

Future of Parasitology Symposium

INSTITUT
Pasteur

Parasites and
Insect Vectors
DEPARTMENT

Inserm

La science pour la santé
From science to health

■ 12th - 13th October 2026

Duclaux Amphitheatre Institut Pasteur,
Paris, France

■ Keynotes

Nicolas BRANCUCCI (Swiss Tropical and Public Health Institute)

Maryse LEBRUN (University of Montpellier)

Speakers

Estefanía CALVO ALVAREZ (University of Milan)

Goylette F. CHAMI (University of Oxford)

Célia DECHAVANNE (Institut de Recherche pour le Développement)

David FIDOCK (Institut Pasteur)

Claudio FRONTERRE (University of Birmingham)

Veerle LEJON (Institut de Recherche pour le Développement)

Gemma MONCUNILL (CaixaResearch Institute)

Miguel PRUDÊNCIO (Gulbenkian Institute for Molecular Medicine)

Chloé ROUMEGOUS (University of Geneva)

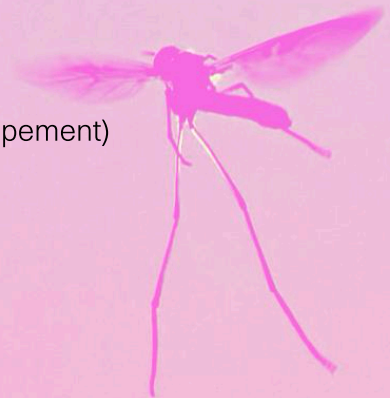
Shazia RUYBAL-PEZANTES (Barcelona Institute for Global Health)

Jeremy SALVADOR (Institut Pasteur du Cambodge)

Maria Luísa SIMÕES (Institute of Tropical Medicine)

Sandra TRINDADE (Gulbenkian Institute for Molecular Medicine)

Richard WHEELER (University of Edinburgh)



**SECURE YOUR SPOT
FOR FREE !**



ORGANIZING COMMITTEE : BABETTE BEHER, CHETAN CHITNIS, MOHAMMAD EL KADRI,
LUCY GLOVER, SÉLIMA MESSAOUDI, JASON ROSADO, BRUNO TESTE

CONTACT : PIVSYMPOSIUM2026@PASTEUR.FR



i Accueil Informations

01 Emile DUCLAUX

02 Gabriel BERTRAND

03 Ernest FOURNEAU

05 Serre

06 Bâtiment Social

07 Le PASTEUR

08 Annexe n° 8

09 Pavillon Louis MARTIN

10 Pavillon Emile ROUX

11 Bâtiment du 205

12 Pasteur BioTop

13 Centre Médical

14

15 CIS

22 André LWOFF

23 Bâtiment Administratif

24

25 Sergent

26 à **28** François JACOB

P Parking sous-sol

Stationnement handicapés

Défibrillateur

Programme — 12 October 2026

13:30–14:00	Registration & Welcome
14:00–14:10	Opening & Introduction by Lucy Glover
BLOCK 1 — VECTORS & TRANSMISSION BIOLOGY	
14:10–15:10	KEYNOTE — Maryse Lebrun (University of Montpellier, France) <i>Open sesame: molecular control of rhoptry release in Apicomplexa</i>
15:10–15:40	Chloé Roumegous (University of Geneva, Switzerland) <i>TTLL1-dependent polyglutamylation is essential for the assembly and motility of the atypical Plasmodium flagellum</i>
15:40–16:10	Maria Luísa Simões (Institute of Tropical Medicine (ITM), Belgium) <i>High fluctuating humidity decouples Anopheles stephensi immunity and increases vector competence for Plasmodium falciparum</i>
16:10–16:30	■ Break
BLOCK 2 — HOST-PARASITE INTERACTIONS & IMMUNE EVASION	
16:30–17:00	Jeremy Salvador (Institut Pasteur du Cambodge, Cambodia) <i>Accessing invasion-competent Plasmodium vivax merozoites reveals antibody-dependent NK cell activation</i>
17:00–17:30	Sandra Trindade (Gulbenkian Institute for Molecular Medicine (GIMM), Portugal) <i>The unexpected army of Trypanosoma parasites in adipose tissue</i>
17:30–18:00	Estefanía Calvo-Alvarez (University of Milan, Italy) <i>Leishmania at the neuroimmune interface: from hidden niches to immune subversion</i>
20:00	■ Dinner — Speakers, Pls & Organizing Committee

Programme — 13 October 2026

BLOCK 3 — VACCINES & DRUG RESISTANCE

09:00–09:30

Gemma Moncunill (CaixaResearch Institute, Spain)

Decoding RTS,S/AS01 vaccine-induced protection: From immune correlates to pre-vaccination immune signatures

09:30–10:00

Miguel Prudêncio (Gulbenkian Institute for Molecular Medicine (GIMM), Portugal)

*A novel surrogate for whole-sporozoite vaccination against *P. vivax* malaria*

10:00–10:30

David Fidock (Institut Pasteur, France)

Resistance–fitness landscapes define multiple routes to K13-mediated artemisinin partial resistance in Africa

10:30–11:00

■ Break

BLOCK 4 — DISEASE BURDEN IN VULNERABLE POPULATIONS

11:00–11:30

Célia Dechavanne (Institut de Recherche pour le Développement (IRD), France)

Placental malaria reshapes neonatal immunity: unraveling the roots of early-life susceptibility

11:30–12:00

Goylette F. Chami (University of Oxford, United Kingdom)

Risk factors for and progression of hepatosplenic multimorbidity associated with intestinal schistosomiasis in the SchistoTrack cohort

12:00–13:30

■ Lunch
Art display by Fleur Mounier

BLOCK 5 — TOOLS FOR ELIMINATION: DIAGNOSTICS & SURVEILLANCE

13:30–14:00

Veerle Lejon (Institut de Recherche pour le Développement (IRD), France)

The future of diagnostics for NTDs: between hope and despair. The case of human African trypanosomiasis

14:00–14:30

Claudio Fronterre (University of Birmingham, United Kingdom)

Spatial statistics for decision-making: a blackfly tale

14:30–15:00

■ Break

Programme — 13 October 2026

BLOCK 6 — AI & COMPUTATIONAL APPROACHES IN PARASITOLOGY

15:00–15:30

Shazia Ruybal-Pezántes (Barcelona Institute for Global Health, Spain)

Inferring the unobservable in Plasmodium genomic epidemiology through simulation and AI

15:30–16:00

Richard Wheeler (University of Edinburgh, United Kingdom)

Discovery biology from the next generation of genome-wide parasite data resources

KEYNOTE

16:00–17:00

Nicolas Brancucci (Swiss TPH, University of Basel)

Stranger things: the peculiar biology of malaria transmission stages

17:00–17:10

Conclusion

Open sesame: molecular control of rhoptry release in Apicomplexa

Maryse Lebrun (University of Montpellier, France)

Apicomplexans are obligate intracellular parasites that cause life-threatening diseases, including malaria and toxoplasmosis. To invade and replicate within host cells, they discharge the contents of a specialized secretory organelle, the rhoptry, into the host cell. Rhoptries are pre-docked at the exocytic site in a primed state, poised for rapid fusion. Secretion is then triggered precisely by parasite–host cell contact, immediately before invasion, delivering rhoptry proteins directly into the host cell.

Despite the importance of this process, the machinery that drives rhoptry exocytosis has remained largely uncharacterized. We have recently elucidated this machinery in *Toxoplasma* and *Plasmodium*, providing both molecular and structural insights. Rhoptry exocytosis depends on a highly intricate, multi-component structure—the rhoptry secretory apparatus (RSA)—which represents a new secretory machinery in eukaryotes. By combining large-scale proteomic analysis of RSA components in *Toxoplasma gondii*, integrative modeling, and yeast two-hybrid assays, we mapped key proteins onto the in situ cryo-ET structure of the RSA. Our functional genetics provide mechanistic insight into this ancient secretory machinery, revealing a gating module that maintains docked organelles in a poised state and enables timely secretion, as well as the critical role of calcium in RSA activation.

TTLL1-dependent polyglutamylation is essential for the assembly and motility of the atypical *Plasmodium* flagellum

Chloé Roumegous (University of Geneva, Switzerland)

In 2024, malaria was still responsible for 610 000 deaths worldwide. *Plasmodium* parasites have a life cycle that alternates between *Anopheles* mosquitos and a mammalian host. Transmission relies on male gamete, whose atypical flagellum powers fertilization of a female gamete within a few minutes after ingestion by the mosquito. The flagellum is composed of the canonical axoneme made of 9+2 microtubules. However, unlike most flagellated cells, *Plasmodium* flagellum is assembled extraordinarily rapidly and entirely within the cytoplasm, thus lacking the traditional intraflagellar transport system. Elucidating the molecular mechanisms that ensure the assembly and function of this atypical flagellum is therefore essential for understanding parasite transmission.

In many eukaryotes, tubulin can be post-translationally modified to regulate microtubules architecture, stability and motility. Among the post-translational modifications (PTMs) that can occur, polyglutamylation is well known to impact flagellum motility in other organisms, yet its roles in *Plasmodium* remain largely unexplored. The addition of glutamate to the primary amino acid chain is catalysed by tubulin-tyrosine ligase-like (TTLLs) enzymes. Bioinformatic analysis identified three putative TTLLs in *Plasmodium*, but their functions were not investigated.

Here, using iterative expansion microscopy, we localised polyglutamylation with sub-axonemal resolution and found that it is specifically enriched on the B-tubule of each axonemal doublet. Genetic analyses further revealed that axonemal polyglutamylation in male gametes depends exclusively on the enzyme TTLL1. We assessed *ttl1*-KO phenotype across several life cycle stages. We showed a drastic impact on axoneme stability during microgametogenesis, leading to a major defect in exflagellation. Together, our findings identify TTLL1-dependent polyglutamylation as a key regulator of axoneme function as polyglutamylation is required both for the structural integrity and motility of the *Plasmodium* flagellum that is essential for parasite transmission to mosquitoes.

High fluctuating humidity decouples *Anopheles stephensi* immunity and increases vector competence for *Plasmodium falciparum*

Maria Luísa Simões (Institute of Tropical Medicine (ITM), Belgium)

The mosquito innate immune system is a crucial determinant of malaria transmission, yet the impact of realistic environmental fluctuations on vector competence remains severely understudied. Because standard laboratory settings typically rely on static conditions, they often mask the true physiological dynamics of vector-pathogen interactions. To start addressing this issue, our laboratory pioneered a novel approach, exposing *Anopheles* mosquitoes from egg to adult to combined diurnal fluctuations in temperature and relative humidity, to investigate the impact of these realistic conditions on gene expression and fitness (Lemos-Silva et al. 2025). Building upon this novel approach, in this study we focused on the specific impact of humidity, which has been neglected in vector ecology studies. Here, we investigated how fluctuating relative humidity, simulating current (Low FH) and projected future (High FH) climate change scenarios, alters *Anopheles stephensi* gene expression and *Plasmodium falciparum* infection in the mosquito. Our analyses revealed that High FH induces a severe, tissue-specific decoupling of the mosquito innate immune system, characterized by suppression of the local midgut complement pathway while priming systemic detoxification machinery. This humidity-driven physiological shift translated into divergent infection phenotypes, where High FH mosquitoes harbored a significantly higher number of *P. falciparum* oocysts. Ultimately, our findings demonstrate that elevated humidity, independent of temperature, drives *Anopheles* toward immune tolerance rather than active resistance, amplifying vector competence and potentially increasing malaria transmission.

Accessing invasion-competent *Plasmodium vivax* merozoites reveals antibody-dependent NK cell activation

Jeremy Salvador (Institut Pasteur du Cambodge, Cambodia)

Malaria pathogenesis and clinical symptoms arise from blood-stage replication of *Plasmodium* parasites, which depends on rapid invasion of red blood cell by merozoites. Despite the central importance of this stage, direct functional studies of *Plasmodium vivax* merozoites have been severely limited by the lack of continuous *in vitro* culture and the inability to routinely access viable, invasion-competent merozoites from clinical isolates. Consequently, key aspects of *P. vivax* merozoite biology and immune recognition remain poorly defined.

Here, we establish a robust platform that enables synchronized release and high-yield isolation of invasion-competent *P. vivax* merozoites directly from *ex vivo* cultures. Reversible inhibition of parasite egress using the cGMP-dependent protein kinase inhibitor ML10 allows precise synchronization at the segmented schizont stage, followed by rapid mechanical liberation of merozoites using a liposome-based extrusion approach. This workflow yields highly pure merozoites with recovery rates exceeding 75% while preserving structural integrity and invasive capacity.

Leveraging this platform, we provide direct functional evidence that antibody-opsonized *P. vivax* merozoites activate human natural killer cells consistent with antibody-dependent cellular cytotoxicity mechanisms. Together, this study overcomes a long-standing technical barrier and enables direct investigation of *P. vivax* merozoite invasion biology and immune effector responses.

The unexpected army of *Trypanosoma* parasites in adipose tissue

Sandra Trindade (Gulbenkian Institute for Molecular Medicine (GIMM), Portugal)

African trypanosomiasis, caused by *Trypanosoma* extracellular parasites, is a major health threat in sub-Saharan Africa, affecting humans, livestock, and wildlife. A hallmark of this disease is weight loss, indicating that infection is associated with major changes in host metabolism potentially linked to parasite colonization of adipose tissue. However, the dynamics and mechanisms of *Trypanosoma brucei* extravascular colonization remains unclear.

We showed that during *T. brucei* pathogenesis, parasites disseminate into extravascular spaces and colonize multiple organs in the mammalian host. We identified the adipose tissue as a major parasite reservoir, where *T. brucei* undergoes extensive metabolic remodeling. Within this niche, parasites rapidly adjust their growth dynamics, with approximately half of the population adopting a reversible slow-growing state. Furthermore, our in vivo RNAi screen targeting parasite surface genes identified 18 proteins whose depletion significantly impaired adipose tissue colonization. Most of these proteins are involved in metabolic processes, like lipid processing, glycolysis and trafficking, highlighting their critical role in parasite adaptation to the lipid-rich adipose environment. Notably, we also showed that parasites residing in adipose tissue can survive drug treatment, suggesting that this anatomical niche may contribute to therapeutic persistence.

Together, our findings demonstrate that *T. brucei* actively adapts to the lipolytic environment of adipose tissue following colonization. These findings provide new insights into the biology and pathogenesis of African trypanosomiasis paving the way for innovative therapeutic strategies.

***Leishmania* at the neuroimmune interface: from hidden niches to immune subversion**

Estefanía Calvo-Alvarez (University of Milan, Italy)

Leishmania parasites persist in diverse host tissues and modulate multiple innate immune pathways, but their interactions with the central nervous system (CNS) remain largely unexplored. Using Akaluc-based bioluminescence imaging in experimental visceral leishmaniasis, we detected persistent *Leishmania donovani* infection in CNS-associated tissues. Complementary ex vivo and tissue-level analyses support parasite localization in meningeal-associated compartments, suggesting that these sites may represent an underappreciated niche during visceral infection.

This led us to investigate whether microglia, the brain-resident macrophages, could serve as a cellular target for visceral *Leishmania* and how infection might modulate their inflammatory responses. We recently showed that *L. infantum* infects murine microglia and suppresses NLRP3 inflammasome activation induced by amyloid- β . To investigate the parasite determinants underlying this phenotype, we focused on the metalloprotease GP63. Preliminary experiments using a *L. mexicana* GP63 mutant panel indicate that GP63 contributes to inflammasome suppression: GP63-deficient parasites showed a reduced ability to inhibit IL-1 β release in primary microglia and increased ASC speck formation compared with parental and GP63 add-back parasites.

Together, these results support CNS-associated persistence during visceral infection and highlight parasite-mediated modulation of microglial inflammasome responses. Identifying the parasite factors responsible may uncover immunoregulatory mechanisms that could inspire new ways to modulate pathological neuroinflammation.

Decoding RTS,S/AS01 vaccine-induced protection: From immune correlates to pre-vaccination immune signatures

Gemma Moncunill (CaixaResearch Institute, Spain)

The RTS,S/AS01 malaria vaccine provides partial and time-limited protection against malaria, with substantial heterogeneity in vaccine-induced immune responses. Understanding the biological determinants of this variability and waning protection is essential for identifying robust correlates of protection and improving the durability and efficacy of malaria vaccines.

Our research has used longitudinal samples from the RTS,S/AS01E phase 3 clinical trial in African children to investigate vaccine-induced immunity across multiple levels. While peak anti-CSP IgG responses are associated with protection, our recent analyses demonstrate that antibody quality is more complex than magnitude alone. Longitudinal assessment of antibodies targeting distinct CSP regions and subclass responses revealed differential dynamics, with more sustained high-avidity responses to the C-terminal region and marked epitope- and age-dependent patterns following primary and booster vaccination.

We have also characterised vaccine-induced cellular immunity, showing that RTS,S/AS01E induces CSP-specific CD4⁺ T-cell and memory responses, including IL-2- and TNF-producing cells, but that these responses are limited in magnitude and the booster fails to induce similar memory responses. These findings highlight the need to understand the cellular mechanisms underlying effective and durable humoral immunity.

Building on this work, we are now investigating whether immune states present before vaccination can predict subsequent vaccine responsiveness. Previous bulk transcriptomic analyses identified pre-vaccination signatures associated with malaria risk, while current analyses focus on children with high or low post-vaccination IgG responses combined with high-dimensional CITE-seq to resolve the cellular populations and immune states underlying differential vaccine responsiveness.

Together, these studies illustrate a progression from conventional immune correlates towards an integrated, multidimensional understanding of RTS,S-induced immunity key for improving the next generation malaria vaccines.

A novel surrogate for whole-sporozoite vaccination against *P. vivax* malaria

Miguel Prudêncio (Gulbenkian Institute for Molecular Medicine (GIMM), Portugal)

Malaria, remains a significant health concern in endemic regions. *Plasmodium falciparum* (*Pf*) is the deadliest among the parasite species that cause malaria in humans, whereas *P. vivax* (*Pv*) is the most geographically widespread. Although *Pf* is responsible for most malaria-associated mortality, *Pv* poses distinct and persistent challenges due to its broader geographical distribution and its ability to form dormant liver-stage hypnozoites that can reactivate weeks or months after the initial infection, causing relapses and sustaining transmission. These biological features complicate elimination efforts and highlight the urgent need for effective vaccines specifically targeting *Pv*.

Whole-sporozoite (WSp) vaccines, based on attenuated *Pf* sporozoites generated through irradiation (RAS), genetic modification (GAP), or administration under chemoprophylaxis (CPS), offer a promising alternative to current RTS,S and R21 subunit *Pf* vaccines, by exposing the immune system to a broad repertoire of parasite antigens. Such vaccines can induce more comprehensive humoral and cellular immune responses than subunit approaches. However, progress toward a *Pv* WSp vaccine has been severely constrained by the inability to maintain continuous culture of *Pv* parasites in a laboratory setting, restricting access to sporozoites to endemic regions and limiting experimental development platforms.

To overcome this barrier, a surrogate vaccination platform was developed using the rodent malaria parasite *P. berghei* (*Pb*) genetically engineered to express antigens from human malaria parasites. Clinical validation of PbVac, a *Pb* parasite expressing the *Pf* circumsporozoite protein (CSP) demonstrated safety together with functional antibody and CD8⁺ T-cell responses. Importantly, the genetic flexibility of the *Pb* platform enables the expression of antigens from different human-infective *Plasmodium* spp., as well as multiple parasite life-cycle stages.

Here, we evaluated *PbvVac*, a transgenic *Pb* line expressing the *PvCSP* either alone or in combination with the transmission-blocking (TB) antigen, Pvs25. *PbvVac* exhibited normal sporogonic development in *Anopheles stephensi* mosquitoes and retained full infectivity in both *in vitro* hepatocyte infection assays and *in vivo* murine models, indicating that genetic modification did not impair parasite fitness. Expression of both heterologous antigens was confirmed, and immunized mice developed robust antibody responses against *PvCSP* and Pvs25. Importantly, immune sera significantly reduced mosquito infectivity in direct membrane feeding assays, demonstrating functional TB activity. Collectively, these findings support *PbvVac* as promising surrogate for WSp vaccination against *Pv* that combines pre-erythrocytic and TB protective immunity in a single immunization agent.

Resistance–fitness landscapes define multiple routes to K13-mediated artemisinin partial resistance in Africa

David Fidock (Institut Pasteur, France)

Artemisinin partial resistance is emerging in Africa, where failure of first-line artemisinin-based combination therapies would have severe consequences. Yet which *Plasmodium falciparum* K13 mutations are most likely to threaten treatment efficacy remains unclear. We generated a panel of 136 gene-edited parasite lines, expressing African mutant *k13* alleles across 17 African genetic backgrounds. Integrating artemisinin survival, competitive fitness, and partner-drug susceptibility revealed that African *k13* variants do not form a single hierarchy of resistance strength. Instead, they occupy distinct regions of a multidimensional resistance–fitness landscape. These findings shift the study of African artemisinin partial resistance from a problem of identifying resistant mutations to one of mapping evolutionary accessibility. Africa is unlikely to face a single K13 trajectory; instead, resistance may emerge through multiple regional routes.

Placental malaria reshapes neonatal immunity: unraveling the roots of early-life susceptibility

Célia Dechavanne (Institut de Recherche pour le Développement (IRD), France)

Malaria during pregnancy or at delivery has been associated with a shorter time to the first malaria episode, a higher number of malaria episodes, and a higher total number of infections during early childhood. It has been demonstrated that neonatal immunity is modulated following placental malaria and that this modulation is related to dampened protection from all kind of infections during first months of life. My work aims to decipher the underpinning cellular and humoral mechanisms of immunomodulation and to depict the association with the susceptibility to infections.

Risk factors for and progression of hepatosplenic multimorbidity associated with intestinal schistosomiasis in the SchistoTrack cohort

Goylette F. Chami (University of Oxford, United Kingdom)

Schistosomiasis is a complex set of conditions caused by parasitic trematodes. Over 700m people live in areas with ongoing schistosome transmission with an estimated 250m infected. Periportal fibrosis is a severe morbidity associated with intestinal schistosomiasis, including *Schistosoma mansoni* and *S. japonicum*. The inflammation, granulomas, and subsequent fibrosis in and around the main portal vein contributes to vascular restructuring within the liver and distinct patterns of fibrosis. Understanding the risk factors and predictors of periportal fibrosis progression within and across individuals is challenging due to interacting and co-occurring conditions (multimorbidity) and the lack of morbidity monitoring from routine mass drug administration programmes.

SchistoTrack is a community-based, prospective cohort in Eastern and Western Uganda that aims to assess causes of periportal fibrosis within and across individuals. 4330 individuals aged five years and older in 52 rural villages are being followed over six years with detailed clinical examinations, including point-of-care ultrasound as well as the diagnosis of a wide range of co-infections. The SchistoTrack Cohort will be introduced, and findings will be shared on the risk factors for periportal fibrosis and timeline for progression. This talk will show that the high burden of hepatosplenic multimorbidity and rapid progression, starting in adolescents and young adults, indicates a need for better morbidity monitoring and case management to improve control in schistosomiasis-endemic areas.

The future of diagnostics for NTDs: between hope and despair. The case of human African trypanosomiasis

Veerle Lejon (Institut de Recherche pour le Développement (IRD), France)

Human African trypanosomiasis (HAT) or sleeping sickness is a neglected tropical disease (NTD) caused by infection with trypanosome parasites. Alongside tsetse fly control, the disease is largely controlled by diagnosis and treatment. Over the last decade, remarkable progress has been made in the fight against in HAT.

As targeted by the NTD roadmap, elimination as a public health problem has been reached for the *Trypanosoma brucei gambiense* HAT form (gHAT) and efforts now focus on eliminating its transmission. The sharp decline in gHAT prevalence requires adjustments to the diagnostic approach. Detection of gHAT is progressively shifting from active population screening by specialized teams, to passive screening integrated in the existing health care system. However, since health care workers rarely, if ever, encounter cases of gHAT, there is a risk that they will lose their knowledge of gHAT and their diagnostic expertise. Alternatives for training, simple diagnostics, and robust quality assessment systems must be implemented.

The elimination of Gambian HAT transmission will be further facilitated by the introduction of a new, user-friendly, single-dose oral medication, acoziborole. Its promising safety profile could pave the way for a simplified gHAT diagnosis, replacing the current “*screen, confirm & treat*” strategy. Until now, parasitological confirmation of screening test positives was inevitable, due to toxicity and complexity of older therapies. However, due to the imperfect sensitivity of the parasitological tests, at least 15% of true HAT cases remained unconfirmed and untreated thereby perpetuating the risk of further transmission of the parasite. Studies are currently underway to evaluate acoziborole treatment of individuals with a positive screening result, employing the so-called “*screen & treat*” strategy, to determine its effect on eliminating HAT transmission and to further document the safety of acoziborole.

The achievements in gHAT control stand in stark contrast with the stagnation in control of rhodesiense HAT (rHAT), the disease form occurring in eastern and southern Africa. In the absence of screening tests, diagnosis of rHAT still relies on outdated microscopic examination of stained blood smears. This practice is under pressure due to the introduction of rapid malaria tests, jeopardizing rHAT diagnosis and depriving rHAT patients of life-saving treatment.

Establishment of WHO target product profiles for NTD diagnostics encourages test developers and funders to create new and appropriate diagnostic tools. Four target product profiles for HAT address the priority needs highlighted above.

Spatial statistics for decision-making: a blackfly tale

Claudio Fronterre (University of Birmingham, United Kingdom)

Onchocerciasis elimination programmes must determine when there is sufficient evidence that transmission has been interrupted. As elimination approaches, infections become increasingly rare and spatially heterogeneous, making the evidence needed to support stopping decisions progressively harder to obtain. Entomological assessments, based on the collection and testing of blackfly vectors, provide a direct measure of ongoing parasite transmission, but raise important questions about where, when and how intensively to sample. In this talk, I will present our ongoing work on the use of spatial statistics to support onchocerciasis elimination decisions. I will discuss how spatial variation in blackfly abundance and parasite transmission can be incorporated into the design and interpretation of entomological assessments, and how sampling strategies can be optimised to provide stronger evidence about whether transmission has been interrupted. I will also introduce our work on adaptive sampling, where information collected during a survey is used to guide subsequent sampling towards locations that are most informative for the elimination decision. Using the blackfly as a common thread, I will illustrate how spatial statistics can help bridge the gap between entomological data and the decisions that ultimately determine whether an elimination programme can safely stop interventions.

Inferring the unobservable in *Plasmodium* genomic epidemiology through simulation and AI

Shazia Ruybal-Pezántes (Barcelona Institute for Global Health, Spain)

Many key questions in malaria epidemiology concern the origin of infections, which is rarely directly observed from empirical data. For instance: *Is a recurrent Plasmodium vivax infection a new infection from a mosquito bite, or a relapse from a dormant hypnozoite? Was this case imported or locally acquired? Who infected whom?* The answers can provide critical information to elimination programmes, from targeting interventions and antimalarial treatment to achieving elimination certification.

Parasite genomics offers a powerful source of evidence because obligate sexual recombination in the mosquito at every transmission event means genetic signals carry information about how recently parasites shared an ancestor. But although many tools are available to estimate ancestry, epidemiological interpretation still largely relies on heuristics. AI methods are increasingly attractive for their ability to learn from high-dimensional data, but they remain limited by biased training data and by the difficulty of knowing what a 'correct' answer looks like.

Simulation-based approaches offer a way forward. I will present work ranging from lightweight statistical models of recombination to full genomic transmission modelling. In the latter, individual-based models can track infections spreading through hosts and mosquitoes, coupled with parasite genome forward simulation, giving every infection a known origin and every genome a known genealogy. These can generate truth-labelled data across a range of epidemiological scenarios, at a scale suited to modern AI methods and for what cannot be observed empirically, such as hypnozoite genotypes, or the true origin of an imported infection. Such simulated ground truth enables exploration of genetic signatures of relapse, benchmarking of existing tools, and training and validation of deep learning for questions such as importation classification. This allows us to move from heuristic interpretation to validated inference in malaria genomic epidemiology.

Discovery biology from the next generation of genome-wide parasite data resources

Richard Wheeler (University of Edinburgh, United Kingdom)

The ability for a unicellular parasite to achieve their intricate multi-host life cycles is encoded in their genome. Dissecting this is challenging because their genomes tend to be both complex and highly divergent from model organisms. This means identification of critical cellular machinery needed for pathogenicity, is a search for a needle in a challenging to annotate haystack. We have addressed this in *Leishmania* through our most recent collaborative project, LeishGEM.

Using *L. mexicana*, we have determined the deletion mutant phenotype of every gene in the genome, using pooled genetically barcoded mutants in *in vitro* and *in vivo* models of the life cycle. We complemented this by mapping the subcellular structure of *Leishmania*, using fluorescent protein tagging of proteins divergent in or specific to *Leishmania*, and with LOPIT-DC. This has comprehensively mapped the structure-function of the cellular protein machinery, independent of bioinformatic predictions, focusing on unbiased detection of pathogenicity factors.

Looking to the future, divergent parasite biology is at risk of being analysed by AI tools over-fitted to model organisms. Such genome-wide experimental datasets, supported by parasite-specific optimisation of genome annotation tools, are critical for discovery biology in these parasites.

Stranger things: the peculiar biology of malaria transmission stages

Nicolas Brancucci, Associate Professor, Swiss TPH, University of Basel

Gametocytes, the sexual transmission stages of *Plasmodium* parasites, are insensitive to most antimalarials. Identifying transmission-blocking drugs is challenging due to the complex biology of gametocytes, the difficulty of cultivating them, and the lack of suitable in vivo models. Using an inducible gametocyte producing line, we established a pipeline that allows going from high-throughput drug screening to evaluating the efficacy of drugs in a preclinical in vivo mouse model.

At maturity, *P. falciparum* gametocytes are believed to acquire a quiescent state that likely contributes to their refractoriness to antimalarial drugs. To learn about essential processes in these stage V gametocytes, we combined our drug screening efforts to resistance selection, whole genome sequencing and drug-target interaction modeling and identified the targets of the three transmission-blocking compounds. All three drugs, ONX-0914 and CR-1-31-B and brusatol, target factors involved in proteostasis, ranging from ribosome loading to proteasomal degradation. Brusatol, a compound known for its anti-tumorigenic activity, blocks translation of stage V gametocytes in the low nanomolar range by binding to the ribosomal A site. Surprisingly, parasites can become resistant to the compound by altering the specificity of a methyltransferase involved in ribosome biogenesis, unraveling both the target and a new rRNA-dependent drug resistance mechanism in *Plasmodium* parasites.

Complementing our efforts on transmission-blocking compounds, we investigated the role of origin recognition complex 2 (ORC2) in asexual parasites and gametocytes and identified non-canonical roles for this replication factor in both asexual and sexual stages. In asexually replicating cells, ORC2 acts as a transcriptional repressor required to maintain silencing across a subset of sexual-stage-specific genes. In male gametocytes, ORC2 is essential for the spatial organization of chromosomes in the highly lobed nucleus of male gametocytes – likely in preparation for the rapid genome replication rounds required for gamete formation.

By combining basic research with work on druggable transmission-blocking targets, we hope to contribute our share to the future of parasitology.