14th Stakeholders’ Meeting
MMV’s longer-term anti-relapse strategy: The discovery of new molecules
Bali | 11 – 12 October 2017

Brice Campo PhD
Director Drug Discovery

Defeating Malaria Together

MMV Medicines for Malaria Venture
Enhanced discovery efforts over the next decade are critical for an eradication agenda over the next 25 years.
MMV Discovery’s portfolio offers multiple compound series against TCPs

Mayday ! Mayday !

- Lead generation
- Lead optimization
- Preclinical
- Human volunteer
- Patient exploratory
- Patient confirmatory
- Regulatory review

2 Counts by compound series  
3 Counts by asset  
4 Based on technical maturity of relevant discovery assays

• Tafenoquine  
• KAF156  
• DSM265  
• KAF156  
• KAE609  
• OZ439  
• DSM265  
• OZ439  
• KAF156  
• KAE609
Discovery priority – TCP3

• WHO Road map for 90% reduction by 2030
• Elimination 2030-2040; Eradication >2040

• Novel drugs without G6PD liabilities are urgently needed:
  • Hypnozoiticidal in vivax and ovale malaria
  • ‘Wake up’ hypnozoites in vivax and ovale malaria
  • Candidates tested in validated haemolysis assay: \textit{in vivo} SCID mouse engrafted with blood from volunteers with low active G6PD (Rochford)
Achieving the ambitious business plan goals: How, When and What?

• **MMV Deliverables (2017–2021)**
  - Support Tafenoquine registration as a single-dose anti-relapse agent in adults and children being treated for *P. vivax* malaria with standard blood schizonticides, and deployed with an appropriate point-of-care G6PD diagnostic

• **Beyond 2021?**
  - 1 new NCE with relapse prevention by 2027+
  - To achieve this ambitious goal, new hits series need to be identified in the next couple of years
  - How? Emergence of new promising Radical Cure *in vitro* *Pv* liver stage assays
What’s the problem?

- Need *P. vivax* sporozoites to establish a liver stage hypnozoite assay
- Membrane feeding of mosquitoes on *vivax* gametocytes
- Human liver cells
- Or alternatively hepatoma cell lines
- Access *vivax* gametocytes from patients
- No blood stage continuous culture

Source: Adapted from Mendis K., *P. vivax* malaria, presentation at the Regional Consultation on Malaria Control and Malaria Elimination, Bhubaneswar, Orissa, India, October 2011
Liver Stage Assays – where were we?

- **2009: BMGF Call, with MMV input, for vivax workstream** (blood culture, *in vitro* and *in vivo* liver stage assays)
  - Excellent progress with *in vitro* and *in vivo* liver stage assays
  - No breakthroughs with continuous vivax blood stage culture

- **2009: NGBS-MMV Wellcome Trust project in 2009 focus on *Pc* liver stages (*in vitro* and *in vivo*)
  - Low/Medium throughput *in vitro* liver stage assays (BPRC)
  - Compounds inhibiting hypnozoite development but no hypnozoiticides

- **2012: MMV funded UCSD to establish a screening center using their *P. berghei* Liver Stage assay**
  - Ultra high throughput (1536w format)
  - Excellent progress and learnings due to high number of compounds tested
1,000,000 compounds screened since start of the program (publication out in 2018)

Several series with dual stage activity (TCP1 and TCP4) currently under development in MMV’s discovery portfolio

First time ever that such high scale screening has been performed on the parasite liver stage

Not human parasite, and no Hypnozoites
Liver Stage Assays – where are we now?

- **Dennis Kyle et al (USF/ Georgia, USA/ SMRU, Thailand):**
  384 well *Pv* liver stage assay using primary hepatocytes
  - Spatial confinement, use of moulded microwell plates
  - Expansion of insectary at SMRU

- **Jetsumon Sattabongkot et al (Mahidol, Thailand):**
  96/384 well *Pv* liver stage assay in development using HC04
  - 8 well assay delivering high quality data
  - HC04 - identify hits that, otherwise, would be inactive after metabolism?

- **Sangeeta Bhatia et al (MIT, USA):**
  384 well *Pv* liver assay - primary hepatocytes and fibroblasts
  - Micropatterned Co-Culture
  - Funded through BMGF Liver Stage consortium

- **Varadha Sundaramurthy et al (NCBS, India):**
  96 well *Pv* liver stage assay in development using HC04 cells
  - Collaboration with NIMR (Santosh Ghosh)
  - Assay in early development
**P. vivax Liver Stage assay:**
Pr D. Sattabongkot’s lab at MVRU, (Thai)

Attributes of novel model system

- Hepatoma cell line (HC-04)
- No co-culture required
- Low metabolism
- Chemical validation with PI4K, atovaquone and 8 Aqs
- First group to deliver data on MMV compounds and on Pv hypnozoites
- Historical platform which is delivering millions of spz

Complete development achieved
P. vivax Liver Stage assay: Pr D. Kyle’s lab at UGA, USA

Attributes of novel model system

- Primary human hepatocytes
- No co-culture required
- Confinement is key
- Primary hepatocyte phenotypes for >3 weeks
- Activation of hypnozoites >Day 21
- Chemical validation with PI4K, atovaquone and 8 AQs

Complete development achieved
Liver Stage Assays – what has been done in the last two years?

• >10,000 compounds screened in prophylaxis and radical cure modes at UGA

• 3 platforms producing sporozoites on a regular basis (2 in Thailand and 1 in India) with a potential 4th one on the way

• Schizonticides and first potential hypnozoiticides identified (under confirmation)

• Strengthen close relationship with BMGF to align strategy of investment

• Size does matter: nb parasites killed vs reduction in size
Gaps and main challenges

• **Still no continuous vivax asexual blood stage culture**
  - No standard clones for studies
  - Restricts where liver stage assays can be run

• **Few clinical sites to access vivax from patients for assays**
  - Requires insectary and full parasitology capabilities
  - Huge logistics often to overcome so that sporozoites ‘meet’ the assay

• **No Pharma or Industrial screening centres in vivax regions**
  - Throughput needs to increase and cost per well decrease
  - Investment in equipment (liquid handling, readers)

• **Sufficient screening capacity for *P. vivax* liver stages?**
  - Many more compounds to screen than capacity
Opportunities

- **P. vivax liver**
  - First substantial screens underway: initial hits requiring confirmation
  - Groundbreaking in science and global health impact

- **P. cynomolgi** as Asexual culture will open up liver stage screening
  - Sporozoite development and infectivity still needs to be confirmed
  - Not vivax
  - Requires sites with insectary and excellent parasitological skills

- **Expand sites**
  - Build capacity for sporozoites and new screening
  - Potential to build off vivax human challenges
  - Cryopreservation would have huge impact
Opportunities

- **P. vivax liver stage assays are delivering**
  - First substantial screens underway: initial hits - requiring confirmation
  - Groundbreaking in science and global health impact

- **P. cynomolgi asexual culture will open up liver stage screening**
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- Expand sites
  - Build capacity for sporozoites and new liver stage screening
  - Potential to build off vivax human challenges
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