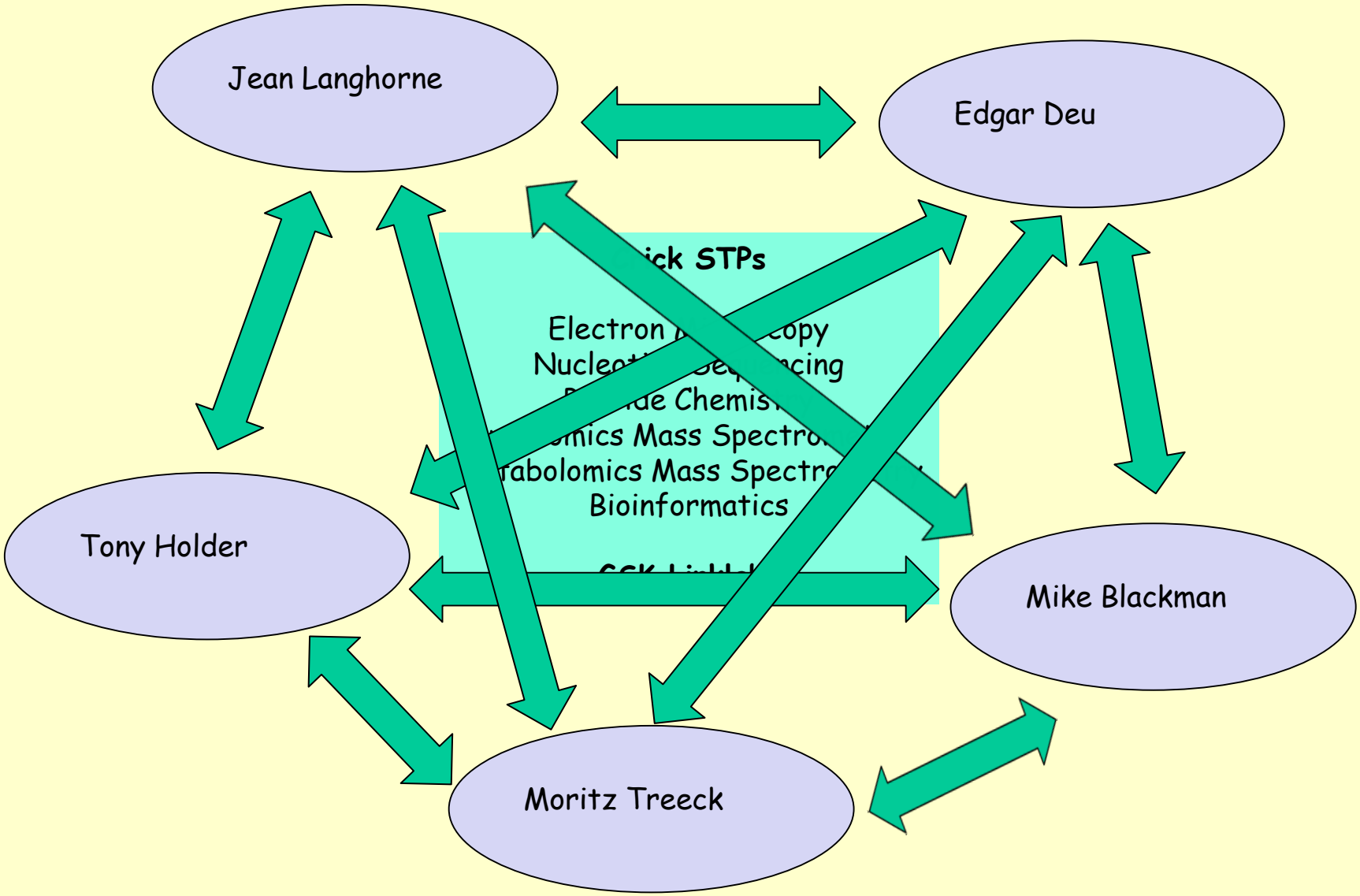
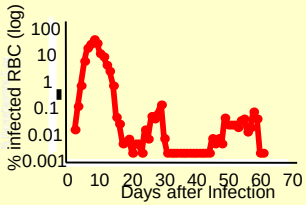
Malaria research at the Crick


Jean Langhorne
Edgar Deu
Tony Holder
Mike Blackman
Moritz Treeck
Bioinformatics

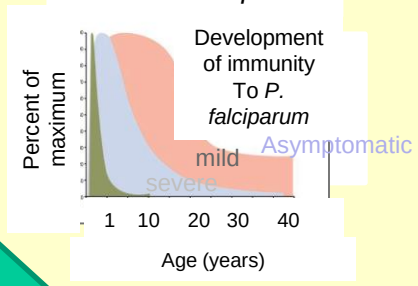
Jean Langhorne - Malaria Immunology Laboratory

Immune mechanisms in virulence and chronicity

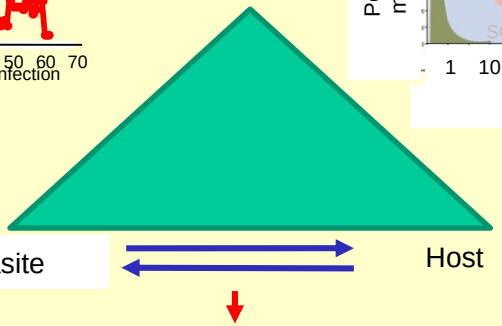
Rodent: *Plasmodium chabaudi*



Human: *P. falciparum*

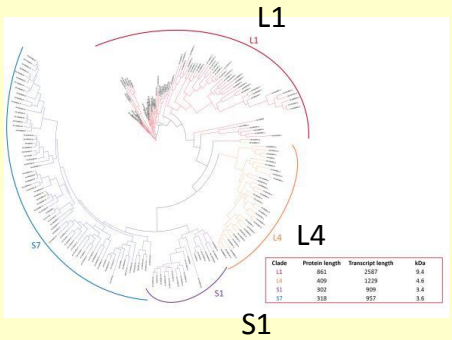


Malaria

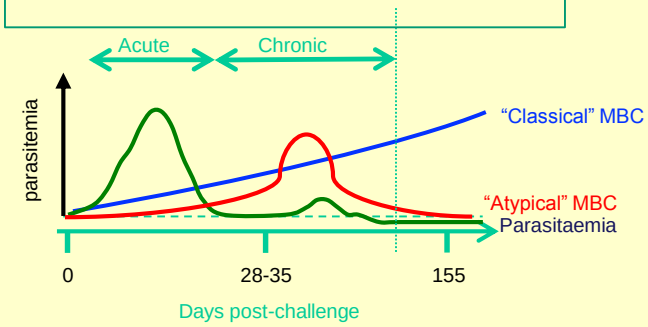


Immunity, chronicity
Immunopathology,Virulence

Understanding the function of the *pir* multigene family



Mouse: Mechanisms of control of chronic infection
Malaria and Burkitt's lymphoma



Human: identification specific immune signatures that predict susceptibility to multiple malaria episodes

Phase 1

Cross sectional bleed
Children 8yrs.
few episodes: ave 2
High no: ave 12

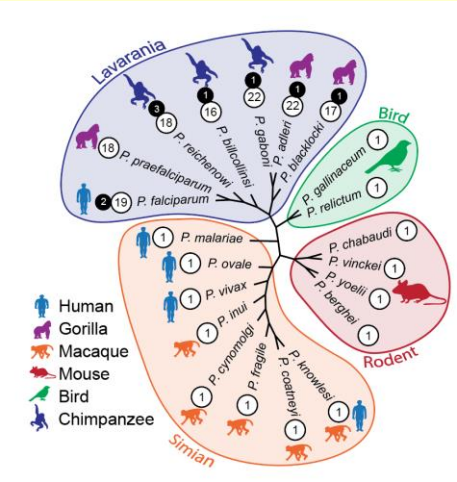
Phase 2

Longitudinal study
(4 years)
Samples annually

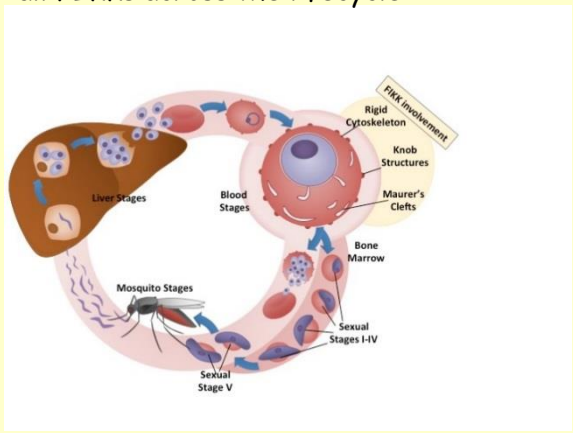
Moritz Treeck – Signalling in Apicomplexan Parasites Laboratory

Species-specific remodeling of host red blood cells by the malaria parasite

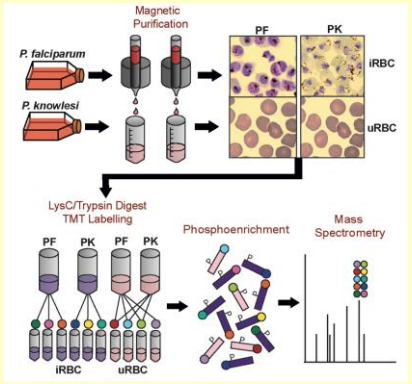
1) FIKK protein kinases expanded in Laverania

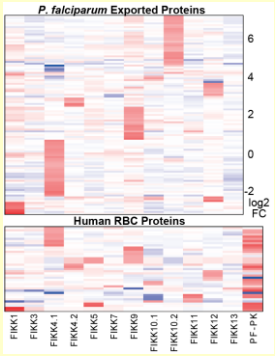


2) Conditional gene deletion of all FIKKs across the lifecycle

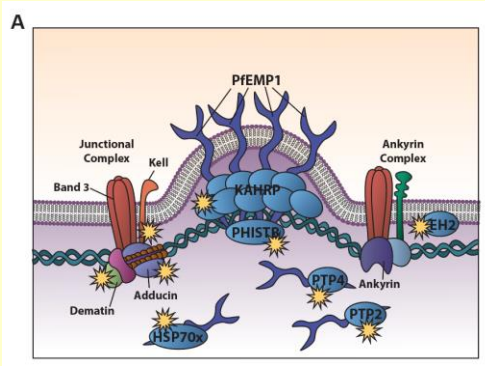


3) Quantitative mass-spectrometry to identify FIKK targets

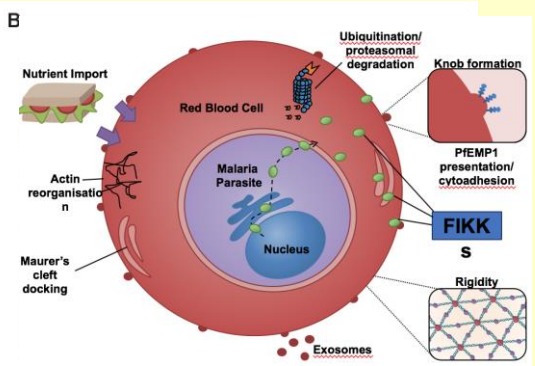




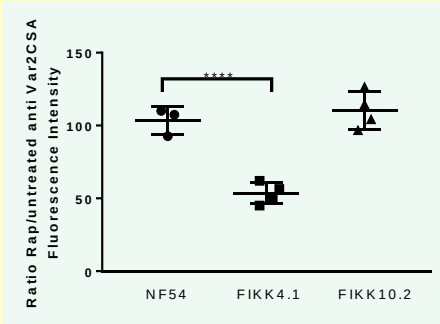
4) Prediction of function from targets



5) Target-specific phenotyping



Example: FIKK4.1 deletion causes a reduction of cytoadhesion due to reduced PfEMP1 surface levels



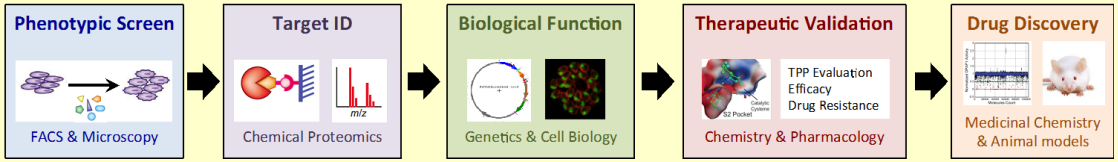
Edgar Deu – Chemical Biology Approaches to Malaria Laboratory

Drug target identification and characterization using chemical biology

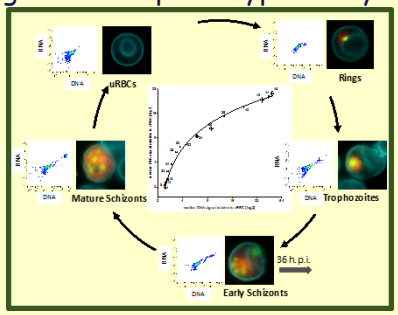
1. **Identification of novel proteases involved in RBC invasion and development of small molecule inhibitors.**

2. **Chemical profiling of metabolic serine hydrolases in *P. falciparum* asexual blood stages.**

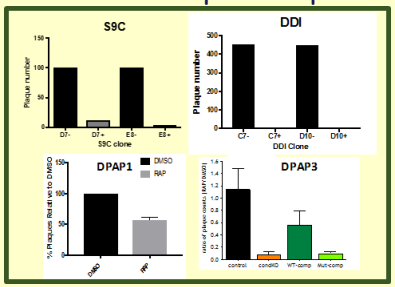
3. **Fragment-based phenotypic screening to identify novel antimalarial targets using chemical proteomics.**



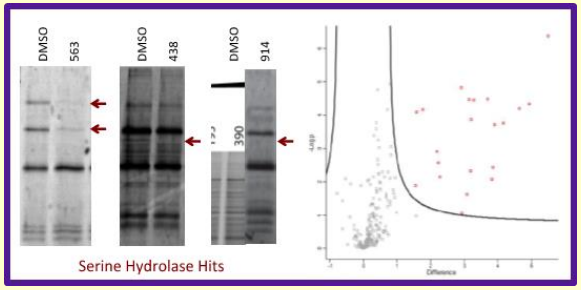
High-content phenotypic assays



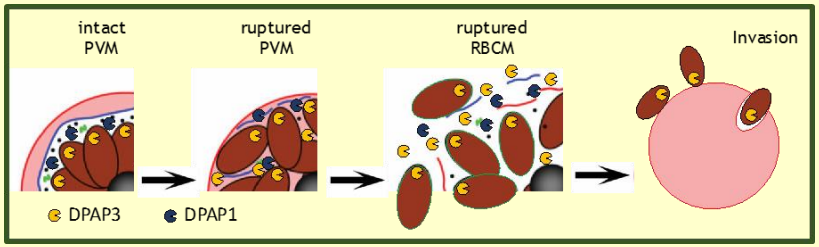
Identification of important proteases



Target ID with Cys-reactive probes, activity-based probes and chemical proteomics



DPAPs are important for efficient RBC invasion



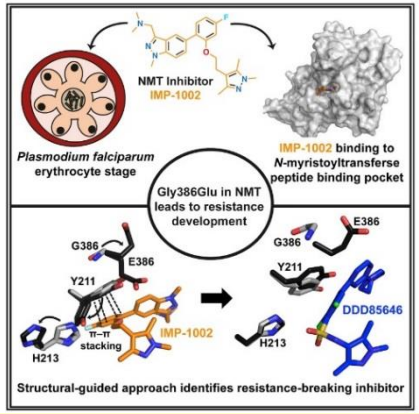
Lehmann et al.
PLoS Path
2018

Tony Holder – Malaria Parasitology Laboratory

Host cell invasion and parasite protein post-translational modification

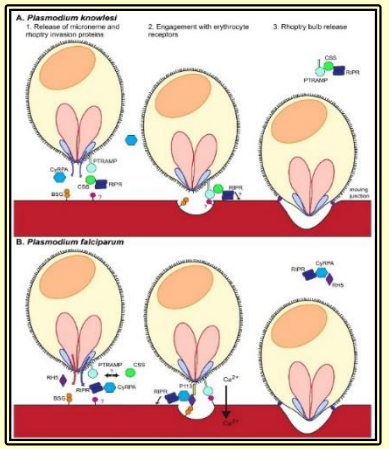
1. Malarial N-myristoyl transferase as a target for the development of new antimalarial drugs

Schlott et al 2019 (Cell Chem Biol): Structure-Guided Identification of Resistance Breaking Antimalarial N-Myristoyltransferase Inhibitors



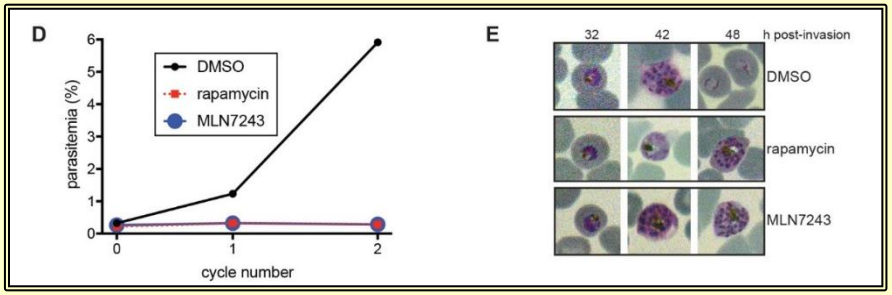
2. Novel molecules for merozoite invasion of erythrocytes

Knuepfer et al 2019 (PloS Pathogens):Divergent roles for the RH5 complex components, CyRPA and RIPR in human-infective malaria parasites



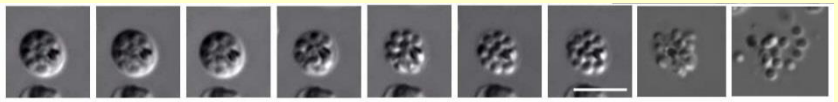
3. Ubiquitylation: protein breakdown and resource recycling

Both a small molecule inhibitor (MLN7243) of ubiquitin activating enzyme (UBA1) and a rapamycin-inducible knock out of the *uba1* gene block schizont maturation and merozoite formation. (Wu et al unpublished)



Mike Blackman – Malaria Biochemistry Laboratory

Enzymes in egress and invasion: function and potential as drug targets



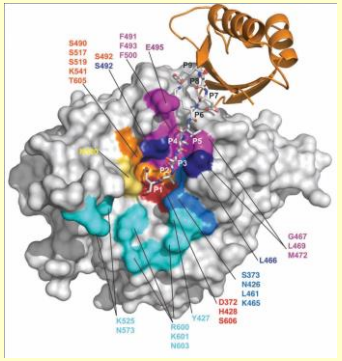
Collins et al. PLoS Pathogens 2017

1. Proteins, proteases and phospholipases in egress and invasion

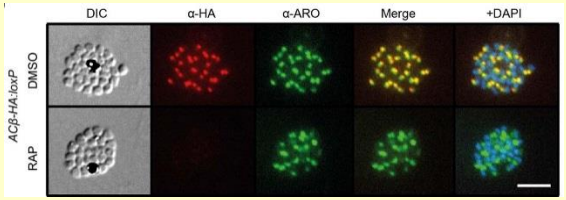
- Subtilisin-like serine proteases (SUB1, SUB2)
- Papain-like proteins and proteases (SERA5, SERA6)
- MSP1 complex and role in egress
- Parasite phospholipases in intracellular development and egress

2. Signalling cascades regulating egress and invasion

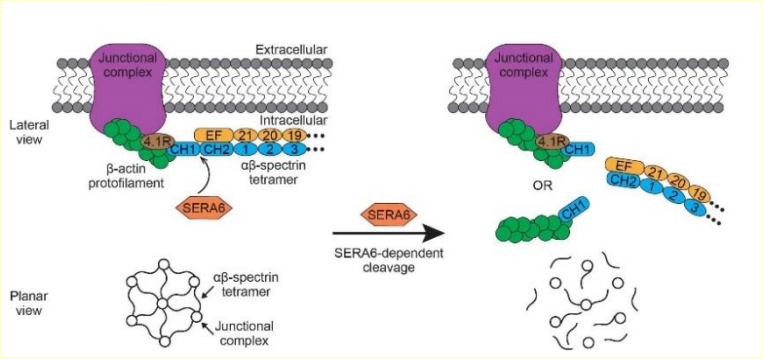
- cGMP-dependent protein kinase PKG – regulation and substrates
- Nucleotide cyclases and phosphodiesterdases



Withers-Martinez et al.
Nature Communications 2014



Patel, Perrin et al. PLoS Biology 2019



Thomas, Tan et al. Nature Microbiol 2018

National and international collaborations

Langhorne (Sanger Institute, IC, Oxford Uni, Exeter Uni)
Treeck (IC, Birkbeck, Cambridge Uni, GSK)
Deu (NIBSC, IC, Sanger Institute, Manchester Uni, GSK)
Holder (LSHTM, IC, GSK, Oxford Uni,
Blackman (LSHTM, KCL, Birkbeck, GSK)

Include WACCBIP (Ghana), MRC The Gambia at LSHTM (in part through the Crick Africa Network), The KEMRI/Wellcome Trust Research Programme (Kenya), Stanford University (CA, USA), etc.