DNDi Australian Discovery Consortium

Early medicinal chemistry to identify new candidate drugs

ICTMM 2012 September 2012
Rio de Janeiro
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Early medicinal chemistry to identify new candidate drugs

- Aim of the discovery effort
- Hit identification
- Profiling and early optimisation
- Flow scheme and assay correlation
- Further optimisation
- Are we there yet?
Aims

• To develop a drug that kills *Trypanosoma cruzi* a kinetoplastid parasite and causative agent of Chagas Disease in humans

• The target product profile:
  – Orally available
  – Cheap
  – Efficacy non-inferior to standard treatment
  – Better tolerated than standard treatment
  – Efficacious against chronic infections, multiple strains
  – No clinically significant interaction with anti-hypertensive, anti-arrythmic and anticoagulants drugs
Hit Identification

- *In vitro screen*: whole parasite assay targeting intracellular amastigote *T. cruzi* forms

- Where to find hits?
  - High-throughput screening (HTS)
  - Compound libraries – (non)-targeted
  - Existing drugs or published compounds
  - Rational design
  - Natural products
Fenarimol as an inhibitor of *T. cruzi*
Profiling and early optimisation: \textit{in vitro}

Design a strategy to define the \textbf{Structure-Activity-Relationship (SAR)}

Profiling of additional \textit{in vitro} properties

\[ E_{H(h)} 0.82 \text{ : Sol}_{\text{pH6.5}} < 25 \mu\text{g/ml} \text{ : CYP3A4 } IC_{50} 7 \mu\text{M} \]
Profiling and early optimisation: *pharmacokinetics*

Oral exposure of compound in mouse plasma

**EPL-BS0177**
- IC₅₀ 12nM
- EH(h) 0.5

*Compound Exposure in Mouse*

[Compound] (µM) over Time (h)

- 20mg/kg *oral* dose

First connection between *in vitro* and *in vivo* assays
Profiling and early optimisation: \textit{in vivo efficacy in a disease model} 
20-day mouse model of \textit{T. cruzi} infection

Control drug

\begin{itemize}
\item \textbf{Posaconazole @ 20 mg/kg}
\end{itemize}

\begin{itemize}
\item \textbf{BS177 @ 20 mg/kg}
\end{itemize}

\begin{itemize}
\item \textbf{Dosing}
\item \textbf{Immunosuppression}
\end{itemize}

\textbf{It works!}
EPL-BS177 efficacious in *T. cruzi* infection model

Highly metabolised

Worked *in vivo* couldn't be optimised

*in vitro/vivo* disconnect

Not active enough

pM activity under active investigation
Pre-Clinical Candidates

**EPL-BS0967** and **EPL-BS1246** both demonstrate 'cure' in the in the *T. cruzi in vivo* efficacy model in mice

Early phase discovery target product profile check-list

- ✔ Orally available and cheap
- ✔ Efficacy non-inferior to standard treatment
- ✔ Efficacious against chronic infection in a discovery model

Late phase discovery profiling ongoing
Acknowledgements

Murdoch University Parasitology: Andrea Khong, Maria Kerfoot, Tanya Armstrong, Adriana Botero, Catherine Perez, Scott Cornwall, Andrew Thompson.
CDCO, Monash University: Karen White, David Shackleford, Sue Charman.
UFOP and IPK