ADVANCES AND CHALLENGES IN THE TREATMENT OF CHAGAS DISEASE - A GLOBAL PERSPECTIVE

ICID 2018
Sergio Sosa-Estani, PhD
History of Chagas disease

- 9,000 BC: People with T. cruzi infection (mummies)
- 1909: Discovery
- 1920: Diagnostic
- 1960-1970: Treatment
- 1995-2018: Treatment – biomarkers

Carlos Chagas

Salvador Mazza
Life cycle of *Trypanosoma cruzi*

**RELATIONSHIP?**
- Dynamic of transmission
- Physiopathogenesis
- Performance of diagnostic tests
- Response to treatment

**CYCLE**
- DOMESTIC
- SELVATIC
Chagas disease: Physiopathology

Parasite

Specific immune response against the parasite

Pathology

Microvascular

Inflammation
CHAGAS DISEASE

PHASES OF INFECTION AND CLINICAL FORMS

ACUTE PHASE (2 months) Prolonged fever syndrome
   Vector transmission
   Congenital transmission
   Accidents

CHRONIC PHASE (decades)
   Without demonstrable disease
   With demonstrable disease
      Cardiac form
      Digestive form (megas)
      Mixed forms and other

REACTIVATION OF CHRONIC INFECTION (eventual)
   Co-infection (HIV/AIDS)
   Other causes of immunodeficiency (oncology, transplant)
Elimination of intra-domiciliary vectorial transmission of Chagas disease in Latin America (2020)

Around 7,000,000 infected and < 18,000 patients treated/year

- Most common parasitic disease in the Americas
- Leading cause of infectious myocarditis worldwide
- Largest disease burden in chronic indeterminate patients
- 20-30% will evolve to cardiomyopathy with important morbidity and mortality
- Only 2 registered compounds: BZN and nifurtimox
A NEW PARADIGM IN THE 21ST CENTURY

**Old Paradigm**
- Autoimmune origin of chronic myocarditis (5,7,21)
- Absence of *T. cruzi* in tissues
- Lack of relationship between acute and chronic stages of the disease, with 30% of heart disease progression due to non-established causes (50)
- Several mechanisms of cardiomyopathy progression: autoimmune, autonomic denervation, disorders of microcirculation (33,51,52)
- No indication of antiparasitic treatment (53,54)

**New Paradigm**
- Inflammatory immune response triggered and sustained by the parasite (25)
- Finding of *T. cruzi* in tissues (19,20)
- Linking acute and chronic stages of disease, correlation with the host’s immune status, and reactivation of the infection by immunosuppression (14,15-18,23)
- The parasitic persistence is postulated as the main mechanism of progression toward cardiomyopathy (14,24,25)
- Antiparasitic treatment (3,11,27,29,30,33-39)

FIG 1 Comparison of concepts belonging to the old and the new paradigms for chronic Chagas disease. Relevant references are given in parentheses.
GOAL OF TIMELY DIAGNOSIS AND TREATMENT

- CURE INFECTION
- PREVENT MORBIMORTALITY
- AVOID CONGENITAL TRANSMISSION
- PERSONAL AND FAMILY WELLBEING

REDUCE DISEASE BURDEN
Guidelines for antitrypanosomal treatment with benznidazole or nifurtimox

Varying strengths of recommendation (A-E) and levels of evidence (I-III)

• All patients in the acute phase (A I; A II)
• Children and young adult patients in the chronic phase (A I)
• Women of childbearing age (A II)
• Adults undergoing the chronic phase (B II; C II)
• Laboratory or surgical accidents (B III)
• Organ transplant recipients or donors (A III)

Oral; 60 days
Timeline of side effects of benznidazole and nifurtimox

- Gastrointestinal
- Haematological
- Peripheral Neurotoxicity
- Dermal
- CNS Toxicity
- Liver toxicity

**Day 1**
- Start

**Day 30**
- Middle

**Day 60**
- End

**Typical completion rates**
- Adults = 83%
- Neonates = 100%

**Monitoring Adverse Events/Drug Tolerance**
- Weekly contact with the patient
- Laboratory testing

Assessing response to etiological treatment

PRIMARY CRITERIA

• Demonstration of no clinical progression
• Wellbeing (clinical evolution)

SECONDARY CRITERIA

• Failure: Detecting parasite presence using molecular tests (PCR)
  – Time range: end of treatment to month/years post-treatment
• Success: serological negativization
  – Acute phase: Follow-up for 24 months post-tx
  – Chronic phase: Long-term follow-up, every 1-3 years.
TREATMENT
impact again infection
Effects during the acute phase

Acute Phase: Decrease in antibodies and parasitemia

Cohort of 206 BZN- treated children

Percentage of positive PCR at follow-up

Figure 1. Serological and parasitological evolution in acute Chagas' infection (51 untreated patients and 550 treated with nifurtimox).
Effects during the early chronic phase
Course of serological outcomes in treated subjects with chronic Trypanosoma cruzi infection: a systematic review and meta-analysis of individual participant data. ELISA test ~ age at treatment

Sguassero et al. Unpublished
TREATMENT
impact on clinical evolution
Trypanocide Treatment of Women Infected with *Trypanosoma cruzi* and Its Effect on Preventing Congenital Chagas

Diana L. Fabbro¹, Emmaria Danesi², Veronica Olivera¹, Maria Olenka Codebo³, Susana Denner¹, Cecilia Heredia³, Mirtha Streiger¹, Sergio Sosa-Estani¹,²,³

<table>
<thead>
<tr>
<th>Grupo</th>
<th>N</th>
<th>ACC (n)</th>
<th>ACC (%)</th>
<th>Tpo seguim. (años)</th>
<th>Edad ult. ECG (años)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tratadas</td>
<td>51</td>
<td>1</td>
<td>1,96</td>
<td>20,6±10,6</td>
<td>44,8±11,6</td>
</tr>
<tr>
<td>No tratadas</td>
<td>39</td>
<td>6</td>
<td>15,38</td>
<td>17,9±8,9</td>
<td>47,6±10,5</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Long-Term Cardiac Outcomes of Treating Chronic Chagas Disease with Benznidazole versus No Treatment

A Nonrandomized Trial

![Figure 2. Kaplan–Meier curves of cumulative percentage of patients who changed clinical group.](image)

Table 5. Logistic regression model. Dependent variable: the occurrence of clinical combined outcomes (heart failure, stroke and total mortality) and independent variables: treatment (BZ), follow-up, male, Caucasian and age in years.

<table>
<thead>
<tr>
<th>Cl (95%)</th>
<th>0.R.</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREATED BZ</td>
<td>0.330</td>
<td>0.115</td>
<td>0.947</td>
<td>0.039</td>
</tr>
<tr>
<td>FOLLOW UP</td>
<td>1.046</td>
<td>0.988</td>
<td>1.110</td>
<td>0.138</td>
</tr>
<tr>
<td>MALE</td>
<td>2.264</td>
<td>0.878</td>
<td>5.834</td>
<td>0.091</td>
</tr>
<tr>
<td>CAUCASIAN</td>
<td>3.029</td>
<td>0.679</td>
<td>13.480</td>
<td>0.147</td>
</tr>
<tr>
<td>AGE</td>
<td>1.021</td>
<td>0.965</td>
<td>1.081</td>
<td>0.463</td>
</tr>
</tbody>
</table>

Table 6. Logistic regression model. Dependent variable: normal ECG maintenance and Independent variables: treatment with BZ, follow-up, male, Caucasian and age in years.

<table>
<thead>
<tr>
<th>Cl (95%)</th>
<th>0.R.</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREATED BZ</td>
<td>5.733</td>
<td>5.5396</td>
<td>12.9420</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FOLLOW UP</td>
<td>0.938</td>
<td>0.8990</td>
<td>0.9789</td>
<td>0.0033</td>
</tr>
<tr>
<td>MALE</td>
<td>0.938</td>
<td>0.8990</td>
<td>0.9789</td>
<td>0.0033</td>
</tr>
<tr>
<td>CAUCASIAN</td>
<td>0.938</td>
<td>0.8990</td>
<td>0.9789</td>
<td>0.0033</td>
</tr>
<tr>
<td>AGE</td>
<td>1.019</td>
<td>0.9886</td>
<td>1.0503</td>
<td>0.2243</td>
</tr>
</tbody>
</table>
**Results:**

Trypanocide effect: $p < 0.05$

Clinical evolution: $p > 0.05$

- **2854 randomized**
- **1431 BNZ**
  - 84% took ≥75% of target dose
  - Discontinuation 192 (13.4%)
  - Lost to follow-up (n=8)
  - 99.5% Complete Follow-up
- **1423 Placebo**
  - 90% took ≥75% of target dose
  - Discontinuation 51 (3.6%)
  - Lost to follow-up (n=7)
  - 99.5% Complete Follow-up

Mean FU 5.4 yrs.
Randomized Trial of Benznidazole for Chronic Chagas’ Cardiomyopathy


### PCR Negativization

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Placebo (Pts with Events%)</th>
<th>Benznidazole (Pts with Events%)</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.O.T.</td>
<td>918</td>
<td>33.5</td>
<td>66.2</td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>673</td>
<td>35.3</td>
<td>55.4</td>
<td></td>
</tr>
<tr>
<td>&gt;5 Years</td>
<td>647</td>
<td>33.1</td>
<td>46.7</td>
<td></td>
</tr>
<tr>
<td><strong>Brazil</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.O.T.</td>
<td>213</td>
<td>24.3</td>
<td>86.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year 2</td>
<td>96</td>
<td>31.1</td>
<td>60.8</td>
<td></td>
</tr>
<tr>
<td>&gt;5 Years</td>
<td>141</td>
<td>27.4</td>
<td>35.3</td>
<td></td>
</tr>
<tr>
<td><strong>Argentina, Bolivia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.O.T.</td>
<td>388</td>
<td>28.6</td>
<td>73.0</td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>332</td>
<td>34.1</td>
<td>62.9</td>
<td></td>
</tr>
<tr>
<td>&gt;5 Years</td>
<td>276</td>
<td>30.2</td>
<td>61.4</td>
<td></td>
</tr>
<tr>
<td><strong>Colombia, El Salvador</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.O.T.</td>
<td>317</td>
<td>45.6</td>
<td>43.9</td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>245</td>
<td>38.5</td>
<td>42.6</td>
<td></td>
</tr>
<tr>
<td>&gt;5 Years</td>
<td>230</td>
<td>40.2</td>
<td>35.4</td>
<td></td>
</tr>
</tbody>
</table>
Primary Outcome - Overall

Some of main limitation:
- Age range
- Severity of disease (Opportunity of treatment)
Randomized Trial of Benznidazole for Chronic Chagas’ Cardiomyopathy


Table 2. Primary Outcome and Its Components, Hospitalizations, and Deaths.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Benznidazole (N = 1431)</th>
<th>Placebo (N = 1423)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>394 (27.5)</td>
<td>414 (29.1)</td>
<td>0.93 (0.81–1.07)</td>
<td>0.31</td>
</tr>
<tr>
<td>Death</td>
<td>246 (17.2)</td>
<td>257 (18.1)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>10 (0.7)</td>
<td>17 (1.2)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>33 (2.3)</td>
<td>41 (2.9)</td>
<td>0.58 (0.27–1.28)</td>
<td></td>
</tr>
<tr>
<td>New or worsening heart failure</td>
<td>109 (7.6)</td>
<td>122 (8.6)</td>
<td>0.80 (0.50–1.26)</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>109 (7.6)</td>
<td>125 (8.8)</td>
<td>0.86 (0.66–1.11)</td>
<td></td>
</tr>
<tr>
<td>CVE or all-cause mortality</td>
<td>54 (3.8)</td>
<td>61 (4.3)</td>
<td>0.33 (0.09–1.22)</td>
<td></td>
</tr>
<tr>
<td>Cardiac transplantation</td>
<td>3 (0.2)</td>
<td>9 (0.6)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Any Hospitalization</td>
<td>358 (25.0)</td>
<td>397 (27.9)</td>
<td>0.89 (0.77–1.03)</td>
<td>0.11</td>
</tr>
<tr>
<td>For cardiovascular causes</td>
<td>242 (16.9)</td>
<td>286 (20.1)</td>
<td>0.74 (0.57–0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>194 (13.6)</td>
<td>203 (14.3)</td>
<td>0.94 (0.77–1.15)</td>
<td>0.55</td>
</tr>
<tr>
<td>Death from or hospitalization for cardiovascular causes</td>
<td>348 (24.3)</td>
<td>380 (26.7)</td>
<td>0.89 (0.77–1.03)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

«Definitive, patient-important outcomes

All results going in the “right direction”...

...but none Statistically significant
TREATMENT
impact on transmission
Trypanocide Treatment of Women Infected with *Trypanosoma cruzi* and Its Effect on Preventing Congenital Chagas

Diana L. Fabbro¹, Emmaria Danesi², Veronica Olivera¹, Maria Olenka Codebó³, Susana Denner¹, Cecilia Heredia², Mirtha Streiger¹, Sergio Sosa-Estani²,³

(RR congenital transmission in treated mothers = 0.04, IC:95%: 0.012 - 0.166; p<0.05)
Treatment of women before pregnancy

Conclusions

• No case was detected among the offspring of mothers treated before pregnancy.

• Specific treatment of young women is useful at the level of secondary prevention.

• Etiological treatment in girls and women of childbearing age is helpful at the primary prevention level to avoid congenital *T. cruzi* transmission.
TREATMENT
new challenges
DNDi’s success is only possible through innovative partnerships

Over 160 partnerships worldwide

CRITERIA FOR SUCCESS

✓ Share the same vision
✓ Mutual understanding
✓ Involvement throughout the whole process
## Chagas Disease – TPP 2015

<table>
<thead>
<tr>
<th></th>
<th>Acceptable</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target population</strong></td>
<td>Chronic indeterminate</td>
<td>Chronic indeterminate and acute</td>
</tr>
<tr>
<td><strong>Geographic Distribution</strong></td>
<td>All regions</td>
<td>All regions</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Non-inferior to benznidazole standard dose* in all parasitological areas</td>
<td>Superior to benznidazole standard dose in different phases of disease (acute and chronic) (parasitological)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Superior to benznidazole* in the frequency of definitive treatment discontinuations due to medical indication (clinical and laboratory)**</td>
<td>Superior to benznidazole* in the frequency of definitive treatment discontinuations due to medical indication (clinical and laboratory)**</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Pregnancy</td>
<td>No contraindications</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>No genotoxicity**; no pro-arrythmic potential</td>
<td>No genotoxicity; no teratogenicity; no pro-arrythmic potential</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>No clinically significant interaction with anti-arrythmic and anticoagulant drugs</td>
<td>No clinically significant interaction with other drugs</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Oral/Parenteral (short POC)***** Age-adapted</td>
<td>Oral Age-adapted</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>3 years, climatic zone IV</td>
<td>5 years, climatic zone IV</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>Oral - any duration Parenteral - &lt;7 days</td>
<td>&lt;30days</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Lowest possible</td>
<td>≤ current treatment cost</td>
</tr>
</tbody>
</table>

* As per WHO recommendation; ** No genotoxicity is a condition only for NCEs; *** Need for parenteral treatment for severe disease
CD Clinical Landscape

Randomized Trial of Posaconazole and Benznidazole for Chronic Chagas’ Disease

Benznidazole and Posaconazole in Eliminating Parasites in Asymptomatic T. Cruzi Carriers

The STOP-CHAGAS Trial

Population Pharmacokinetic Study of Benznidazole in Pediatric Chagas Disease Suggests Efficacy despite Lower Plasma Concentrations than in Adults

Systematic Review and Meta-analysis of the Pharmacokinetics of Benznidazole in the Treatment of Chagas Disease

Treatment of adult chronic indeterminate Chagas disease with benznidazole and three E1224 dosing regimens: a proof-of-concept, randomised, placebo-controlled trial

SUMMARY OF RECENT RCTs

- Posaconazole (monotherapy or in combination) and E1224 (monotherapy) were effective during treatment and relapsed after EOT (demonstrated by PCR Positive)

- Fexinidazole x 60 days (suspended for safety issues) was effective during treatment with sustained response (PCR negative 100%) at 12 months FUP

- Benznidazole was effective during treatment with sustained response (PCR negative ~ 80%) at 12 months FUP

- Pharmacokinetic studies suggest that doses of benznidazole could be reduced

- PCR proved useful for assessing treatment response to antitrypanosomal drugs
Treatment of adult chronic indeterminate Chagas disease with benznidazole and three E1224 dosing regimens: a proof-of-concept, randomised, placebo-controlled trial

Faustino Torraca, Jaquem Gascón, Lourdes Orta, Cristina Alonso-Vega, María Jesús Pina, Alejandro Schilman, Igor C Almeida, Fabiano Alves, Nathalie Strob-Wouer, Isabel Ribeiro, on behalf of the E1224 Study Group
Strategies for Improving Efficacy and Tolerability

- BNZ is an effective drug
  ... but
- Efficacy gap
  - About 20% exhibit failure on PCR at 12 months
- Tolerability gap
  - 15-20% do not complete treatment
  - Majority due to ADRs

Reduce BNZ exposure
- Improve tolerability while maintaining efficacy
  - *Does not address the efficacy gap
- Combination therapy
  - Improve efficacy while maintaining or improving tolerability
  - *May not address the tolerability gap
Chagas Landscape 2018

**Research**
- Various Groups Worldwide
- GSK Tres Cantos
- Chagas DD Consortium
- Celgene
- EU-FP7 Consortia - PDE4NPD

**Translational**
- Pre-clinical
- Hit to Lead
- Screen

**Development**
- Phase I
- Phase IIa / PoC
- Phase IIb / III
- Registration
- Implementation

**DNDi Activities**
- LOAUS-LOUS-LOLA
  - Series from partners and sources
  - Abbvie
  - GSK “Chagas” Box
  - Sanofi
  - Celgene
  - others

- LSHTM STPH LMPH
- IPK Dundee Eskitis

- Fexinidazole
- Benznidazole New Regimen / Comb Forsa
- ATTACH Amiodarone UNB
- BERENICE Benznidazole VHIR EU-FP7 consortia
- CHICO Pediatric Nifurtimox Bayer
- EQUITY Benznidazole / Nifurtimox UNB
- BERENICE Pediatric Nifurtimox Bayer

**Biomarkers**
- LAFEPE Bra
- ELEA Arg
- Pfizer / UGA
- GSK Eisai/Broad GSK DDU
- Various Groups Worldwide

**Additional Information**
- DNDi only
- DNDi in collaboration
- Other

**Notes**
- 5/8
- 2/3
BENDITA overall design
Bolivia

- Adults (18 – 50 years old) at Chronic Indeterminate CD stage
- 210 subjects - 30 patients/arm

Follow-up at 10 wk, 12 wk, 4M, 6M, 12 M

Primary endpoint at 6M
Follow-up until 12M

Clinically significant adverse events

BZN 300 8W
E1224 PBO 8W
BZN 300 4W
BZN PBO 4W
E1224 PBO 8W
BZN 300 2W
BZN PBO 6W
E1224 PBO 8W
BZN 150 4W
BZN PBO 4W
E1224 PBO 8W
BZN 150 4W
BZN PBO 4W
E1224 8W
BZN PBO 8W
E1224 PBO 8W

Futility stopping rule
10 and 12-week interim analysis (safety and efficacy)

Screening period
randomisation

ClinicalTrials.gov Identifier: NCT03378661
FEXI 012 overall design
Spain

- Adults (18 – 50 years old) at Chronic Indeterminate CD stage
- 45 subjects - 15 patients/arm

Screening period

- Futility stopping rule
- 12-week interim analysis (safety and efficacy)

Randomisation

10 day treatment phase

Historical Control

Follow-up at 1-4; 6; 10; 12 wk, 4M, 6m, 12 M
Primary endpoint at 4M
Follow-up until 12M

Partners
ISGlobal
Hosp Vall d´Hebron
Hop Clinic
Hop Moises Broggi
Hosp Univ Valencia
INGEBI

- Fexi 600 mg
  - 3 days
- Fexi 1200 mg
  - 3 days
- PBO
  - 7 days
- Fexi 600 mg
  - 4 days
- PCO
  - 3 day

- Fexi 1200 mg
  - 4 days
- PCO
  - 3 day
**MULTIBENZ overall design**

**Argentina, Brazil, Colombia, Spain**

- Adults (18 – 50 years old) at Chronic Indeterminate CD stage
- 240 subjects - 80 patients/arm

**BZ 300 mg**
- 60 days

**BZ 150 mg**
- 60 days

**BZ 400 mg**
- 15 days

**PLACEBO**
- 45 days

Follow-up at 4; 6; 8; 12 M

Follow-up until 12M

**ClinicalTrials.gov Identifier:** NCT03191162
Current alternatives under evaluation

• Different old courses of benznidazole and nifurtimox (30 vs 60 days)

• New regimens of benznidazole in monotherapy (low dose and/or short regimen or intermittent): Next step, policy change?

• NCE: New regimen of Bz in combination with E1224: Next step, Move to Phase 3?

• NCE: Fexinidazole, short course of treatment: Next step, Move to Phase 3?
Biomarkers to improve assessment of response of etiological treatment

### POTENTIAL BIOMARKER. SECONDARY SURROGATES

**NHEPACHA Pilot Study 2017-2018**

<table>
<thead>
<tr>
<th>PARASITE ANTIGENS</th>
<th>Expression level in % (vs no T. cruzi)</th>
<th>% of decreasing after treatment</th>
<th>Elapsed time to decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoML anti rTc24 ab</td>
<td>80</td>
<td>38 – 19</td>
<td>6-24m/ 24-36m</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>38 – 19 // 80*</td>
<td></td>
</tr>
<tr>
<td>KMP11</td>
<td>100</td>
<td>74-67</td>
<td>6m -24m</td>
</tr>
<tr>
<td>HSP70</td>
<td>100</td>
<td>74-50</td>
<td>6m-9m</td>
</tr>
<tr>
<td>F29</td>
<td>80</td>
<td>35 – 62</td>
<td>6m - 48 m</td>
</tr>
<tr>
<td>Ab 3</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
</tbody>
</table>

**Next-generation ELISA diagnostic assay for Chagas Disease based on the combination of short peptidic epitopes**

Juan Mucci1*, Santiago J. Carmona1**, Romina Volovich2, Jaime Altehe2, Estefania Bracamonte5, Jorge D. Marco5, Morten Nielsen1**, Carlos A. Buscaglia1, Fernán Agüero1,5

**Fig2. Reactivity pattern of example optimal peptide subsets. Two peptide combinations were created using the EpiSelect algorithm to achieve a**
Progress in developing NCEs for Chagas disease

* = preclinical candidate

Preclinical development

Lead optimisation

2016 2017 2018

OXABOROLE
GSK Box Series 1
GSK Box Series 2
GNF
GSK DDU
...

Nitroheterocyclic drugs cure experimental *Trypanosoma cruzi* infections more effectively in the chronic stage than in the acute stage

Amanda Fortes Francisco¹, Shiromani Jayawardhana¹, Michael D. Lewis³, Karen L. White¹, David M. Shackleford², Gong Chen², Jessica Saunders², Maria Osuna-Caballero³, Kevin D. Read³, Susan A. Charman³, Eric Chakelstein³ & John M. Kelly²

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**DNDi**

Drugs for Neglected Diseases initiative
OUTLOOK FOR 2020 BEYOND….

- NEW TRYPANOCIDE CHEMOTHERAPY

- TRYPANOCIDE CHEMOTHERAPY PLUS IMMUNOTHERAPY (?)

- TRYPANOCIDE CHEMOTHERAPY PLUS MODULATION OF PHYSIOPATHOGENESIS (?)

- TRYPANOCIDE CHEMOTHERAPY PLUS IMMUNOTHERAPY PLUS MODULATION OF PHYSIOPATHOGENESIS (?)
Chagas Access Plan: Current Outlook

Regional Initiatives Ministries of Health INCOSUR, IPA, IPCAM, IAMAZON, NonEC

Colombian Pilot Project, initial Y1 results:
- Increase in screening: 900%
- Coverage of dx confirmation: 100%
- Reduction in delays, dx confirmation: from > 1 year to <2 weeks

Available Medication:
- BZ 12.5; 50; 100 mg
- NFT 30; 120 mg

Registration of Bz in NA (FDA-USA and COFEPRIS-Mexico) 2017
International Federation of Associations of People Affected by Chagas disease - FINDECHAGAS

http://www.youtube.com/watch?v=t3yVr8N3XmU
THANK YOU!!

https://www.dndi.org/
ssosa@dndi.org