# Understanding the Liver Stage Biology of Malaria to Enable and Accelerate the Development of a Highly Efficacious Vaccine

Location: RmLD20AB, 5601 Fishers Lane, Rockville, MD 20852

Date: August 8-9, 2017

**Background and Objective**

Development of a highly efficacious malaria vaccine with at least 75% protective efficacy is one of the R&D targets identified by the Global Vaccine Action Plan and the Malaria Vaccine Technology Roadmap. However, the most advanced vaccine product, RTS,S/AS01B (MosquiRix®) developed by GSK, elicits only a moderate level of efficacy against clinical malaria (33-50%) in older infants. Thus, the development of a second-generation malaria vaccine with improved efficacy is a crucial global health priority.

As global malaria control and elimination efforts continue, measures to reduce infection with both *P. falciparum* and *P. vivax* become extremely important. The liver stage represents a bottleneck in the malaria life cycle and, as such, is an attractive vaccine target for both *P. falciparum(Pf)* and *P. vivax(Pv)*. Recently, great progress has been made in the development of whole sporozoite vaccine strategies targeting to the liver stage of *Pf* parasites. These include radiation attenuated sporozoites (RAS), genetically attenuated sporozoites (GAP), or Chloroquine prophylaxis with (live) sporozoites (CPS). Evaluation of these strategies in a controlled human malaria infection (CHMI) setting indicated that CPS immunization using live sporozoites was ~10-times more effective at eliciting protection compared to a RAS strategy and achieved >75% protective efficacy; protective immunity elicited by CPS is believed to be directed against pre-erythrocytic (most likely liver stage) parasites. This increase in potency is thought to reflect the greater ability of live *Pf* parasites to multiply in the liver for at least 6-7 days to complete their liver stage replication before being terminated by drug treatment, while RAS only supports liver stage development for approximately 2-3 days.

Efforts are ongoing in multiple laboratories to develop and test several *Pf* GAP approaches, especially GAP that can support longer liver stage development. To date, however, only mutations that arrest parasite development in the early liver stage have been made, and the development of a stable *Pf* GAP with a late liver stage replication comparable to those of CPS has not been successful. Undoubtedly, there remain knowledge gaps in malaria parasite liver stage biology for *Pf* as well as for *Pv* in human infections as compared to that observed in experimental infections in animal models. ***The overall objective of this workshop is to gather relevant investigators to discuss malaria liver stage biology and immunology with an ultimate goal of identifying targets and strategies that will assist in the design and development of a safe, efficacious GAP vaccine for malaria.***

**Agenda**

*Tuesday, August 8*

8:00-8:15 **Opening Remarks**
Emily Erbelding, MD, Director, Division of Microbiology and Infectious Diseases (DMID)

8:15-8:25 **Welcome & Logistics**
Annie Mo & Glen McGugan

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**Main Session**

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**8:25-11:20** **Overview: Progress and Challenges on Sporozoite Vaccine R&D**
Chair &Co-Chair: Miguel Prudencio, Hernando Del Portillo

8:25-8:50 Overview of Whole Parasite Vaccine R&D Targeting Pre-erythrocytic Lifecycle Stage of Malaria
Stephen Hoffman, Sanaria Inc.; 20+5 mins

8:50-9:15 Current Progress and Challenges in R&D for Genetically Attenuated Parasites (GAP)
Stefan Kappe, CIDR; 20+5 mins

Specific Topics

9:15-9:50 Liver Stage Immunity
William Heath, U of Melbourne; Robert Sauerwein, Radboud UMC; 30+5 mins

9:50-10:15 Liver Stage Biology and Omics
Elizabeth Winzeler, UCSD; 20+5 mins

10:15-10:30 Break

10:30-10:55 Genetic Manipulation of Model Organisms
Sebastian Lourido, MIT; 20+5 mins

10:55-11:20 Technologies for GAP Parasite Selection
Shahid Khan, LUMC; 20+5mins

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**Small Panel Gathering**

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11:20 -12:20 **Breakout Groups**

Panel members divide into groups for discussion (total of five groups: main session, sub-session I, II, II, IV). Please see the end of the agenda for group/role assignment.

12:20-1:20 Lunch break

| Big Group Discussion | |
|---|---|
| 1:20-1:35 | **Main Session Wrap Up** (by Chair and Co-Chair) |
| 1:35-3:05 | **Sub-Session I: Liver Stage Immunity**<br>Panel members: William Heath, Robert Sauerwein, John Harty, Fidel Zavala, Sumana Chakravarty |
| 3:05-3:20 | Break |
| 3:20-4:50 | **Sub-Session II: Liver Stage Biology and Omics**<br>Panel members: Elizabeth Winzeler, Isabelle Coppens, Norman Waters, Volker Heussler |
| 4:50-5:00 | **Day 1 wrap up** |

*Wednesday, August 9*

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| 8:15-9:30 | **Sub-Session III: Genetic Manipulation of Model Organisms**<br>Panel members: Sebastian Lourido, Jacquin Niles, John Adams, Boris Striepen |
| 9:30-10:45 | **Sub-Session IV: Technologies for GAP Parasite Selection**<br>Panel members: Ashley M. Vaughan, Shahid Khan, Dennis Kyle, Kim Lee Sim |
| 10:45-11:00 | Break |
| 11:00-12:00 | **Sub-Session V: Challenges for Pv Sporozoite Vaccine Discovery**<br>Panel members**:** John Adams, Elizabeth Winzler, Hernando Del Portillo |
| **Final Wrap Up** | |
| 12:00-12:50 | **Whole Workshop Wrap Up/Summary**<br>Each sub-session for 10 mins |
| 12:50-1:00 | **Meeting Adjourn** |

**Workshop Organization**

Main Session

There will be six, 20-min presentations on each topic outlined in the agenda (except Sub-Session I, which will have 2x15mins presentations). It is not expected that these presentations include data-heavy slides, or exclusively summarize or emphasize the research progress of the speaker alone, but rather provide a high level overview intended to educate the group on the current state of the field for the representative topic. Following each presentation, there will be a brief, 5-minute period for clarification questions. More involved discussions will be covered in later sessions.

No more than 15-20 slides are expected (except for Sub-Session I, 10-15 slides for each speakers). While presentations should focus primarily on *Pf*, speakers may also include up to 3 slides to cover *Pv* if desired.

Small Panel Breakout Groups

Following the opening session and the overview of priority topics, there will be five (5) breakout groups based on topic (see Panel Members and Role Assignments) which will meet in separate locations for 1 hour. During this time, it is expected that panel members will assess information presented during the main session, as it relates to their assigned topic area, and identify gaps, issues, opportunities, and refine a list of questions to guide a larger discussion with the entire workshop panel. Each group can also determine at this time how they want to lead the subsequent large panel discussion on their assigned topic areas.

Large Panel Discussion

Following breakout discussions, all workshop members will once again assemble as one large panel. The Overview Group (see Panel Members and Role Assignments) will open the large group discussion period for 15 mins with an overall summary or suggestion of challenges and major issues that should be addressed during the subsequent large panel discussions.

Sub-Session I, II, III, and IV: Each Sub-Session group will lead, facilitate, and stimulate discussions with all the workshop panel members on their assigned Sub-Session topic for ~1.5 hours. Sub-Session group members can present the outcome of their group breakout discussion, including gaps and opportunities, or use questions generated to guide an overall discussion with the entire workshop panel. They may also incorporate the Overview Group's summary/suggestion into the discussion. All the discussions (Overview Group and Sub-Session I, II, II, and IV) are encouraged to focus on *Pf*.

Sub-Session V: This Sub-Session is dedicated to *Pv* discussion. A high level summary/discussion around potential challenges/opportunities unique to *Pv* is arranged for ~1 hr. This Sub-Session is expected to draw information from the above *Pf* discussions, and develop a strategy for future *Pv* vaccine research with a potential for future in depth discussions.

Panel Members and Proposed Roles:

| Name | Role |
|---|---|
| **Main Session: Overview** | |
| Stefan Kappe | Overview Talk |
| Steve Hoffman | Overview Talk |
| Miguel Prudencio | Chair/Wrap Up |
| Hernando Del Portillo | Co-Chair/Wrap Up |
| **Sub-Session I: Liver Stage Immunity** | |
| William Heath | Overview Talk/Mice |
| Robert Sauerwein | Overview Talk/Human |
| John Harty | Lead Discussant |
| Fidel Zavala | Commentator |
| Sumana Chakravarty | Wrap Up |
| **Sub-Session II: Liver Stage Biology and Omics** | |
| Elizabeth Winzeler | Overview Talk |
| Isabelle Coppens | Lead Discussant |
| Norman Waters | Commentator |
| Volker Heussler | Wrap Up |
| **Sub-Session III: Genetic Manipulation of Model Organisms** | |
| Sebastian Lourido | Overview Talk |
| Jacquin Niles | Lead Discussant |
| Boris Striepen | Commentator |
| John Adams | Wrap Up |
| **Sub-Session IV: Technologies for GAP Parasite Selection** | |
| Ashley M. Vaughan | Lead Discussant |
| Shahid Khan | Overview Talk |
| Kim Lee Sim | Commentator |
| Dennis Kyle | Wrap Up |
| **Sub-Session V: Challenges for *Pv* Sporozoite Vaccine Discovery** | |
| John Adams | Lead Discussant |
| Hernando Del Portillo | Commentator |
| Elizabeth Winzeler | Wrap Up |