Open Source Drug Discovery at The Medicines for Malaria Venture

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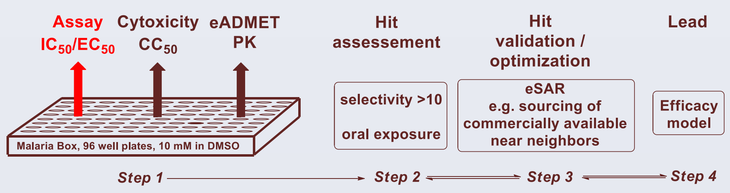
Introduction

- Despite recent treatment advances 610,000-971,000 lives were lost to malaria in 2011, 86% of those who die are under the age of 5
- MMV was established in 1999 with a mission to discover, develop and deliver safe, effective and affordable antimalarial drugs
- The low commercial value of medicines for malaria gives an opportunity to exploit the extended pre-competitive space and explore alternate drug discovery models
- Initial results from some MMV Open Source Drug Discovery projects will be discussed

MMV Open Access Malaria Box

- Screening set of 400 diverse compounds with antimalarial activity, assembled by MMV and Scynexis[1].
- Provided free to requestors in a bid to catalyse malaria and neglected disease drug discovery and research. Requestors agree to put results back into public domain.
- MMV has generated data including mouse oral PK on all 400 compounds and can provide advice to groups wishing to exploit hits



Process for advising groups on progressing hits

Preliminary results

Malaria

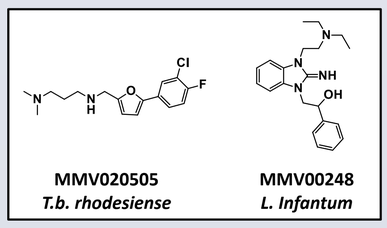
Screened against key plasmodium biological targets: aids drug discovery prioritization

Compounds being used to identify novel biological targets

Compounds have shown activity in several other neglected diseases:

Human African Trypanosomiasis and Leishmaniasis

In a collaboration with DNDi and University of Antwerp, MMV020505 and MMV000248 showed *in vitro* potency and oral exposure in mice: rapid progression to efficacy models



Request the Malaria Box at http://www.mmv.org/malariabox

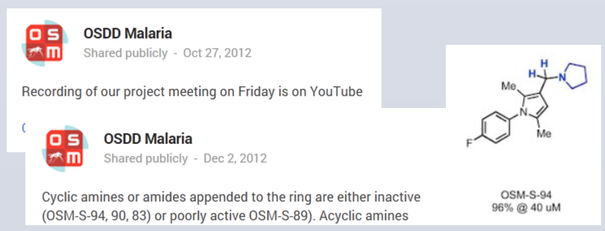
Open Source Drug Discovery

- 2011: MMV started an Open Source Drug Discovery project with M. Todd (U Sydney)
- All project data posted online: electronic lab note book, screening results, discussions
  http://opensourcemalaria.org
- Anyone can contribute experimentally or with scientific advice
- Open Project Meetings where decisions made: anyone can connect and contribute

1. All data are open and all ideas are shared
2. Anyone can take part at any level of the project
3. There will be no patents
4. Suggestions are the best form of criticism
5. Public discussion is more valuable than email
6. Project is bigger than, and not owned by, any given lab

GOAL: Find a good drug to treat malaria, by any means, as quickly as possible

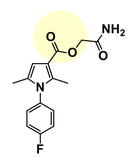
Laws for OSDD Project



Screenshots from Website

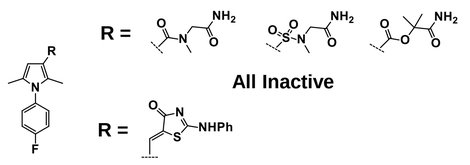
Pyrrole Series Initially Investigated

Ester: Key Liability
Compound inactive *in vivo* malaria model
Stable in Human Plasma
Mouse Plasma $t_{1/2}$ = 112min
HLM Cl_{int} 29µL/min/mg protein



Hit from GSK TCAM set
TCAM123812
IC_{50} (3D7) 330nM

Many Ester replacements prepared: most inactive



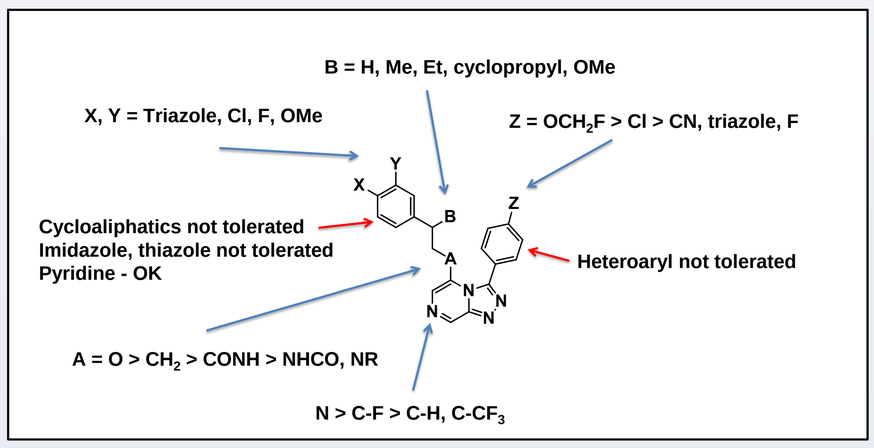
IC_{50} (3D7) 46nM
Solubility <1.6µg/ml
HLM Cl_{int} 19µL/min/mg protein
No improvement in overall properties

- Series parked, key liabilities not overcome. New series under investigation
- Open source drug discovery team established, external groups contributed synthesis and screening resources
- Drug discovery scientists contributed via website and participated in project meetings
- Encouraging start, increased participation of med. chem. experts would be beneficial

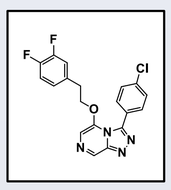
Triazolopyrazines

Identified from screening 160,000 Pfizer compounds against *P. falciparum* (3D7 strain) at the Eskitis Institute for Cell and Molecular Therapies in Brisbane (For further info see D. Waterson poster #58)

Initial SAR



Lead Molecule: MMV639565 Summary



MWt 386.7, logD 3.36

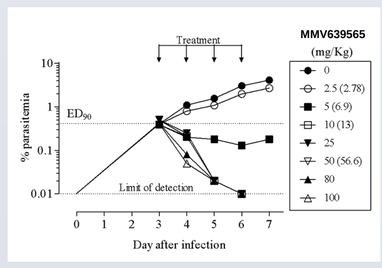
P. falciparum (3D7) IC_{50} 38nM
No cross-resistance with K1 strain
HLM 16µl/min/mg
RLM 70µl/min/mg

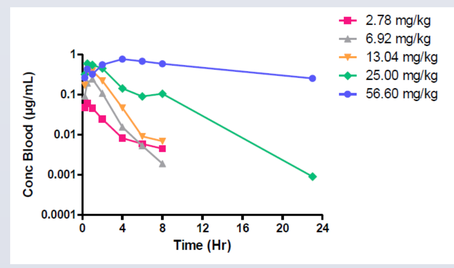
Dofetilide binding IC_{50} 23.8µM
Cerep panel: no significant hits @ 10µM for close analogues

Rat PK (iv 0.5mg/kg; po 3 mg/kg)
Cl 44 ml/min/kg
Vss 0.9 L/kg
$T_{1/2}$ 0.6hrs
Oral F 16%

MMV639565: *In vivo* efficacy

Screened against *P. falciparum* growing in peripheral blood of NODscidIL2Rγnull mice engrafted with human erythrocytes - po dosing, qd for 4 days





In brackets: Dose corrected according to quality control of formulation

Rapid parasite clearance - ED_{90} 6.3mg/kg

Triazolopyrazines: New Open Source Series

Further optimisation of the triazolopyrazine series to deliver a drug candidate will be carried out in an Open Source Drug Discovery project with Dr Mat Todd (U. Sydney)

Series Strengths

- Good *in vivo efficacy* and rapid parasite clearance
- Known biological mechanism: PfATP4 inhibitor

Series Issues

- Metabolic stability, particularly in rat

Get Involved in Open Source Drug Discovery

- Can you offer drug discovery advice to the project?
- Can you prepare or screen compounds for the project?

Visit the website and participate: http://opensourcemalaria.org

Conclusions

Open science is able to play a role in advancing neglected disease research. Further increasing the participation of drug discovery experts will be key to future progress.

Acknowledgements

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References

1. Spangenberg T, Burrows JN, Kowalczyk P, McDonald S, Wells TNC, Willis PA. (2013) The Open Access Malaria Box: A Drug Discovery Catalyst for Neglected Diseases. PLoS ONE 8(6): e62906