The Lead Optimization Latin America (LOLA) consortium: collaborative drug discovery for Neglected Tropical Diseases (NTDs)

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⁴Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland
# Building a DNDi LOLA consortium

<table>
<thead>
<tr>
<th>Key component</th>
<th>Chagas</th>
<th>VL</th>
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</thead>
<tbody>
<tr>
<td>Medicinal chemistry &amp; DMPK leadership&lt;br&gt;Data analysis, screen progression &amp; compound design</td>
<td>UNICAMP &amp; AbbVie &amp; Simon Campbell</td>
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<tr>
<td>Synthetic chemistry&lt;br.Route design, problem solving and synthesis</td>
<td>UNICAMP</td>
<td>UNICAMP</td>
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<tr>
<td>Biology&lt;br&gt;in vitro&lt;br&gt;in vivo</td>
<td>LMPH &amp; USP, Sao Carlos TBA</td>
<td>LMPH &amp; USP, Sao Carlos LMPH (temporary)</td>
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<tr>
<td>DMPK – in vitro &amp; in vivo</td>
<td>AbbVie &amp; Wuxi</td>
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<td>Drug safety &amp; toxicology</td>
<td>TBA</td>
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<td>Formulations &amp; solid form</td>
<td>Wuxi</td>
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<td>Consortium coordination</td>
<td></td>
<td>Leandro Christmann</td>
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<td>• Other specialist services available via additional CROs</td>
<td></td>
<td>Charlie Mowbray &amp; Eric Chatelain</td>
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Consortium leaders
Early screening cascade

Design and Analysis of new targets
Collaborative effort by UNICAMP, AbbVie, Simon Campbell & DNDi

Synthesis
UNICAMP, Campinas

Primary Parasitology
USP São Carlos and LMPH, Antwerp

in vitro ADME
AbbVie, Chicago

Secondary Parasitology
Swiss Tropical Institute

Formulation – in vivo PK
Wuxi AppTech, Shanghai

Mouse model of Chagas Disease
LSHTM, London
Origins of leads against *T. cruzi*

Early leads for new drugs for Chagas disease

- **Monocyclic series**
  - TDR30139
  - IC$_{50}$ = 0.34 µM (*in vitro*)
  - TDR screening campaign
  - TDR optimisation project

- **Bicyclic series**
  - LOLA4
  - IC$_{50}$ = 0.03 µM (*in vitro*)
  - NIH funded screen of the Broad Institute compound collection

Medicinal Chemistry Centre for Chagas Disease in Brazil

**World Health Organization**

New Medicinal Chemistry Centers to Join Drug Discovery Networks

T24/181/136 ID No. A80141

The Special Program for Research and Training in Tropical Diseases

TDR/UNICEF/UNDP/WB/WHO

**Principal Investigators**

- Adriano D. Andricopulo
  - University of Sao Paolo
  - Medicinal Chemistry and Drug Design

- Glaucius Oliva
  - University of Sao Paolo
  - Structural Biology and Strategic Planning

- Luitz Carlos Dias
  - UNICAMP
  - Organic Synthesis
MOA is not CYP51 inhibition

- **TDR30139 & TDR91219** have promising *in vitro* activity against *T. cruzi*
- Hit to lead chemistry in progress at University of Campinas
- Check for CYP51 inhibition before investing too much effort:

  ![Chemical structures](image)

  **TDR30139**
  - *T. cruzi* IC$_{50} = 0.34$ µM
  - CYP51 IC$_{50} > 10$ µM

  **TDR91219**
  - *T. cruzi* IC$_{50} = 0.7$ µM
  - CYP51 IC$_{50} > 10$ µM

- Experiment kindly carried out by collaborators at GSK, Tres Cantos, and Dundee Drug Discovery Unit
Recovery of T. cruzi amastigotes: Standard assay vs. wash-out

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (µg/ml)</th>
<th>IC90 (µg/ml)</th>
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<tbody>
<tr>
<td>TDR91219</td>
<td>0.166</td>
<td>3.23</td>
</tr>
<tr>
<td>TDR30139</td>
<td>0.263</td>
<td>2.65</td>
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</table>

- Further confirmation of good *in vitro* activity
- Aim to test relevance of residual parasites in an *in vivo* assay

25 August 2014
General Synthesis

**monocyclic cyanopyridines**

\[
\text{Me} - \text{C} - \text{Me} + \text{NC} - \text{C} - \text{NH}_2 \xrightarrow{\text{Et}_3\text{N, ethanol, reflux, 30 min}} \text{thiopyridone}
\]


**bicyclic cyanopyridines**

\[
\text{H} - \text{Ar} + \text{NC} - \text{C} - \text{NH}_2 \xrightarrow{\text{Et}_3\text{N, ethanol, reflux, 30 min}} \text{thiopyridone} \xrightarrow{\text{then piperidine, reflux, 18 h}} \text{NIH lead analogues}
\]

Scaleup

BWS036

1) Br

2) TsOH-H_2O, EtOAc, 55 °C
then 2N NaOH
(96%)

LOLA3

LOLA4

MAD997

LOLA67
Synthesis of TDR30139 derivatives

LOLA4
IC$_{50}$ = 0.03 µM

LOLA3
IC$_{50}$ = 0.31 µM

LOLA48
IC$_{50}$ = 7.9 µM

LOLA67
IC$_{50}$ = 0.58 µM

TDR91228
IC$_{50}$ = 1.2 µM

TDR100612
IC$_{50}$ = 70 µM

TDR100524
IC$_{50}$ = 26 µM

TDR95696
IC$_{50}$ = 2.0 µM

MAD328
IC$_{50}$ > 100 µM

TDR30139
IC$_{50}$ = 0.34 µM

monocyclic

bicyclic
T. Cruzi IC$_{50}$ vs. Selectivity Index on MRC5 cells

Good potency and SI possible within the series.
Good potency possible over a useful range of AlogP within the series, especially with AlogP > 3.
Encouraging HLM metabolic stability possible within the series even at AlogP 3-4

Chose 4 examples for in vivo evaluation:
- 1 monocyclic, 3 bicyclic
- 2 neutral, 1 tertiary & 1 secondary amine

Encouraging RLM metabolic stability also possible within the series even at AlogP 3-4:
- Important for in vivo pk and efficacy studies
Metabolite identification for LOLA3

Routes of metabolism observed:
- Amide hydrolysis
- Dehydrogenation
- Dehydrogenation & oxidation
- Aromatisation

Use this information to:
- Remove soft spots
- Block soft spots
Summary

- Cyanopyridine series
  - Encouraging *in vitro* profiles
  - Leads scaled up for formulation and *in vivo* studies
  - Mouse pk results awaited
  - Apply metabolite ID to guide design
  - Test leads in a mouse model of Chagas disease soon

- Apply medicinal chemistry & drug discovery principles to other new chemical series

- Extend the LOLA consortium
  - DMPK, *in vivo* models, chemistry, safety/toxicology,…
Acknowledgements

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Manu De Rycker

James Mills

Wen Hua

Charlie Mowbray, Eric Chatelain, Leandro Christmann and Simon Campbell