Challenges in Chagas Disease R&D

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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


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

- 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

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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