Challenges in Chagas Disease R&D

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DNDi

Drugs for Neglected Diseases *initiative*

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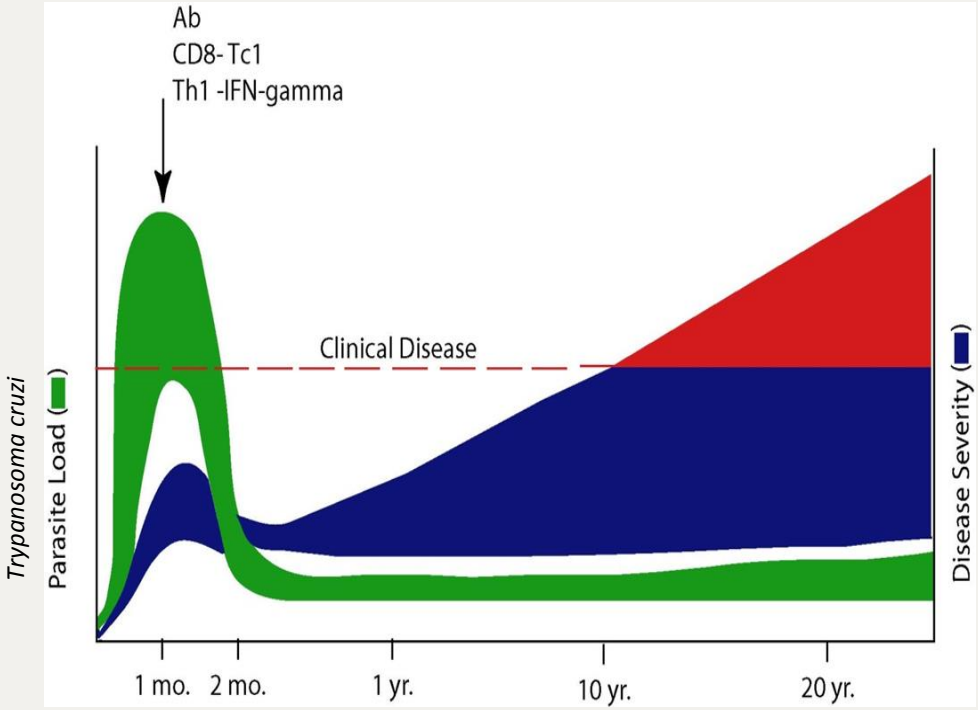
What is Chagas Disease?

- Poor understanding of the disease, its pathology, factors related to its progression



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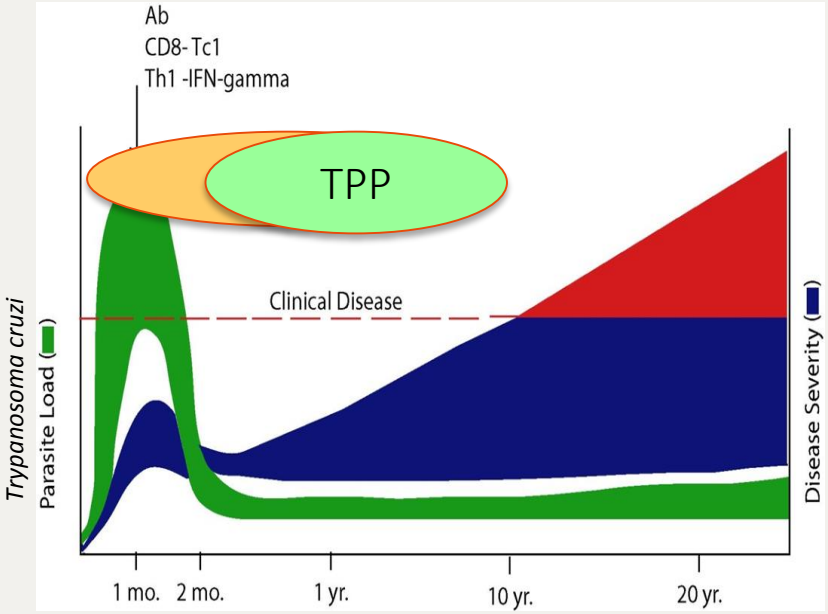
➡ What Type of Drug/Treatment is Needed?

Still Unanswered Questions

- Is killing *T. cruzi* parasite enough? Does absence of parasites means cure?
- Are we sure that removal of parasites will prevent development/progression of the disease?
- What is our understanding of the host/parasite interactions?
- Why will some infected people develop the disease (up to 30-40%) and others not?
- Is the progression of the disease due to an accumulation of the damages? Are there genetic factors playing a role? Markers?

Target Patient Population



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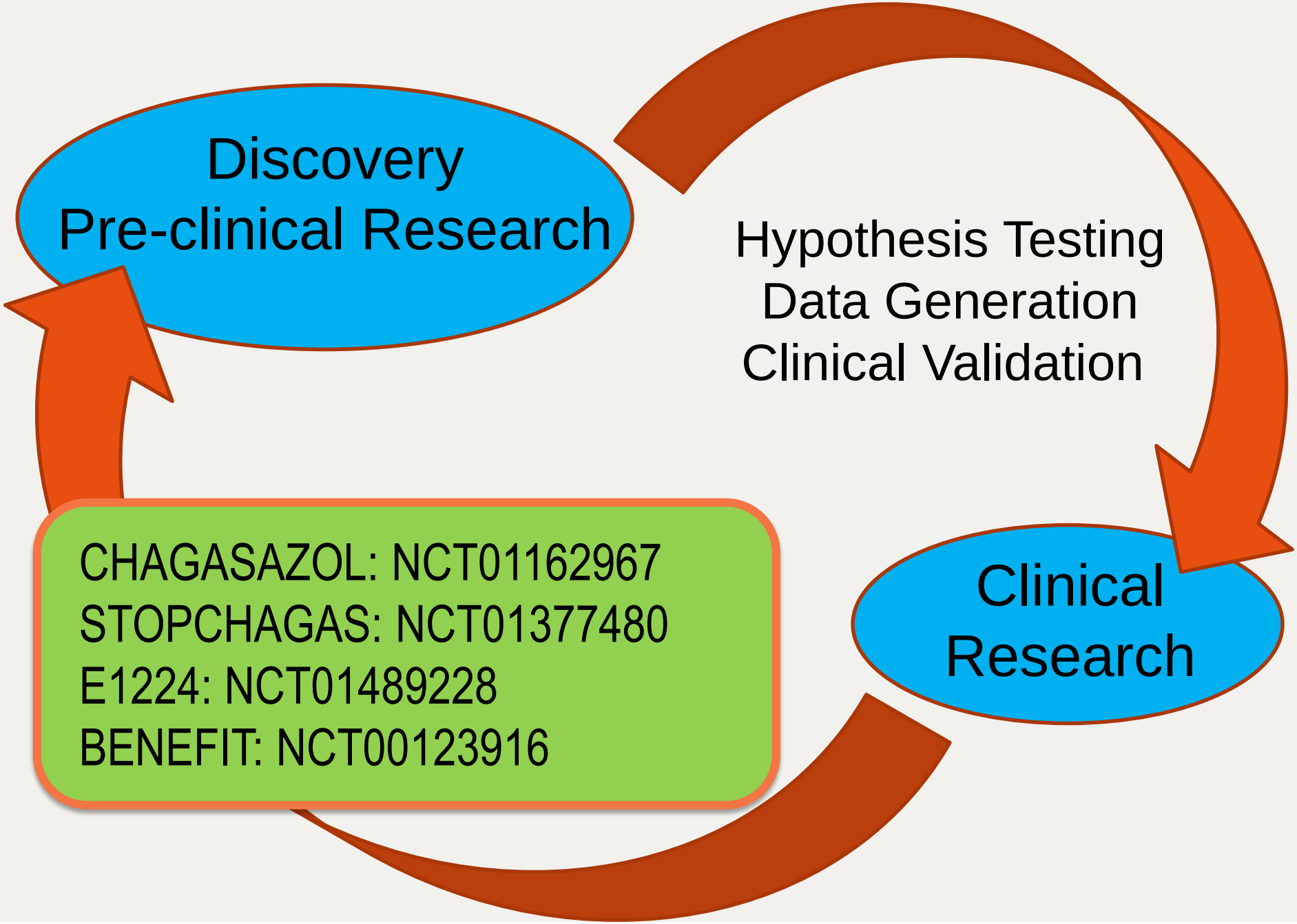
- Important for designing the Target Product Profile (TPP) and Target Candidate Profile (TCP)
- Risk / Benefit Ratio: Asymptomatic «healthy» people carriers of *T. cruzi*

➡ Get rid of the parasite (parasitological cure)

How do We Assess Clinically the Efficacy (Parasitological Cure) of a Chagas Drug?

- Parasitemia by PCR: Current State of the Art
  - Selected primary endpoint for Phase 2 PoC clinical trials
  - Standardized technique; multicenter validation
- But…
  - Give an idea of treatment failure NOT efficacy
  - Fluctuating parasitemia → Limit of detection
  - Is Parasitemia representative of tissue parasitism?
  - 20-60% of Chagas infected people are PCR-negative
- What about Phase 3 clinical trials? Regulatory requirement to show efficacy? How?

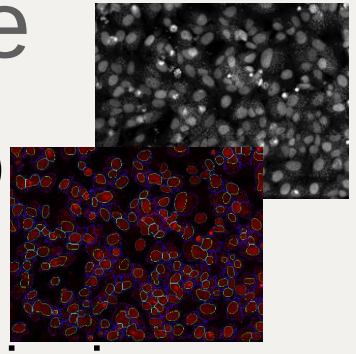
Need to identify a surrogate marker that is quicker and more sensitive than seroconversion


Discovery
Pre-clinical Research
Hypothesis Testing
Data Generation
Clinical Validation
Clinical
Research
CHAGASAZOL: NCT01162967
STOPCHAGAS: NCT01377480
E1224: NCT01489228
BENEFIT: NCT00123916

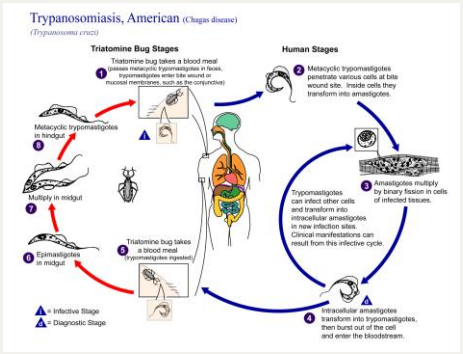
Implications for Delivery of Future Chagas Candidates

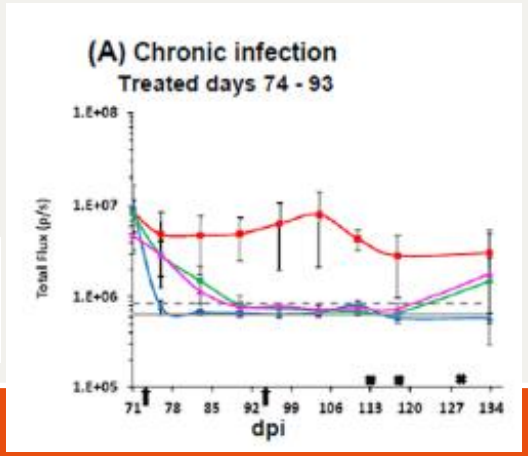
- Highlighted Major Translational Challenges with the failure of Azoles (Posaconazole, Ravuconazole)
  - Need for better translation *in vitro/in vivo* models and the clinic
  - Need to translate research data to assays compatible with Drug Discovery & Development process
  - Address the right questions in models but also consider the Critical Path
  - Better understanding of PK/PD relationships
- Break dogma and test hypothesis

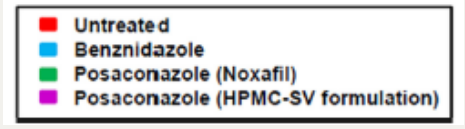
Chagas Disease Drug Discovery
A Very Dynamic Landscape



- New technologies (Imaging, BLI, -omics, WGS,…)
- New HTS assays for *T. cruzi (High content)*
- New secondary screening assays for compound triaging
  - *T. cruzi* strains specific assays, Time-kill/Reversibility/ Cidal assays, Parasite stage-specific assays
  - Functional *T. cruzi* CYP51 inhibition assay
- Moving towards assay standardization
- *In vivo* models reproducing clinical trials outcomes (GNF, LSHTM)





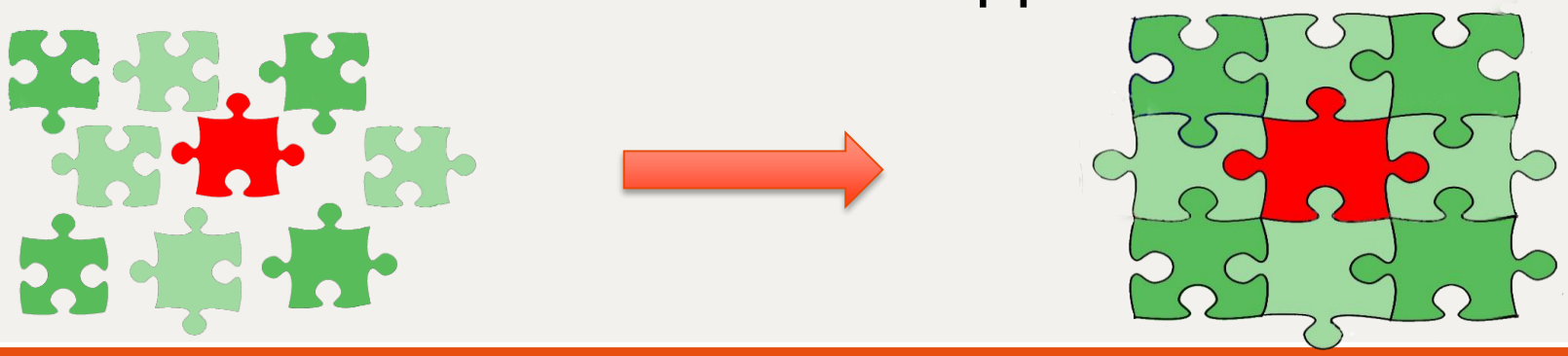


Priorities / Needs: Next Steps

- Assess optimal benznidazole regimen in chronic indeterminate patients
- Follow-up cohort of indeterminate patients to assess/understand the impact of treatment on progression of the disease
- Move new drug(s) in clinical trials PoC; Fill the pipeline for new drug candidates
- Need for surrogate markers of cure / treatment efficacy
- Need for more research

Conclusions

- Drug discovery & development process is already a challenge per se
- Still a lot of challenges and unanswered questions in the Chagas disease arena
- Major changes have shaken the Chagas drug discovery landscape during the last 5 years
- Still a lot to achieve but more confidence today
- With a broader collaborative approach



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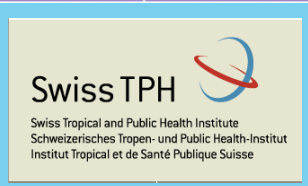


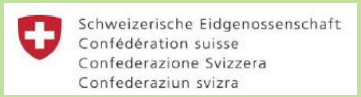


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SCIENCE
FOR THE MOST
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Thank you
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