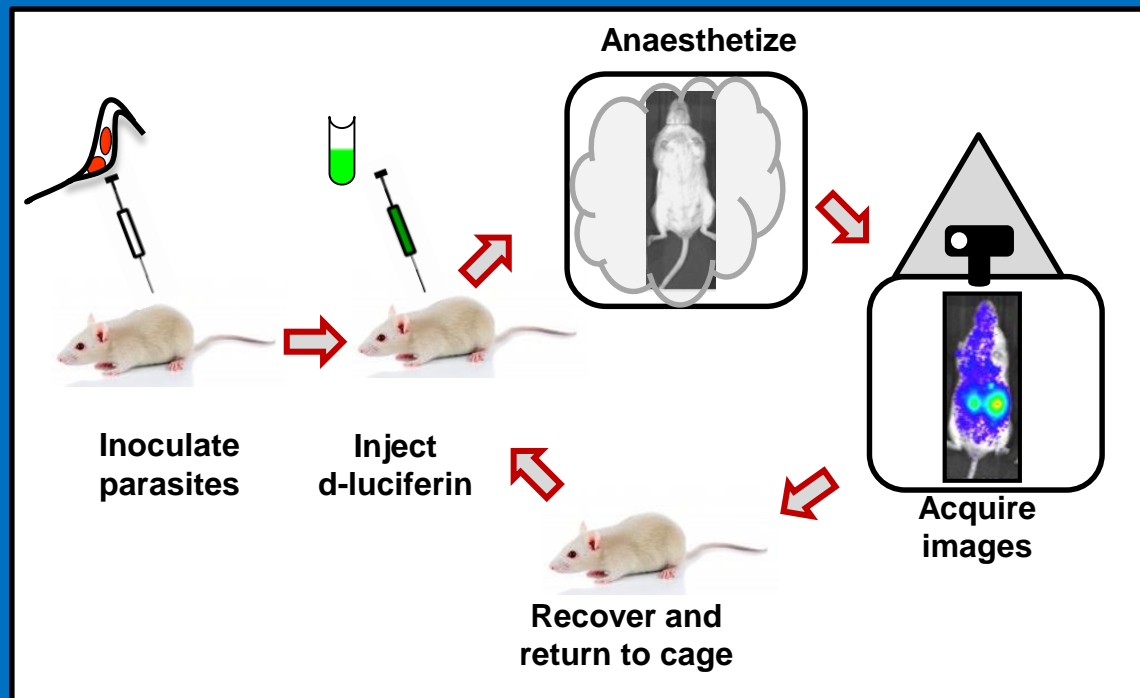
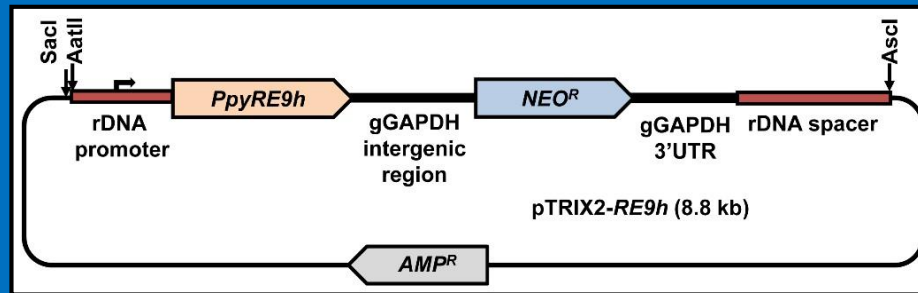


“Exploring drug efficacy in experimental Chagas disease using highly sensitive bioluminescence imaging”

John Kelly

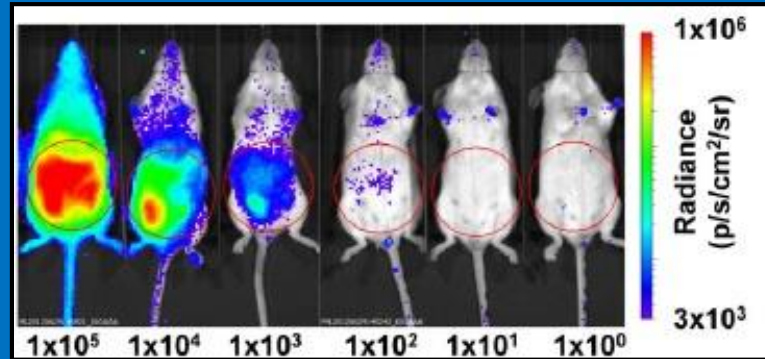
Department of Pathogen Molecular Biology
London School of Hygiene and Tropical Medicine

In vivo imaging

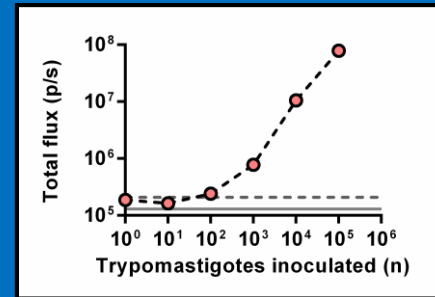
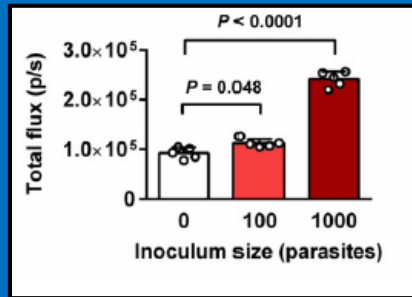


Validating the model

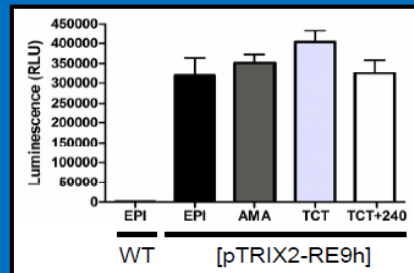
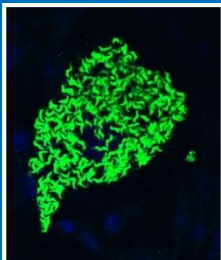
The limit of detection



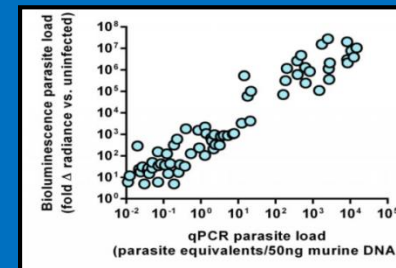
Correlation between bioluminescence and parasite burden



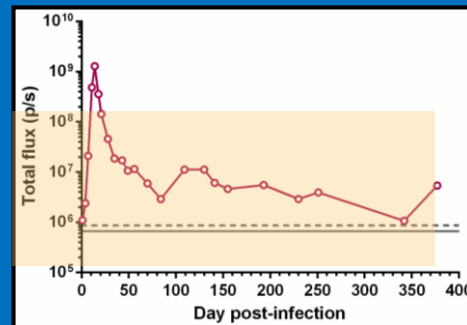
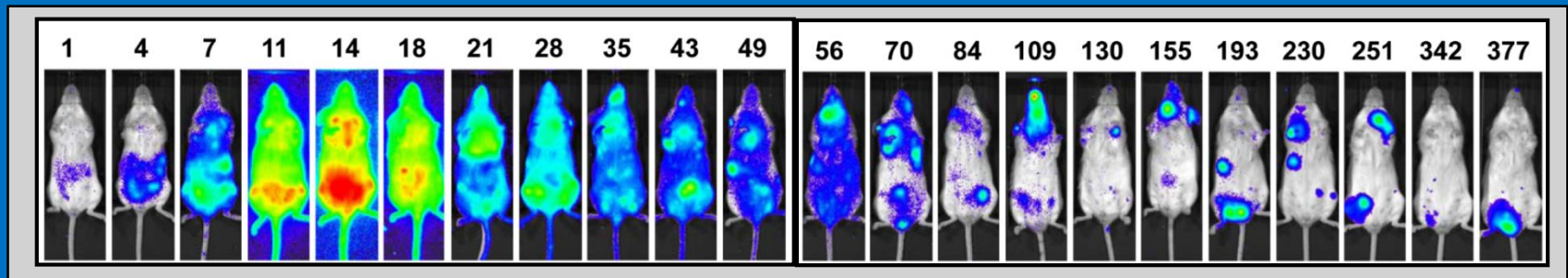
Profile of expression



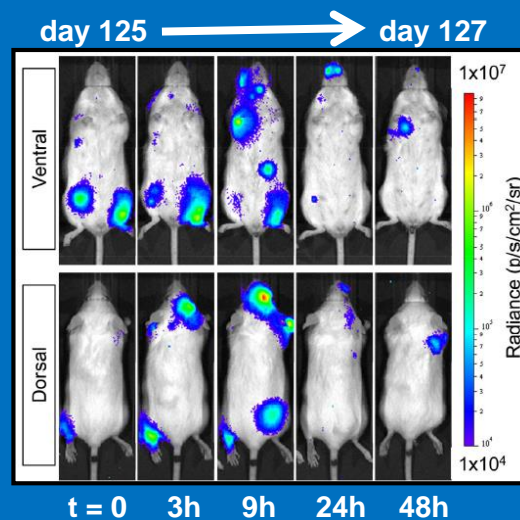
Correlation with qPCR



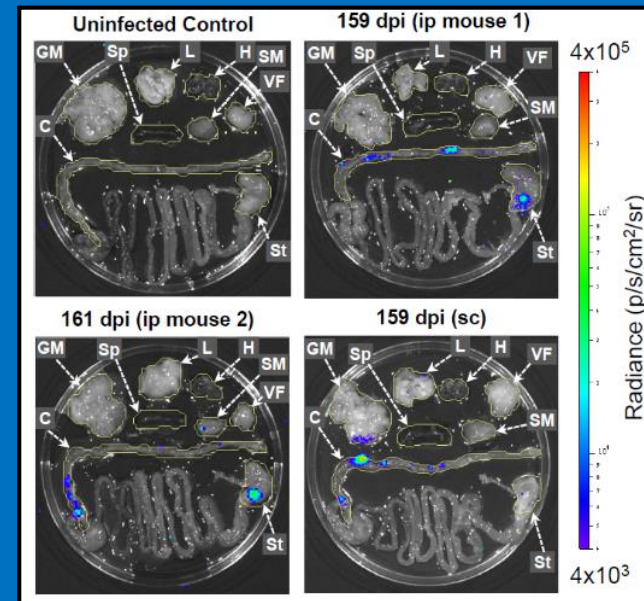
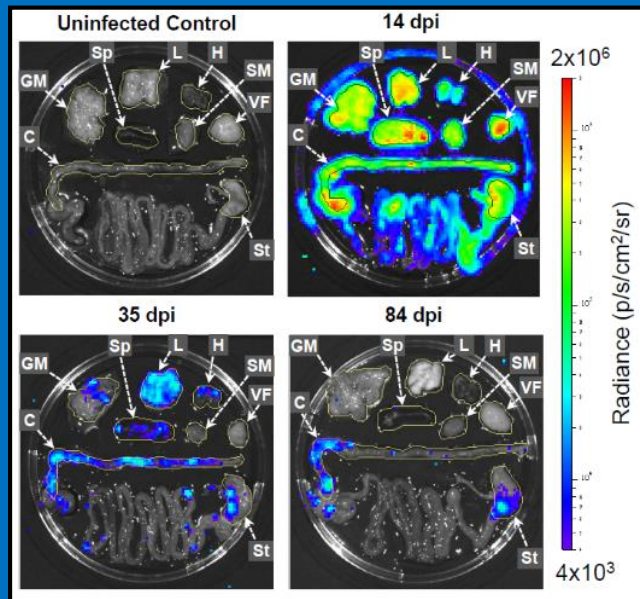
Visualising chronic *Trypanosoma cruzi* infection



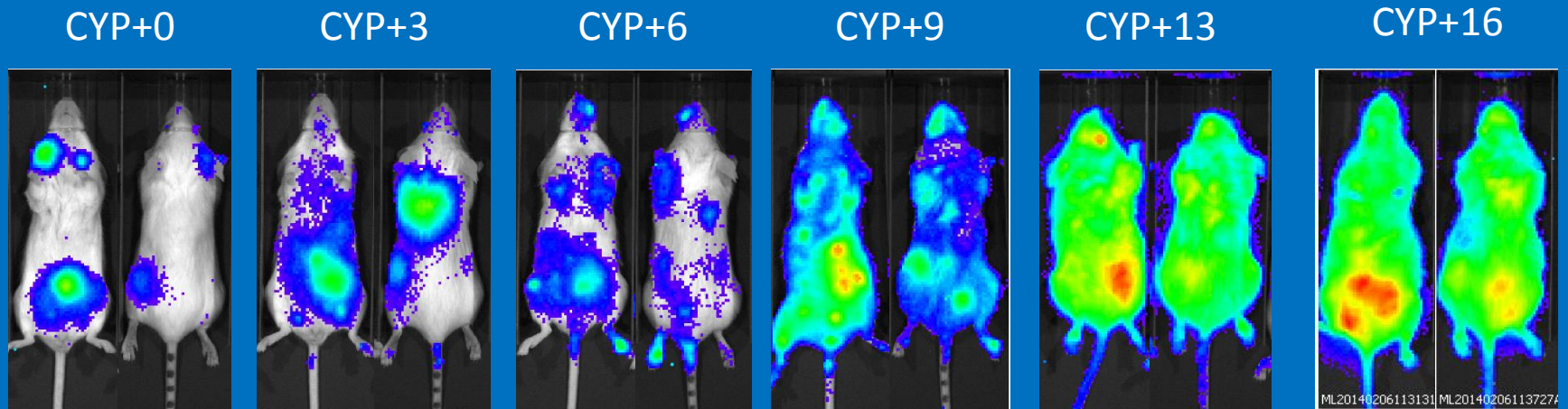
Chronic *T. cruzi* infection : dynamic not latent!



The GI tract is the major site of parasite persistence in chronic infections



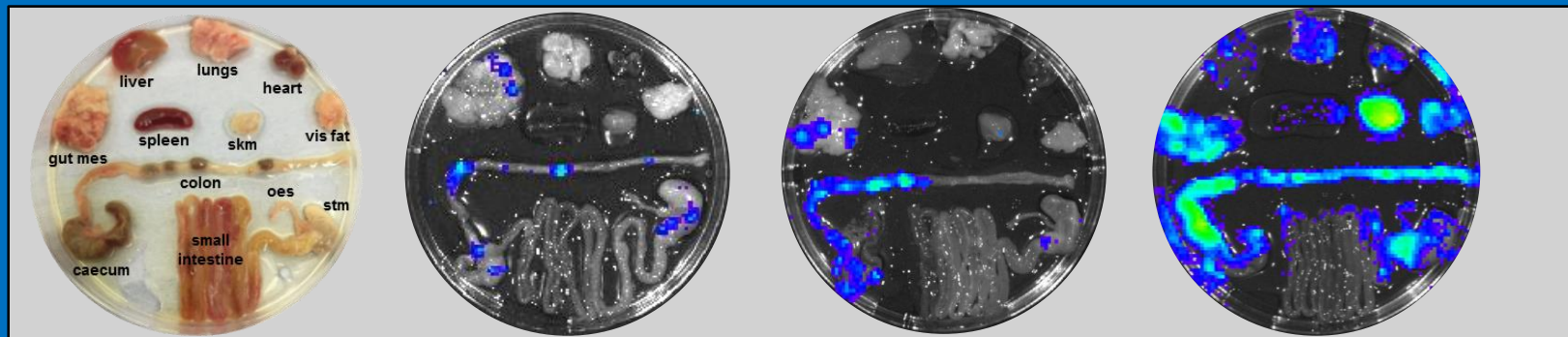
Inducing relapse by immunosuppression



Day 0

Day 6

Day 9



cyclophosphamide



Summary - 1

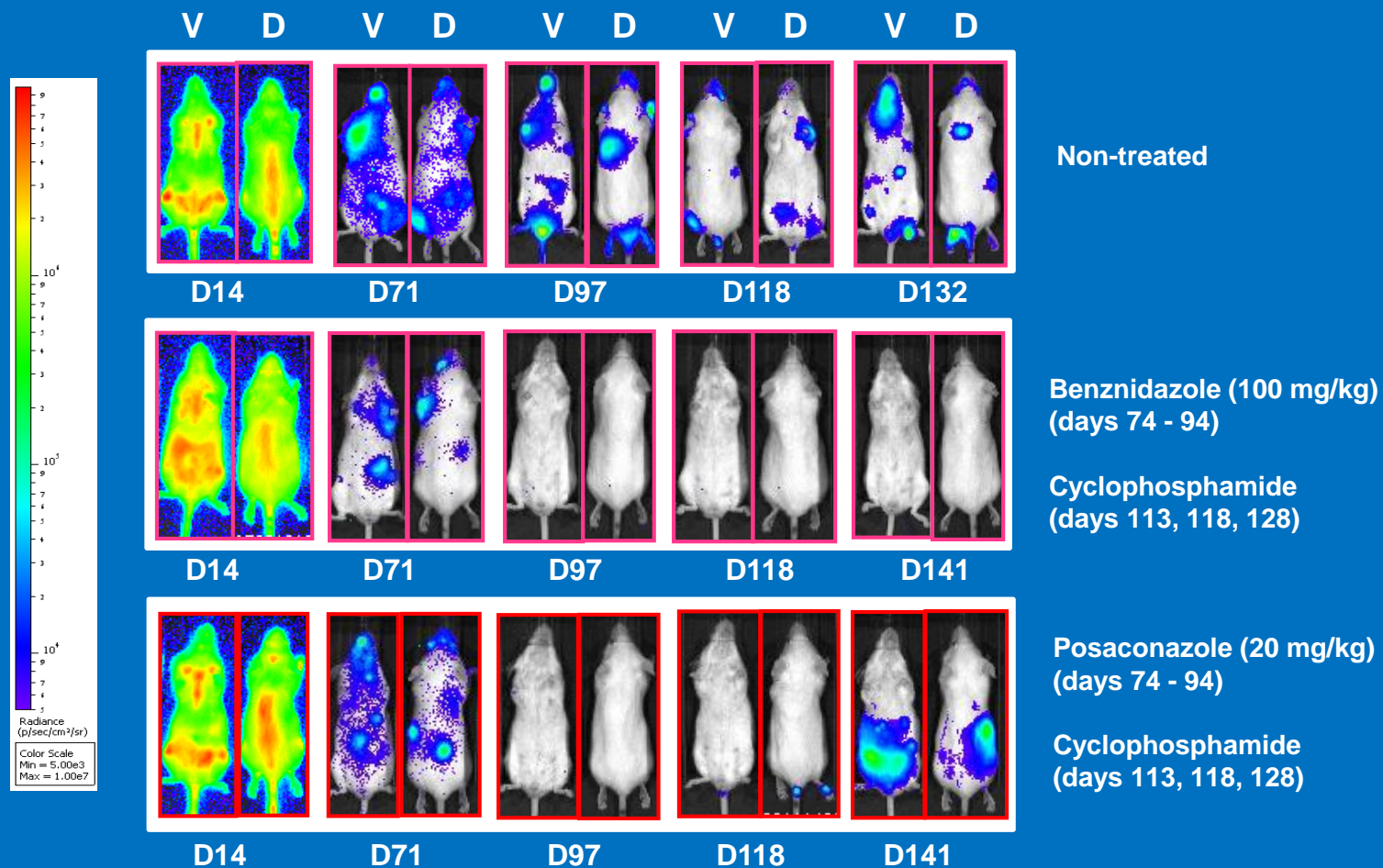
- BLI can be used to track chronic *T. cruzi* infections in mouse models
- The GI tract is the major site of parasite persistence in chronic infections
- Chronic *T. cruzi* infections are highly focal and spatiotemporally dynamic
- BLI can be used as a tool to:

Phenotype genetically engineered parasite mutants

Investigate the mechanisms of pathogenesis

Assess drug efficacy

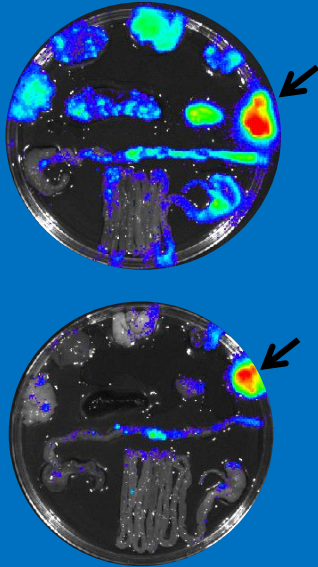
Chronic stage infection: Comparing benznidazole and posaconazole



Drug	Disease state	Treatment time	Daily dose	Number cured
Benznidazole	chronic	20 days	100 mg/kg	5/5
Benznidazole	acute	20 days	100 mg/kg	5/5
Posaconazole	chronic	20 days	20 mg/kg	0/9
Posaconazole	acute	20 days	20 mg/kg	3/19

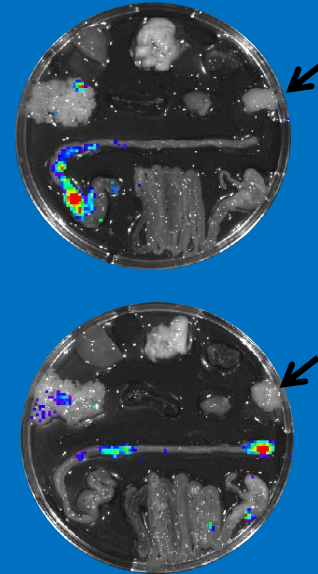
Parasite recrudescence following posaconazole treatment

Treated days 14 – 33
Immunosuppressed
Imaged day 74

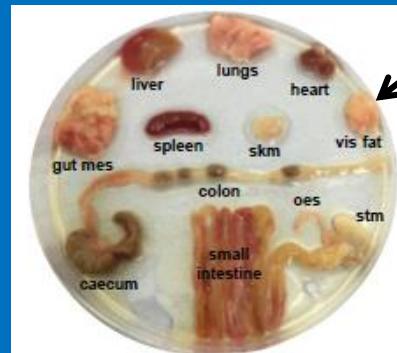


9/16 display high level
infection in adipose tissue

Treated days 74 – 93
Immunosuppressed
Imaged day 147

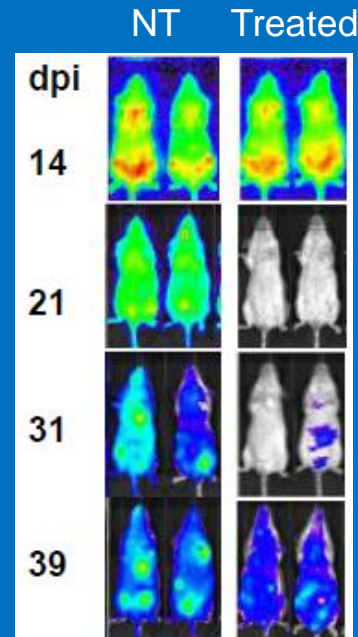
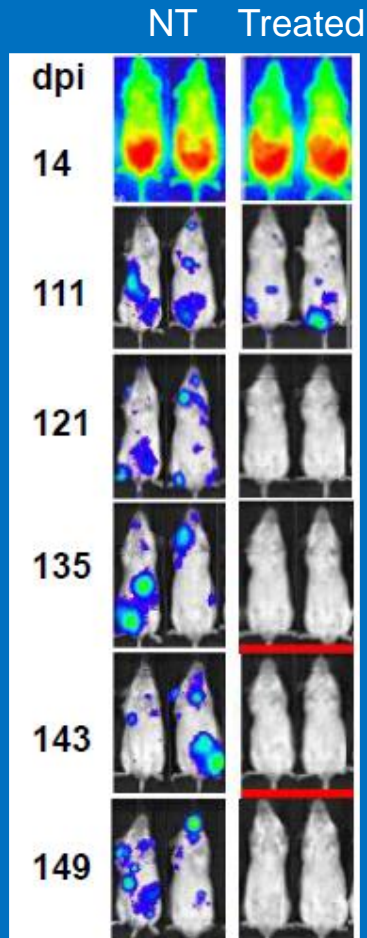
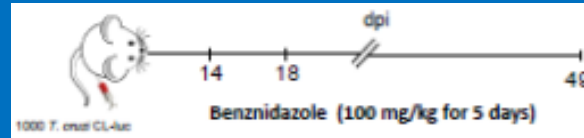
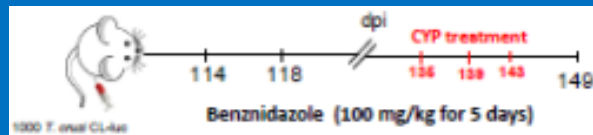


1/9 display high level
infection in adipose tissue



Benznidazole cures chronic stage infections more readily than acute stage infections

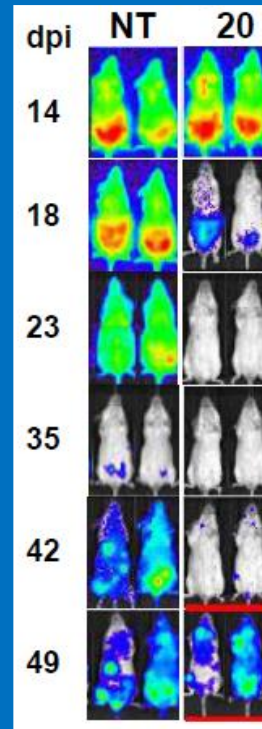
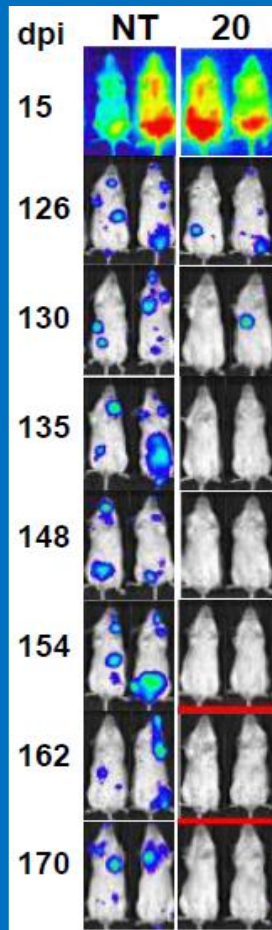
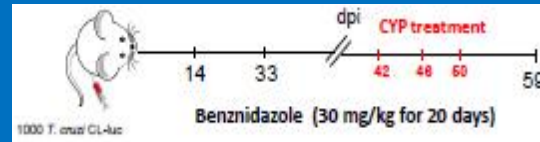
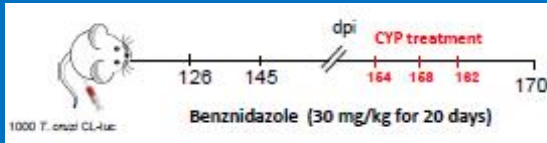
100 mg/kg qd for 5 days



Drug	Treatment (days)	Dose (mg/kg)	Cure rate Chronic	Cure rate Acute
Benznidazole	20	100	100% (11/11)	93% (14/15)
Benznidazole	10	100	100% (15/15)	0% (0/6)
Benznidazole	5	100	100% (11/11)	0% (0/30)

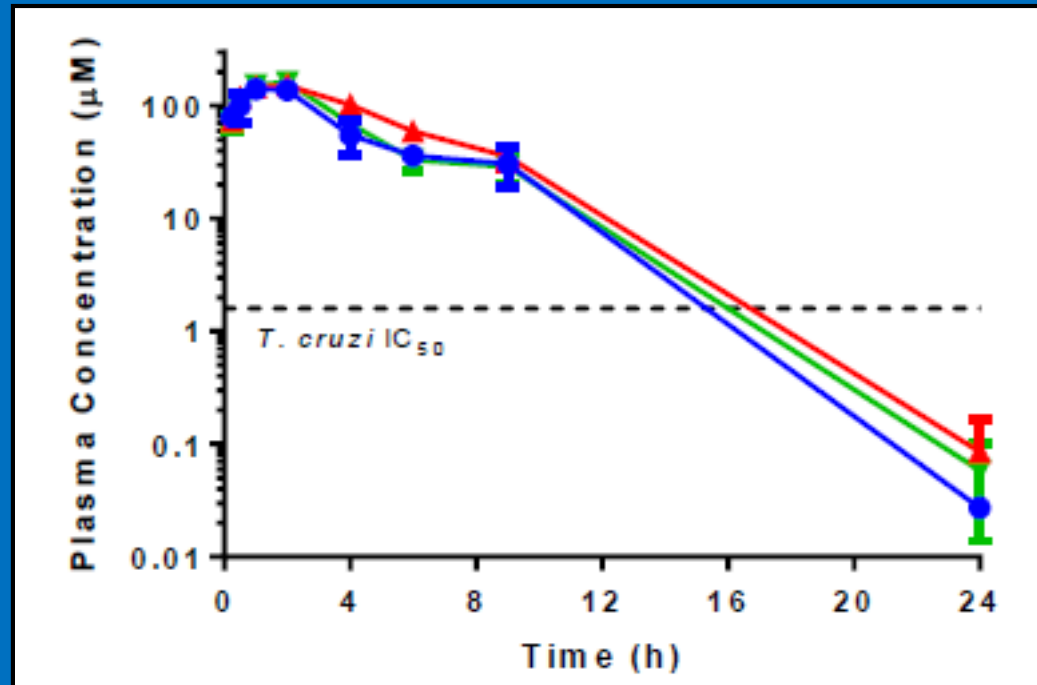
Benznidazole cures chronic stage infections more readily than acute stage infections

30 mg/kg qd for 20 days

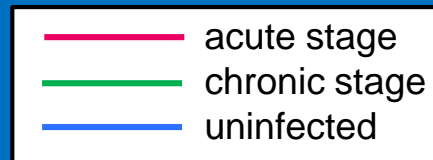


Drug	Treatment (days)	Dose (mg/kg)	Cure rate Chronic	Cure rate Acute
Benznidazole	20	30	100% (6/6)	33% (2/6)
Benznidazole	10	30	67% (4/6)	0% (0/6)
Benznidazole	5	30	0% (0/6)	-

Does differential drug exposure account for disease stage-specific benznidazole efficacy?

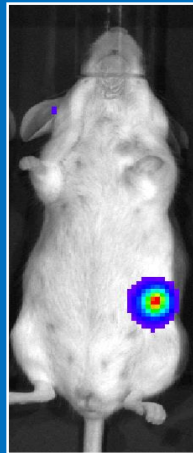
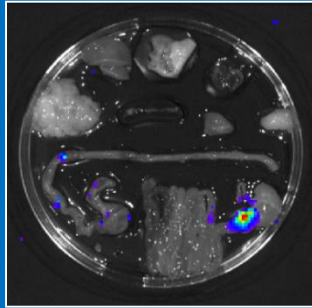


100 mg/kg single oral dose

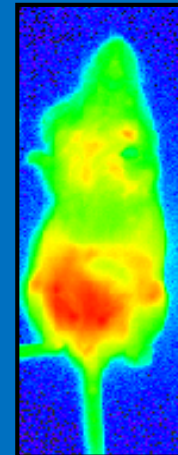
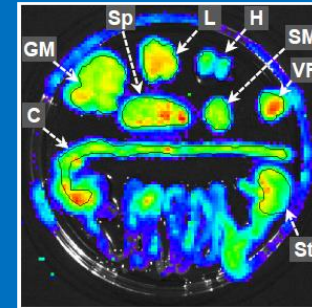


Why is benznidazole more effective against the chronic stage?

CHRONIC

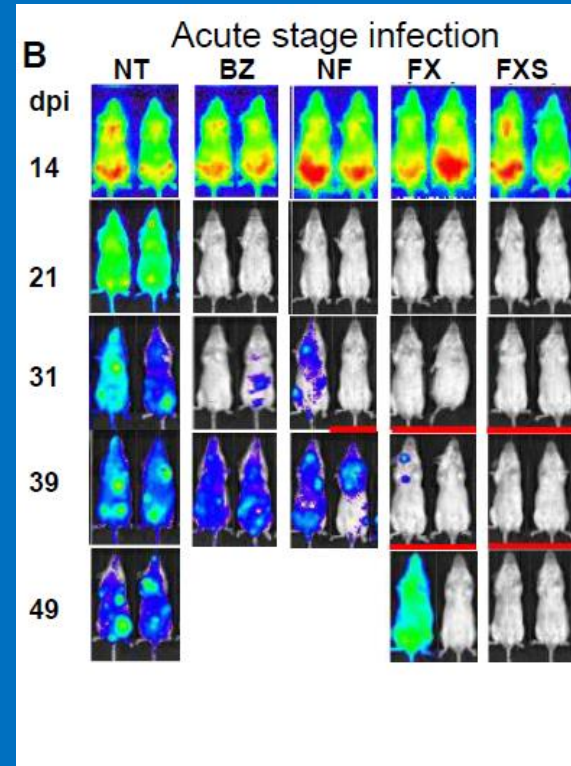
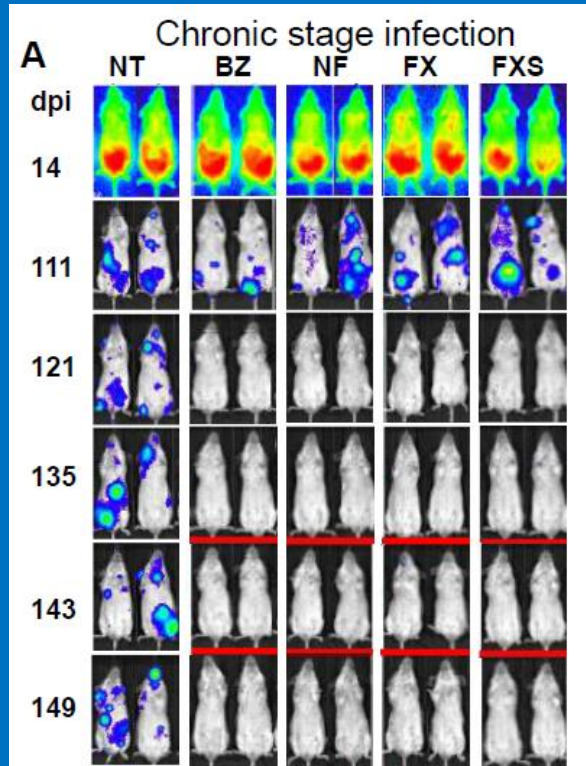


ACUTE



Do other nitroheterocycles show the same stage-specific profile?

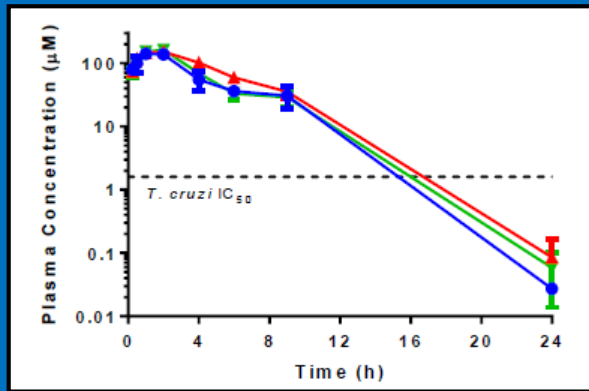
100 mg/kg qd for 5 days



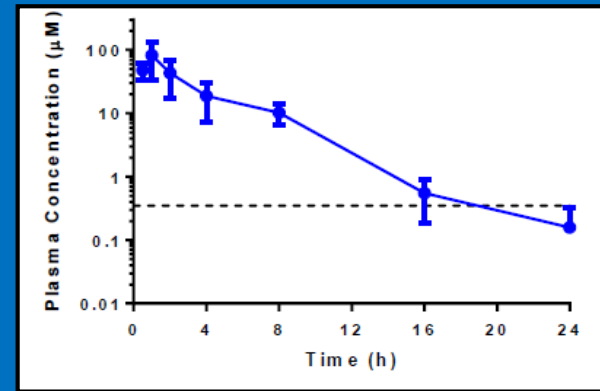
Drug	Treatment (days)	Dose (mg/kg)	Cure rate Chronic	Cure rate Acute
Benznidazole	5	100	100% (11/11)	0% (0/30)
Nifurtimox	5	100	90% (9/10)	0% (0/6)
Fexinidazole	5	100	100% (8/8)	67% (4/6)
Fexinidazole sulfone	5	100	100% (7/7)	100% (15/15)

Pharmacokinetic parameters

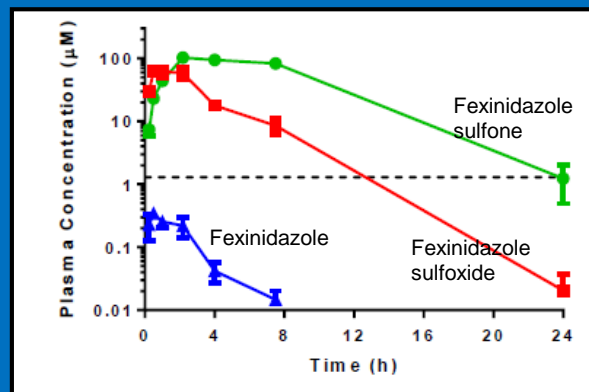
Benznidazole



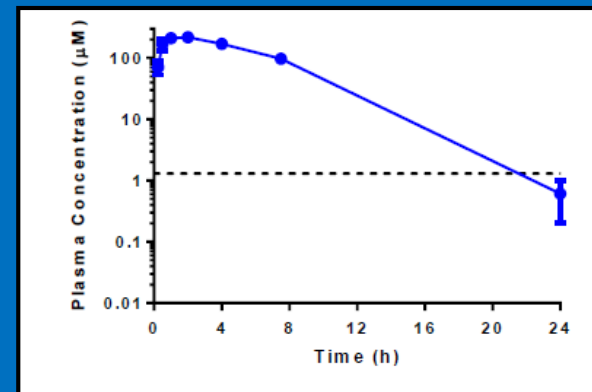
Nifurtimox



Fexinidazole



Fexinidazole sulfone

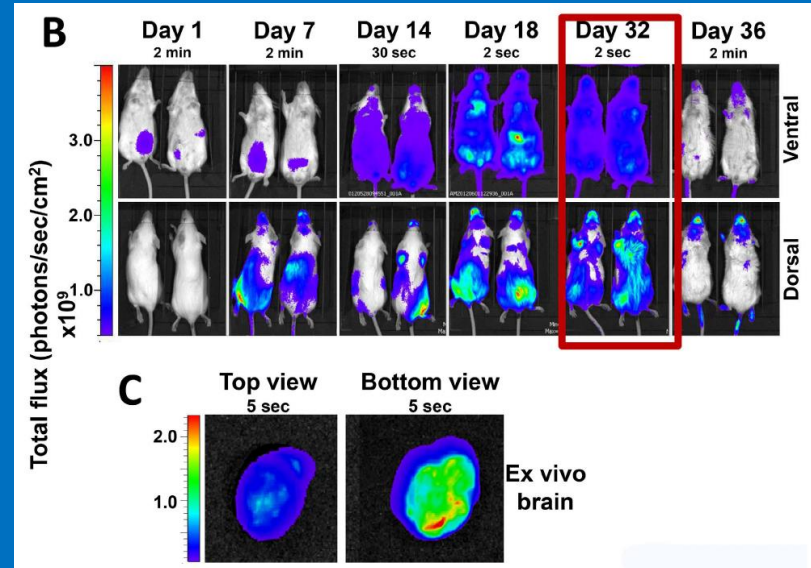
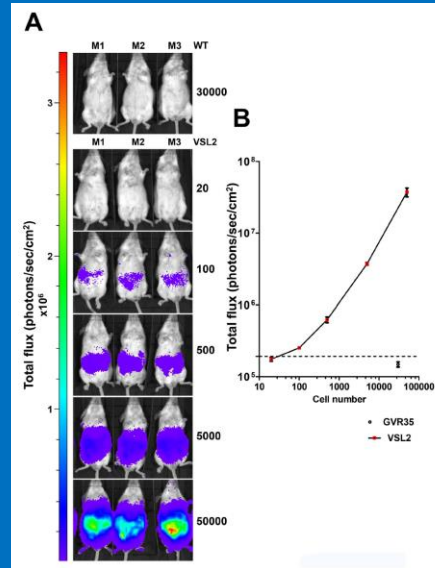


Summary – 2

- Posaconazole has limitations as a treatment for experimental Chagas disease
- Adipose tissue is an important site of parasite recrudescence following posaconazole treatment of acute stage infections
- Benznidazole cures chronic stage infections more effectively than acute stage infections
- At the same dose, fexinidazole sulphone is more effective than benznidazole as a curative treatment for acute stage *T. cruzi* infections
- PCR-based methodologies have a tendency to over-estimate cure rates

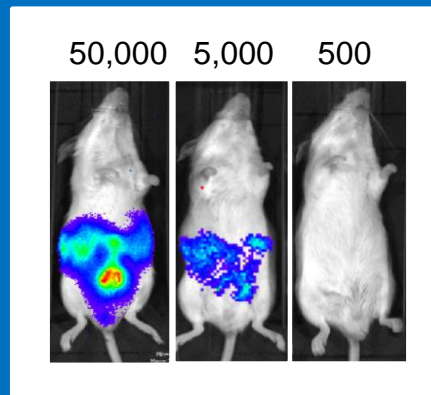
In vivo imaging of other trypanosomatid infections

Trypanosoma brucei
GVR35 strain



McLatchie A. et al (2013) *PLOS NTD*

Leishmania donovani
(DD8 strain)



Taylor M.C. (unpublished)



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