Latest Developments in Chagas Biomarker Research

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Drugs for Neglected Diseases *initiative*

Session 82: Overcoming Challenges in Screening and Diagnosis of Chagas Disease
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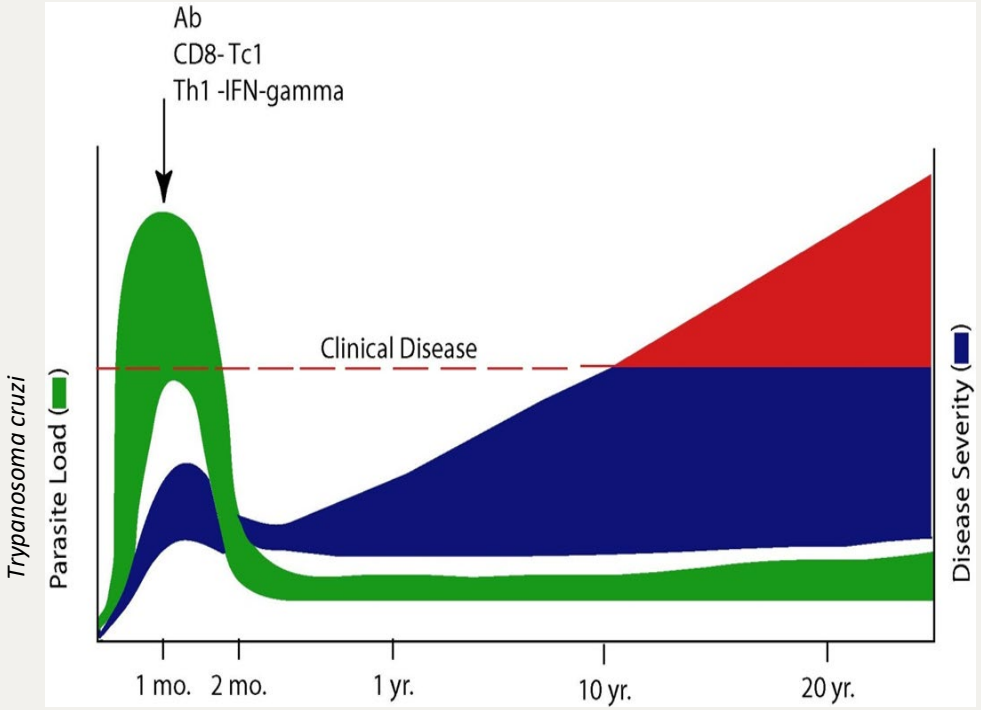
Chagas Disease & Target Patient Population

- Poor understanding of the disease, its pathology, factors related to its progression
- Target Patient Population
  - Risk / Benefit Ratio: Asymptomatic «healthy» people carriers of *T. cruzi*
  - Children vs adults



Reproduced from Tarleton, R. L. *Trypanosoma cruzi* and Chagas Disease: Cause and Effect. In *American Trypanosomiasis*; Tyler, K. M., Miles, M. A., Eds.; Springer: New York, **2003**, pp 107–116

What Type of Drug / Treatment is Needed?
What Marker(s)? Disease progression risk, Cure?

Dogmas & Unanswered Questions

- 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 damages with time since infection? Are there genetic factors playing a role? Markers?
- Does parasite removal correlates with lack of disease development / progression? Definition of clinical cure in asymptomatic «healthy» carriers of *T. cruzi*?

➡ Assumption: Parasitological cure = Clinical cure(?)

- Does negative PCR following treatment mean absence of *T. cruzi* parasites, therefore cure?
- Does positive serology following treatment mean still presence of the parasite *T. cruzi*, therefore treatment failure?

Some definitions

- Biomarker: a characteristic objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention

- Clinical End point: A characteristic or variable that reflects how a patient feels, functions or survives

- Surrogate end point: a biomarker intended to substitute for a clinical end point aiming to predict clinical benefit (or harm, or lack of benefit or harm) on the basis of epidemiological, therapeutic, pathophysiological or other scientific evidence

Different roles of Biomarkers

- Prognostic: Identifying the risk of developing an illness
- Screening: screening for subclinical disease
- Diagnostic: recognizing overt disease
- Staging: categorizing disease severity

- Predictive: baseline characteristic that predicts future disease course/response to therapy
- Pharmacodynamic: assessment that shows that a biological response has occurred in a patient after having received a therapeutic intervention

→ Surrogate markers are a subset of pharmacodynamic biomarkers

Chagas Disease Biomarkers: The Need

Need to identify / define surrogate marker(s) for absence of parasites -and develop a test- that is quicker and more sensitive than seroconversion

- To support drug development (Test of “Cure”)
- To help patient counselling

→ Surrogate of a surrogate of Clinical Cure / Benefit

Current Regulatory Views on the Topic
Benznidazole FDA Approval for Chagas Disease

Approved for children of 2 to 12 years of age

- Approval based on 2 studies showing in around 50-60% of the children patients an effect (seroconversion after FU) on surrogate endpoints (F29 and AT *T. cruzi* antigens) that are reasonably likely to predict clinical benefit in this population
- Post Marketing Requirement: Additional studies needed to be performed to further confirm these results
  - Prospective, single-arm, multicenter trial, with historical controls, to evaluate safety, efficacy, and PK of benznidazole tablets for treatment of Chagas disease in children

Chagas Disease Biomarkers - Current Status

So far, No validated surrogate of seroreversion

- PCR: pharmacodynamic marker but no proof / validation for its potential use as surrogate
  - Give an idea of treatment failure NOT efficacy
  - Fluctuating parasitemia
  - Limit of detection (Parasitemia representative of tissue parasitism?)
  - 20-60% of Chagas infected people are PCR-negative
- A lot of emphasis on titer reduction of specific anti-*T. cruzi* antibodies (lytic antibody, specific epitopes –e.g. F29- or *T. cruzi* lysate antibodies)
  - Time till seroreversion, Serodiscordance issue
  - Does decrease in Ab titers correlates with future seroreversion?

See Pinazo 2014, Pinazo 2015, Pinho 2016, Ruiz Lancheros *in press*

Chagas Disease Biomarkers - Current Status (2)

- Looking at the host
  - Host T-cell responses → No clear positive evidence
  - Parasite signatures in the host
    - Apo-A1 and Fbn fragments, others to be characterized
- New Technologies for the ID of new markers
  - Gene expression profiling / Transcriptomics
  - - Omics: Metabolome, proteome, lipidome, glycome
  - High-density microarrays for the ID of *T. cruzi* antigens and epitopes (see oral presentations 1413 and 1416)
  - Aptamers, loop-mediated isothermal amplification (LAMP) (See oral presentations 570 and 1414 resp.)

Chagas Disease Biomarkers - Current Status (3)

- Development of a multiplex test incorporating the new potential markers identified e.g. ApoA1 and Fibronectin fragments in combination with Ab3 from Infynity Biomarkers to allow “high-throughput” testing of samples
  - Monoparametric prototype assays development, optimization and validation for use in multiplex - ongoing
  - Multiplex assay development and optimization (1H2019)
  - Further validation for use in multiplex

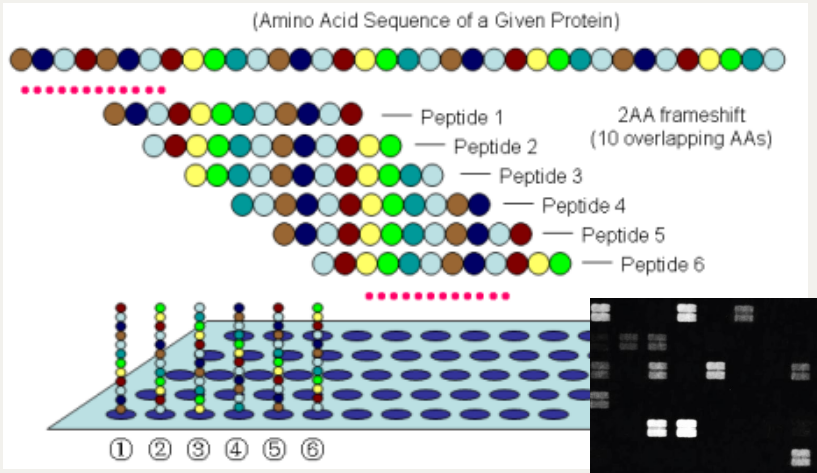
Assess further the potential of these new host markers (ApoA1 and Fbn fragments)
Combines Parasite and host markers

Chagas Disease Biomarkers - Current Status (4)

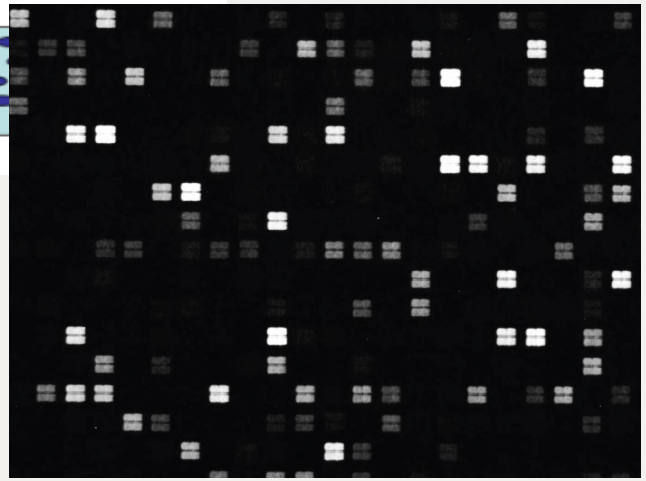
- «NHEPACHA» study (Ongoing)

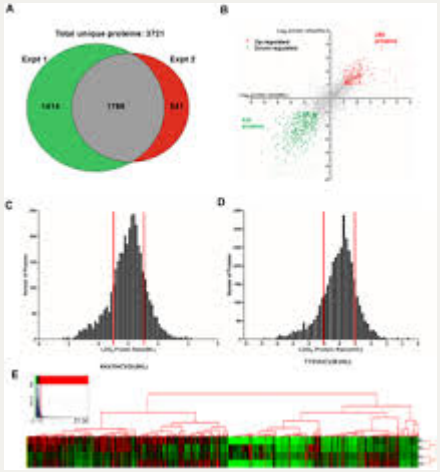
  - Retrospective study with control, patients in the chronic stage and 2 years or more follow-up after treatment
  - Objective: Assess *T. cruzi* antigens for their potential as biomarkers
    - F29, K11-H70-PFR2-3073, Anti-alpha-galactosyl mucin
    - Compare with PCR
    - Samples also run on the fifteen antigens «chip» from Infynity Biomarkers
    - Currently being run on a CE validated Chagas kit commercially available, BioKit
- Review of the current CD Biomarker TPP (biased towards PCR)

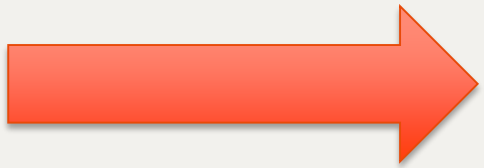
Path towards clinical validation / qualification of identified markers with potential



A Long Way till regulatory acceptance of a Biomarker







Big difference between a differentially expressed protein and a validated surrogate

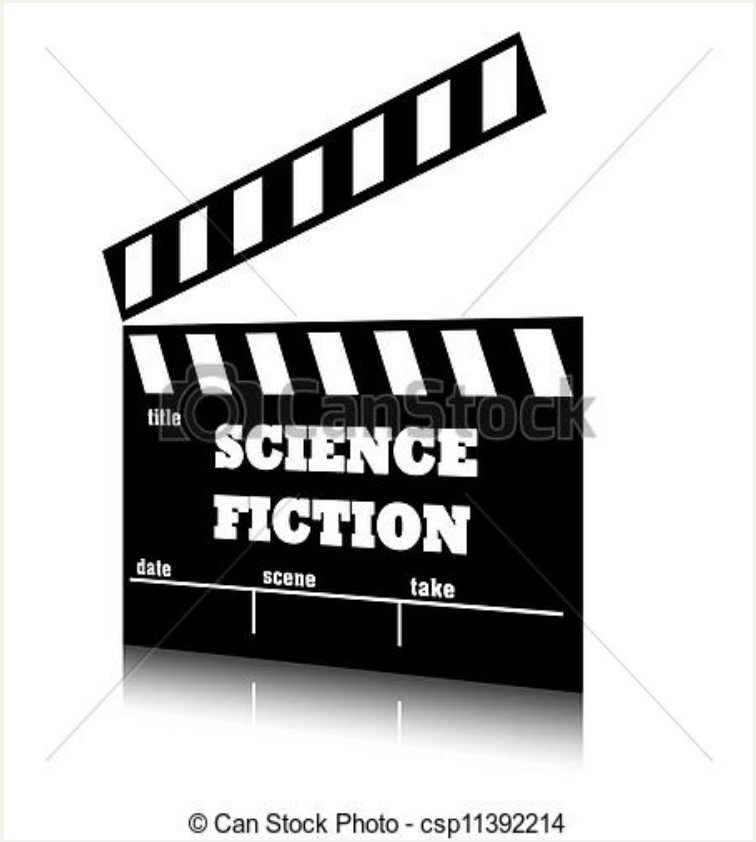
Path towards clinical validation / qualification of identified markers with potential

Basically 2 pathways for biomarkers to be accepted by regulators for use in drug development

- Acceptance through an IND (drug approval process); Use the biomarker in a single drug development program
- Biomarker qualification: Establish the biomarker(s) for use in multiple development programs; process involving the RA and usually biomarker consortium

The Ideal Biomarker Program for Chagas Disease?

- Biomarker or set of Biomarkers identified and validity assessed
- Assay/test validated; industrialization possible, adapted to the field
- Clinical validation plan established and agreeable to regulators
  - Well designed and powered Retrospective study: Access to well characterized cohort(s) and high-quality samples; biostatistical plan
  - Alternatively, prospective study with long follow-up planned and funded; Entire Chagas community working together for that common goal
  - Get input from regulators



A Process that needs a Collaborative & Community wide Effort

Conclusions

- Biomarker ID and validation process is a challenge *per se*
- Chagas disease and its definition of cure is another known challenge
- Biomarker for Chagas disease is a huge challenge to tackle, but a serious and necessary step to consider for CD drug development and adequate patient counseling
- Still a long way till clinical validation / qualification of any identified biomarker with potential; Phase 3?
- Need for adequate budget and resources
- Need to advocate for Biomarkers for Chagas

Thank you

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