Catalyzing neglected diseases drug discovery

THE PATHOGEN BOX
Open Source Drug Discovery: From screen to Malaria Box
Timothy N.C. Wells
**Malaria Box (MB)**

- 400 Diverse Compounds with Antimalarial activity
- Launched Dec 2012
- Generated many neglected diseases projects

**Pathogen Box (PB)**

- 400 Diverse Compounds Active against a range of pathogens
- Launches Q4 2015
- Will stimulate neglected Disease research

**Exploiting the Pathogen Box**

- Hit series + biological targets From PB
- Planned start 2015
- Delivers drug discovery project opportunities
Next generation: target based

Genome: All drugable targets → Validate Knock-out organisms → Assay Set-up Validation → HTS Specific Target

DHFR: Yuthavong Y et al., 2012 in preparation
DHODH: Coteron JM et al., 2011 J Med Chem 54 5540-61
Next Generation: ask the parasite

- **New business model:** ‘screen first’
- **Screened over five million compounds,** 25’000 hits
- **Fast:** screen to human trials in less than four years
- **Eight molecules** already in clinical or preclinical
- **Identifies new targets** (resistance or pull-down)

Wells TNC Science 329 1153-1154 (2010)
## Lessons from phenotypic screening

<table>
<thead>
<tr>
<th>Compound Collection</th>
<th>Compounds screened</th>
<th>Number of hits(^1)</th>
<th>% Hit-rate</th>
<th>Public?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis</td>
<td>810’000</td>
<td>5930</td>
<td>0.73</td>
<td>Yes</td>
</tr>
<tr>
<td>GSK</td>
<td>1,986,056</td>
<td>13,533</td>
<td>0.68</td>
<td>Yes</td>
</tr>
<tr>
<td>St Jude</td>
<td>309,474</td>
<td>561</td>
<td>0.18</td>
<td>Yes</td>
</tr>
<tr>
<td>Pharma A</td>
<td>502,868</td>
<td>3274</td>
<td>0.65</td>
<td>Some hits</td>
</tr>
<tr>
<td>Pharma B</td>
<td>155,554</td>
<td>1147</td>
<td>0.74</td>
<td>Some hits</td>
</tr>
<tr>
<td>Diversity A</td>
<td>256,263</td>
<td>339</td>
<td>0.13</td>
<td>2013?</td>
</tr>
<tr>
<td>Sanofi(^2)</td>
<td>1600</td>
<td>306</td>
<td>19.1</td>
<td>No</td>
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<tr>
<td>Broad Institute</td>
<td>100’000</td>
<td>465</td>
<td>0.47</td>
<td>2014</td>
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<tr>
<td>Diversity B</td>
<td>35,000</td>
<td>222</td>
<td>0.63</td>
<td>Hits</td>
</tr>
</tbody>
</table>

**Screening new diversity deck (500k) against multiple pathogens**

\(^1\) Exact definitions variable – usually confirmed hit is non-cytotoxic and has IC\(_{50}\) < 2μM

\(^2\) Compounds selected inhibited human targets that have orthologues in *Plasmodium*
**New chemical entities since 2007**

- **2022+**: 10%
- **2020+**: 20%
- **2018**: 50%
- **2016**: >90%

**New presentations of existing molecules**

- Artemether-Lumefantrine Dispersible Novartis
- Artesunate for injection Guilin
- DHA - Piperaquine Sigma-Tau
- Pyronaridine-Artesunate Shin Poong
- Artesunate Amodiaquine Sanofi/DNDi
- Artesunate-Mefloquine CIPLA/DNDi

**Launch Probability**
Case Study 1: Spiroindololone
New target and new compound class

Singleton “Hit”
EC$_{50}$ NF54 90nM

EC$_{50}$ NF54 9.2nM
Cl$_{int}$ (hu, m) unstable

EC$_{50}$ NF54 0.7nM
Cl$_{int}$ (hu, m) stable
ED$_{90}$ Pb 2.7mg/kg

7- to 6- ring
Enantiomer
Bromo- to chloro-

Fix metabolic Instability with halo-substitution

NITD-609
Currently in phase IIa trials in Thailand

Case Study 2: Aminopyridine
Drug discovery built from Africa

- Original hit donated by Diversity Company
- Compound optimized by African led project team
- Moving towards First in Human in Cape Town

\[ \text{EC}_{50}\text{ NF54 49nM}\]
Metabolic instability
\[ E_H 0.48 \]

\[ \text{EC}_{50}\text{ NF54 51nM}\]
Improved stability
\[ E_H 0.26 \]

\[ \text{EC}_{50}\text{ NF54 25nM}\]
\[ E_H < 0.07 \]
Rat F: 51%

\( \text{J Med Chem 2012, 55, 3479} \)
New models for lead optimisation: teams need high quality validated starting points

- New Hits to leads paradigm
- Dedicated teams: medicinal chemists, cell pharmacology
- Academic and industrial consortia
- Partnering in disease endemic countries
  - India, South Africa, Thailand, Brazil
- MMV experienced Mentors
- Experienced in-house project directors
More than 20’000 compounds in the public domain

Researchers want ‘physical compounds’ to test

Chose 400 compounds - based on being commercially available

Available without restriction
malariabox@mmv.org
• 153 Copies shipped

• Requests by Disease Area

- Malaria whole cell screen
- Malaria target based assay
- Neglected diseases
- Infectious diseases
- Others

- Excellent exposure, oral bioavailability
- Rapid Progression of leads to *in vivo* models
- Mechanistic studies ongoing, target ID
- Encouraging groups to deposit/publish data
- Sharing the success with the NTD17 and beyond

Drug discovery in neglected diseases has limited access to new starting scaffolds.

Early access to data on pharmacokinetics and metabolism is key to progressing compounds.

Successful projects have spun out collaborations with research teams in disease endemic countries.

Better to specifically make compounds: more novelty, less supply issues.

Start with diversity from screens against different pathogens, not just malaria.
MMV in Open Source: powering three projects

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