Open Innovation and MoA Tools for Kinetoplastids and Antimalarial Drug Discovery

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FiS_NeglectedDiseases
Sao Paulo, Nov 14th, 2014

Agenda

- DDW focused research in diseases of the developing world
- Three different units and models sharing a common goal
- Strategy of Kinetoplastids Discovery Unit
- Objectives of Malaria DPU
- Mode of action tools to identify differentiated antimalarials
- Case study: result of strategy

"All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EU and the GSK Policy on the Care, Welfare and Treatment of Animals."

Tres Cantos Medicines Development Campus

DDW: One site and three DPUs with different business model

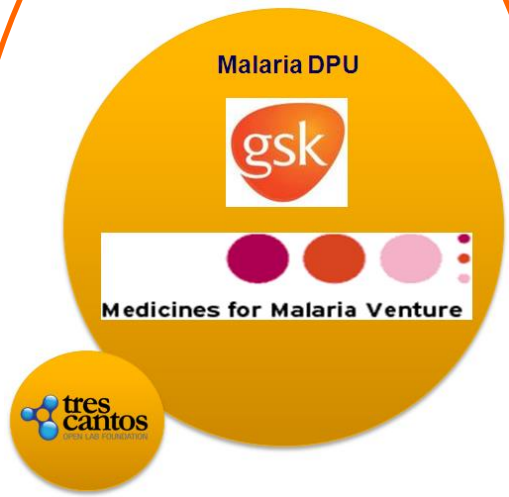
Kineto DPU

- Virtual unit acting as catalyst
- Untapped area where DDW can add value
- Key partnerships formed

TB DPU

- Partnerships formed place GSK at the cutting edge of TB research
- Pooling of TB expertise through collaborative consortia

Malaria DPU



- GSK has world class malaria research capability
- Scientific advances have provided new opportunities
- Key strategic partnership with MMV

Kinetoplastids DPU – Strategy

•Through a virtual model, act as a catalyst to discover medicines in Sleeping Sickness, Chagas Disease and Leishmaniasis

Build a Sustainable Pipeline	Fill Scientific capability gaps	Partnership model
•Focus Lead ID through phenotypic assays •Target-based approach opportunistically (Open lab) • BD • Repositioning	• Focus on scientific needs and tools for DD. • In vitro assays • Translational studies; animal models; PK/PD • Biomarkers, diagnostic, etc • MoA, etc	• Partners bring parasite and disease expertise. • GSK brings Drug Discovery expertise

Kinetoplastids DPU: Kinetoplastid-Porfolio Highlights

1.
- GSK (HTS GSK Comp. Coll.)
- NYU (HTS GSK Comp. Coll.)
- GSK (HTS GSK Comp. Coll.)

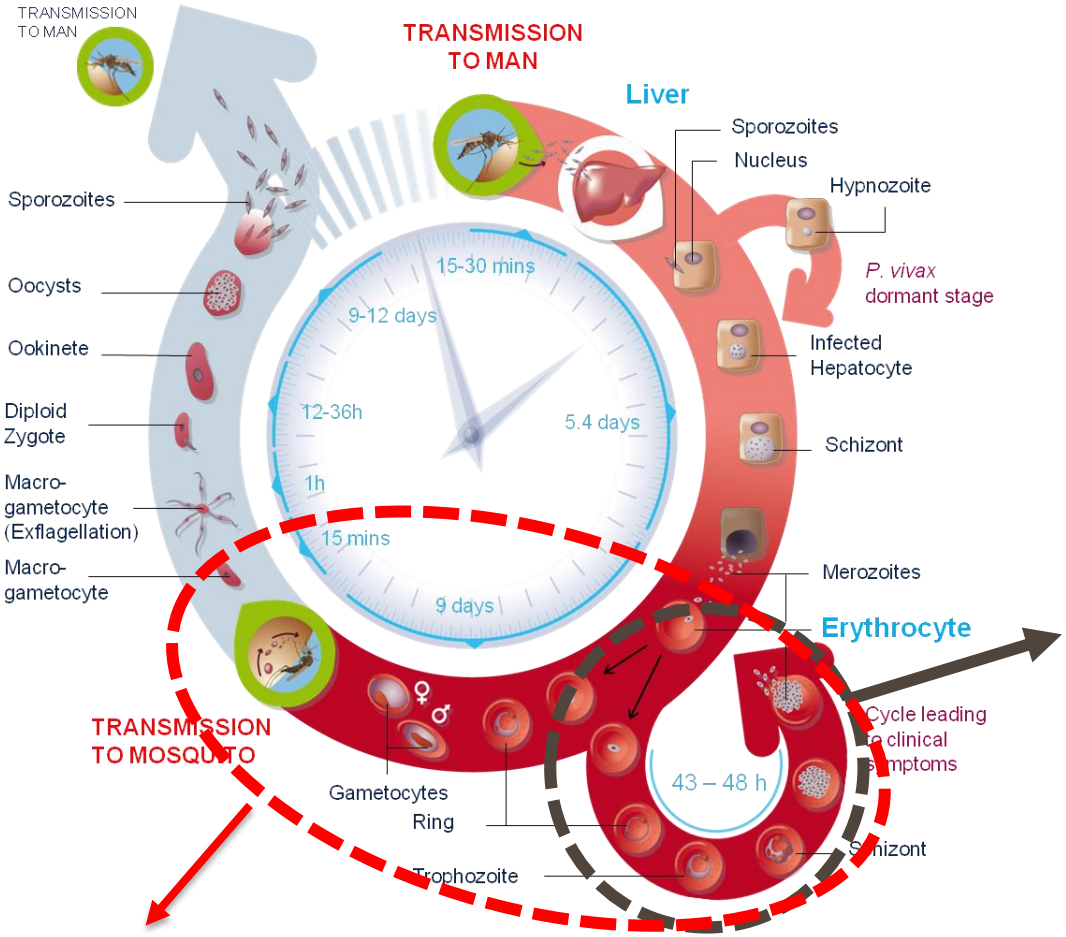
2.
- New chemical diversity (HTS Efforts)

3.
- DNDi (3 Series)
- Wellcome T. DD Engine (1 Series)
- Dundee DDU / Wellcome T (3 series).
- Dundee DDU / Wellcome T. (2 series)
- Wellcome T. DD Engine (1 series)

4.
- Dundee DDU / Wellcome T.
- Dundee DDU / Wellcome T.
- Wellcome T. DD Engine

- Leishmaniasis
- Chagas Disease
- Sleeping Sickness
- Multiple Diseases

Malaria DPU: identifying differentiated antimalarials



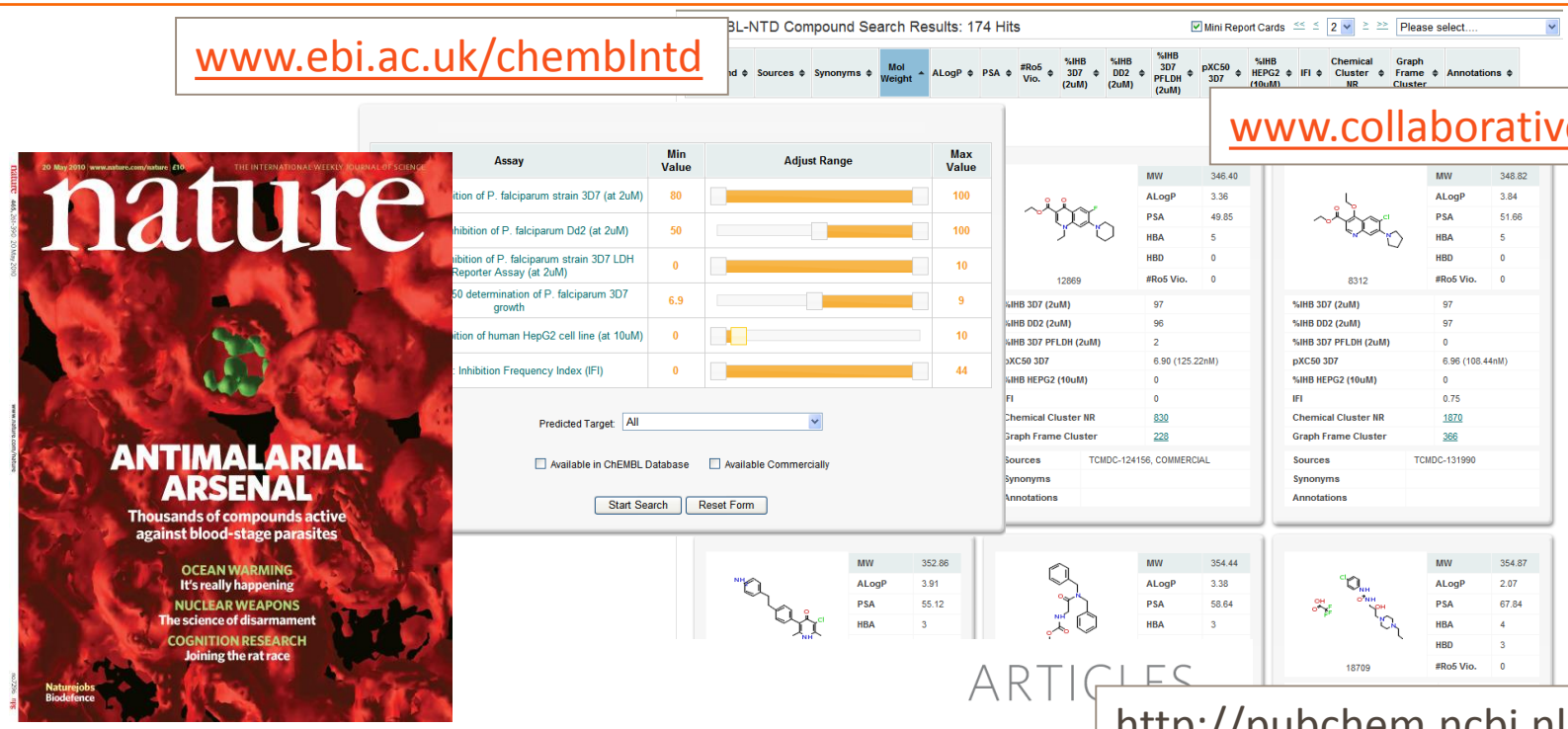
Deliver next generation of fast-acting antimalarials to deliver new front-line treatment options and mitigate the risk that ACTs become compromised

Deliver a new class of dual acting antimalarial drugs that are schizontocidal and eliminate mature gametocytes resulting in the blockade of transmission

Phenotypic screening as main source of antimalarial hits

TCAMS: 13,500 hits publicaly available

www.ebi.ac.uk/chemblntd



www.collaborativedrug.com

http://pubchem.ncbi.nlm.nih.gov/

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Thousands of chemical starting points for antimalarial lead identification

Francisco-Javier Gamo[1], Laura M. Sanz[1], Jaume Vidal[1], Cristina de Cozar[1], Emilio Alvarez[1], Jose-Luis Lavandera[1], Dana E. Vanderwall[2], Darren V. S. Green[3], Vinod Kumar[4], Samiul Hasan[4], James R. Brown[4], Catherine E. Peishoff[5], Lon R. Cardon[6] & Jose F. Garcia-Bustos[1]

Malaria is a devastating infection caused by protozoa of the genus *Plasmodium*. Drug resistance is widespread, no new chemical class of antimalarials has been introduced into clinical practice since 1996 and there is a recent rise of parasite strains with reduced sensitivity to the newest drugs. We screened nearly 2 million compounds in GlaxoSmithKline's chemical library for inhibitors of *P. falciparum*, of which 13,533 were confirmed to inhibit parasite growth by at least 80% at 2 μM concentration. More than 8,000 also showed potent activity against the multidrug resistant strain Dd2. Most (82%) compounds originate from internal company projects and are new to the malaria community. Analyses using historic assay data suggest several novel mechanisms of antimalarial action, such as inhibition of protein kinases and host–pathogen interaction related targets. Chemical structures and associated data are hereby made public to encourage additional drug lead identification efforts and further research into this disease.

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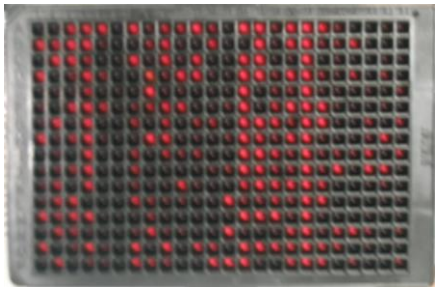
Sharing of TCAMS across the malaria community



Imperial College London

Institut Pasteur Korea

HARVARD MEDICAL SCHOOL

FIAT LUX Walter+Eliza Hall Institute of Medical Research

University of Dundee

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STUDIUM GENERALE CIVITATIS PERUSII A.D. MCCCVIII

JOHNS HOPKINS MEDICINE

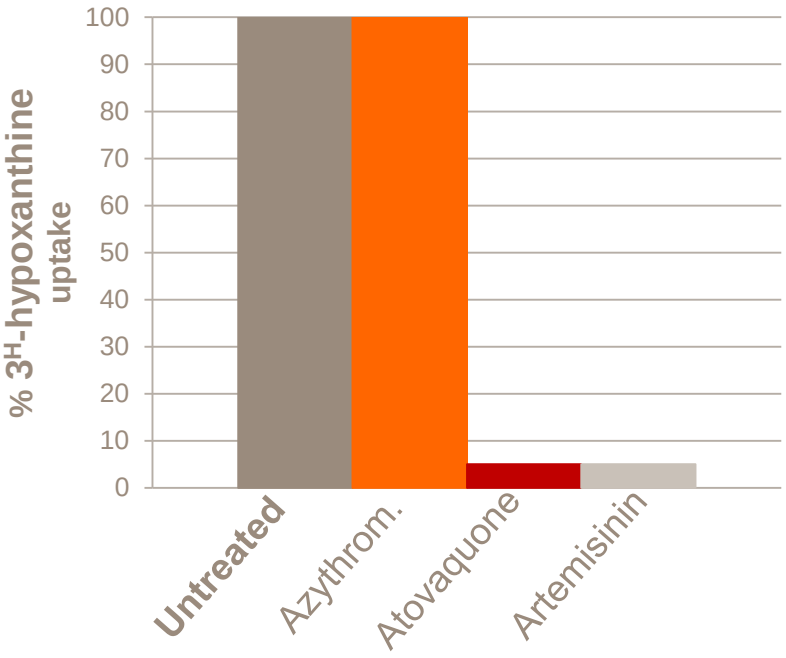
MONASH University

UNIVERSITY OF WASHINGTON 1861

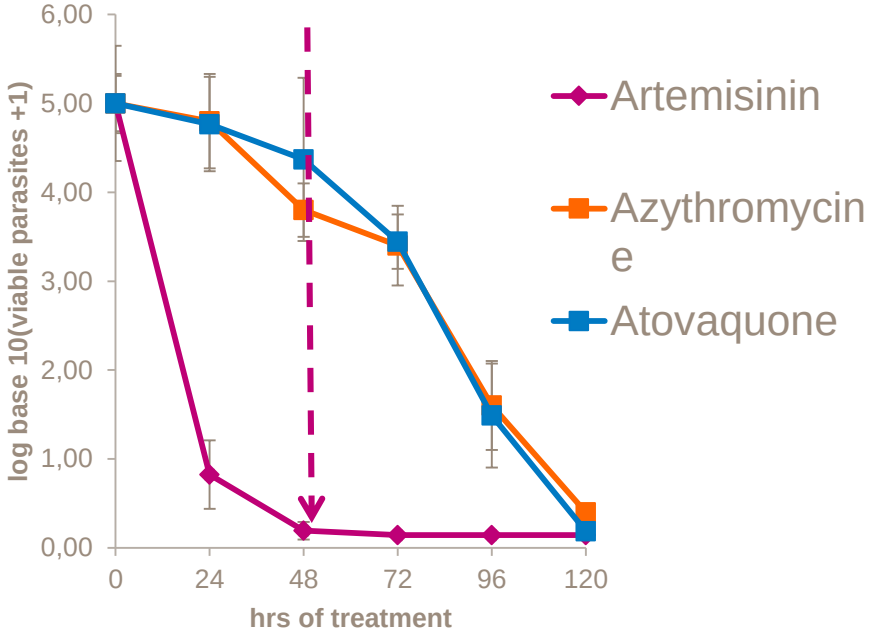
Griffith UNIVERSITY

Killing rates determination to prioritize fast acting compounds

48h treated parasites at 10xIC$_{50}$

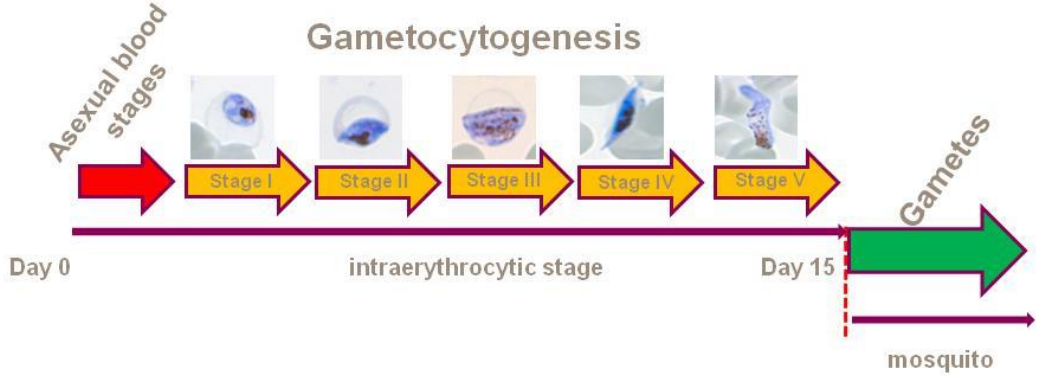


Parasites viability at 10xIC$_{50}$



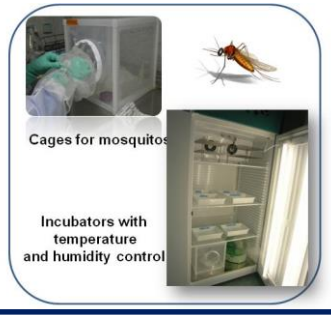
- Metabolism is not a good surrogate of parasite viability
  - Growth stopped but viable parasite and viceversa

Transmission blocking assays to prioritize gametocytocidal compounds



- Gametocytocidal activity needed for malaria eradication
- Assay for activity against mature gametocytes in place

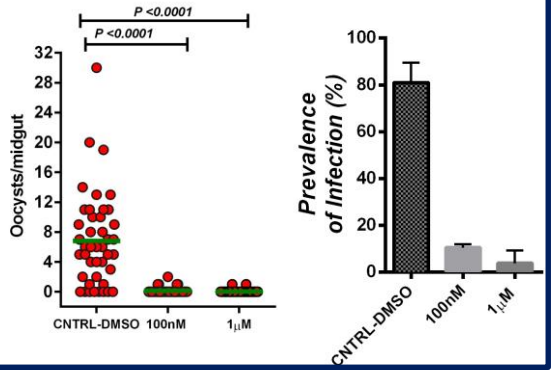
- Fully operational *in-house* insectary to validate TrB potencial



SMFA

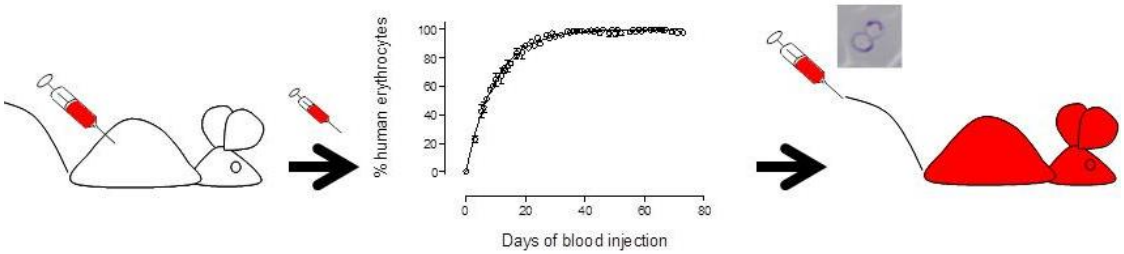
Mosquito feeding
Infection of *A. stephensi* mosquitoes

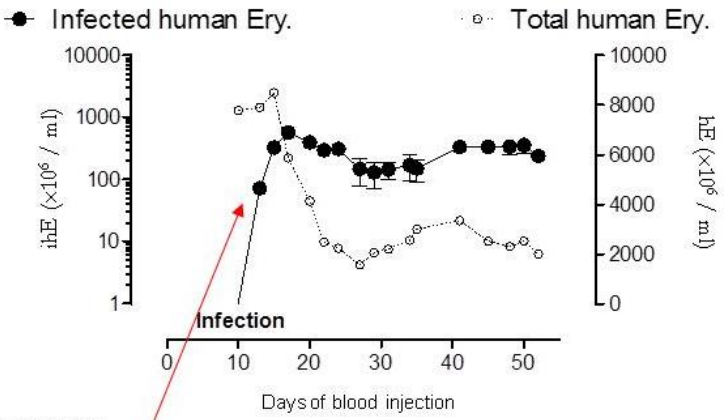
Decapitation, dissection and oocysts counting

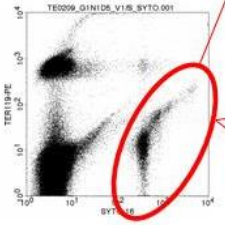


P. falciparum murine malaria model

Working with the human pathogen

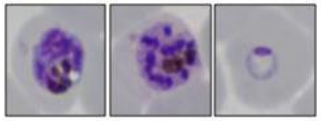


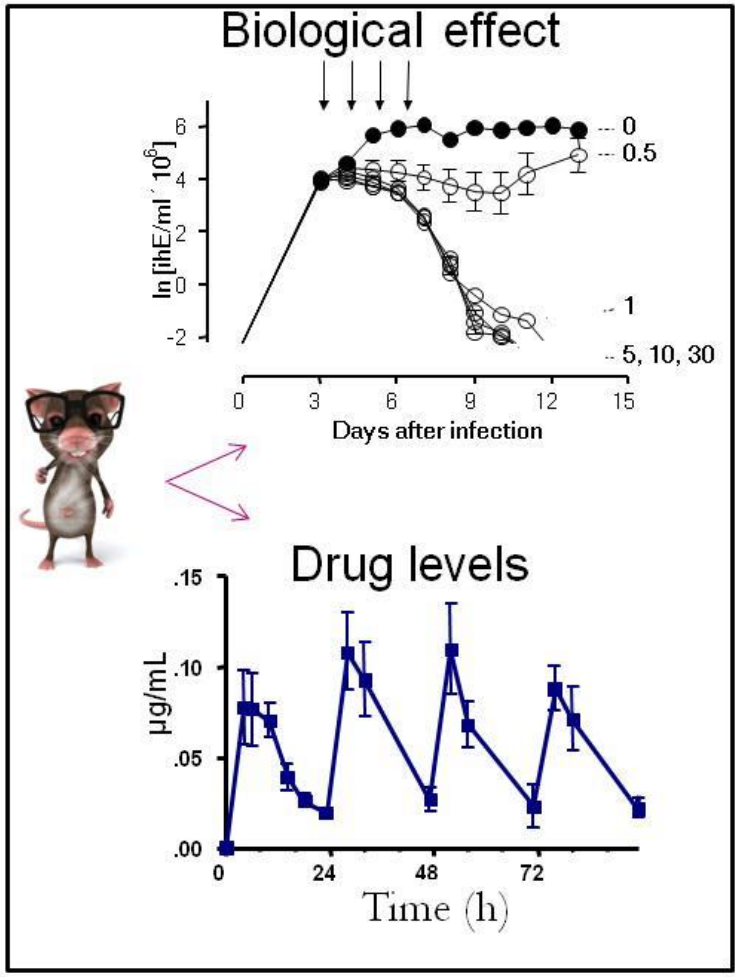




Not synchronized

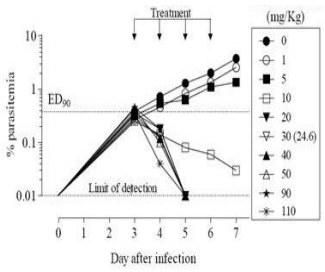
All erythrocytic stages



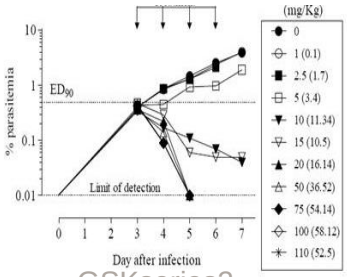


Strategy is being successful

Fast acting and TrB potential embedded in the same molecule



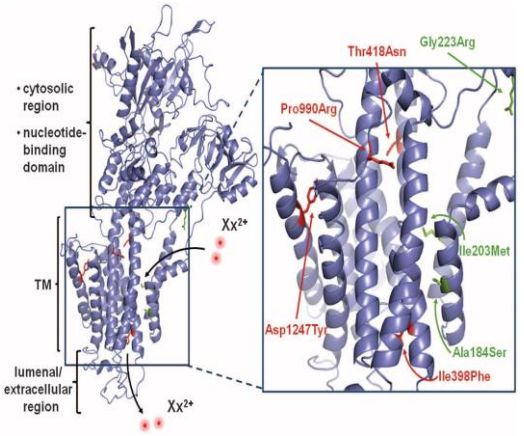
GSKseries1



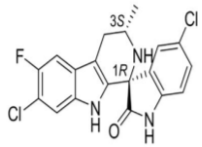
GSKseries2

- Target ID efforts to assist lead optimization program
- Linkable analogs designed for proteomic approach
  - Pull down experiments ongoing
- Genomic approach selected resistant mutants for both series
  - Sequencing has revealed mutations in PFL0590c *locus*

- PFL0590c locus encodes **PfATP4** (P-type ATPase4)
- First described by Novartis as causing resistance to spiroindolone NITD 609
- Additional chemotypes displaying cross-resistance with PfATP4-R mutants



Science. 2010 September 3; 329(5996): 1175–1180.



spiroindolone

- Multiple chemotypes sharing same mechanism of resistance

Thank you