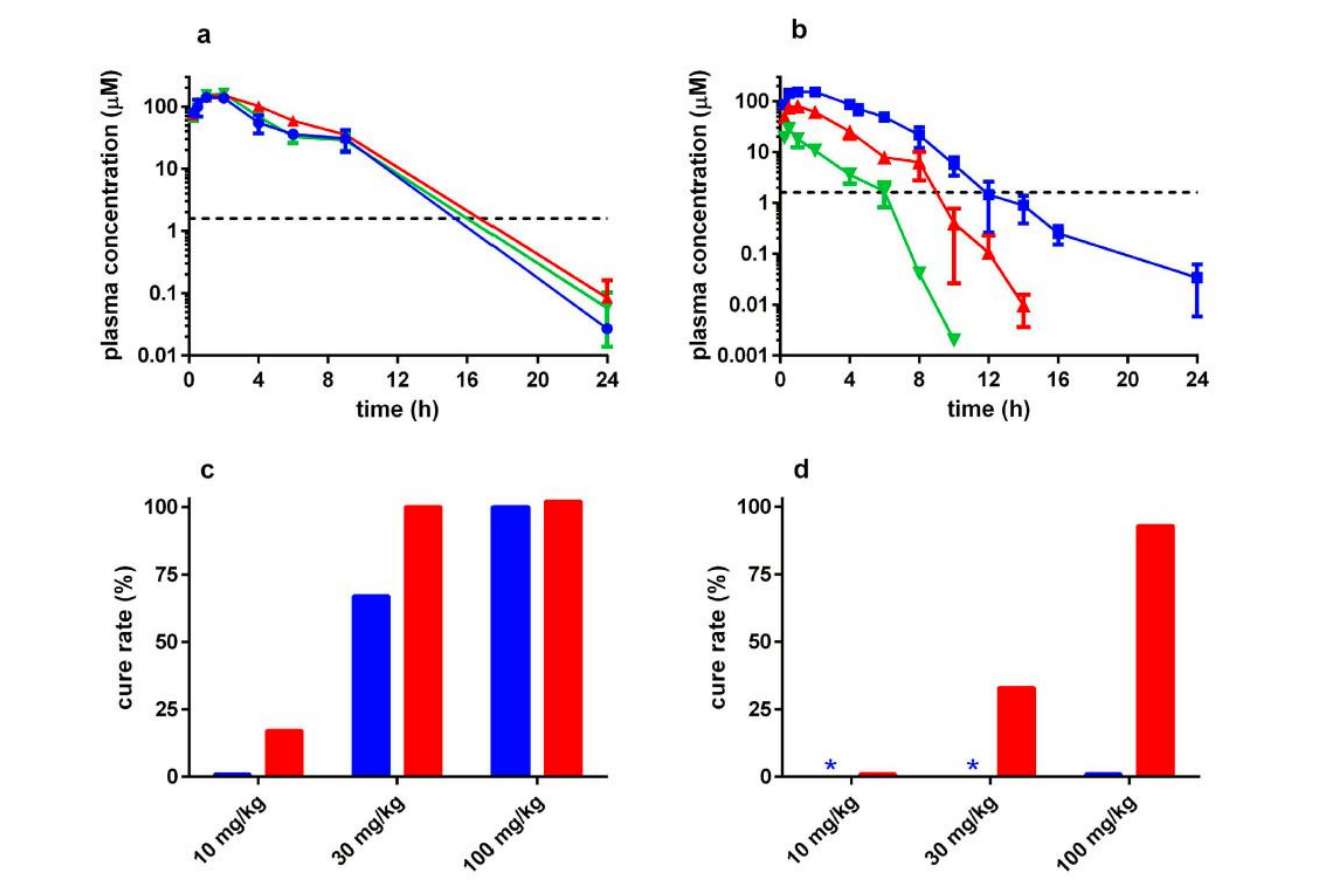
Pharmacokinetic and cure data for BZN



A. Plasma concentration versus time after 100 mg/kg uninfected, acute and chronic

- No difference in PK between acute and chronic

B. Plasma concentration with single dose 10, 30, 100 mg/kg

C. Cure rates after10, 20 days in chronic stage mice

D. Cure rates after 10, 20 days in acute stage mice

- Association between dose/exposure and effectiveness

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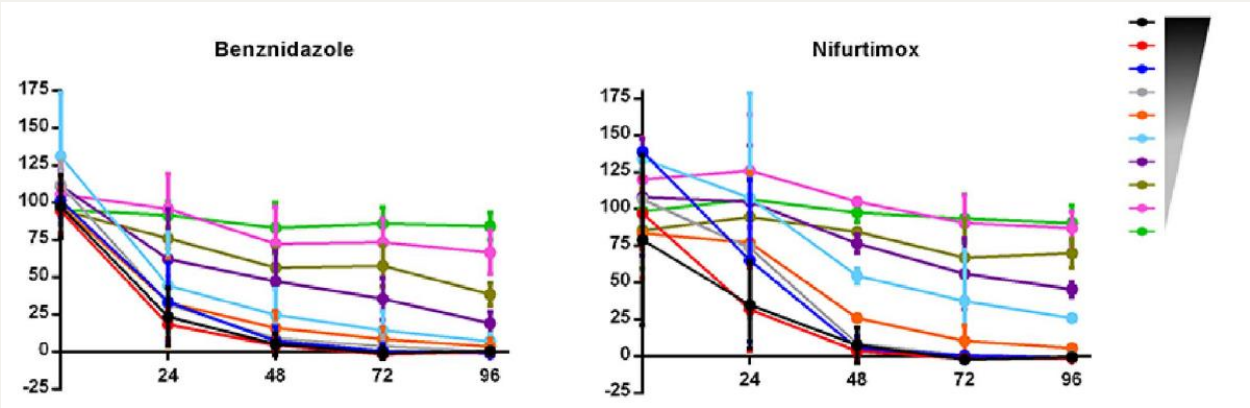
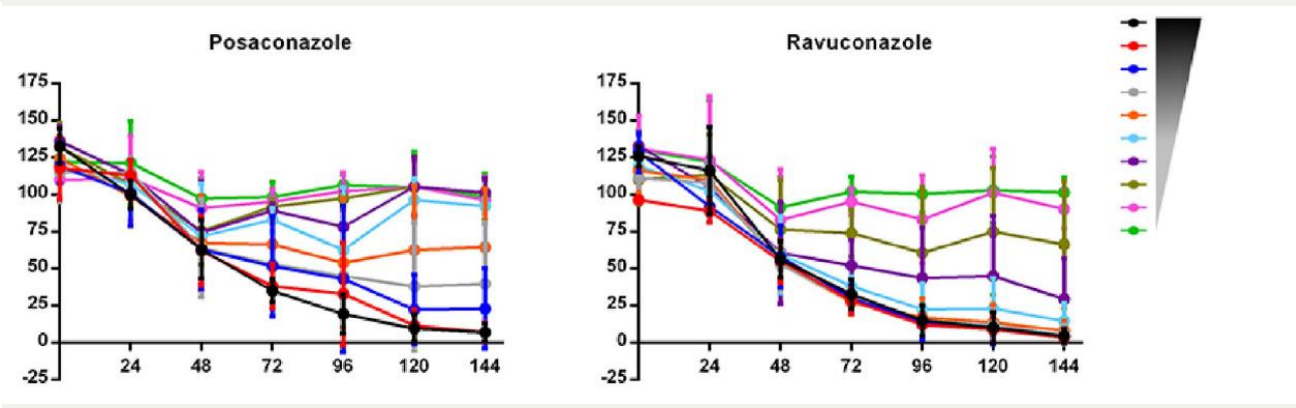
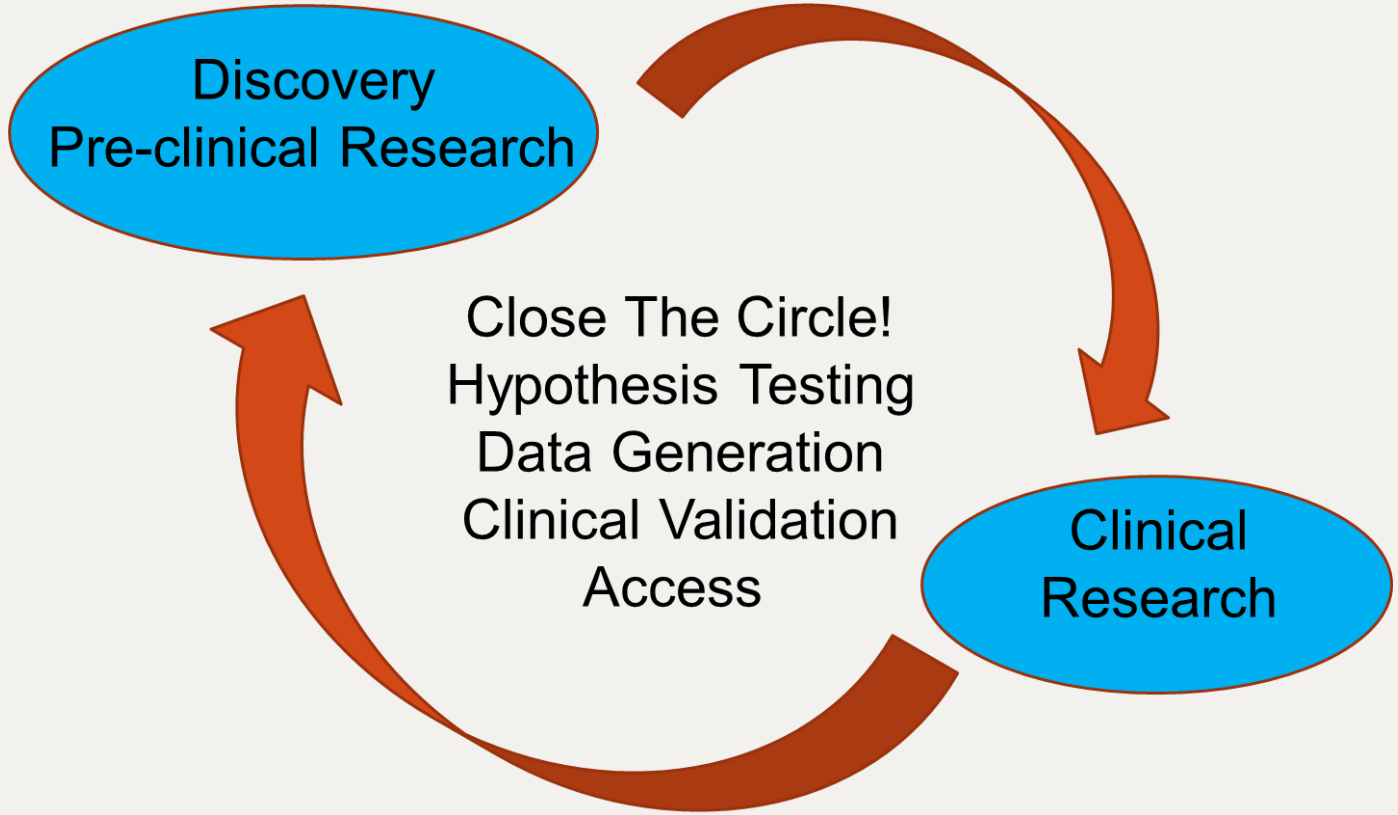




Implications for R&D

“The greatest enemy of knowledge is not ignorance, but the illusion of knowledge”
Stephen Hawking



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