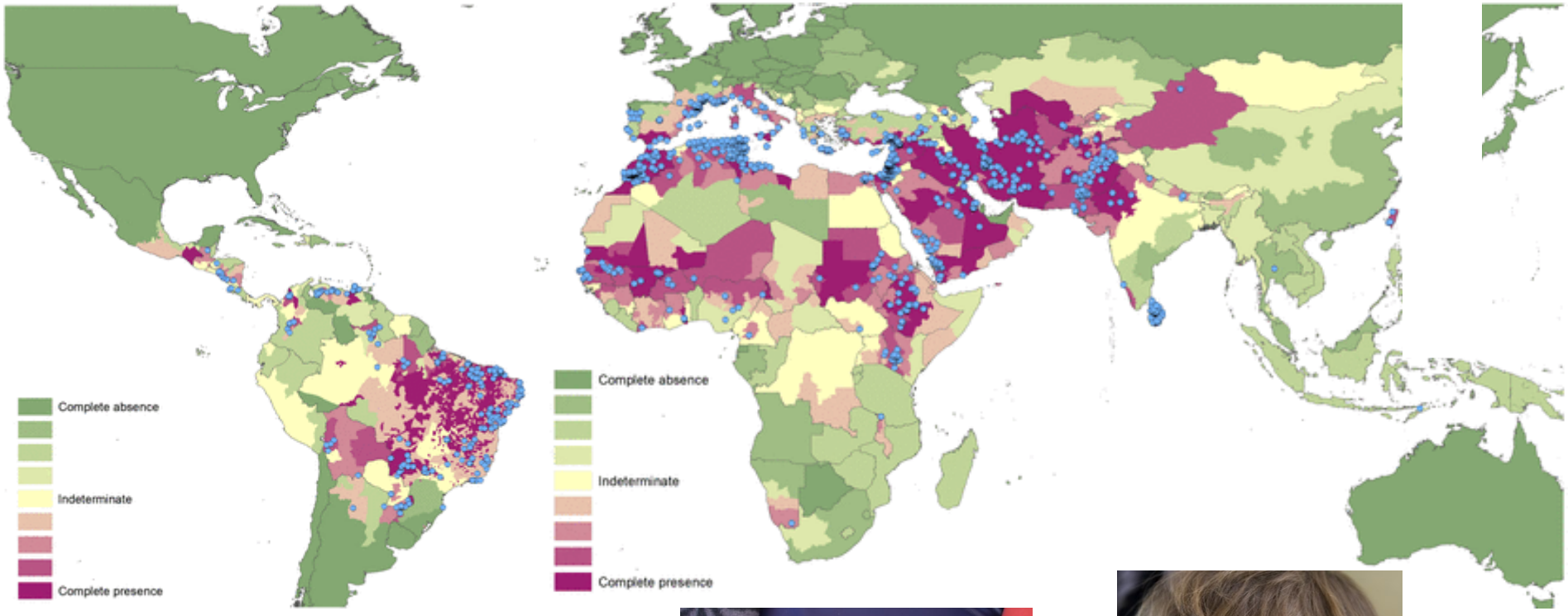
UC San Diego

Targeting Leishmaniasis:
Disease Models and Drug Repurposing

Laura-Isobel McCall, PhD

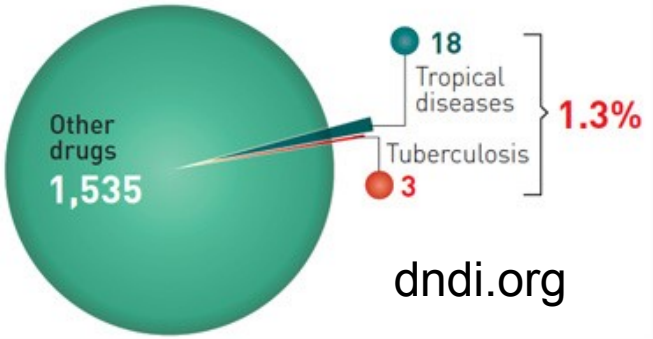
Leishmaniasis: a global problem



WHO / S. Stammers / C. Black
Pigott *et al,* eLife 2014

Bridging the divide: leishmaniasis and poverty

- A disease affecting the poorest of the poor
  - Sudan, India, Nepal, Bangladesh: <1$/day in endemic areas
- Overall neglected by drug companies
  - Pentavalent antimonials (1922)
  - One new chemical entity since 1975
  - Some recent progress, e.g. AmBisome
- Imbalanced with the need
  - Leishmaniasis: >2 million DALYs
  - Endemic in >90 countries worldwide
  - 350 million people at risk
- Academic and non-profit groups take up the challenge.
  - Center for Discovery and Innovation in Parasitic Diseases, UC San Diego



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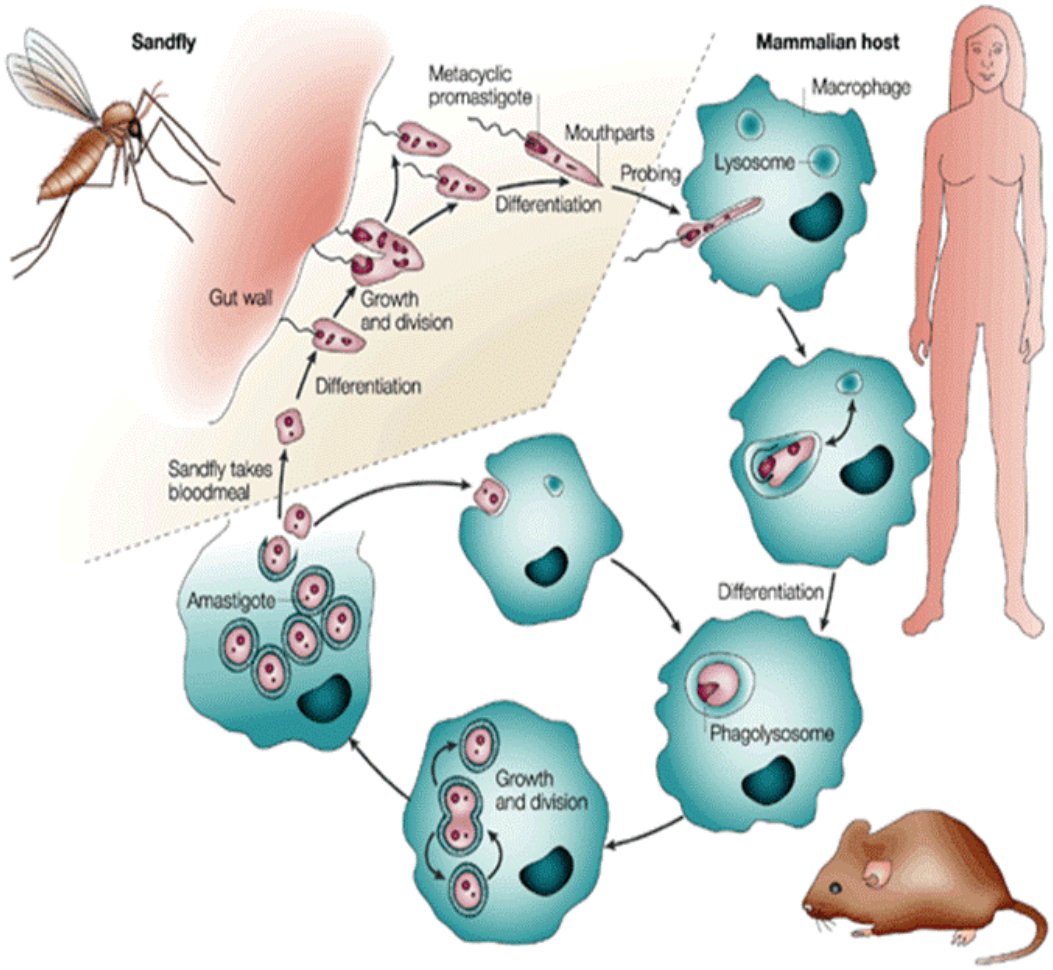
CENTER FOR DISCOVERY AND INNOVATION IN PARASITIC DISEASES

Leishmania lifecycle

Sandfly vector

Promastigote stage

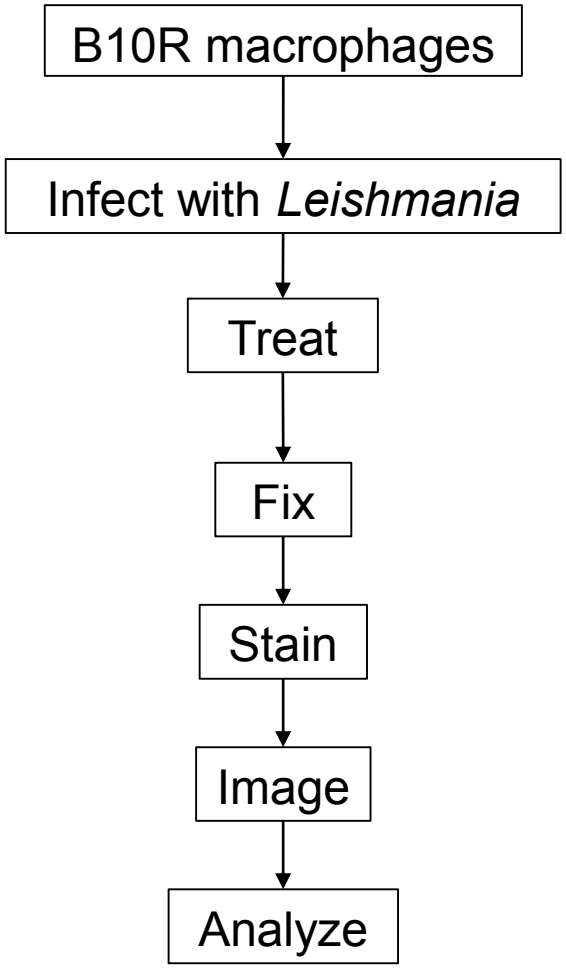


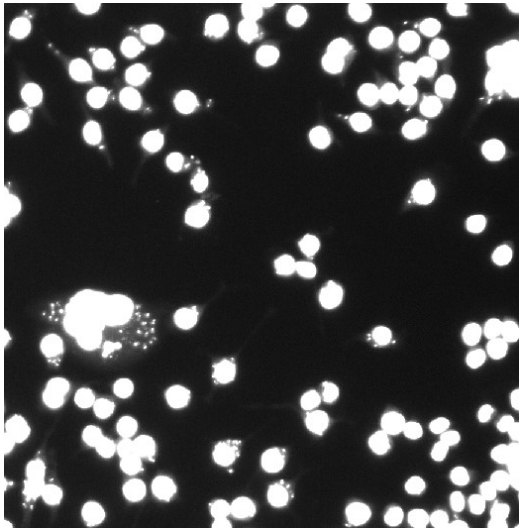
Mammalian host

Amastigote stage

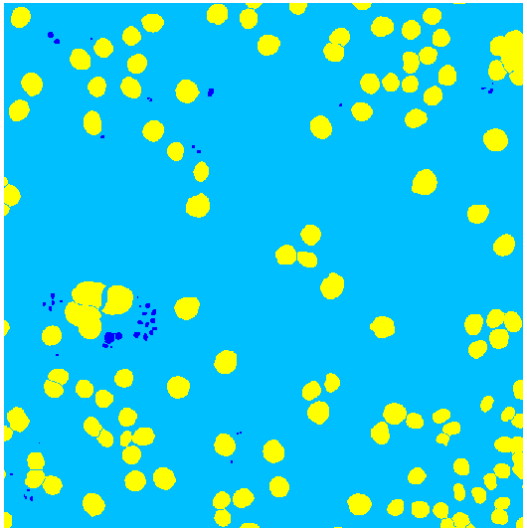
Sacks *et al,* Nat. Rev. Immunol. 2002

High-content assay





DAPI

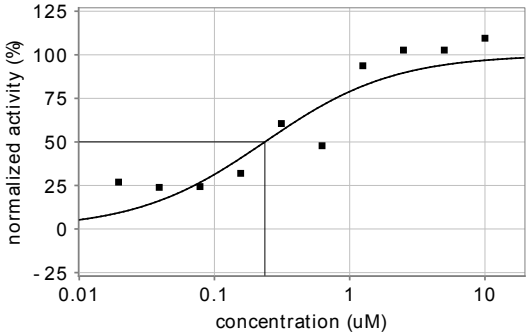


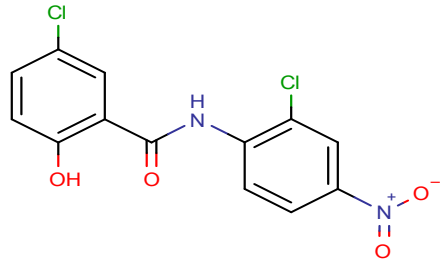
segmentation

Drug and target repurposing: accelerating the path to the clinic

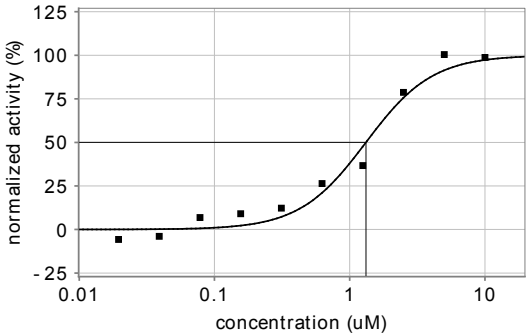
- Drug repurposing
  - FDA-approved drugs (1,640)
  - 21 preliminary hits

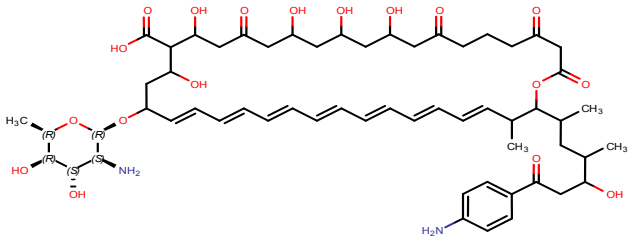
Niclosamide
(antihelminthic)
IC50=0.236 μM





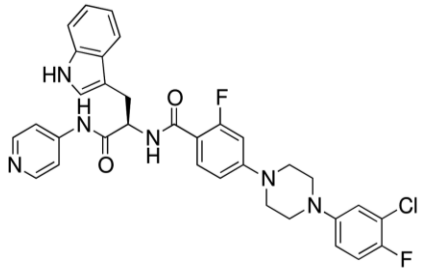
Candicidin
(antifungal)
IC50=1.32 μM





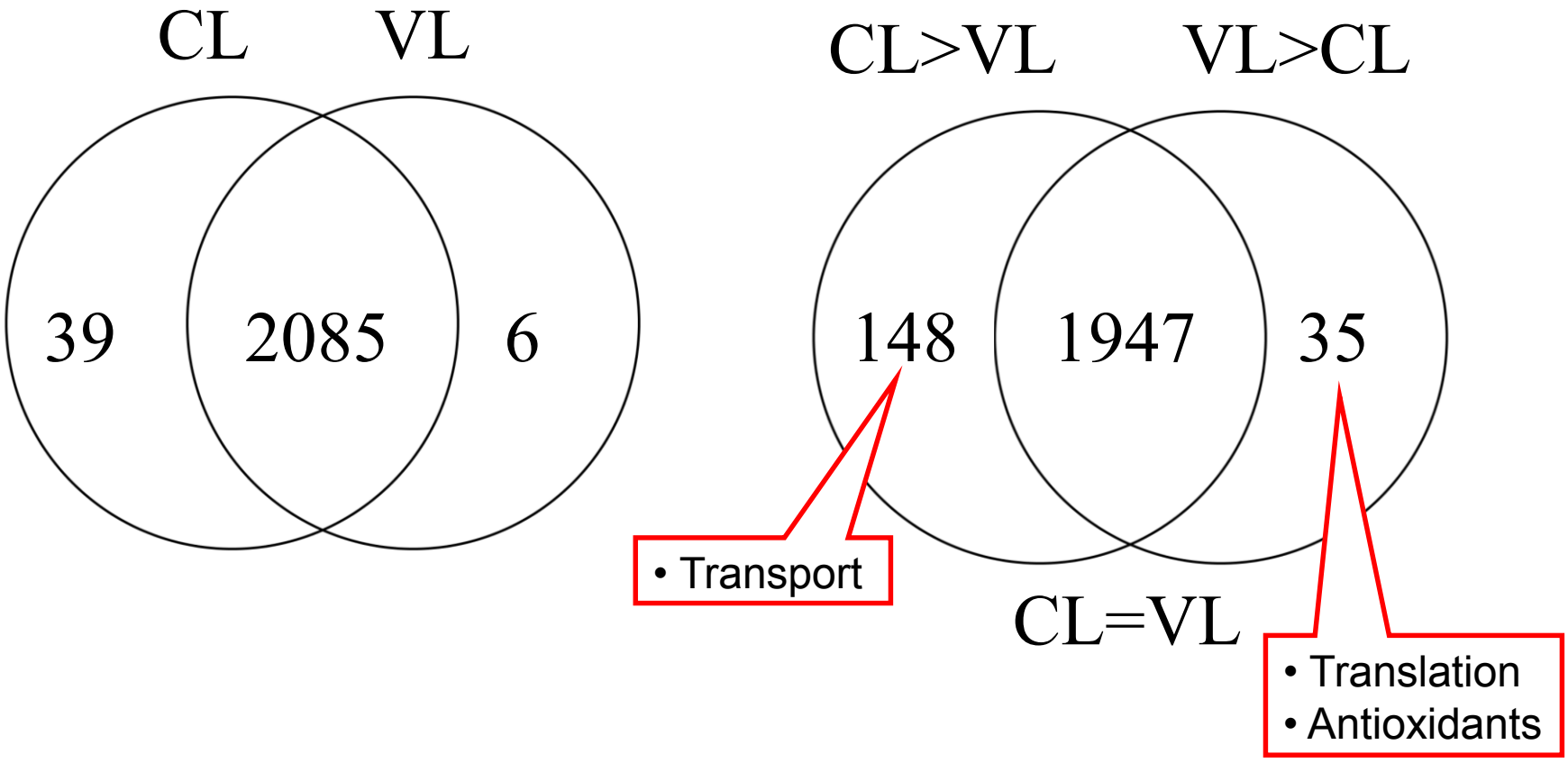
Drug and target repurposing: accelerating the path to the clinic

- Target repurposing
  - Sterol biosynthesis inhibitors
  - Essentiality of CYP51 in *Leishmania donovani*
  - CYP51 inhibitor activity dependent on CYP51 expression levels

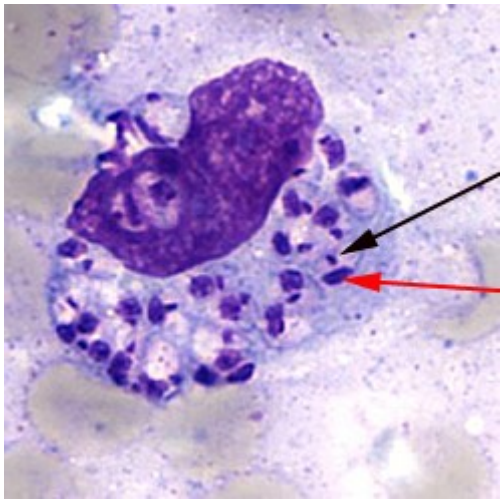
Structure	Name	*T. cruzi* cell-based (μM)	WT	HKO	HKO + C	HKO + CYP	P-Value (one-tailed Student's t-test) [a]
	10 (II-279)	0.00064 ±0.0008	8.59 ±0.25	4.50 ±3.44	0.29 ±0.09	5.18 ±0.48	0.03

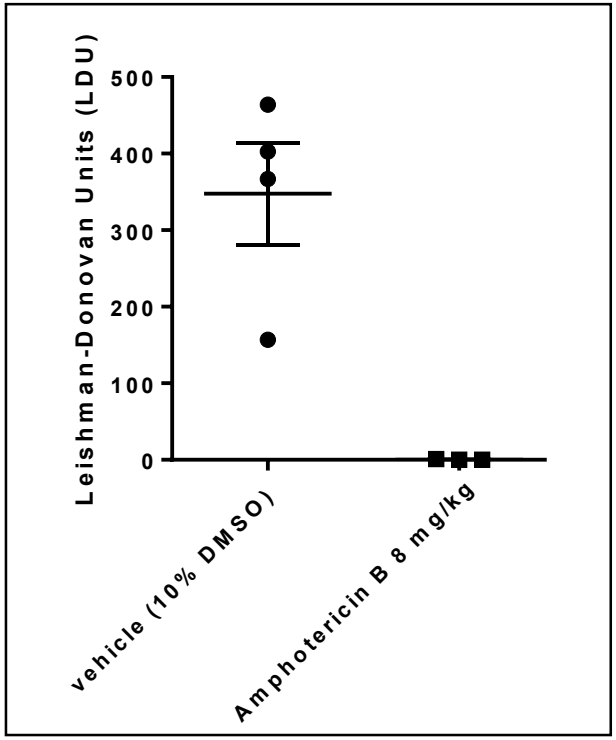
Identification of new drug targets

- Proteomic comparison of cutaneous and visceral parasites

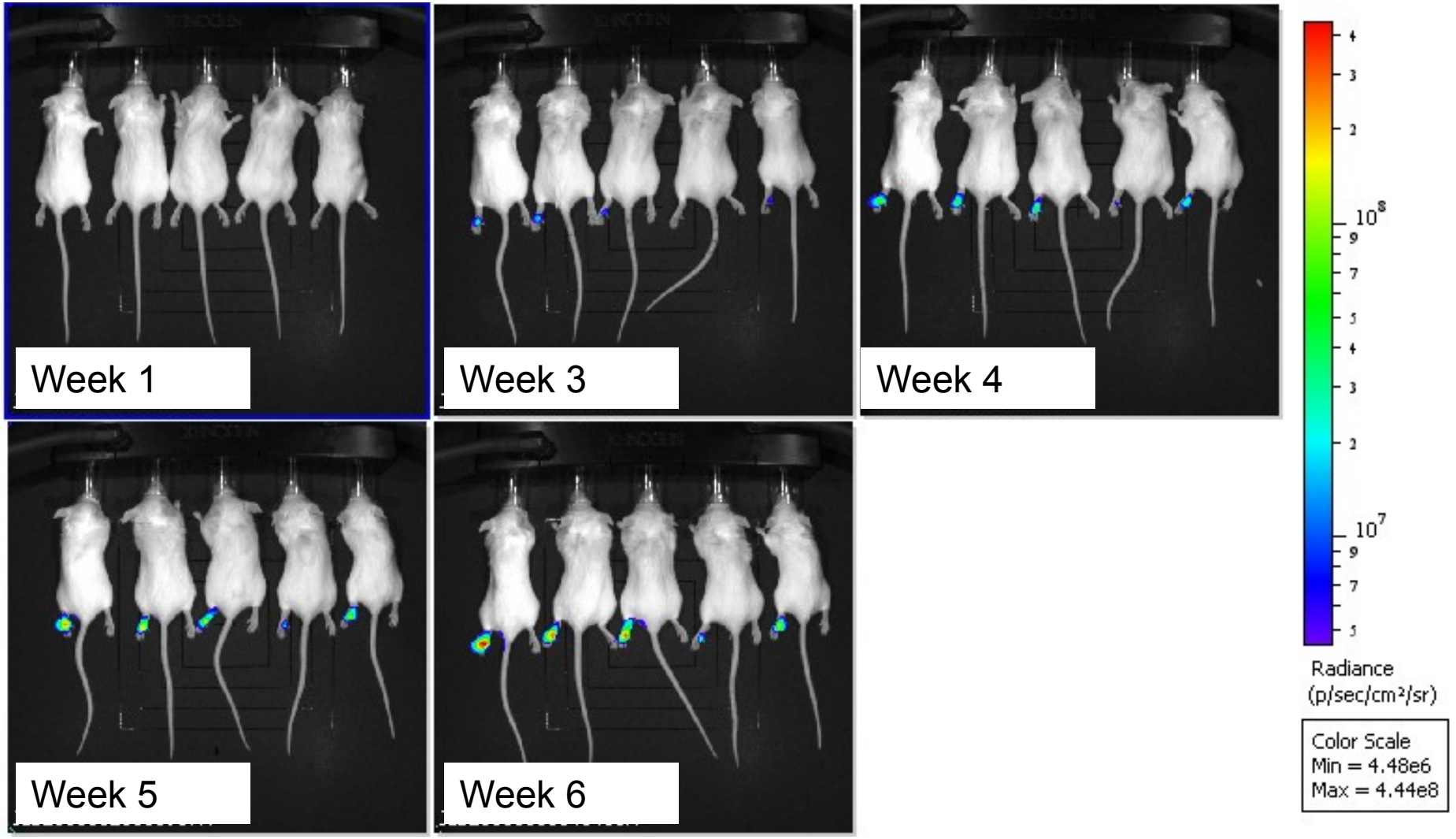


Visceral leishmaniasis model

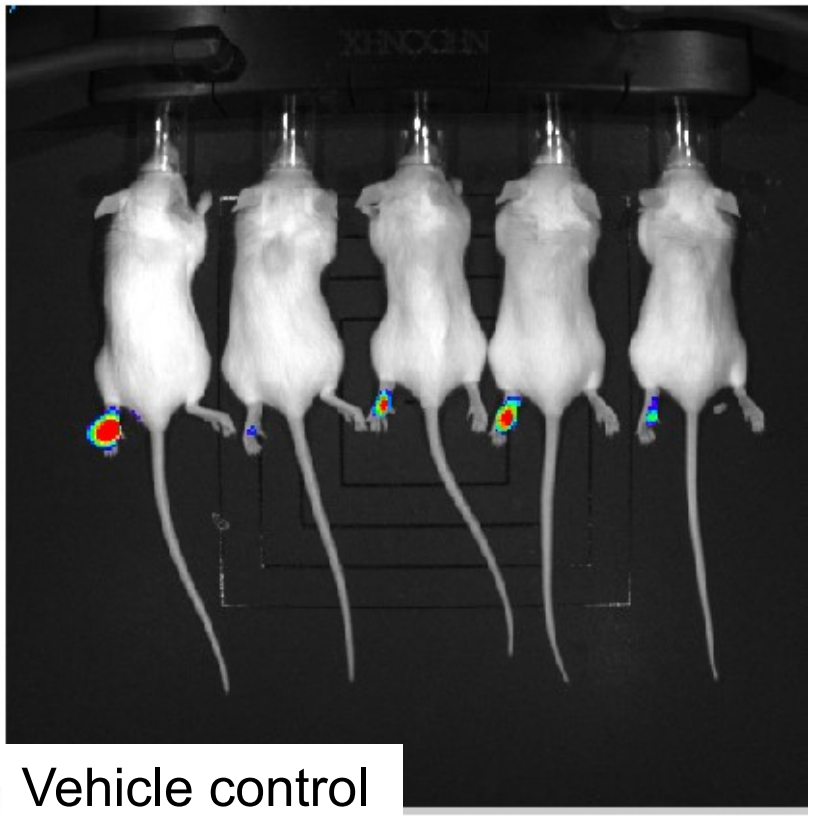




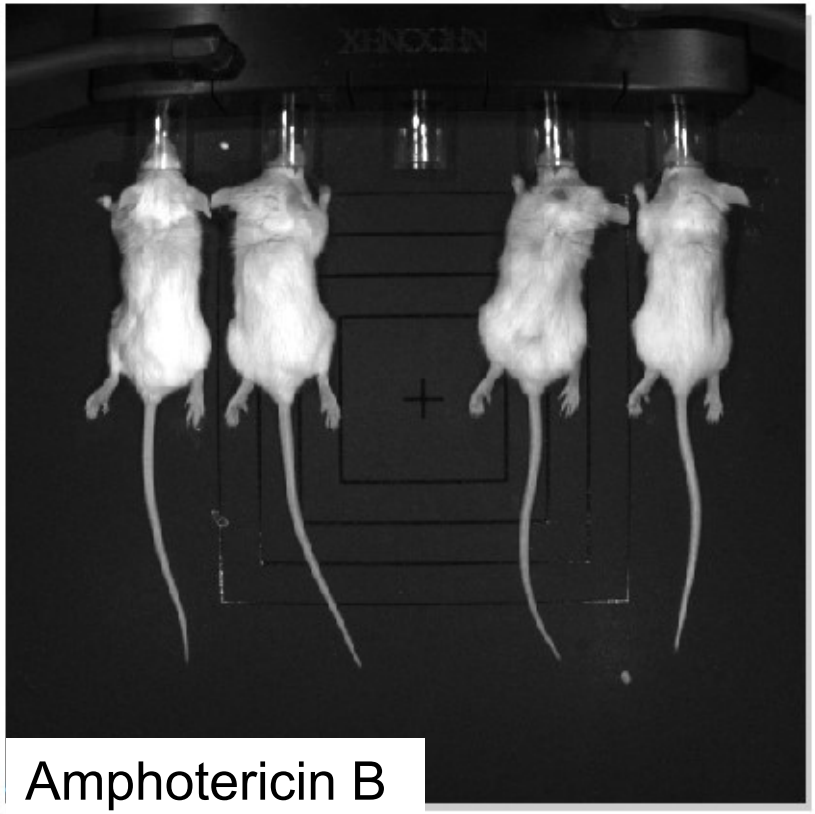
Cutaneous leishmaniasis model: luminescence time course



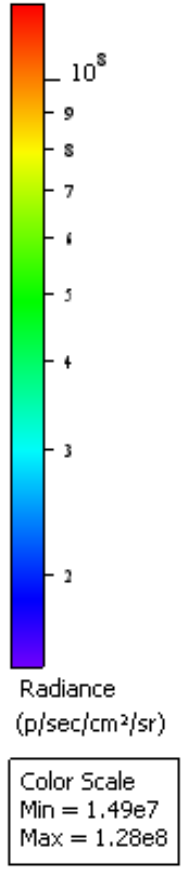
Cutaneous leishmaniasis model: treatment efficacy



Vehicle control



Amphotericin B



Conclusions

- The need for new leishmaniasis treatments is being filled by groups like the Center for Discovery and Innovation in Parasitic Diseases :
  - Drug repurposing to accelerate the path from bench to bedside
  - Target repurposing e.g. ergosterol biosynthesis inhibitors
  - Identification of new drug targets
- Further research and support is still needed

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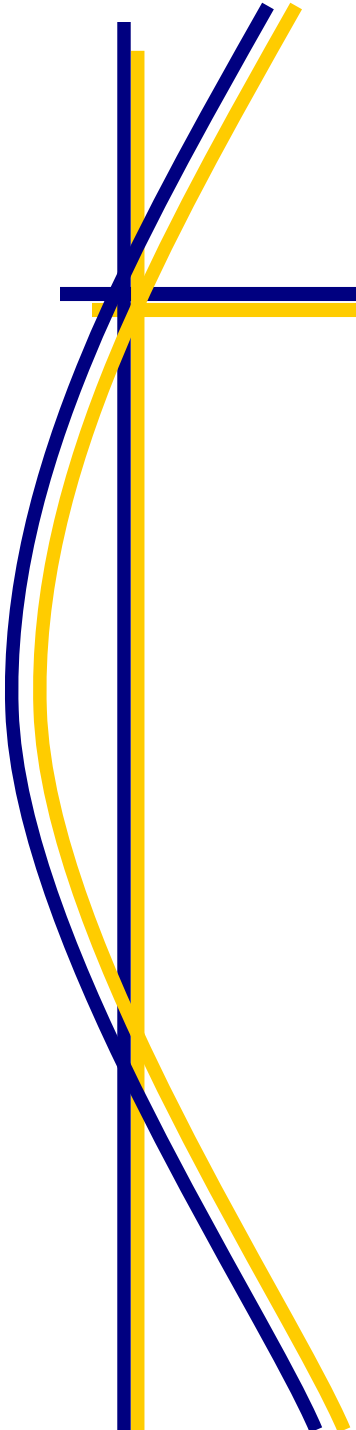

Questions?