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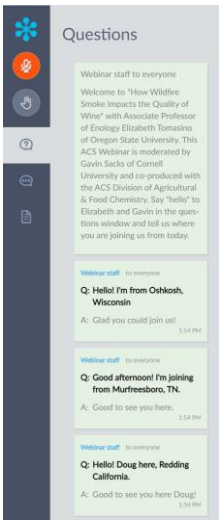

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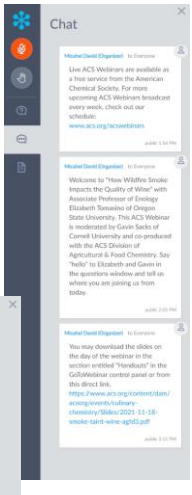

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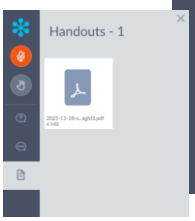

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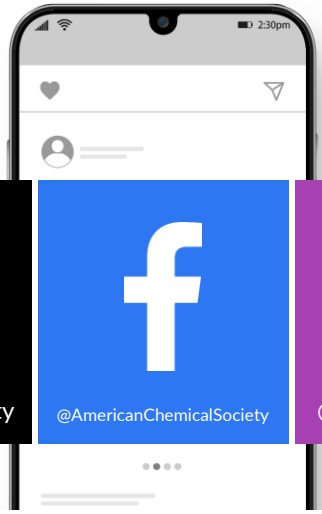

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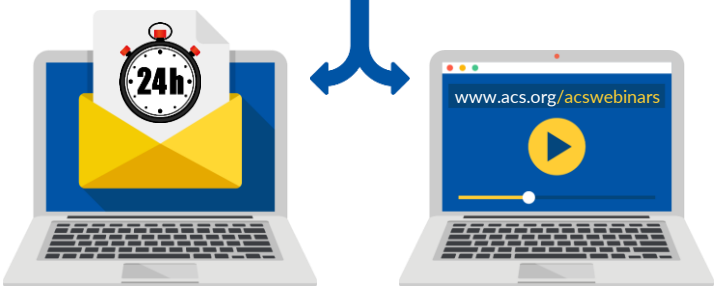

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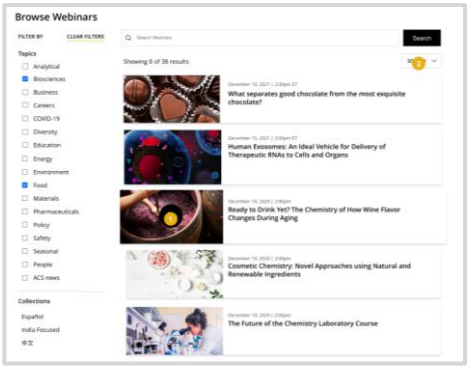

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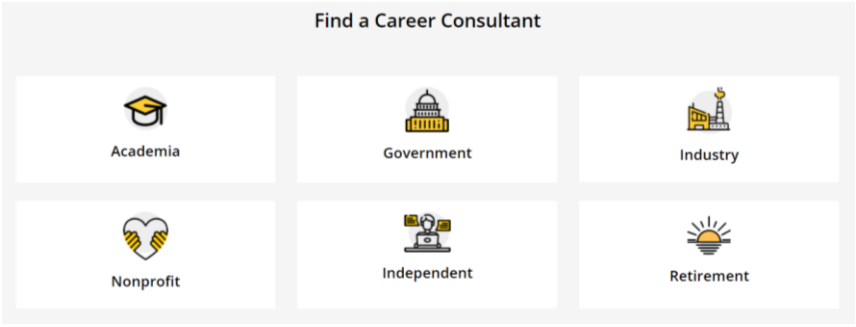
Career Consultant Directory



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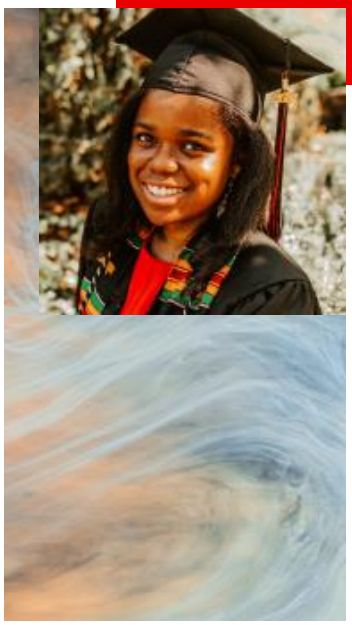

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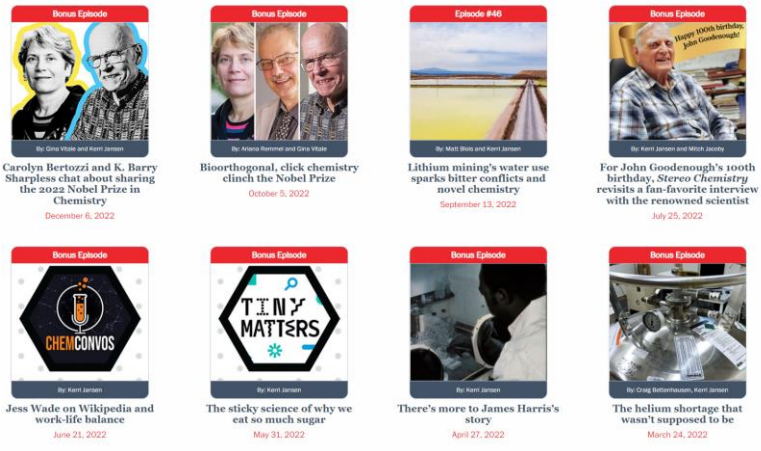

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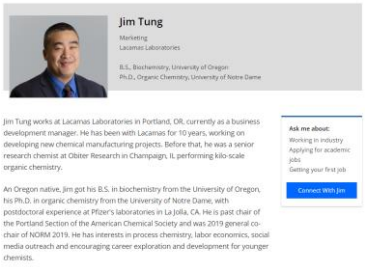

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Advancing ACS' Core Value of Diversity, Equity, Inclusion and Respect

Resources

- **Inclusivity Style Guide** — Designed to help staff and members use language and images that respect diversity in all its forms.
- **ACS Webinars on Diversity** — Covering diversity and inclusion at the workplace
- **ACS Publications DEIR Hub** — See what ACS Publications is doing for fostering inclusivity in scholarly publishing
- **ACS Volunteer and ACS Meetings Code of Conduct** — Fostering a positive and welcoming environment for attendees, volunteers and staff.
- **C&EN Trailblazers** — C&EN highlights scientists from different backgrounds who are making an impact in chemistry.
- **NEW! Download DEIR Educational Resources** — Download this educational guide for additional recommendations on videos, articles, books, podcasts, and more on diversity, inclusion, and related topics.
- **Quick Guide: Inclusion Moments** — Learn more about what Inclusion Moments are and see ideas to host them during your meetings.
- **Quick Guide: How to host inclusive in-person events** — Recommendations and best practices to ensure that your events can accommodate everyone.

Diversity, Equity, Inclusion, and Respect

**Adapted from definitions from the Ford Foundation Center for Social Justice:

Equity**
Seeks to ensure fair treatment, equality of opportunity, and fairness in access to information and resources for all. We believe this is only possible in an environment built on respect and dignity. Equity requires the identification and elimination of barriers that have prevented the full participation of some groups.

Diversity**
The representation of varied identities and differences (race, ethnicity, gender, disability, sexual orientation, gender identity, national origin, tribe, caste, socio-economic status, thinking and communication styles, etc.), collectively and as individuals. ACS seeks to proactively engage, understand, and draw on a variety of perspectives.

Inclusion**
Builds a culture of belonging by actively inviting the contribution and participation of all people. Every person's voice adds value, and ACS strives to create balance in the face of power differences. In addition, no one person can or should be called upon to represent an entire community.

Respect
Ensures that each person is treated with professionalism, integrity, and ethics underpinning all interpersonal interactions.

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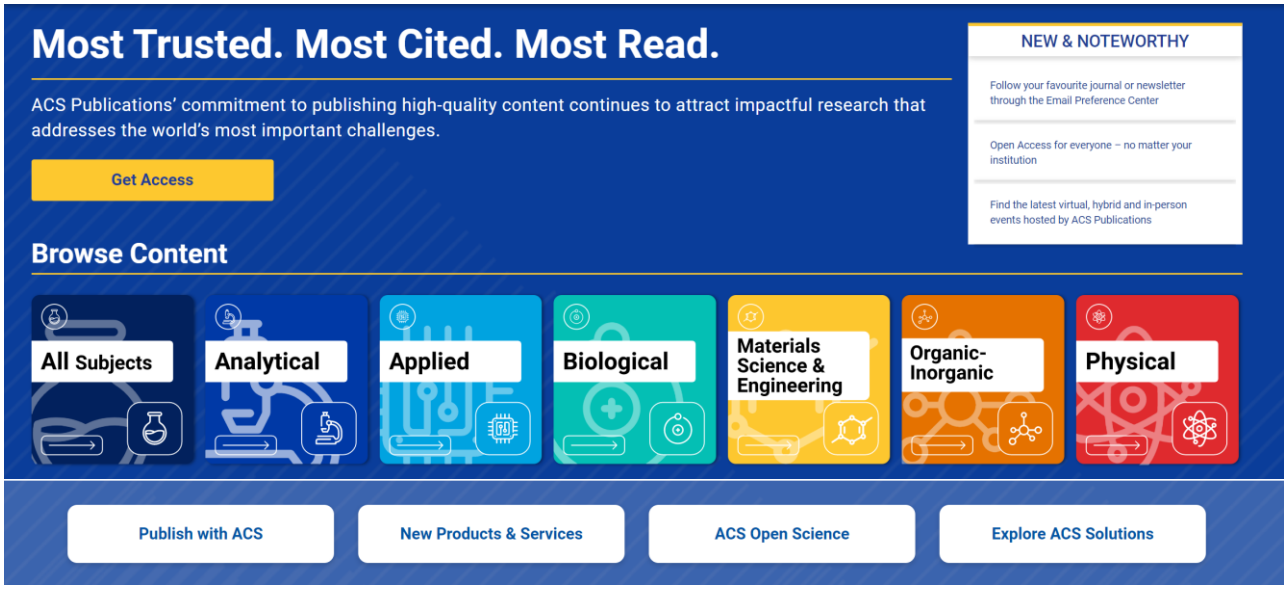

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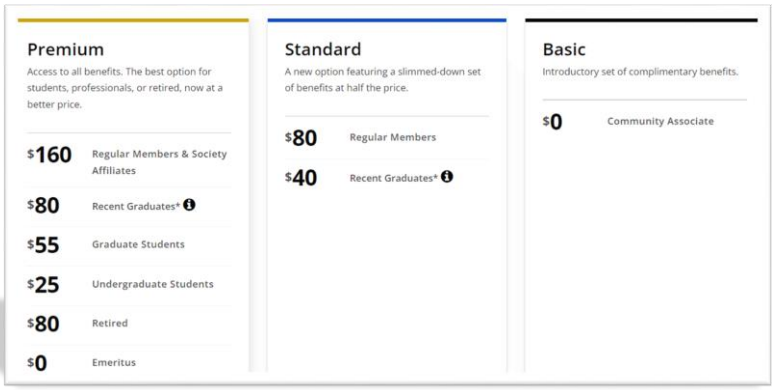

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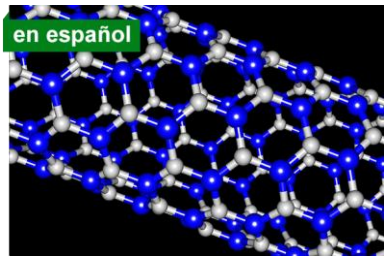

Wednesday, May 1, 2024| 3pm-4pm ET

La Creación de Materiales Macroscópicos a Través del Ensamblaje de Nanotubos de Nitruro de Boro

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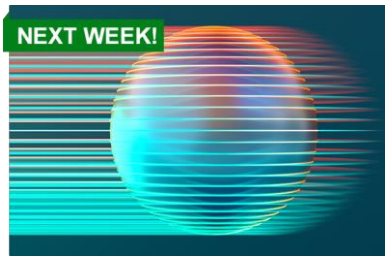

Thursday, May 2, 2024| 2pm-3:30pm ET

Better Biodegradable Vinyl Polymer Materials by Improving Radical Ring-Opening Polymerization (rROP)

Co-produced with ACS Division of Polymer Chemistry

Wednesday, May 8, 2024| 2pm-3:30pm ET

How Nanoscale Materials in Biosensors are Innovating Health from Concept to Care

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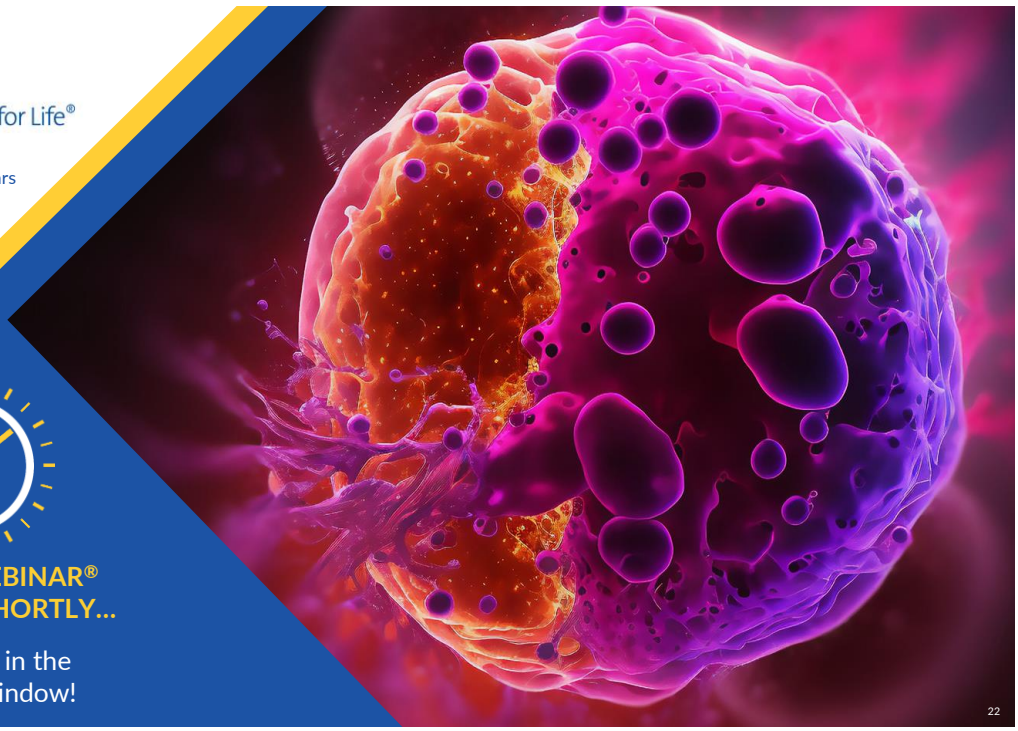

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Eliminating Malaria: Unraveling the Mysteries of Parasitic Transmission and Metamorphosis
LYN-MARIÉ BIRKHOLTZ, PhD
Professor of Biochemistry & South African Research Chair in Sustainable Malaria Control, University of Pretoria, South Africa
EMILY R. DERBYSHIRE, PhD
Associate Professor of Chemistry and Molecular Genetics & Microbiology, Duke University
JEREMY BURROWS, PhD
VP & Head of Drug Discovery, Medicines for Malaria Venture, Switzerland
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MMV
Medicines for Malaria Venture
25 YEARS
Eliminating Malaria: Unraveling the Mysteries of Parasitic Transmission and Metamorphosis
Moderator
Jeremy N. Burrows MA D.Phil FRSC
VP Head of Research Drug Discovery
Medicines for Malaria Venture
ACS Webinar – 25th April 2024
Ending malaria, rewriting the future
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Today is World Malaria Day

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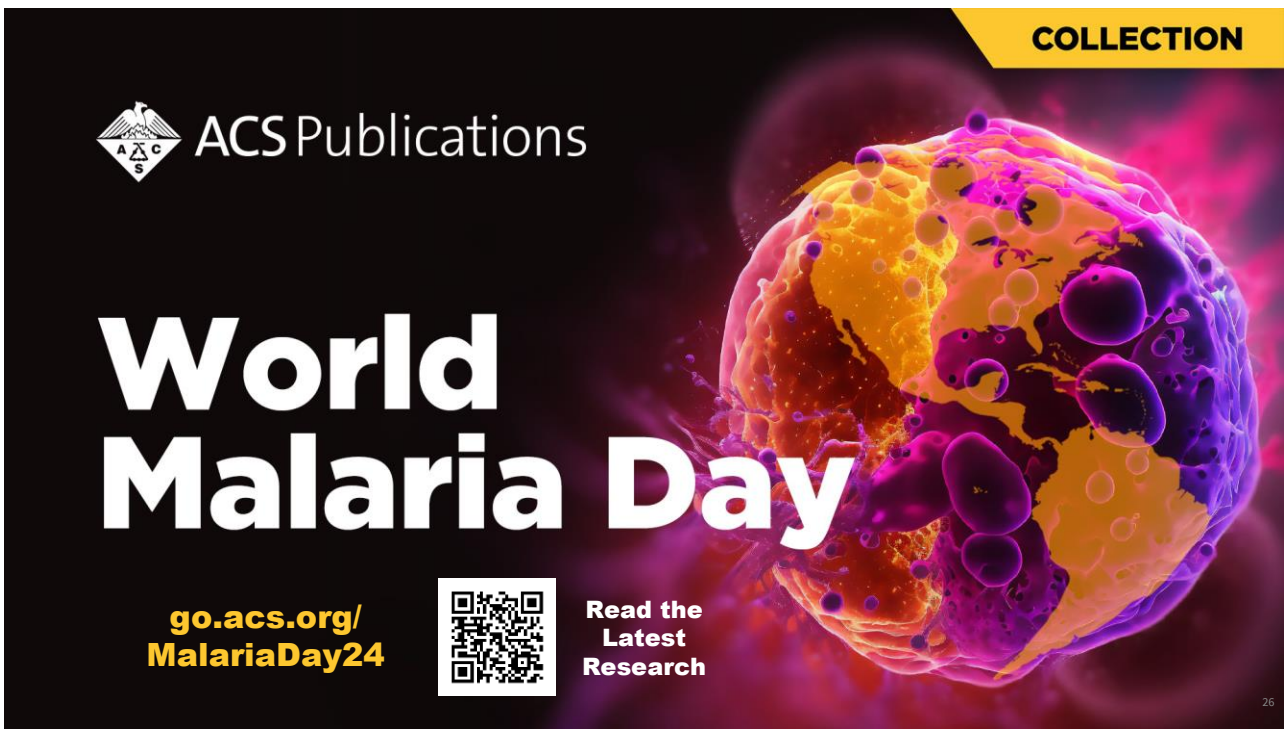

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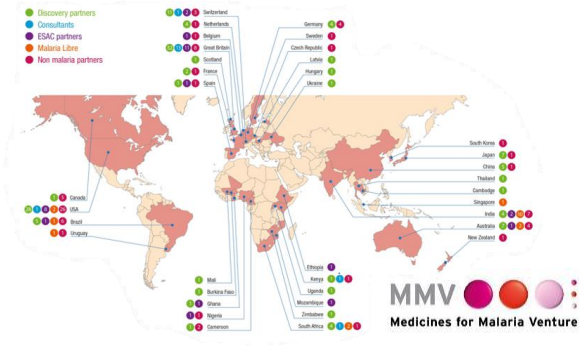
Medicines for Malaria Venture – Who are we?

- We are a not-for-profit PDP, headquartered in Geneva, ~100 people
- Our Mission - to reduce the burden of Malaria in disease endemic countries and ultimately to eradicate malaria
- Work with our network of partners to discover, develop and support access to affordable, effective antimalarial drugs. Funded by private and public organisations
- 15 products approved for malaria treatment or chemoprotection – strong pipeline



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Transmission-blocking antimalarials:

A tool to elimination?

L Birkholtz

SARChI – Sustainable Malaria Control
Malaria Parasite Molecular Laboratory (M2PL)
University of Pretoria

https://www.up.ac.za/malaria-parasite-molecular-laboratory-m2pl

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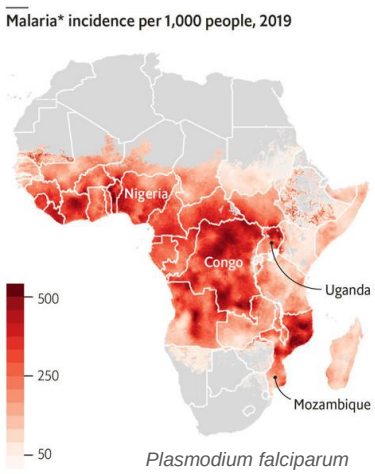
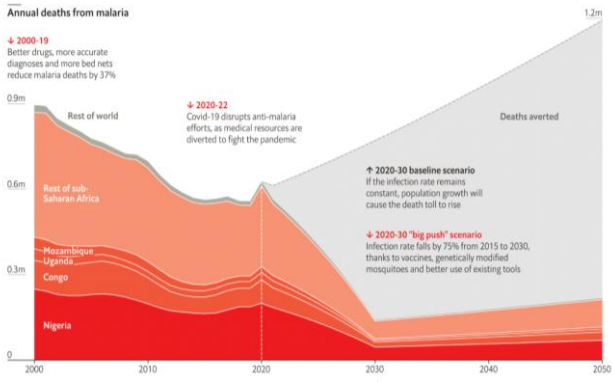
Malaria in Africa



Plasmodium falciparum
Anopheles gambiae & funestus



WHO target
>90% reduction in mortality and incidence

Source: The Economist

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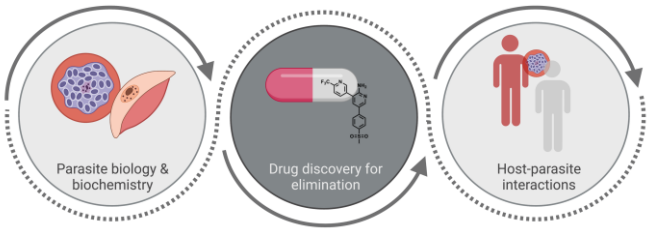
Malaria Parasite Molecular Laboratory (M2PL)

Malaria parasite biology to identify sustainable malaria control measures for malaria elimination



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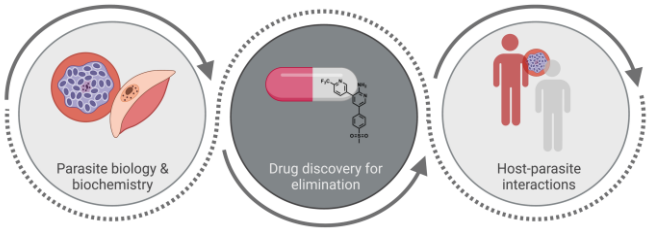
Malaria Parasite Molecular Laboratory (M2PL)

M2PL

Malaria parasite biology to identify sustainable malaria control measures for malaria elimination



South African Antimalarial Drug Discovery Consortium

https://www.up.ac.za/malaria-parasite-molecular-laboratory-m2pl

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GC ADDA - African Drug Discovery Accelerator – Antimalarial Drug Discovery

M2PL

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MMV Medicines for Malaria Venture

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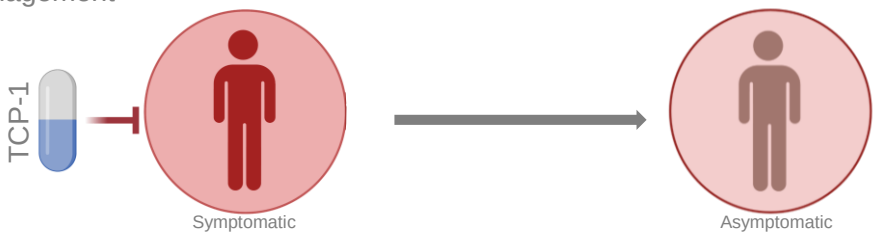
Antimalarials – from cure to elimination

TPP-1
Case management



- Curative
- Safe, effective & affordable
- Quick-acting & long-lasting
- Available to vulnerable populations

Birkholtz *et al.*, 2016, 2022 33

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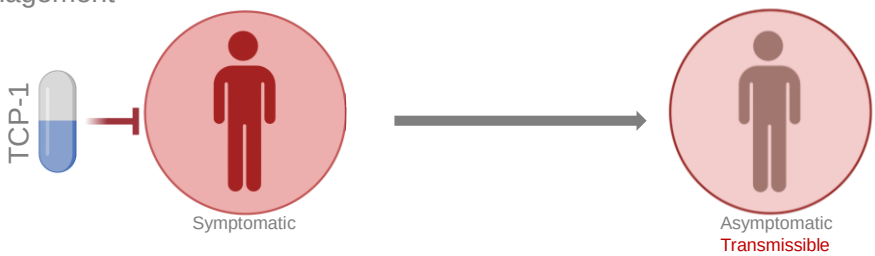
Antimalarials – from cure to elimination

TPP-1
Case management



'Unmet medical need' for new antimalarial combinations

- Circumvent resistance and/or have a low resistance risk (novel mode-of-action)
- Contribute to elimination (and eradication)
  - Target multiple stages of the parasites' life cycle

Birkholtz *et al.*, 2016, 2022 34

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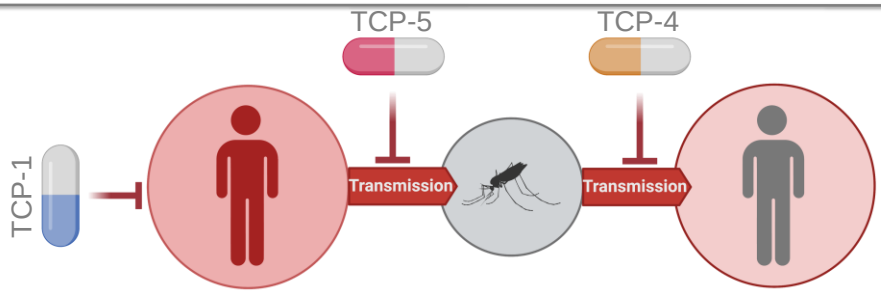
Antimalarials – from cure to elimination



Birkholtz *et al*., 2016, 2022

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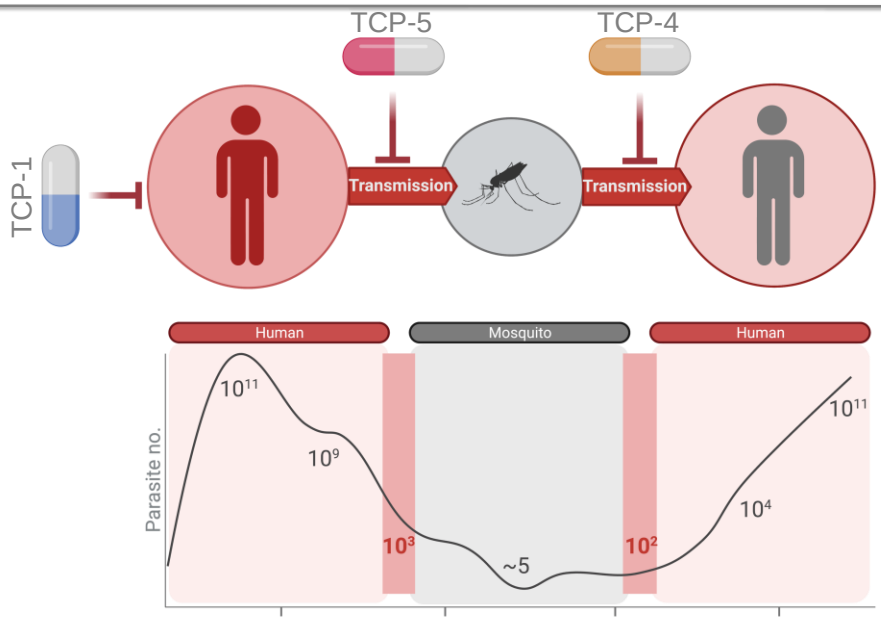
Antimalarials – from cure to elimination



Birkholtz *et al*., 2016, 2022

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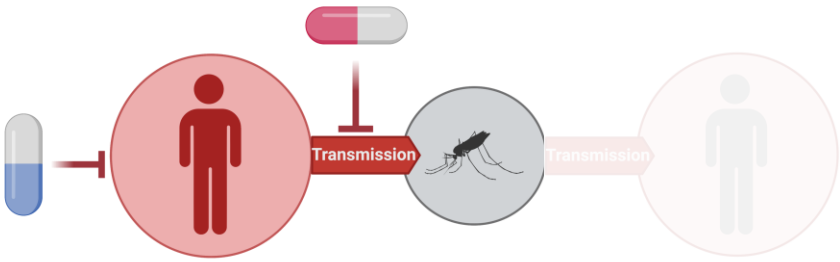
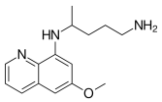
Antimalarials for malaria elimination



Advantages

- **Decrease parasite burden (even in high-transmission settings)**
- **Target asymptomatic carriers**
  - >90% contribution to onwards transmission (Andolina *et al.*, Lancet, 2021)
- **Protect lifespan of antimalarials by preventing transmission of resistance**
  - Art resistance transferred to transmissible stages (Witmer *et al.*, AAC, 2021)

Low-dose primaquine (Graves, Cochrane review, 2018; WHO, 2012)



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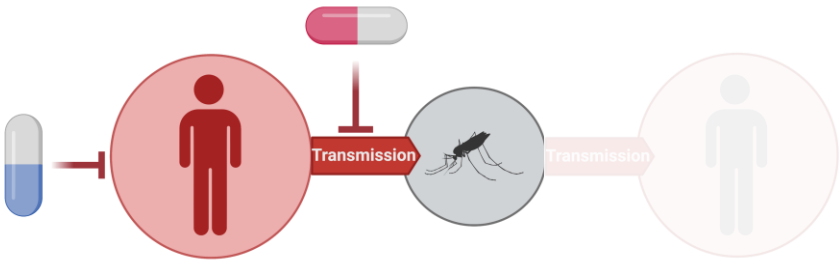
Antimalarials for malaria elimination



Development objective

- **To develop a transmission-blocking (reducing) agent (TrB agent) to add on to current enhanced standard measures (ESM) plus MDA to prevent person-to-person transmission through mosquitoes, at the community level**

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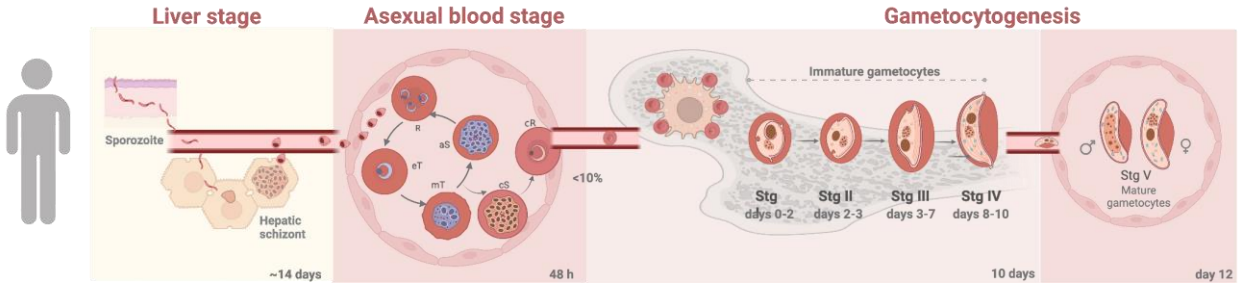
Plasmodium falciparum parasite biology



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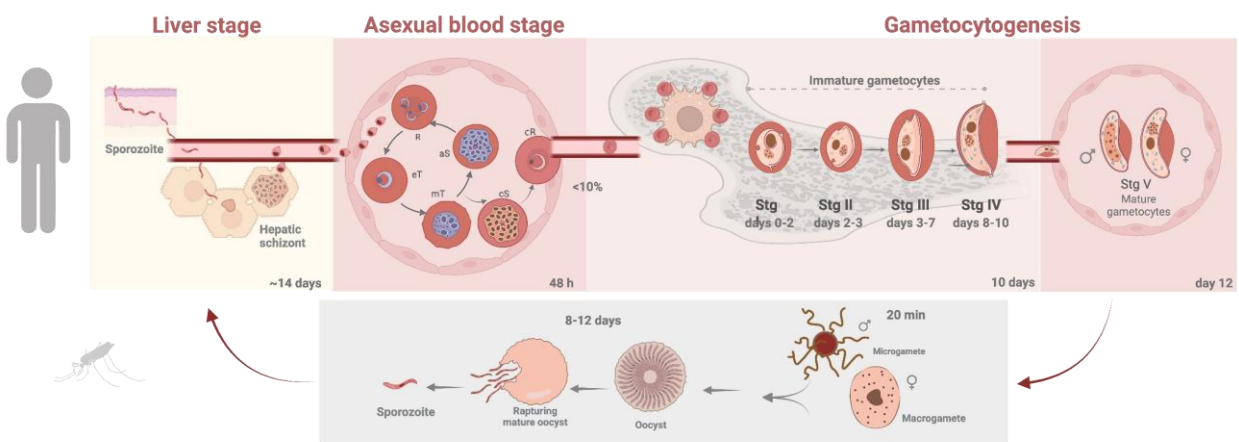
Plasmodium falciparum parasite biology



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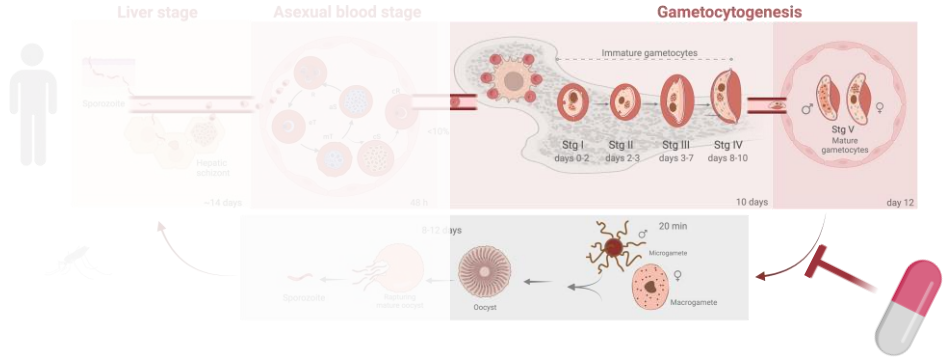

TrB discovery challenges

1) **How do we identify compounds with TrB activity?**
   - At scale, robust evaluation of multiple stages
   - What are the characteristics of an ideal TrB compound?
2) **What to target in transmissible stages?**
   - Unique MoA indications required to prevent resistance transmission

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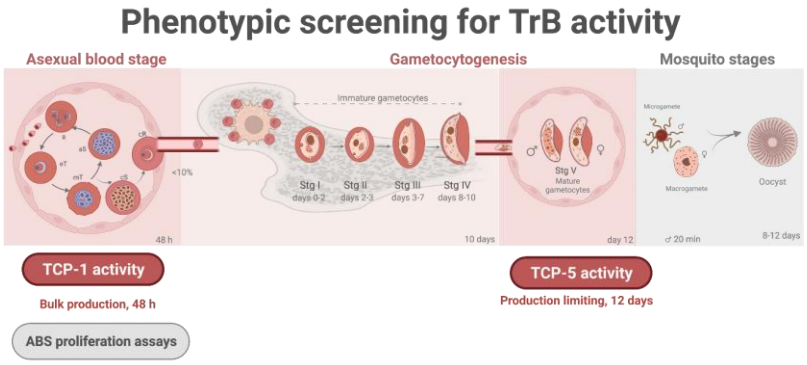
Enabling technology



Reader *et al.*, Mal J 2016, Frontiers, 2022

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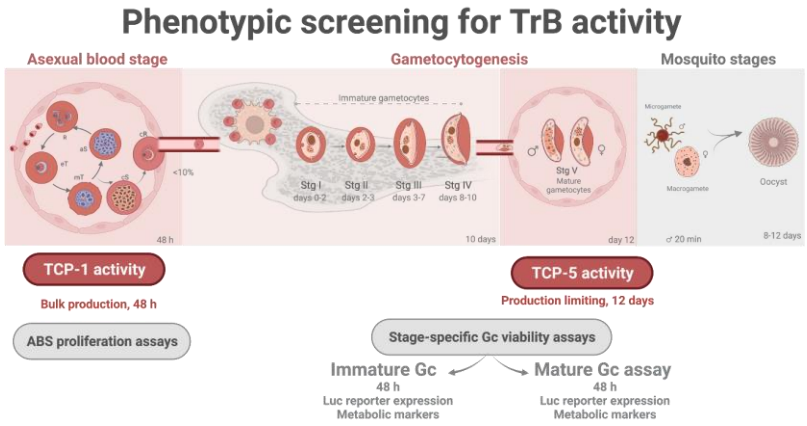
Enabling technology



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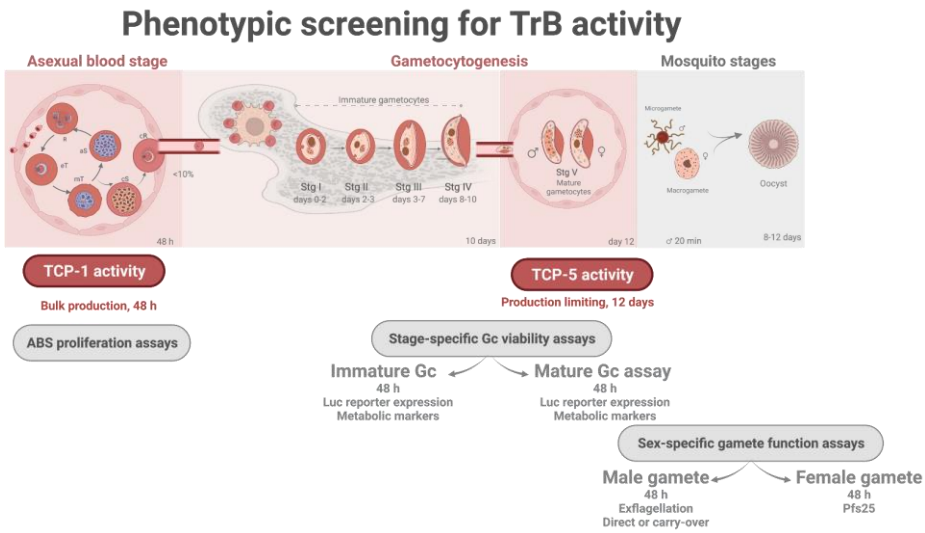
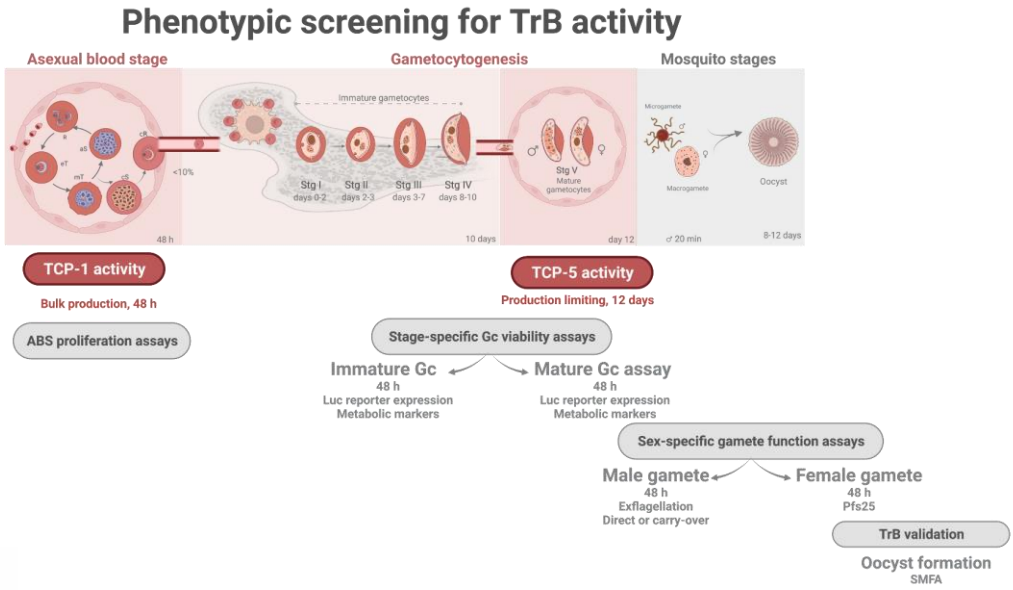
Enabling technology



Reader *et al.*, Mal J 2016, Frontiers, 2022

44

Enabling technology



Reader *et al.*, Mal J 2016, Frontiers, 2022

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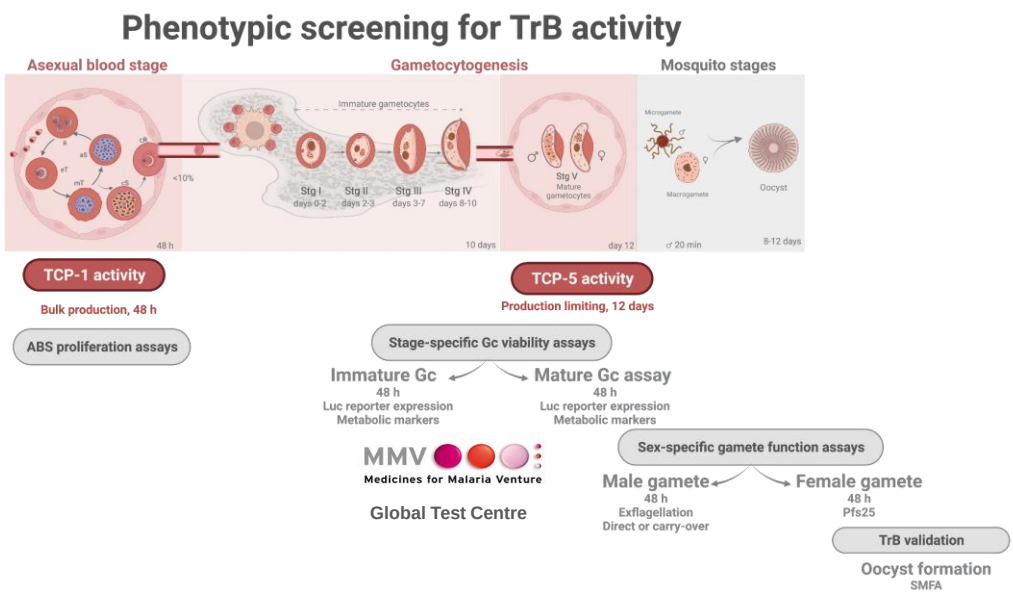
45

Enabling technology



Reader *et al.*, Mal J 2016, Frontiers, 2022

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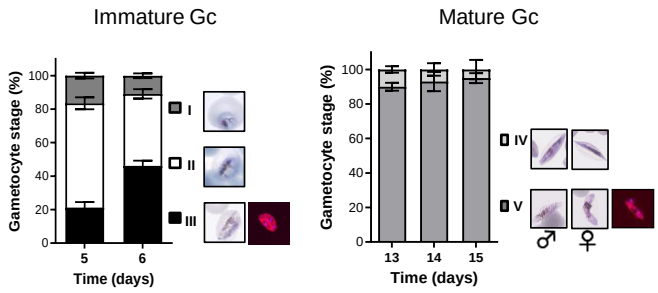
Transmission-blocking platform



>90% stage II/III

Gametocytemia:
3.3 ± 0.2%, (day 5, n=50)

Luc assay Z factor:
0.83 ± 0.02 (n=81)

>95% stage V

Gametocytemia:
2.7 ± 0.2%, (day 15, n=50)

Luc assay Z factor:
0.84 ± 0.02 (n=80)

Reader *et al.*, Mal J 2016, Frontiers, 2022 47

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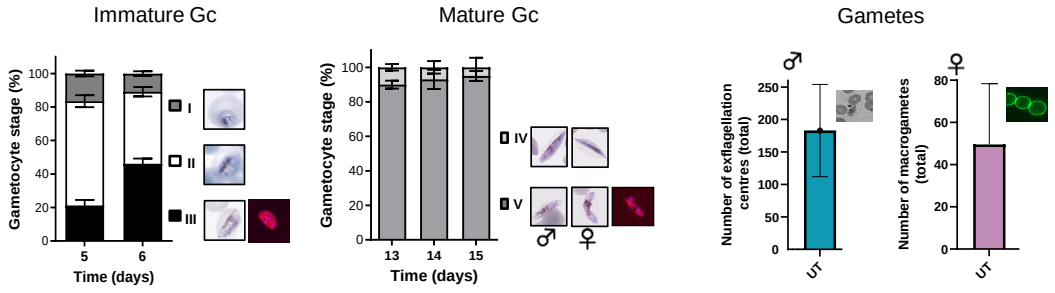
Transmission-blocking platform



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2.7 ± 0.2%, (day 15, n=50)

Luc assay Z factor:
0.84 ± 0.02 (n=80)

Male:
150 exflagellation centres (n>25)

Female:
>30 macrogametes (n>25)

Reader *et al.*, Mal J 2016, Frontiers, 2022 48

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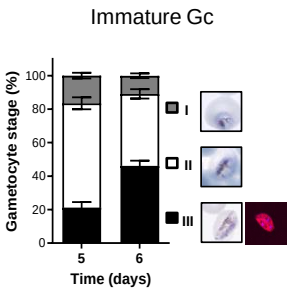
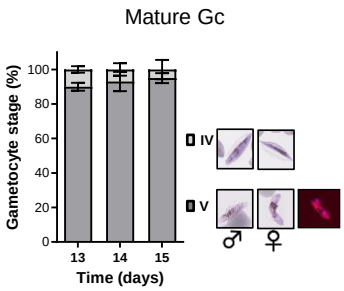
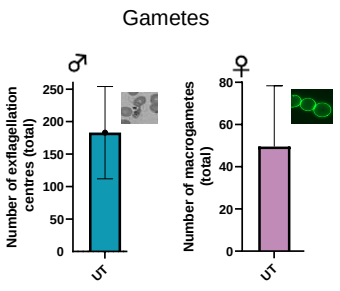
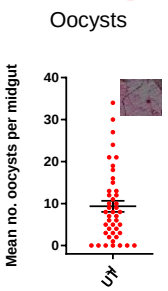
Transmission-blocking platform









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2.7 ± 0.2%, (day 15, n=50)

Luc assay Z factor:
0.84 ± 0.02 (n=80)

Male:
150 exflagellation centres (n>25)

Female:
>30 macrogametes (n>25)

Feeding rage ~80%

Prevalence ~75%

Oocyst intensity ~10

African *Anopheles sps.*

Reader *et al.*, Mal J 2016, Frontiers, 2022

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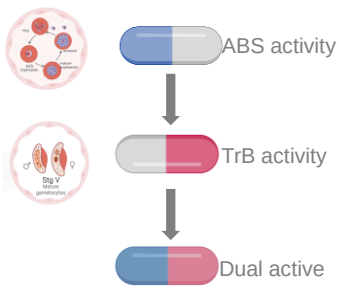
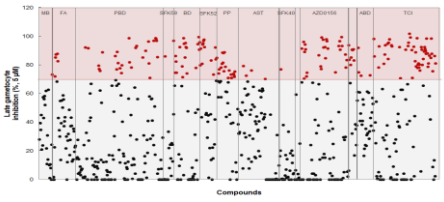
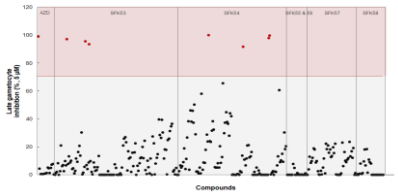
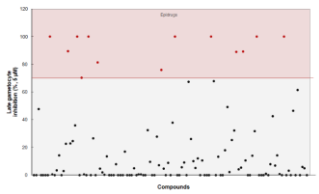
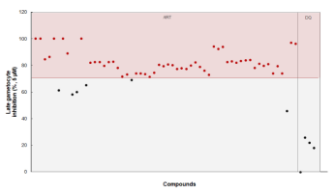
TrB as additional activity to antimalarials





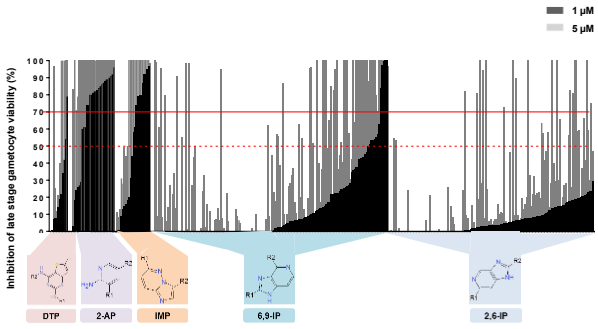






50

Exploring the kinase inhibitor space for transmission-blocking antimalarials



Van der Watt, JAC, 2018; Paquet, Science Transl Med, 2017; Brunswig, AAC, 2018

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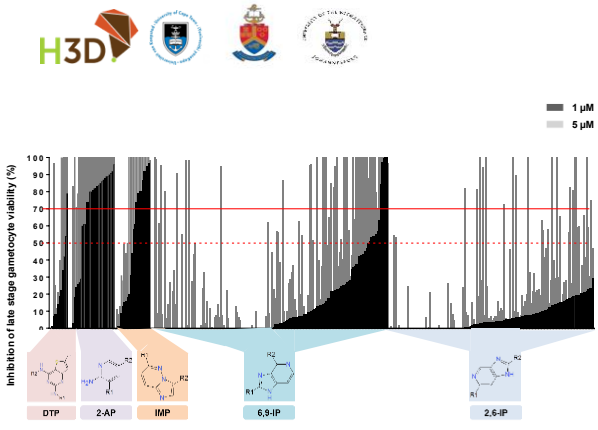
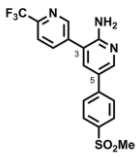
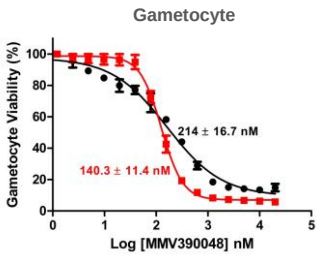
Exploring the kinase inhibitor space for transmission-blocking antimalarials





MMV048

PfPI4K inhibitor



Van der Watt, JAC, 2018; Paquet, Science Transl Med, 2017; Brunswig, AAC, 2018

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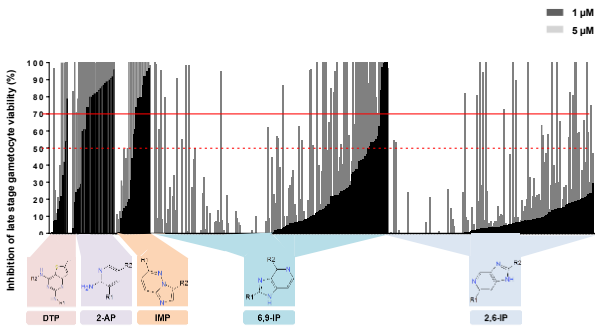
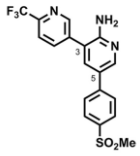
Exploring the kinase inhibitor space for transmission-blocking antimalarials

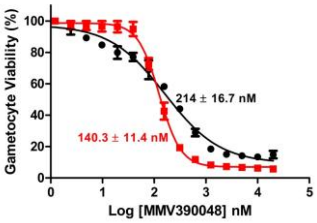




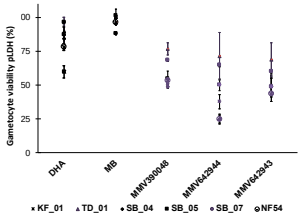
PfPI4K inhibitor

MMV048

Gametocyte



Ex vivo gametocyte efficacy



Clinical isolates

Van der Watt, JAC, 2018; Paquet, Science Transl Med, 2017; Brunswig, AAC, 2018

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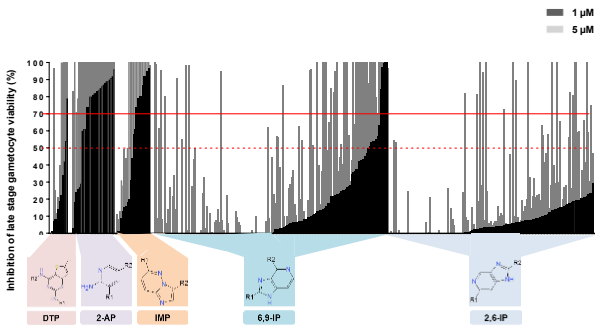
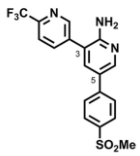
Exploring the kinase inhibitor space for transmission-blocking antimalarials

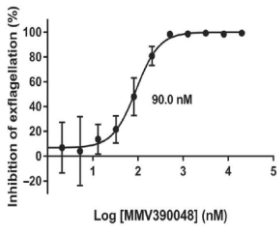




PfPI4K inhibitor

MMV048

Gamete



Van der Watt, JAC, 2018; Paquet, Science Transl Med, 2017; Brunswig, AAC, 2018

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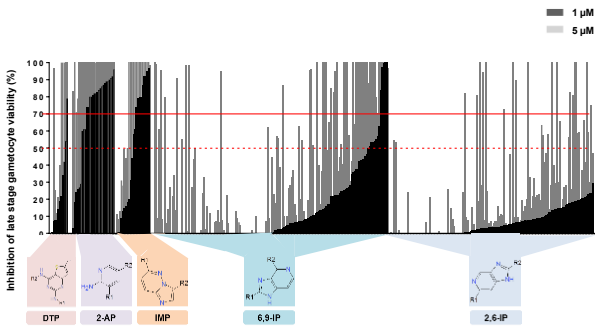
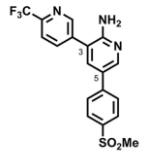
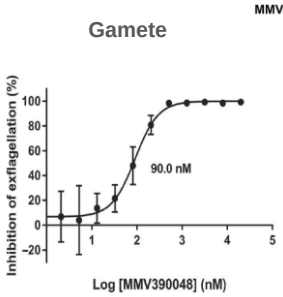
Exploring the kinase inhibitor space for transmission-blocking antimalarials

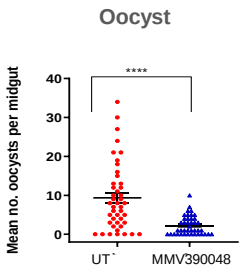




PfPI4K inhibitor

MMV048





Van der Watt, JAC, 2018; Paquet, Science Transl Med, 2017; Brunswig, AAC, 2018

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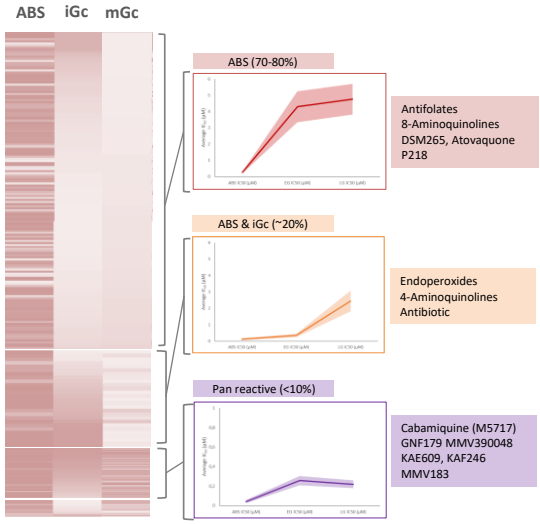

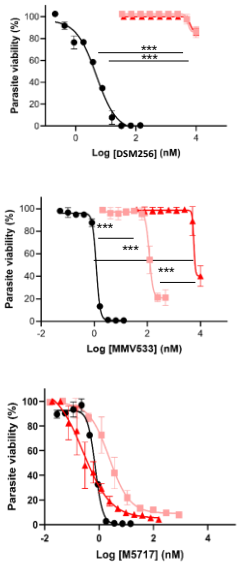

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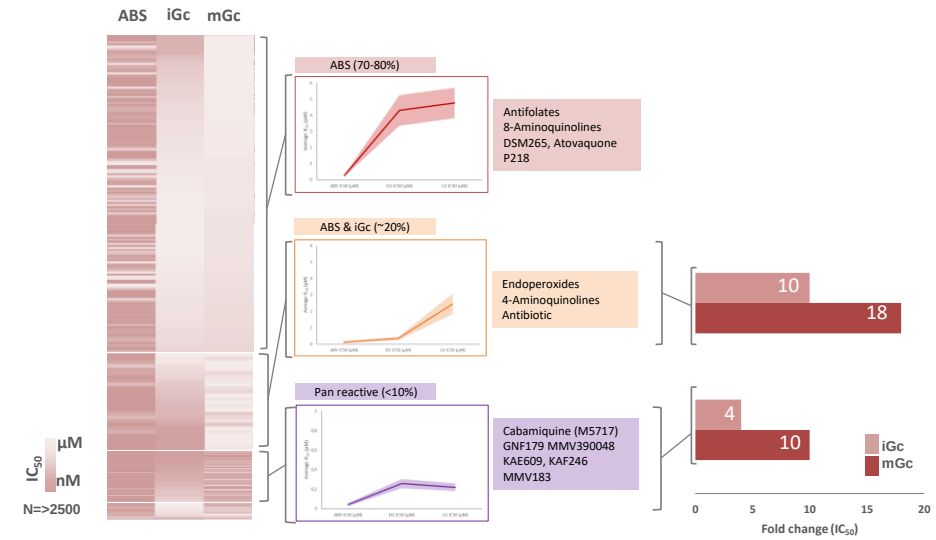

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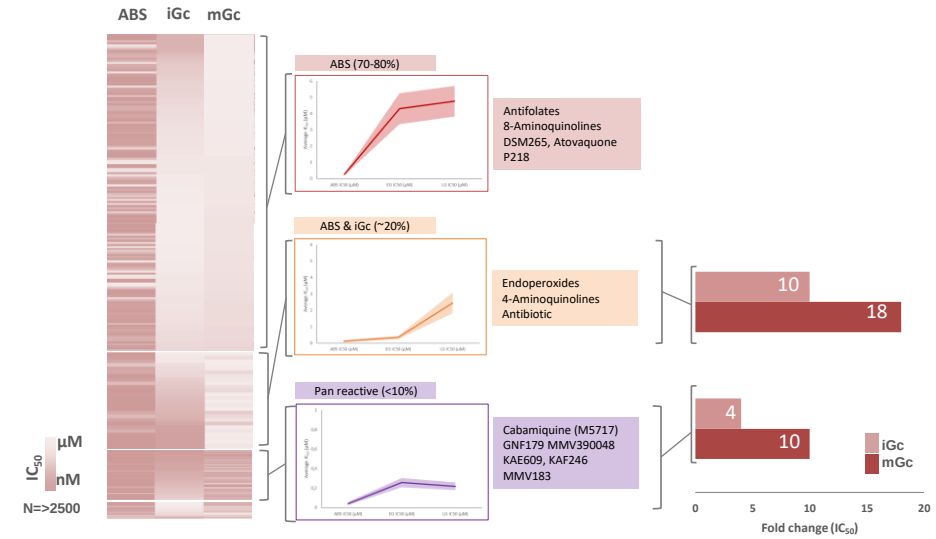

Will gametocyte maturation be prevented?

Will effective gametocytocidal activity be achieved at therapeutic doses?

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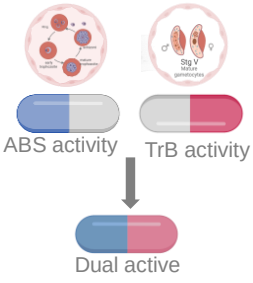
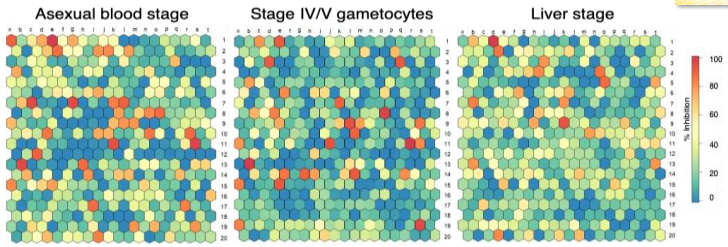
De novo parallel screens against multiple life cycle stages





Reader *et al.*, Nature Comms, 2021

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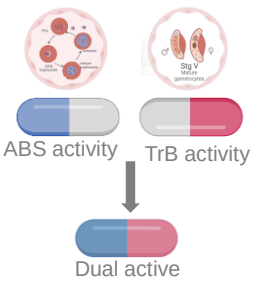
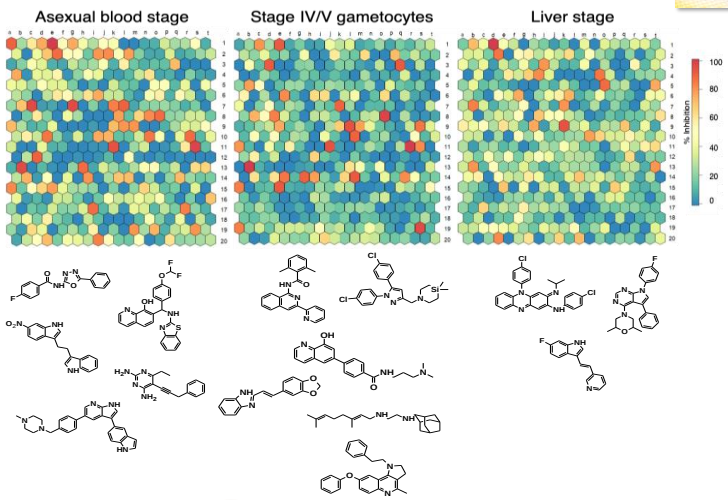
De novo parallel screens against multiple life cycle stages





Reader *et al.*, Nature Comms, 2021

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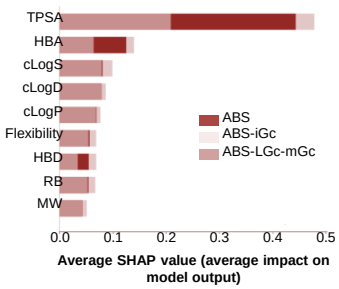
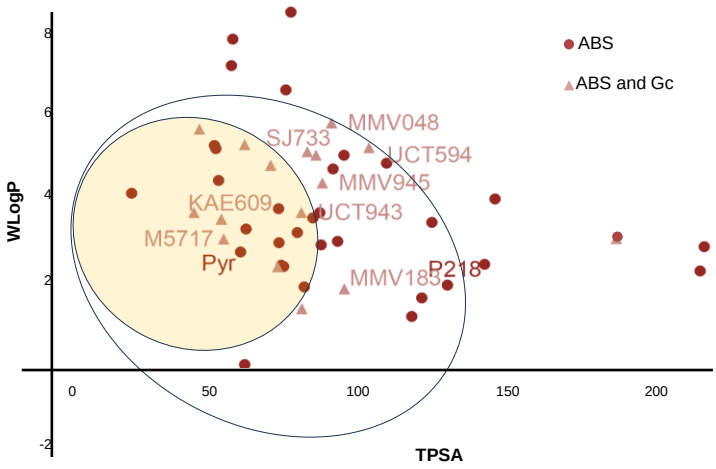
Required properties of dual-active antimalarials





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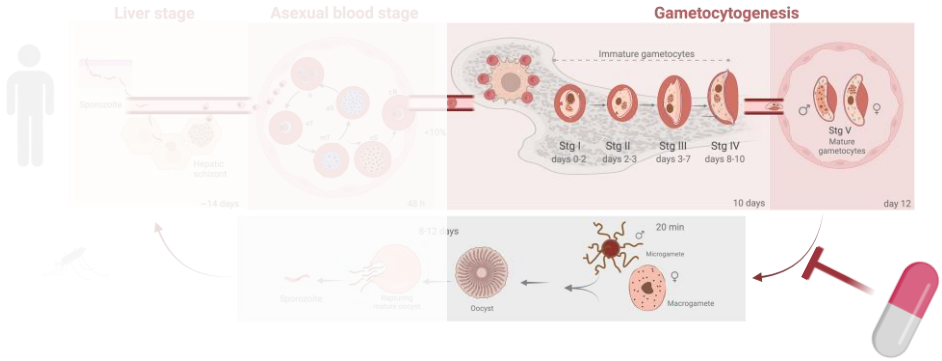

TrB discovery challenges

1) How do we identify compounds with TrB activity?
   - At scale, robust evaluation of multiple stages
   - What are the characteristics of an ideal TrB compound?
2) What to target in transmissible stages?
   - Unique MoA indications required to prevent resistance transmission

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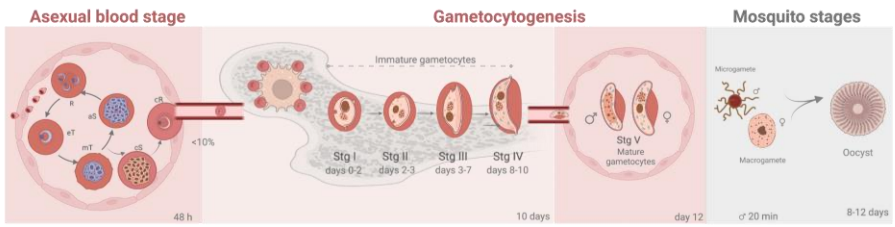
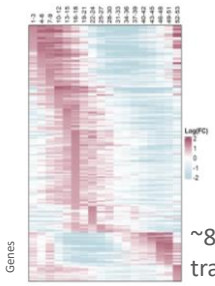
TrB to prevent the spread of resistance

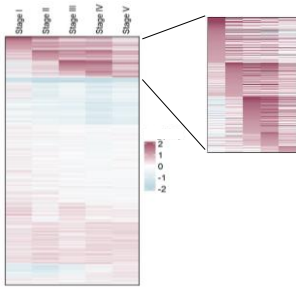


Proliferative state



~80% of genome transcribed

Differentiative state



- Divergence from ABS
  - Stage-stratified
  - Sexual dimorphism
- Only 45% of genome transcribed

Bozdech, 2003

Van Biljon *et al.*, 2019 ; Van Wyk *et al.*, 2021

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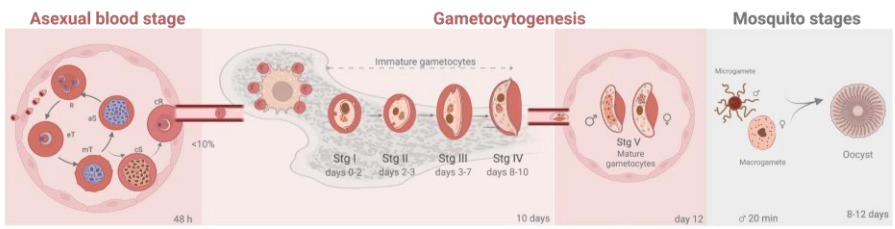
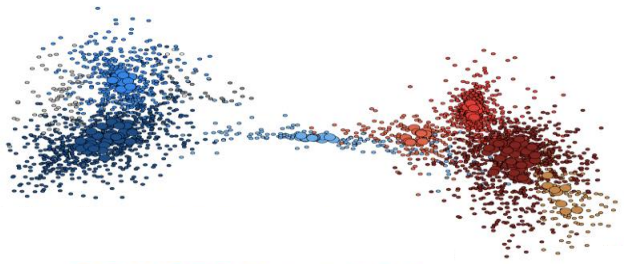
TrB to prevent the spread of resistance



Proliferative state



Differentiative state

Van Biljon *et al.*, 2019 ; Van Wyk *et al.*, 2021, van der Watt *et al.*, 2022

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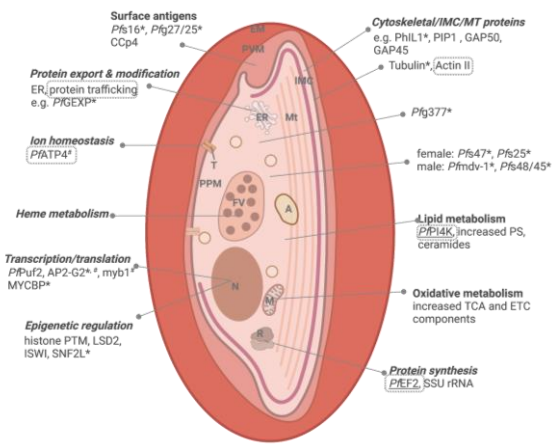
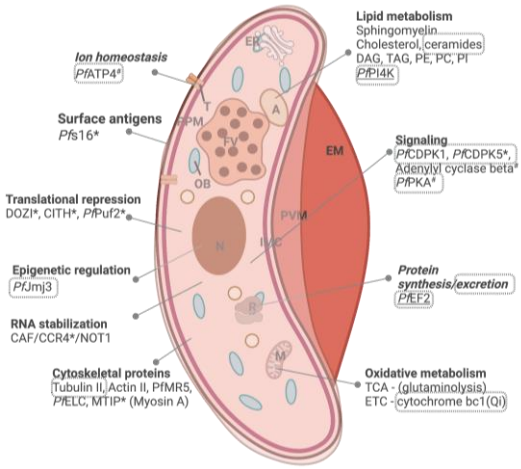
TrB to prevent the spread of resistance



Immature gametocyte



Mature gametocyte

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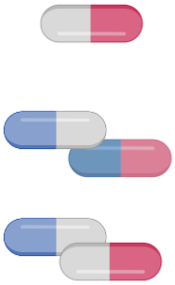
Summary & future directions

TrB agents

- **Routine platform to assign TrB activity to antimalarial candidates**
- **Physicochemical space defined**
  - Uptake as a main barrier to efficacy
- **Targetable biology becoming evident**
  - Resistance transmission can be circumvented
  - Polypharmacology enticing



Development challenges

- **Can we achieve equipotency for the effective therapeutic window for TrB in dual-active compounds?**
- **Can we achieve PK/PD and half-life matching in combinations?**
- **Which *in vitro* activities translate to good activity *in vivo*?**

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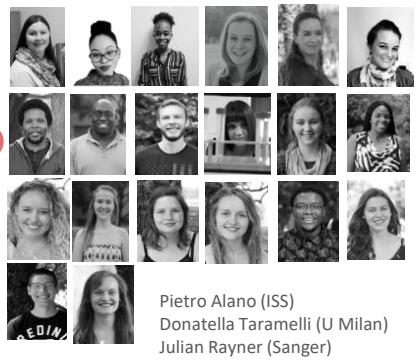
Thank you….



Pietro Alano (ISS)
Donatella Taramelli (U Milan)
Julian Rayner (Sanger)
Marcus Lee (DDU)
Manuel Llinas (Penn State)
Ben Garcia (Uni Penn)
Simone Sidoli (Uni Penn)
Micheal Delves (LSHTM)
Mathieu Brochet (Uni Geneva)
Moritz Treeck (Crick)

Kelly Chibale
Andre Horatscheck
Greg Basarab
Multiple members of H3D

Lizette Koekemoer (WITS)
Theresa Coetzer (WITS)
Dalu Mancama, Anjo Theron (CSIR)

Didier Leroy, James Duffy & Anna Adam

Elizabeth Winzeler (UCSD)
Dan Goldberg (WU)
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Giovanna Poce (Sapienza)
Kenny Onajole (Rooseveldt)
Eric Oldfield (Ilinois)
Amanda Rossouw (WITS)
Winston Nxumalo (UL)
Richard Amewu (UGhana)

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Unraveling the mysteries of malaria parasites

Emily Derbyshire, Duke University
Departments of Chemistry and
Molecular Genetics & Microbiology

ACS Webinars
World Malaria Day
April 25, 2024

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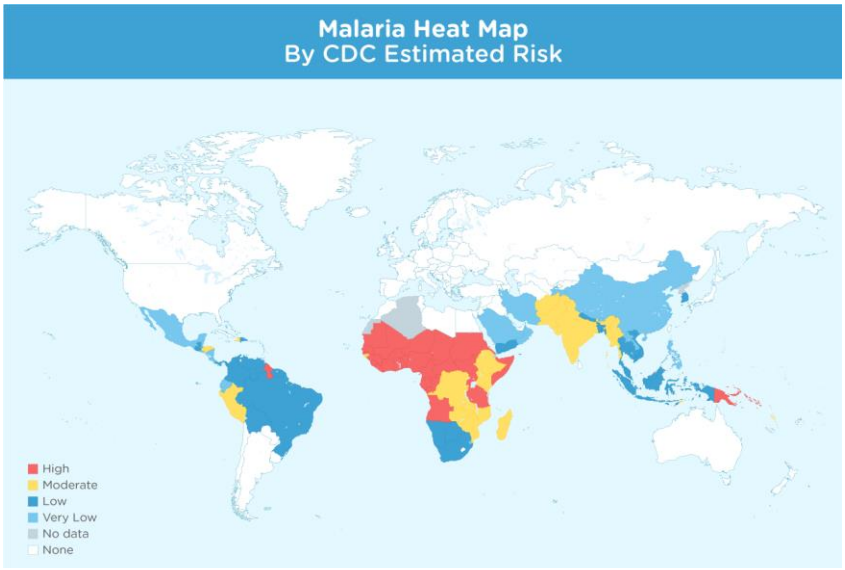
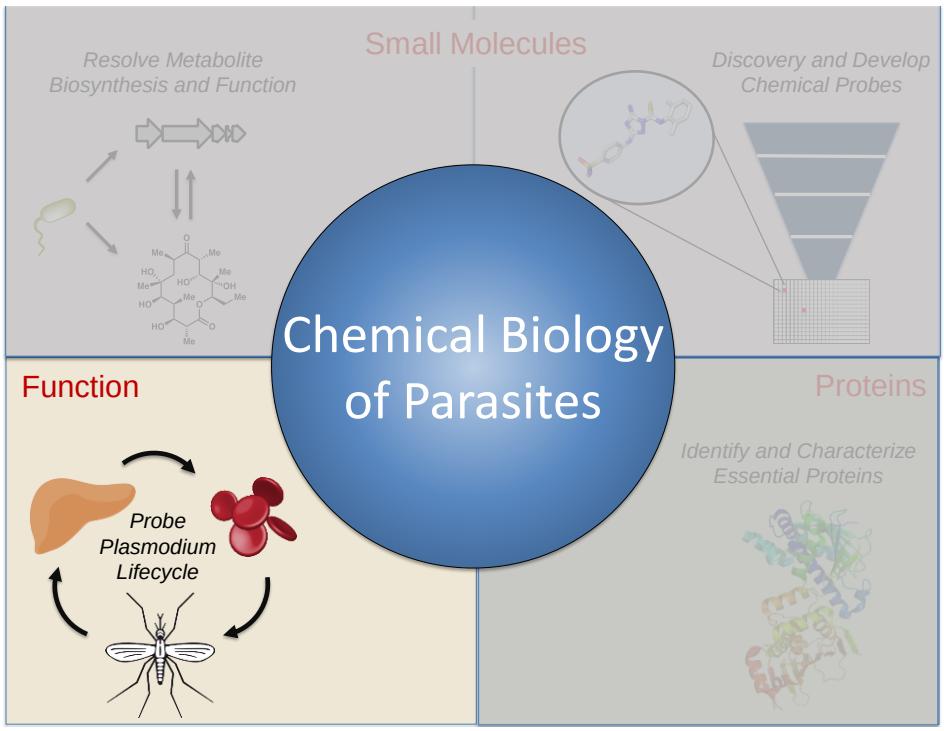
Malaria Progress 'Stalled'



Drug resistance is greatest risk to disease control

70

70



71

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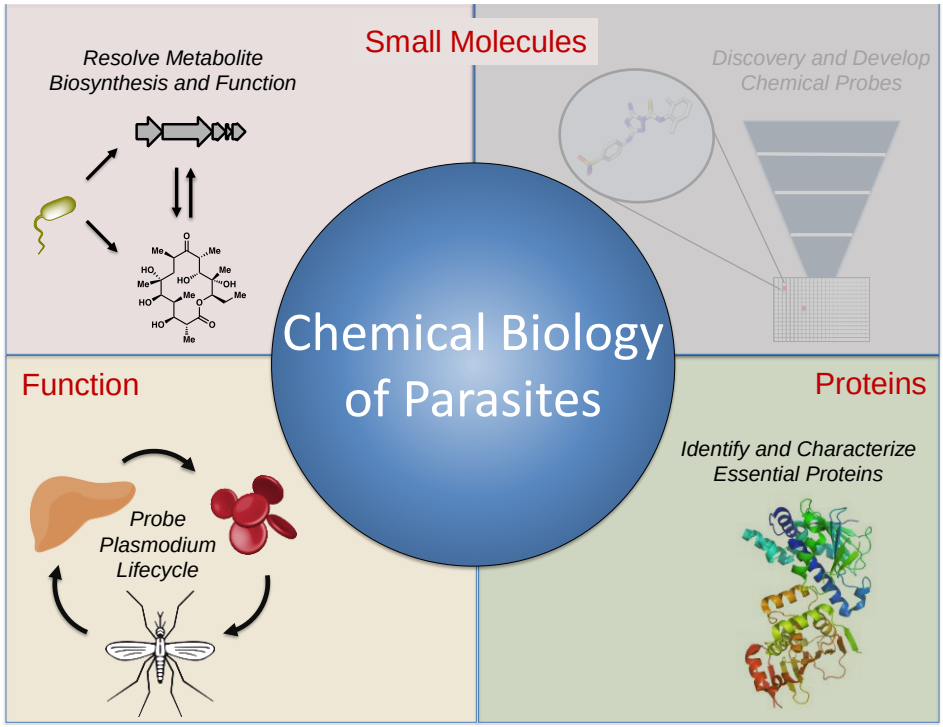
Small Molecules
Resolve Metabolite Biosynthesis and Function
Discovery and Develop Chemical Probes
Chemical Biology of Parasites
Function
Probe Plasmodium Lifecycle
Proteins
Identify and Characterize Essential Proteins

72

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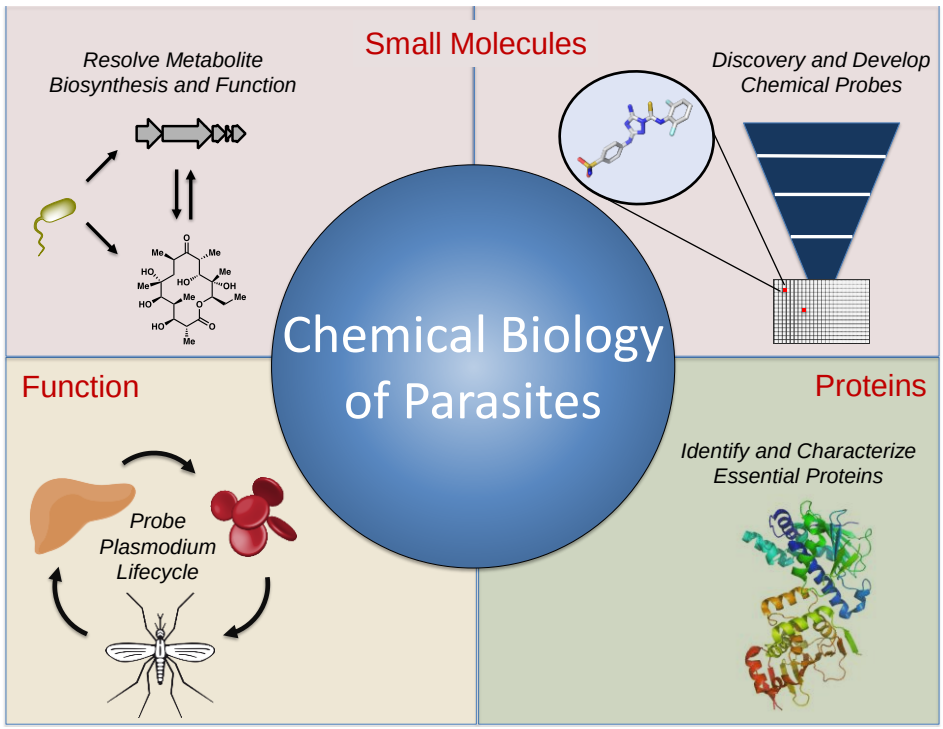
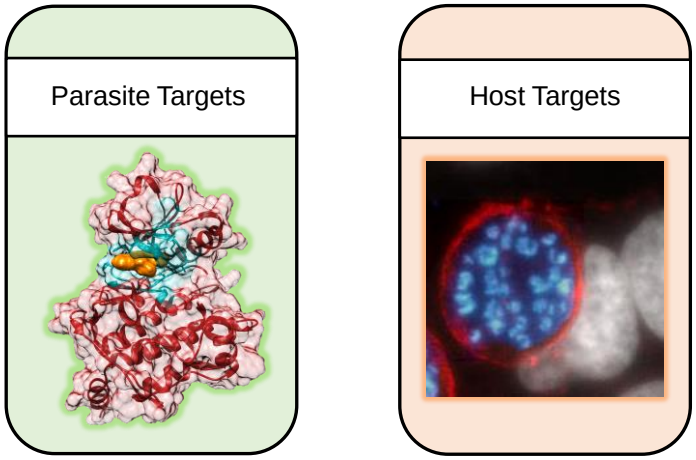

Small Molecules
Resolve Metabolite Biosynthesis and Function
Discovery and Develop Chemical Probes
Chemical Biology of Parasites
Function
Probe Plasmodium Lifecycle
Proteins
Identify and Characterize Essential Proteins

73

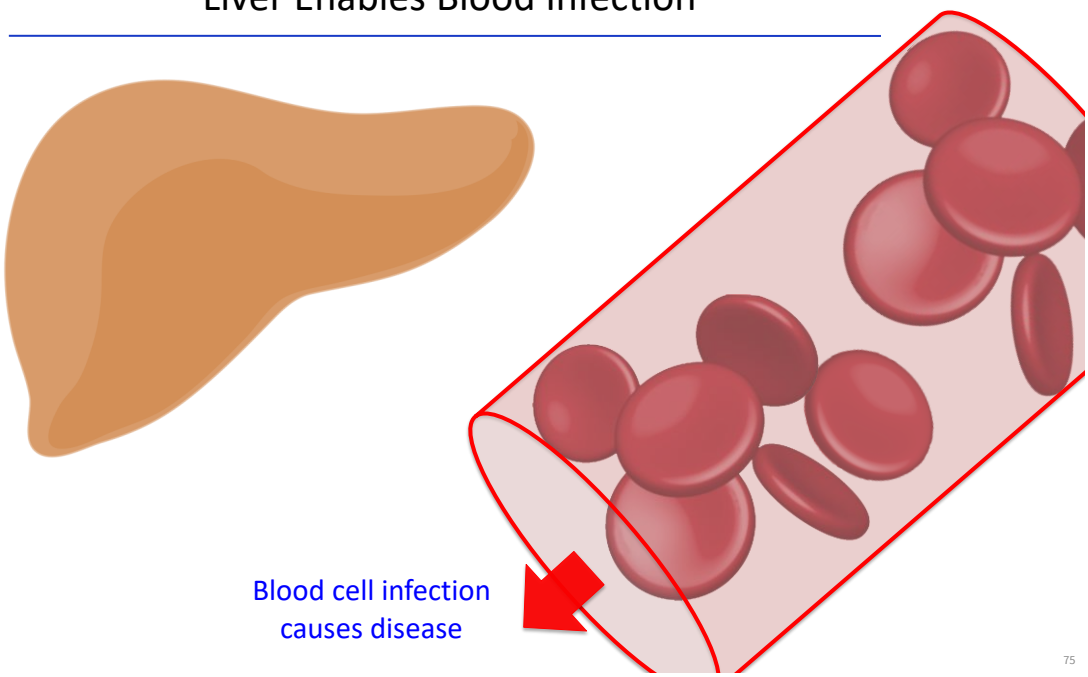
73

Chemical Biology of Parasites



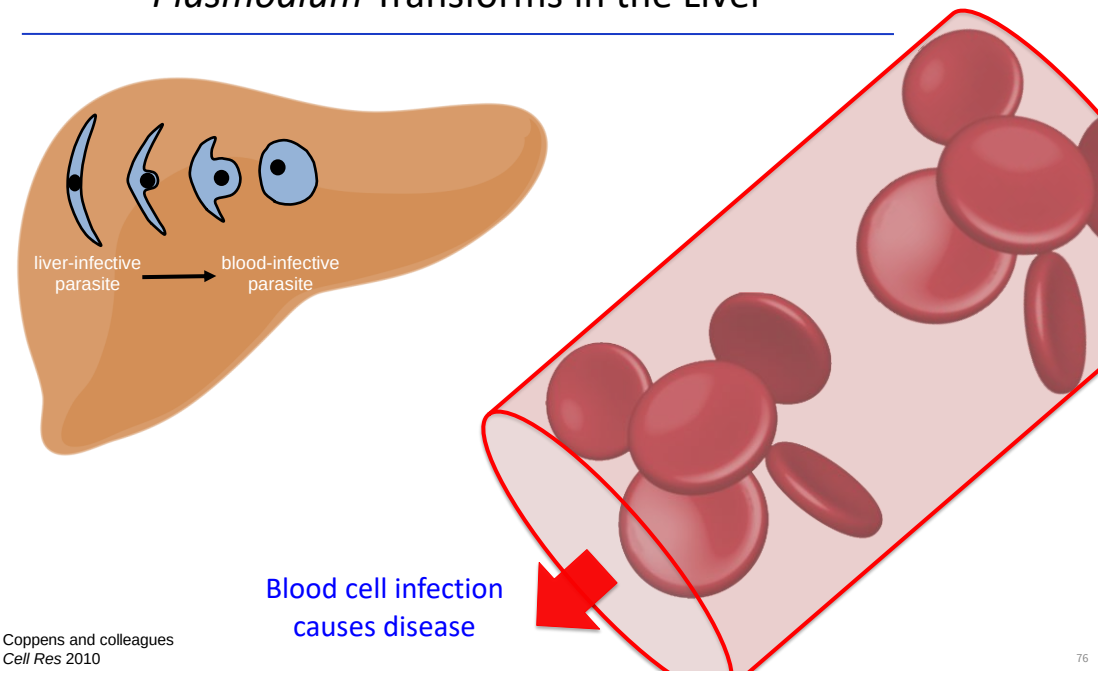
74

Liver Enables Blood Infection



75

Plasmodium Transforms in the Liver

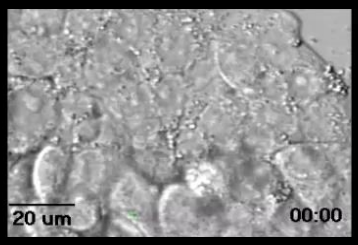


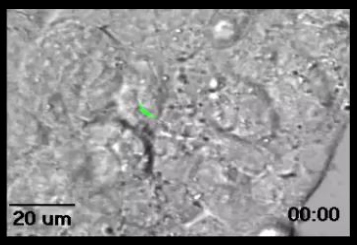
Coppens and colleagues
Cell Res 2010

76

76

Plasmodium Transforms in the Liver



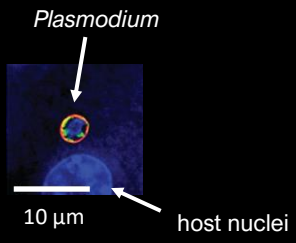


Dr. Dora Posfai

77

77

Plasmodium Replicates Massively

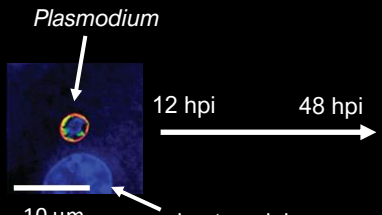


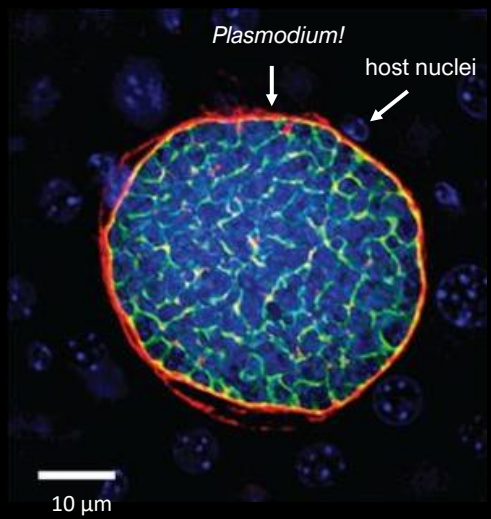
Images adapted from Vaughan & Kappe *Cold Spring Harb Perspect Med* 2017

78

78

Plasmodium Replicates Massively



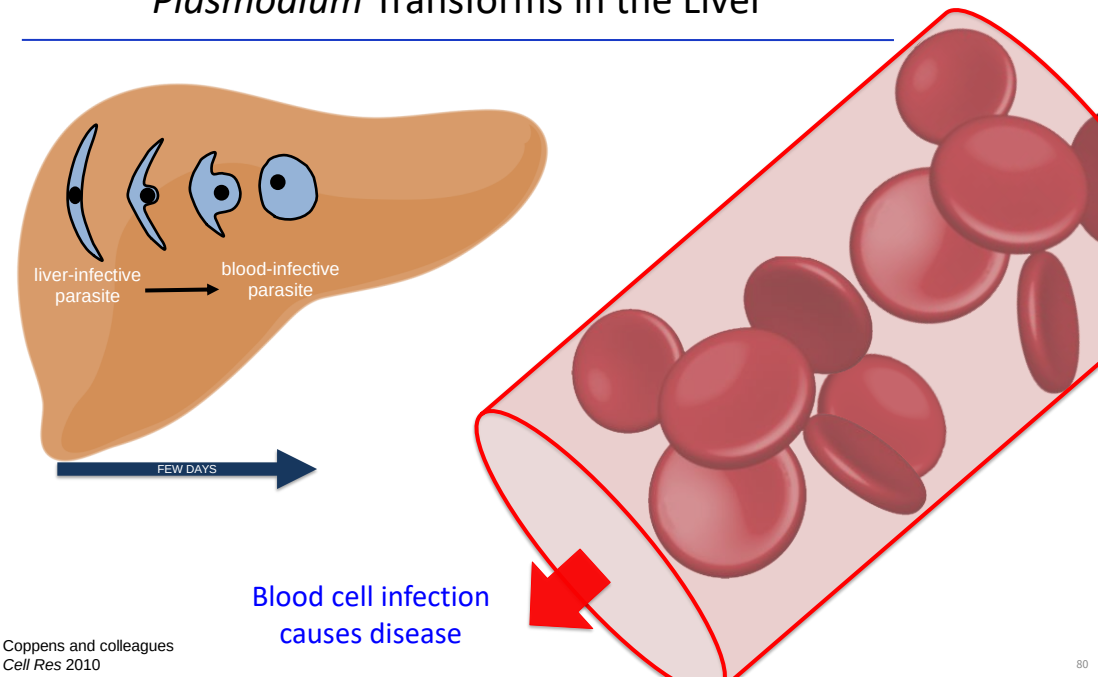


Images adapted from Vaughan & Kappe *Cold Spring Harb Perspect Med* 2017

79

79

Plasmodium Transforms in the Liver



Coppens and colleagues
Cell Res 2010

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Challenges of Liver Stage Research

We need thousands of live malaria-infected mosquitoes

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Challenges of Liver Stage Research

We ne es

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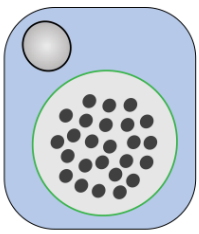
Malaria Liver Stage Model System

Hepatocytes

P. berghei-Infected Mosquitoes

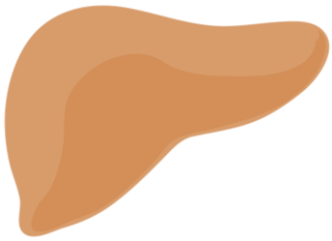


P. berghei-Infected Hepatocytes

83

83

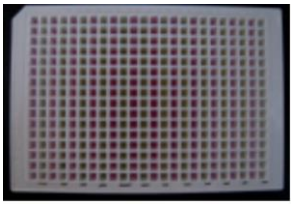
Malaria Liver Stage Model System



Hepatocytes

P. berghei-Infected Mosquitoes

Ong et al *Eur J Med Chem* 2023
Viswanathan et al *Bioor Med Chem Let* 2023
Galal et al *J Med Chem* 2022
Mughal et al *ACS Infect Dis* 2022
Bang et al *Nat Comm* 2021



384-well plate
Plasmodium-infected liver cells

84

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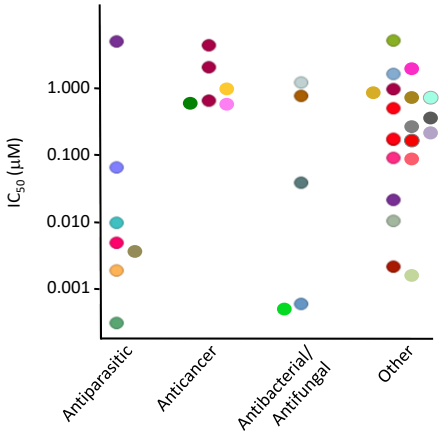
We aim to leverage small molecules to reveal druggable proteins

85

85

FDA-Approved Compounds Inhibit LS *Plasmodium*



Hits exhibit different IC_{50}s & diverse chemical scaffolds

Derbyshire *PNAS* 2012

86

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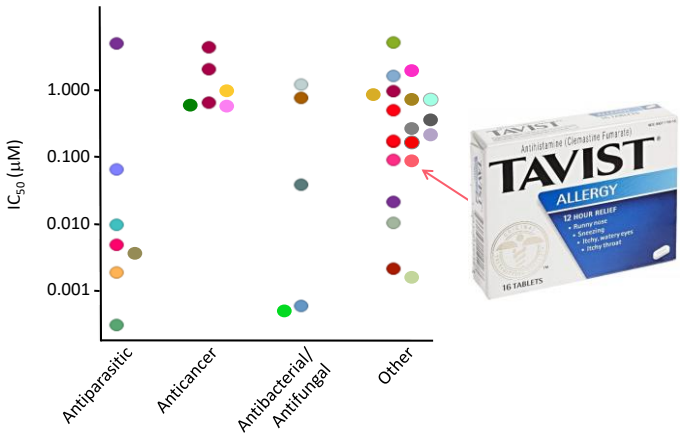
FDA-Approved Compounds Inhibit LS *Plasmodium*



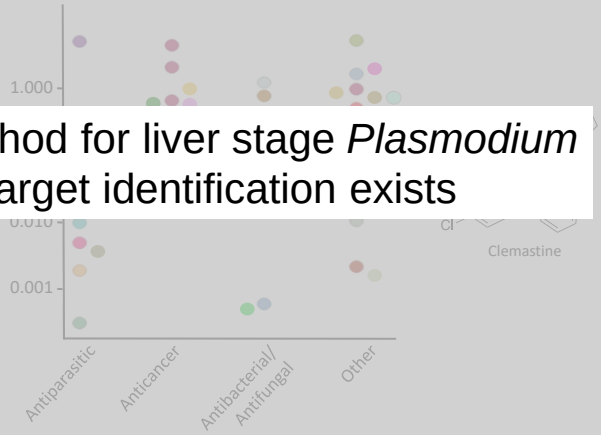
Hits exhibit different IC_{50}s & diverse chemical scaffolds

Derbyshire *PNAS* 2012

87

87

FDA-Approved Compounds Inhibit LS *Plasmodium*



No method for liver stage *Plasmodium* target identification exists

Hits exhibit different IC_{50}s & diverse chemical scaffolds

Derbyshire *PNAS* 2012

88

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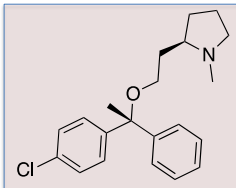
Plasmodium Blood Stage Target Identification

Kills *Plasmodium*



Clemastine
FDA-approved

?

Protein

Dr. Kuan-Yi Lu

Collaboration with Prof. Fitzgerald

Dr. Baiyi Quan

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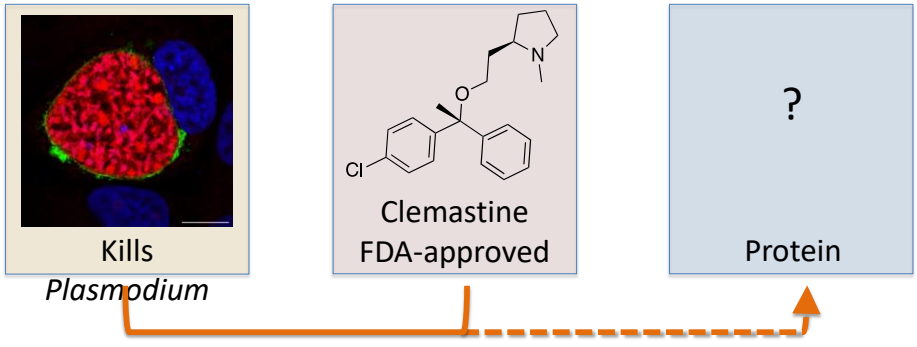
Plasmodium Blood Stage Target Identification



Chemoproteomics: CETSA (cellular thermal shift assay)
TPP (thermal proteome profiling)
SPROX (stability of proteins from rates of oxidation)

Molina et al *Science* 2013, Franken et al *Nat Protoc* 2015, West et al *Anal Chem* 2008

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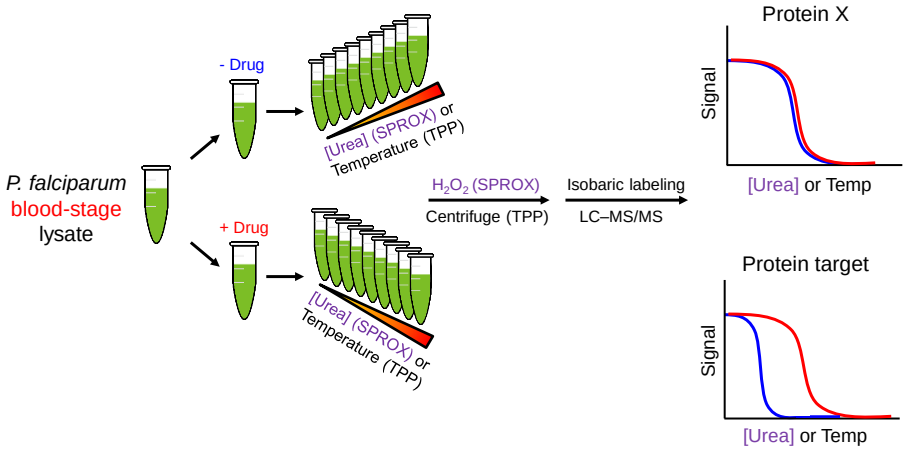
Proteomics Approach to *Plasmodium* Target ID



Lu *ChemBioChem* 2020
Collaboration with Prof. Fitzgerald (Duke) and Dr. Baiyi Quan

Dr. Kuan-Yi Lu

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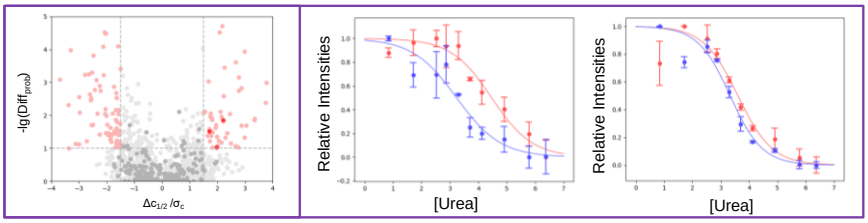
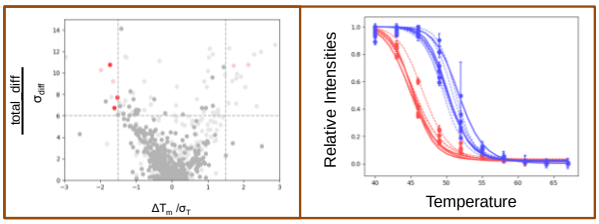
Proteomics Approach to *Plasmodium* Target ID

SPROX



TPP

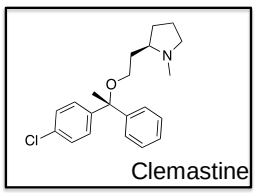


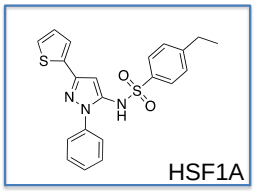
TCP-1 delta is reproducible hit in SPROX and TPP

Lu et al *PNAS* 2020

Clemastine Destabilizes *Pf*TRiC but not *Hs*TRiC

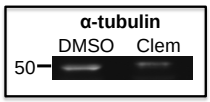
TRiC is an essential molecular chaperone that folds tubulin

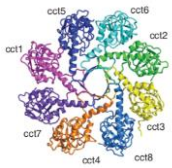




Neef 2014 *Cell Reports*

Clemastine binds and destabilizes *Plasmodium* TRiC but not human





Dekker *EMBO J* 2011

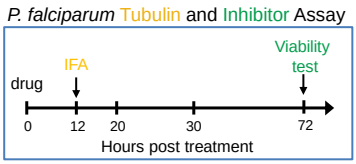
HSF1A binds and destabilizes human TRiC but not *Plasmodium*

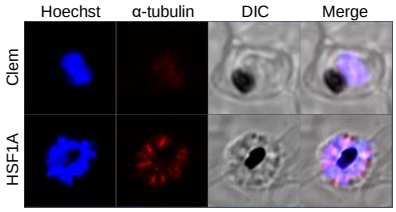
tubulin decreases tubulin destabilizes

Lu et al *PNAS* 2020

*Hs*TRiC: Frydman and colleagues *Cell* 2022
*Pf*TRiC: Goldberg and colleagues *Cell Microbiol* 2017

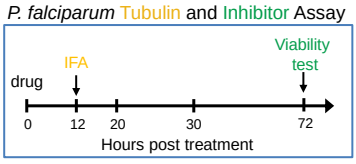
Clemastine Inhibits *Pf*TRiC Activity in Cells

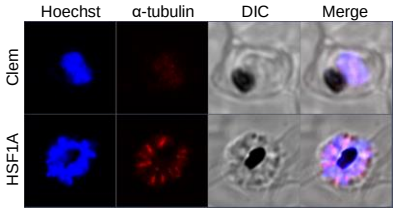


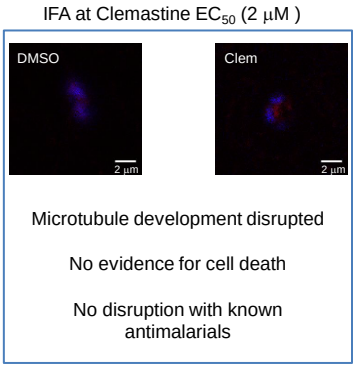


Lu et al *PNAS* 2020

Clemastine Inhibits *Pf*TRiC Activity in Cells



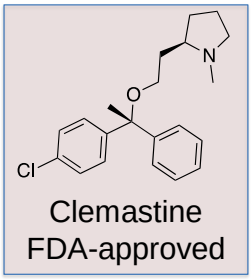




Proteomics-based target ID from HTS reveals potential to selectively target *Plasmodium* TRiC

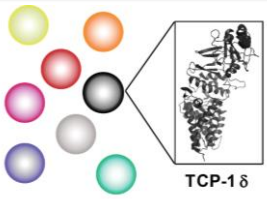
Lu et al *PNAS* 2020

Clemastine Inhibits *Plasmodium* Chaperone TRiC



Clemastine
FDA-approved

TRiC



Binds TCP-1 δ $K_{d\ app}$ ~ 10 μM
Complex destabilization

Phenotype: Decrease in tubulin levels
Aberrant tubulin morphologies
Protein aggregation

MS Target ID: Fidock and colleagues *Cell Chem Bio* 2020; Bozdech and colleagues *Nat Protoc* 2020; Cowman and colleagues *Cell Host & Microbe* 2020; Nordlund and colleagues *Science Trans Med* 2019

Lu et al *PNAS* 2020

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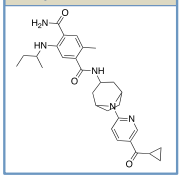
Targeting Essential Parasite Proteins

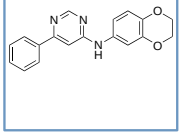
Screening and affinity-based chemoproteomics reveal protein function and structure

Heat shock protein 90



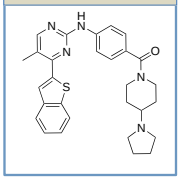
Mansfield el al *Cell Chem Bio* 2024

Heat shock protein 70



Keeler et al *unpublished*

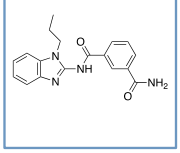
Protein kinase 6



Galal et al *J Med Chem* 2022

Dr. Chris Mansfield

Protein kinase 9



Totzke et al *Cell Chem Bio* 2017
Raphemot et al *Cell Chem Bio* 2019

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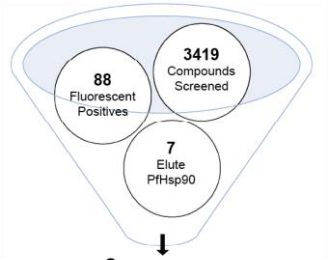
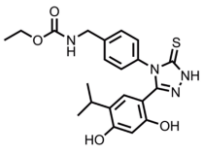
Identifying *Pf*Hsp90 Inhibitors

High-throughput screen



BX-2819

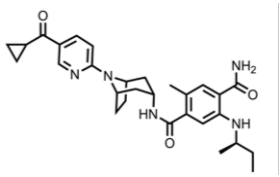


Protein binding:
*Pf*Hsp90 K_i = 24 ± 4.4 nM
*Hs*Hsp90 K_i = 49 ± 4.3 nM

Parasite inhibition:
BS EC_{50} = 1.2 ± 0.027 µM
LS EC_{50} = 1.5 ± 0.41 µM

2-fold selective

XL888



Protein binding:
*Pf*Hsp90 K_i = 27 ± 7.8 nM
*Hs*Hsp90 K_i = 130 ± 30 nM

Parasite inhibition:
BS EC_{50} = 0.78 ± 0.12 µM
LS EC_{50} = 0.24 ± 0.045 µM

5-fold selective

Collaboration with Prof. Tim Haystead (Duke)

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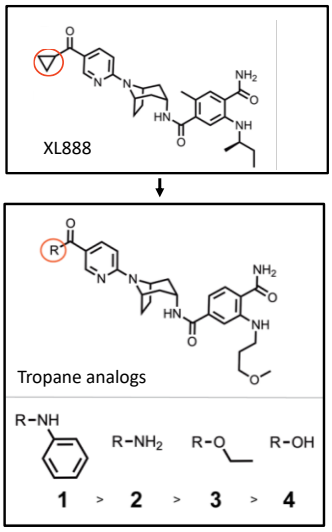
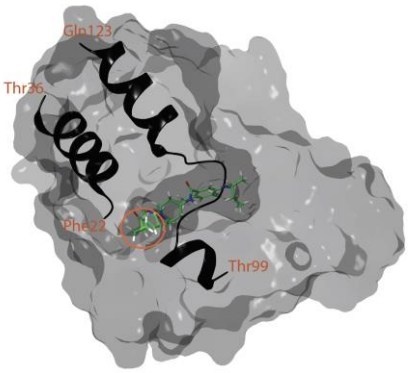
XL888 SAR to Improve Species Selectivity



XL888 bound *Hs*Hsp90



PDB: 4AWO
Constructed in Schrodinger Maestro

Collaboration with Prof. Leahy (USF) and Dr. Benjamin Eduful

99

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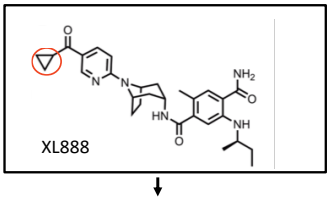
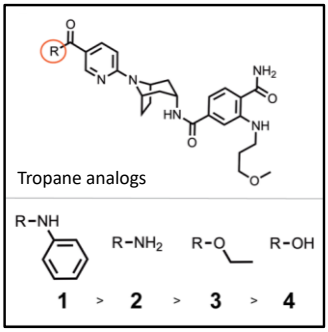
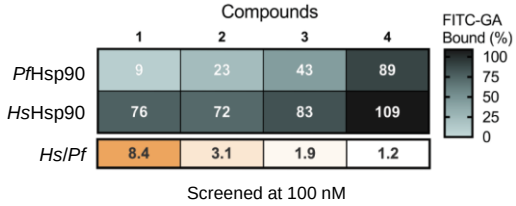
XL888 SAR to Improve Species Selectivity







Screened at 100 nM

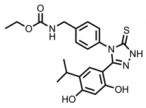
Apparent K_i (nM)	*PfHsp90*	*HsHsp90*	Selectivity
	46 ± 6.8	440 ± 130	**9.6-fold**

Tropane **1** is an XL888 analog with improved *Pf*Hsp90 selectivity

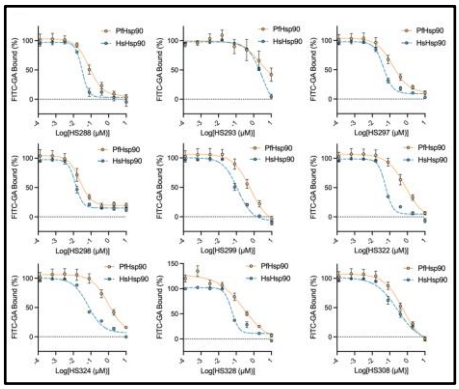
Collaboration with Prof. Leahy (USF) and Dr. Benjamin Eduful

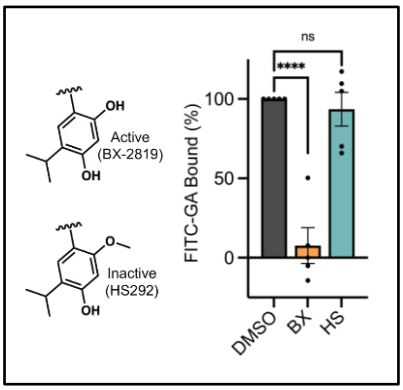
BX-2819 SAR

Can we improve BX-2819 selectivity?
Not within +30 compounds



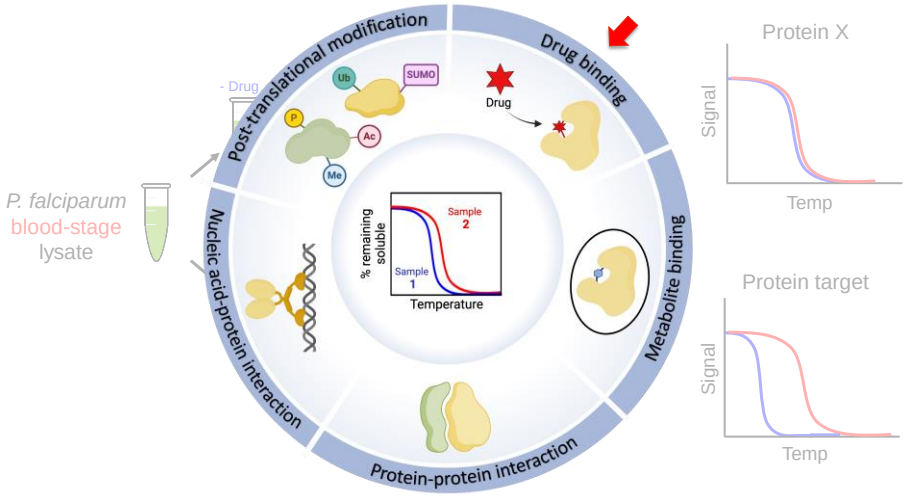
Are any derivatives useful?
Yes, as a negative control





Collaboration with Prof. Haystead (Duke) and Dr. Philip Hughes

TPP Approach to *Plasmodium* Target ID



BioRender
Figure inspired by Mateus & Kurzawa et al *Mol Syst Biol* 2020

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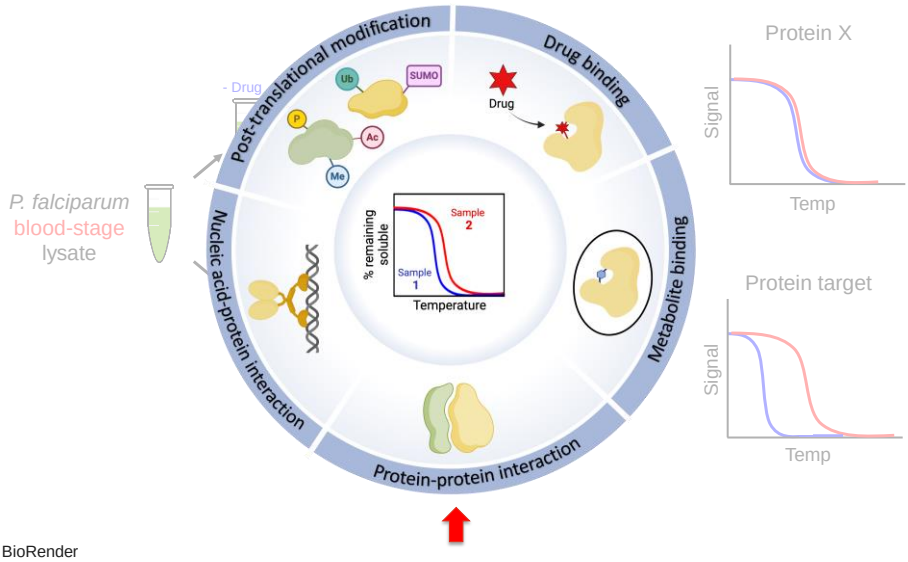
TPP Approach to Reveal Protein Interactions



BioRender
Figure inspired by Mateus & Kurzawa et al *Mol Syst Biol* 2020

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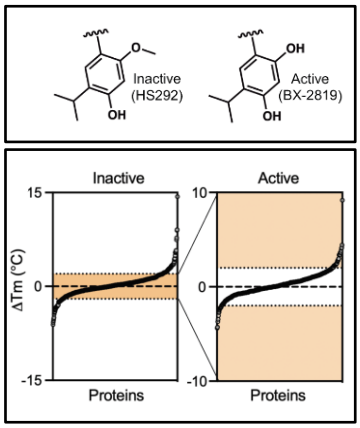
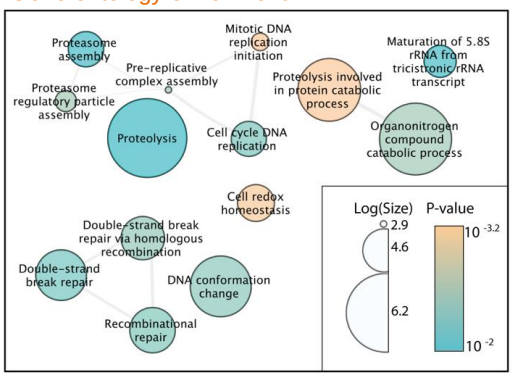
TPP Highlights Putative *Pf*Hsp90 Interactors

Interrogating specific perturbations from *Pf*Hsp90 inhibition



Gene ontology enrichment



GO analysis for biological process conducted in PlasmoDB and REVIGO

Collaboration with Prof. Fitzgerald (Duke)

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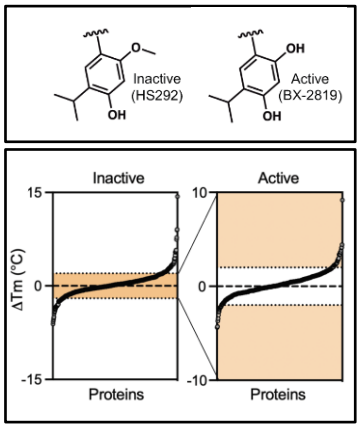
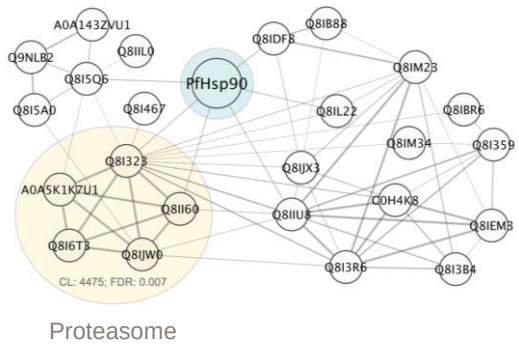
TPP Highlights Putative *Pf*Hsp90 Interactors

Interrogating specific perturbations from *Pf*Hsp90 inhibition



Predicted interaction network



Proteasome

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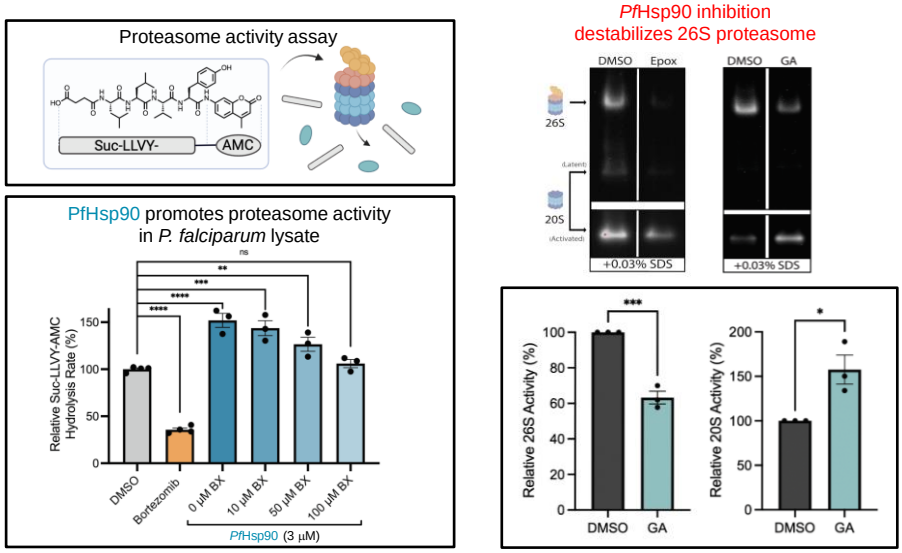
*Pf*Hsp90 Chaperones the 26S Proteasome



Mansfield et al *Cell Chem Bio* 2024

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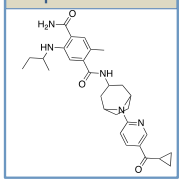
Targeting Essential Parasite Proteins

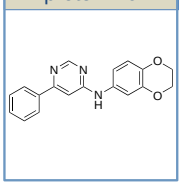
Screening and affinity-based chemoproteomics reveal protein function and structure

Heat shock protein 90



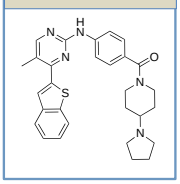
Mansfield el al *Cell Chem Bio* 2024

Heat shock protein 70



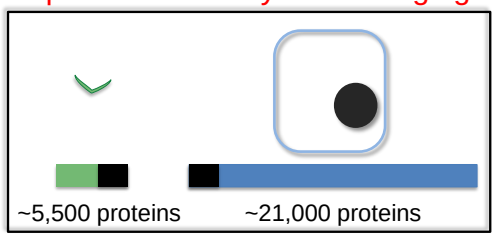
Keeler et al *unpublished*

Protein kinase 6

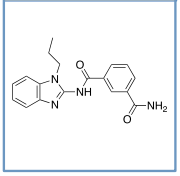


Galal et al *J Med Chem* 2022

Species selectivity is challenging



Protein kinase 9



Totzke et al *Cell Chem Bio* 2017
Raphemot et al *Cell Chem Bio* 2019

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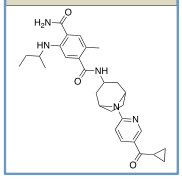
Targeting Essential Parasite Proteins

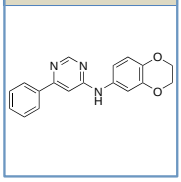
Screening and affinity-based chemoproteomics reveal protein function and structure

Heat shock protein 90



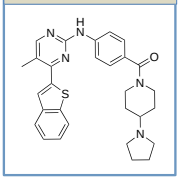
Mansfield el al *Cell Chem Bio* 2024

Heat shock protein 70



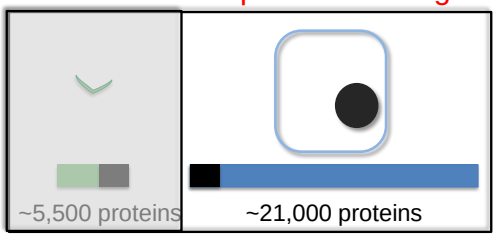
Keeler et al *unpublished*

Protein kinase 6



Galal et al *J Med Chem* 2022

Embrace human proteins as targets

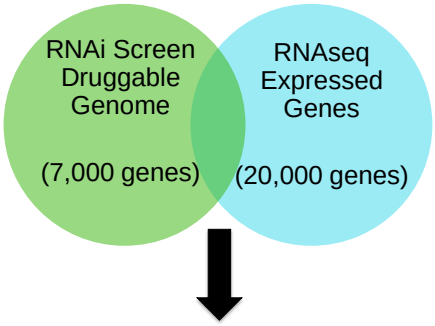


Reveal host processes essential to *Plasmodium*

Systematic Approaches to Uncover Host Processes

Dr. Rene Raphemot

Dr. Maria Toro Moreno



Host Factors Important to *Plasmodium*

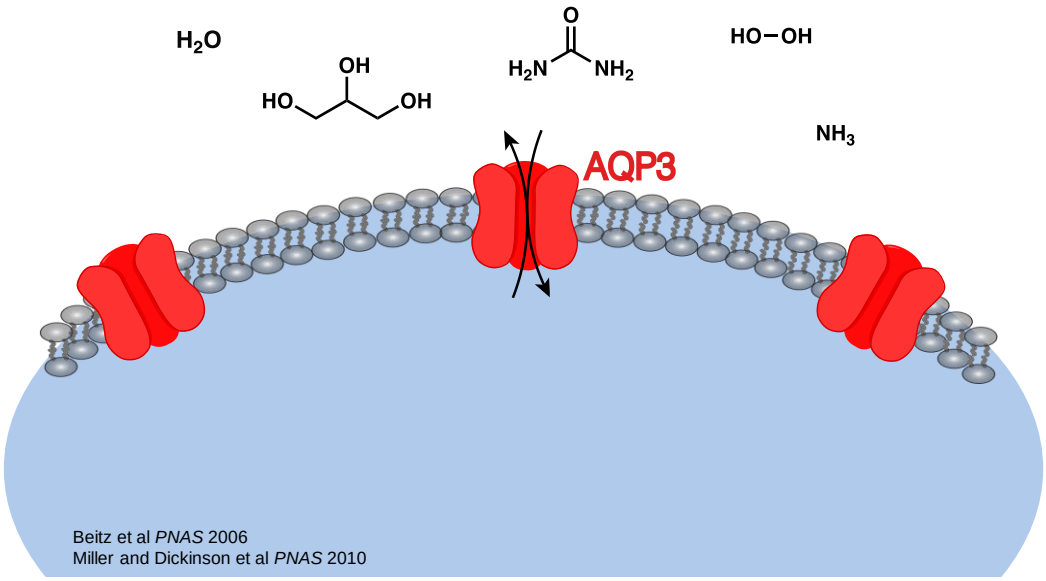
Dr. Dora Posfai

Dr. Kayla Sylvester

Raphemot & Toro-Moreno et al *Cell Chem Bio* 2019

Posfai et al *Plos Pathogens* 2018

Aquaporin 3 is Upregulated During Infection



Beitz et al *PNAS* 2006
Miller and Dickinson et al *PNAS* 2010

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Aquaporin 3 is Upregulated During Infection

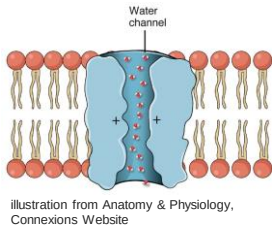
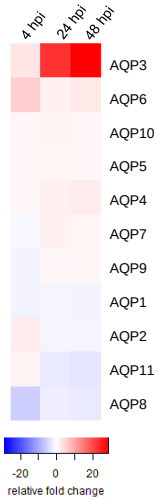
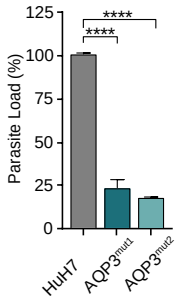


illustration from Anatomy & Physiology, Connexions Website

AQP3 is not generally expressed in hepatocytes



CRISPR disruption AQP3 inhibits *Plasmodium*



Collaboration with Prof. Sandeep Dave (Duke) and Dr. Dr. Anupama Reddy

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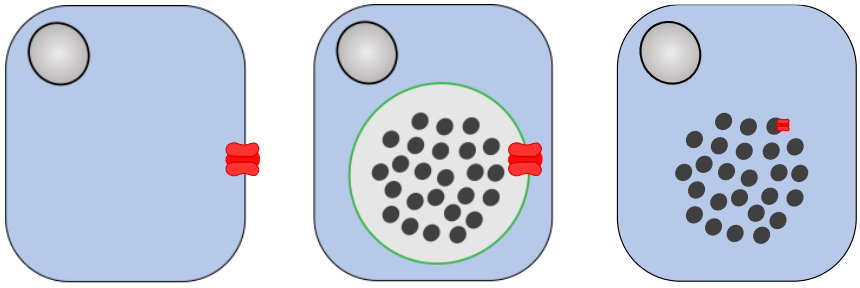
Where Does AQP3 Localize During Infection?

Parasitophorous vacuole membrane (PVM) interface that protects parasite



Host Cell Membrane | Host-Parasite Interface | Parasite Cell Membrane

1 **2** **3**

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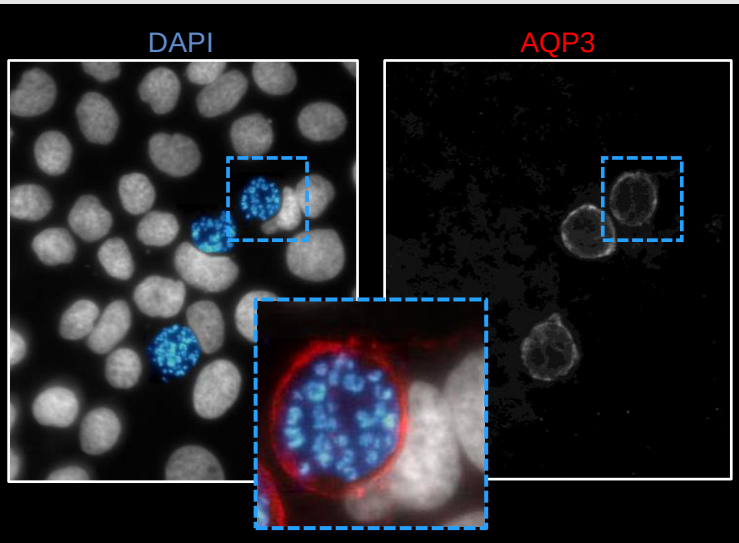
AQP3 Localizes to Parasitophorous Vacuole



Recruitment to parasite occurs 24-28 hpi

Posfai et al *Plos Pathogens* 2018

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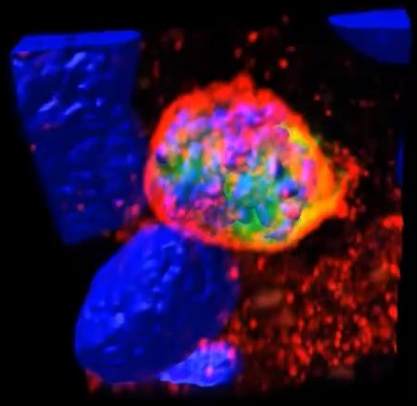
AQP3 Localizes to Parasitophorous Vacuole



Nuclei
*Hs*AQP3
*Pb*Hsp70

Recruitment to parasite occurs 24-28 hpi

Posfai et al *Plos Pathogens* 2018

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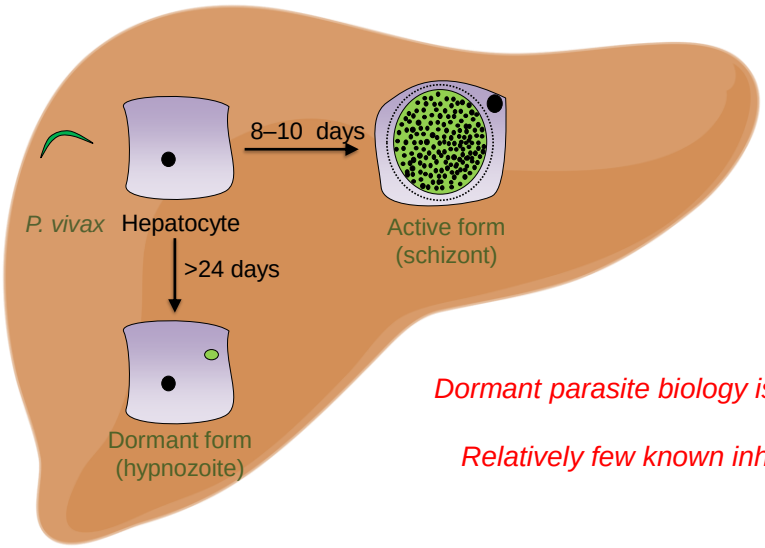
Dormant Liver Stage

P. vivax dormant forms cause disease <u>months</u> after exposure



Dormant parasite biology is elusive

Relatively few known inhibitors

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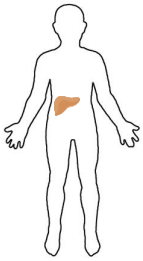
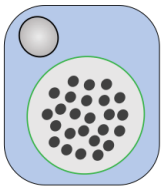
Challenges of Liver Stage Research



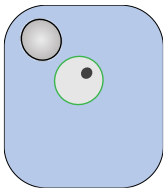
Primary Human Hepatocytes

P. vivax-Infected Mosquitoes

Active



Dormant



P. vivax-Infected Hepatocytes

Roth et al *Nat Comms* 2018

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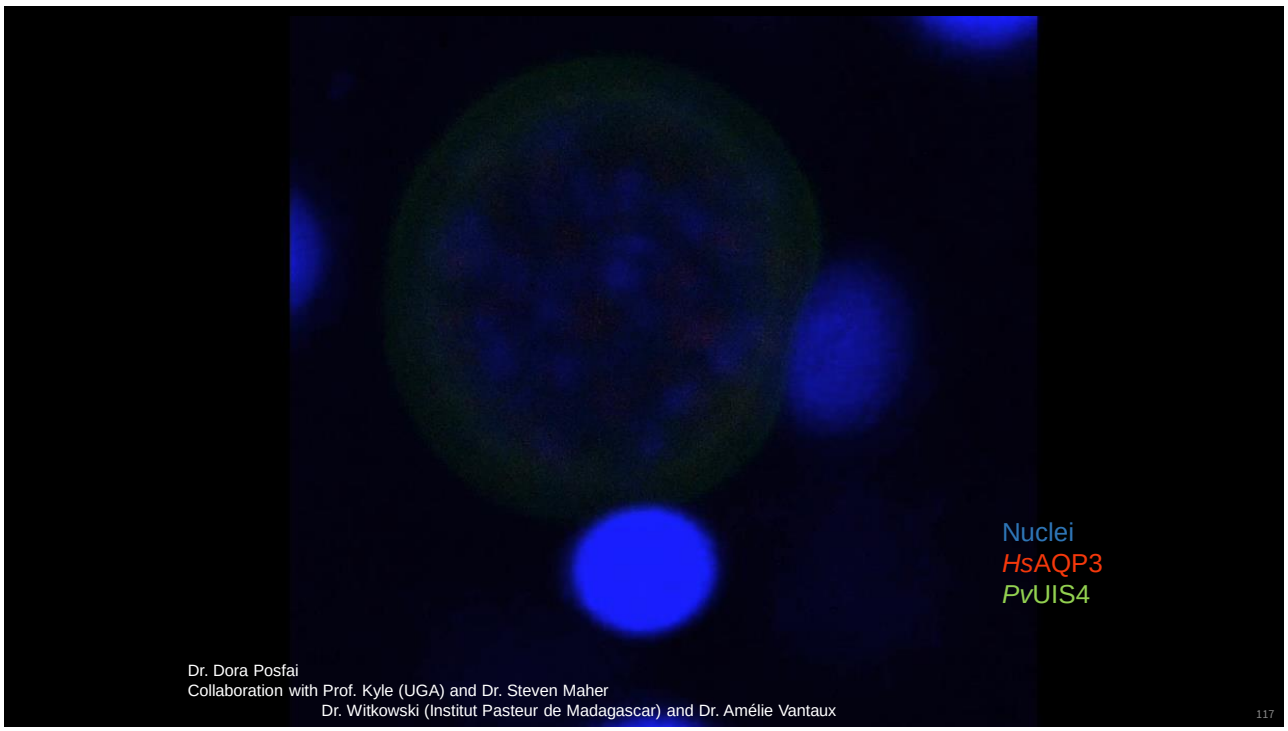

Dr. Dora Posfai
Collaboration with Prof. Kyle (UGA) and Dr. Steven Maher
Dr. Witkowski (Institut Pasteur de Madagascar) and Dr. Amélie Vantaux

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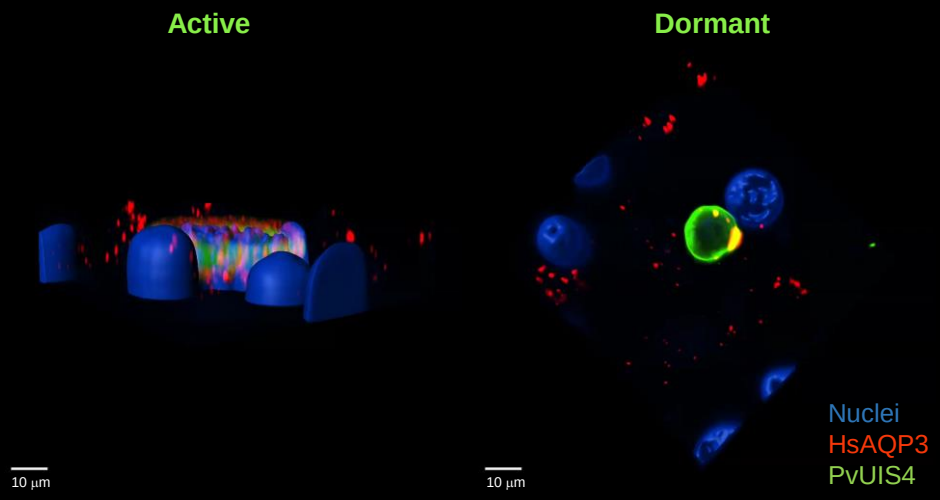
Differential Recruitment to Active vs Dormant Forms



What is the function of AQP3?

Posfai & Maher et al *Cell Chem Bio* 2020

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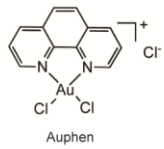
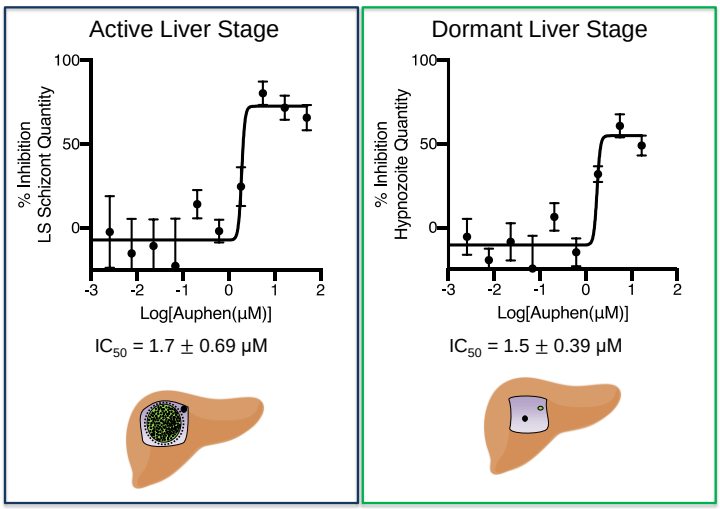
Auphen Inhibits *P. vivax* Liver Stages

AQP3 Inhibitor (glycerol flux)





Auphen inhibits *P. vivax* active and dormant forms

Collaboration with Prof. Kyle (UGA) and Dr. Witkowski (Institut Pasteur de Madagascar)

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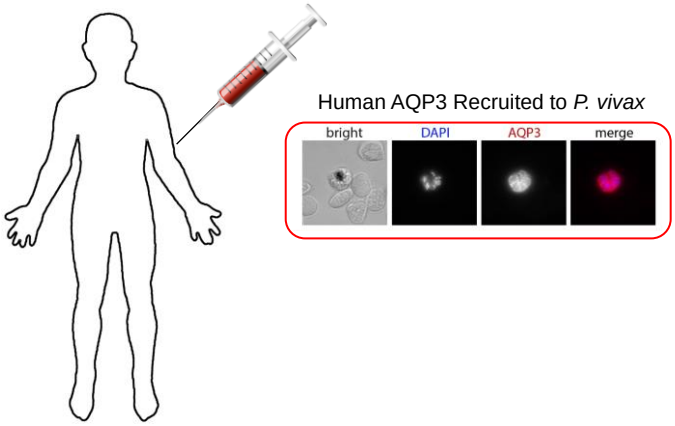
Does Auphen Inhibit Blood Stage *P. vivax?*



Posfai & Maher et al *Cell Chem Bio* 2020

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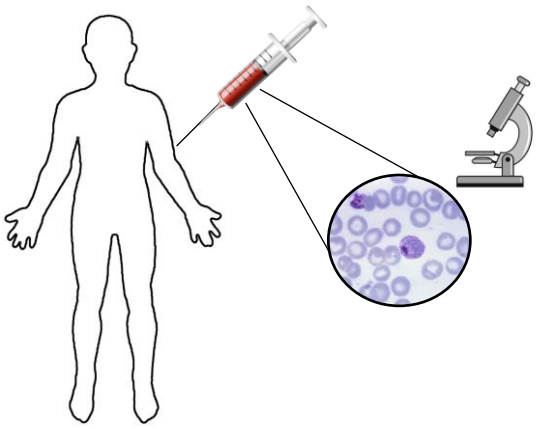
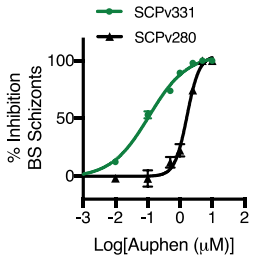
Auphen Inhibits Blood Stage *P. vivax*





Isolates ID	EC_{50} (μM)
SCPv280	1.6 ± 0.24
SCPv341	1.6 ± 0.53
SCPv443	1.5 ± 0.40
Kim102	0.94 ± 0.25
SCPv339	0.57 ± 0.096
SCPv367	0.53 ± 0.23
SCPv328	0.42 ± 0.18
SCPv452	0.24 ± 0.061
Kim100	0.18 ± 0.046
SCPv331	0.097 ± 0.012

Dr. Amélie Vantaux
Posfai & Maher et al *Cell Chem Bio* 2020

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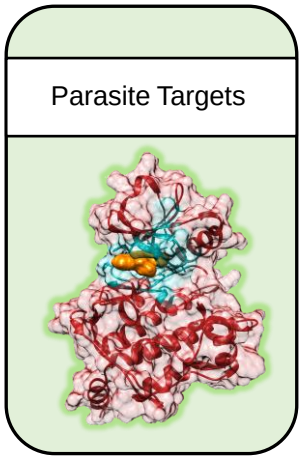
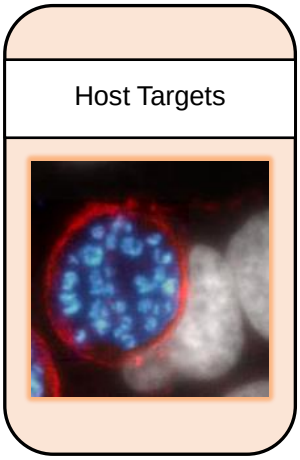
Chemical Biology of Parasites





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The Team

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Dr. Jack Ganley (Princeton)
Dr. Maria Toro Moreno (FHCC)
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Dr. Hannah D'Ambrosio (Moderna)
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Dr. Aaron Keeler
Dr. Chris Mansfield
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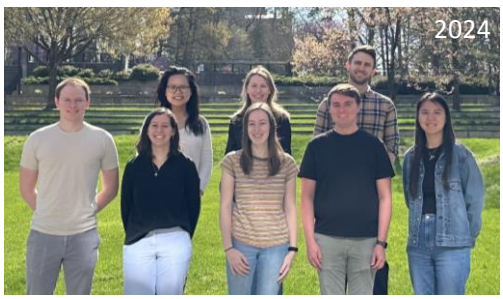
Daniel Ryan (NIH)
Tamanna Srivastava (UPenn)
Grace Wang (Caltech)
Kaitie Choe
Elizabeth Boger
Porter Petruziello
Isabel Colon
Xeno Hu



Duke University
Prof. Michael Fitzgerald
Dr. Baiyi Quan

Prof. Tim Haystead
Dr. Philip Hughes

Prof. Sandeep Dave
Dr. Anupama Reddy

USF
Prof. James Leahy
Dr. Benjamin Eduful

UGA
Prof. Dennis Kyle
Dr. Steven Maher

Institut Pasteur de Madagascar
Dr. Benoit Witkowski
Dr. Amélie Vantaux

Light Microscopy Core
(Dr. Lisa Cameron)
SporoCore, UGA
(Dr. Ash Pathak)

Funding
R01AI173295, R01AI173042, R21AI174151, R44AI150237,
Sloan Foundation, Camille Dreyfus Foundation, Duke University

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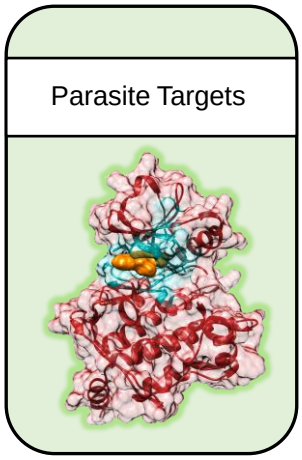
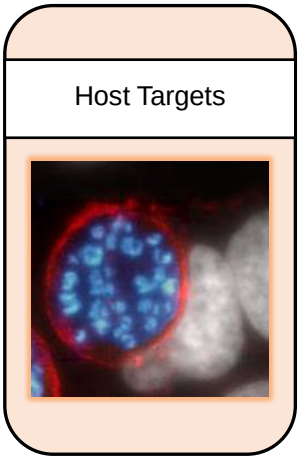
Questions?





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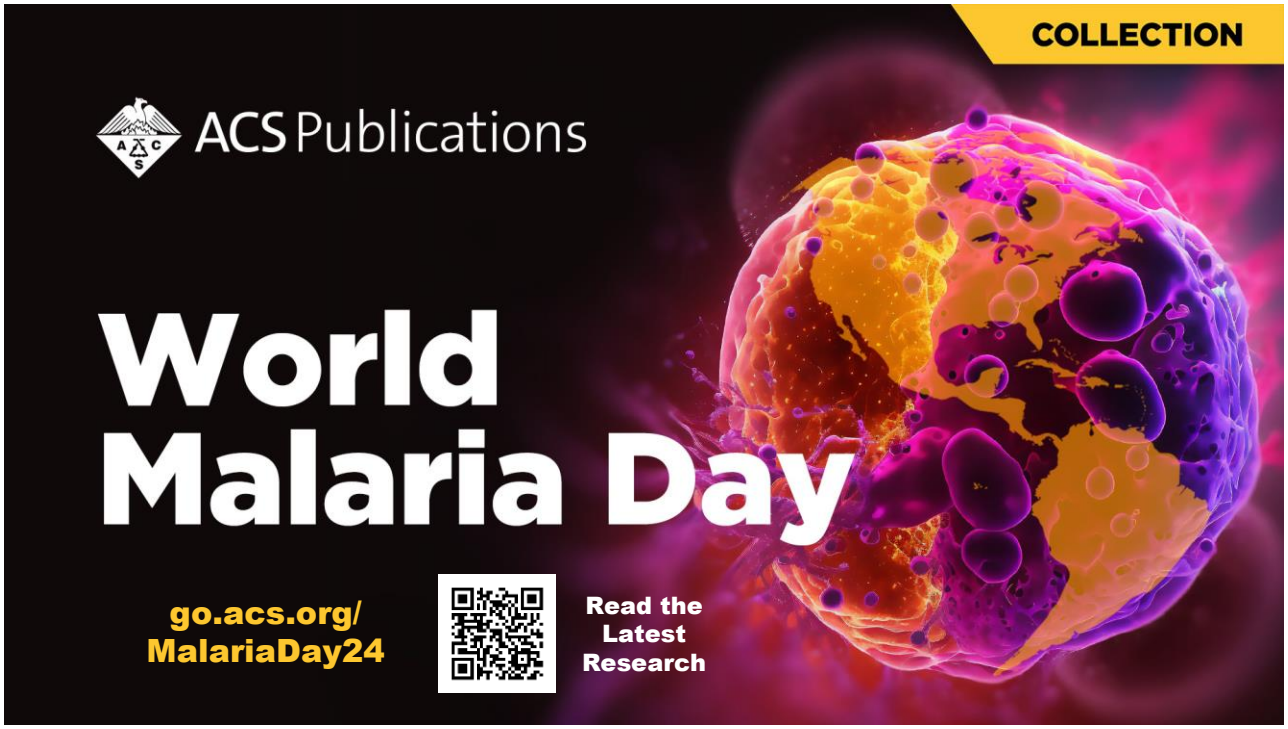

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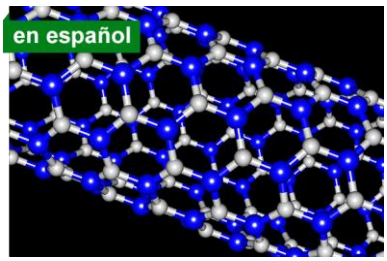
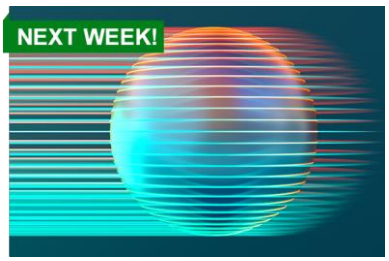


Wednesday, May 1, 2024| 3pm-4pm ET

La Creación de Materiales Macroscópicos a Través del Ensamblaje de Nanotubos de Nitruro de Boro

Co-produced with the Sociedad Química de Mexico



Thursday, May 2, 2024| 2pm-3:30pm ET

Better Biodegradable Vinyl Polymer Materials by Improving Radical Ring-Opening Polymerization (rROP)

Co-produced with ACS Division of Polymer Chemistry

Wednesday, May 8, 2024| 2pm-3:30pm ET

How Nanoscale Materials in Biosensors are Innovating Health from Concept to Care

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