Structure-guided Drug Discovery for Malaria
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Program Manager, SDDC
Crystal Structures and how they inform drug discovery
Crystal Structures and how they inform drug discovery
2010 – Massive influx of phenotypic hits for malaria

Data from MMV-supported research now in the public domain

In an unprecedented move, data from three new projects supported by MMV have been made available in the public domain.

20 May 2010

The first MMV-supported project, conducted by GlaxoSmithKline (GSK) has identified promising leads to develop new antimalarials. The second, the screening of compounds of the Genomics Institute of the Novartis Research Foundation (GNF) has been released to the European Bioinformatics Institute (EMBL-EBI). The third, conducted by Prof. Kip Guy at St Jude Children’s Research Hospital, Memphis, will also be released to the EMBL-EBI this week. Placing the combined data of over 20,000 active compounds into the public domain will give the global malaria community a considerable resource to drive forward the development of new medicines for malaria.
SDDC – the premise

Phenotypic Actives; genetic validation

Structural Genomics
Gene to protein, assay, crystal w/ hit SSIGCID/MCSG/SGC/CSGID

Combine the strengths of phenotypic and target-directed drug discovery
Bringing it together for quality Drug Leads

- Essentiality & Validation
- Chemical Validation
- Protein/Structure Ure/Assay
- Progressible Chemistry
SG-Lead-ID multidisciplinary project teams

Structural Genomics  In vitro  Chemistry  DMPK/TOX  In vivo

Drug Leads for High Value Targets
Malaria and Tuberculosis

MedChem & DMPK

In vitro biology

External Support
- CEREP
- AbbVie
- WUXI
- GSK
- Schrodinger
Pf ProRS project: SG Lead-ID

- Essential process in Pf
  - Protein synthesis inhibition

- Potent phenotypic inhibitors available – febrifugine, halofuginone (HF)
  - Chemical validation with HF (resistant parasites, WGS)
  - Active in blood-stage, liver-stage and gametocytes

- HF drugable but non-selective vs human ProRS
  - HF, FF toxic, HF low safety margin

- Phenotypic libraries (TCAMS, St Judes) screened for selective hits

Inhibitors with high selectivity vs human enzyme would be attractive drug-candidates
Initial crystal structure with halofuginone
Initial crystal structure with halofuginone
Phenotypic Library Screening: Plasmodium versus Human
Crystal structures w/ hits show completely new, allostERIC binding site and abrogated active site
### Hit-to-Lead: PfProRS

<table>
<thead>
<tr>
<th>ID</th>
<th>Early Lead Criteria</th>
<th>Initial Hit</th>
</tr>
</thead>
<tbody>
<tr>
<td>pIC50 vs PfProRS</td>
<td>&gt;7</td>
<td>6.1</td>
</tr>
<tr>
<td>pIC50 vs Pf(3D7)</td>
<td>&gt;7</td>
<td>6.3</td>
</tr>
<tr>
<td>pIC50 vs Pf(NF54)</td>
<td>&gt;7</td>
<td></td>
</tr>
<tr>
<td>pIC50 vs Pf(K1)</td>
<td>&gt;7</td>
<td></td>
</tr>
<tr>
<td>pIC50 vs HEPG2</td>
<td>&gt;100 fold difference calculated</td>
<td>&lt;4.3</td>
</tr>
<tr>
<td>LE, LLE, LELP</td>
<td>&lt;5</td>
<td>4.4</td>
</tr>
<tr>
<td>logP (CHIlogD)</td>
<td>&lt;5</td>
<td>4.4</td>
</tr>
<tr>
<td>MW</td>
<td>&lt;500</td>
<td>396</td>
</tr>
<tr>
<td>Clearance Microsomes ml/</td>
<td>Stable (&lt;5 ml/min/g)</td>
<td>2.9</td>
</tr>
<tr>
<td>Mouse PPB</td>
<td>&lt;99%</td>
<td></td>
</tr>
<tr>
<td>Solubility (uM)</td>
<td>&gt;10 uM</td>
<td>&gt;250</td>
</tr>
</tbody>
</table>

**Structure-guided drug discovery is underway**
Early Lead Candidates (AA assay - UW)

Pfal ProRS compound inhibition

- Pf(3D7) pEC$_{50} = 7.1$
- HsHEPG2 pIC$_{50} = 4.7$
- Sol (µM) > 250
- Mouse Cli (ml/min/g) 0.5

- Pf(3D7) pEC$_{50} = 7.7$
- HsHEPG2 pIC$_{50} = < 4.3$
- Sol (µM) > 250
- Mouse Cli (ml/min/g) 0.5

- Pf(3D7) pEC$_{50} = 7.2$
- HsHEPG2 pIC$_{50} = < 4.3$
- Sol (µM) > 250
- Mouse Cli (ml/min/g) 1.2

Pro 15
Pro 16
Pro 17
PfKRS1 project (Hit to Lead)

- Essential process in Pf
  - Protein synthesis inhibition

- Potent phenotypic inhibitor available – Cladosporin (CLAD) (Winzeler)

- Chemical validation with CLAD (resistant parasites, WGS)

- CLAD active against blood-stage and liver-stage parasites

- Phenotypic hit (CLAD) selectivity vs human is high but CLAD poorly druggable

Drug-like inhibitors of Pf LysRS with high selectivity vs human enzyme desirable
Hit to Lead: Pf LysRS

Proteins and assay at SSGCID:
Phenotypic hits screened Structure from Amit Sharma

Novel drug-like heterocyclic hits have similar pharmacology to CLAD (IC$_{50}$ 300nM Pf krs1, selective vs Hs KRS1)

MedChem, Computational Chem, DMPK from DDU

VanVoorhis, Sharma, DDU
Cladosporin, hits, and computational chemistry
Hit to Lead: Pf LysRS

CLADOSPORIN – probe compound

Drug-like heterocyclic “hit”

Novel compounds based on initial hits and computational chemistry, structure-activity relationship established

DDU, STPHI, UW
Tracking SAR: *Pf* kr1 vs *Pf*(3D7) for novel heterocycles

Good correlation between biochemical and phenotypic assays

Colour coded metabolic stability (green stable, red high Cl)
Hit to Lead: Pf LysRS

Early Lead Criteria (MMV) | Early Lead
--- | ---
plC$_{50}$ vs. PfKRS1 > 7 | 6.9
plC$_{50}$ vs. HsKRS1 > 100 fold | < 4.3
pEC$_{50}$ vs. Pf(3D7) > 7 | 6.5
pEC$_{50}$ vs. HEPG2 > 100 fold | 4.3
LE, LEE, LELP calculated | 0.4, 4.1, 6.7
clogP (CHI logD) < 5 | 2.4(1.7)
MW < 500 | 355
Clearance: Liver Microsomes mouse/human Stable (< 5 ml/min/g) | 1, < 0.5
Mouse PPB % < 99% | 51
Solubility (µM) > 10 µM | 250
hERG IC$_{50}$ (µM) > 1 µM | > 100
Pf dose response in Pf SCID mouse (oral) ED$_{90}$ < 50 mg/kg | 99.2% reduction of parasitemia at 20 mg/kg (oral)

Lead orally active in SCID mouse model
### PfKRS1 Compounds vs MMV Early Lead Criteria

#### Early Lead Criteria

<table>
<thead>
<tr>
<th></th>
<th>Compound 1</th>
<th>Compound 2</th>
<th>Compound 3</th>
<th>Compound 4</th>
<th>Compound 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>pIC&lt;sub&gt;50&lt;/sub&gt; vs. PfKRS1</td>
<td>&gt; 7</td>
<td>6.9</td>
<td>7.3 (hill slope 2.5)</td>
<td>7.3 (hill slope 2.4)</td>
<td>7.0 (hill slope 1.9)</td>
</tr>
<tr>
<td>pIC&lt;sub&gt;50&lt;/sub&gt; vs. HsKRS1</td>
<td>&gt; 100 fold</td>
<td>4.3 (max. effect 47%)</td>
<td>4.9 (max. effect 64%)</td>
<td>4.7 (max. effect 64%)</td>
<td>4.3 (max. effect 40%)</td>
</tr>
<tr>
<td>pEC&lt;sub&gt;50&lt;/sub&gt; vs. Pf(3D7)</td>
<td>&gt; 7</td>
<td>6.5</td>
<td>7.3</td>
<td>7.1</td>
<td>6.9</td>
</tr>
<tr>
<td>pEC&lt;sub&gt;50&lt;/sub&gt; vs. HEPG2</td>
<td>&gt; 100 fold</td>
<td>4.3</td>
<td>4.5</td>
<td>&lt; 4.3</td>
<td>4.4</td>
</tr>
<tr>
<td>logP (CHIlogD)</td>
<td>&lt; 4</td>
<td>2.4 (1.7)</td>
<td>2.1 (0.4)</td>
<td>2.1 (0.4)</td>
<td>1.9</td>
</tr>
<tr>
<td>MW</td>
<td>&lt; 450</td>
<td>355</td>
<td>335</td>
<td>371</td>
<td>335</td>
</tr>
<tr>
<td>Clearance Microsomes m/ h</td>
<td>Stable (&lt; 5 ml/min/g)</td>
<td>1, &lt; 0.5</td>
<td>1.1 (4% glucuronidated)</td>
<td>&lt; 0.5 (9% glucuronidated)</td>
<td>&lt; 0.5 (2% glucuronidated)</td>
</tr>
<tr>
<td>Mouse PPB %</td>
<td>≤ 98%</td>
<td>48</td>
<td>74</td>
<td>58</td>
<td>39</td>
</tr>
<tr>
<td>Solubility (µM)</td>
<td>&gt; 50µM</td>
<td>&gt; 250</td>
<td>146</td>
<td>&gt; 250</td>
<td>&gt; 250</td>
</tr>
</tbody>
</table>
Acknowledgements

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