RUTGERS
THE STATE UNIVERSITY
OF NEW JERSEY

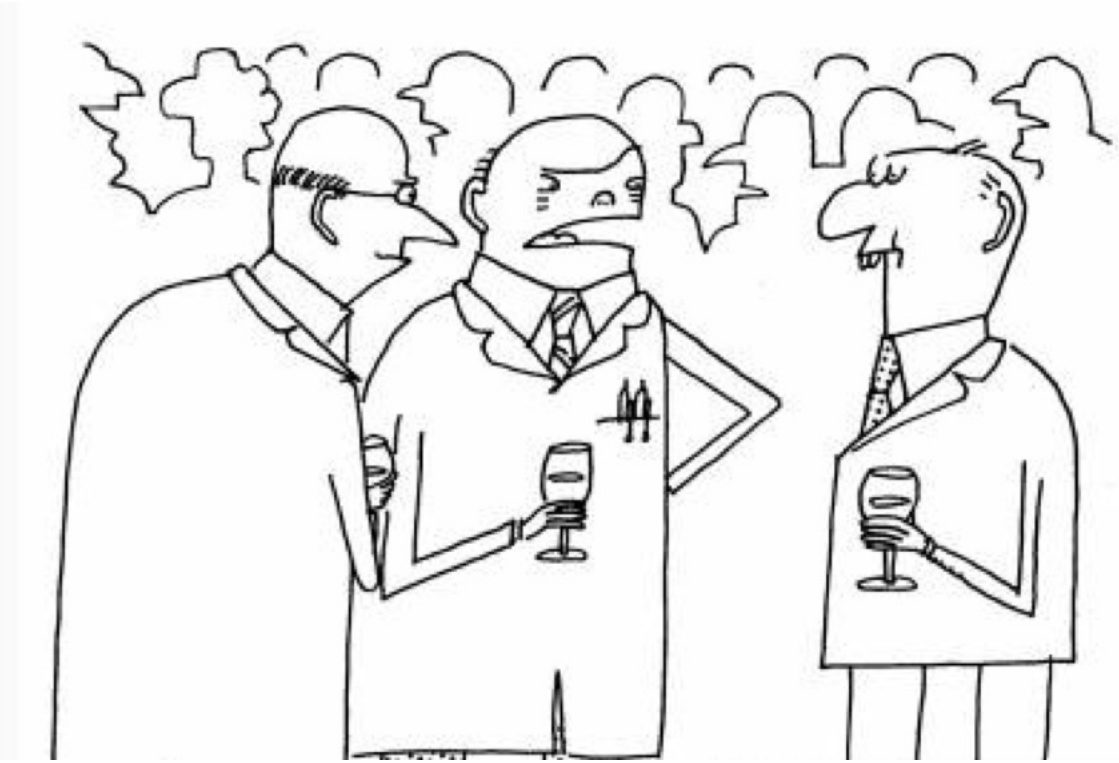
Multilateral modes of drug development: An antimalarial success story

Presentation to First Year Grad Students

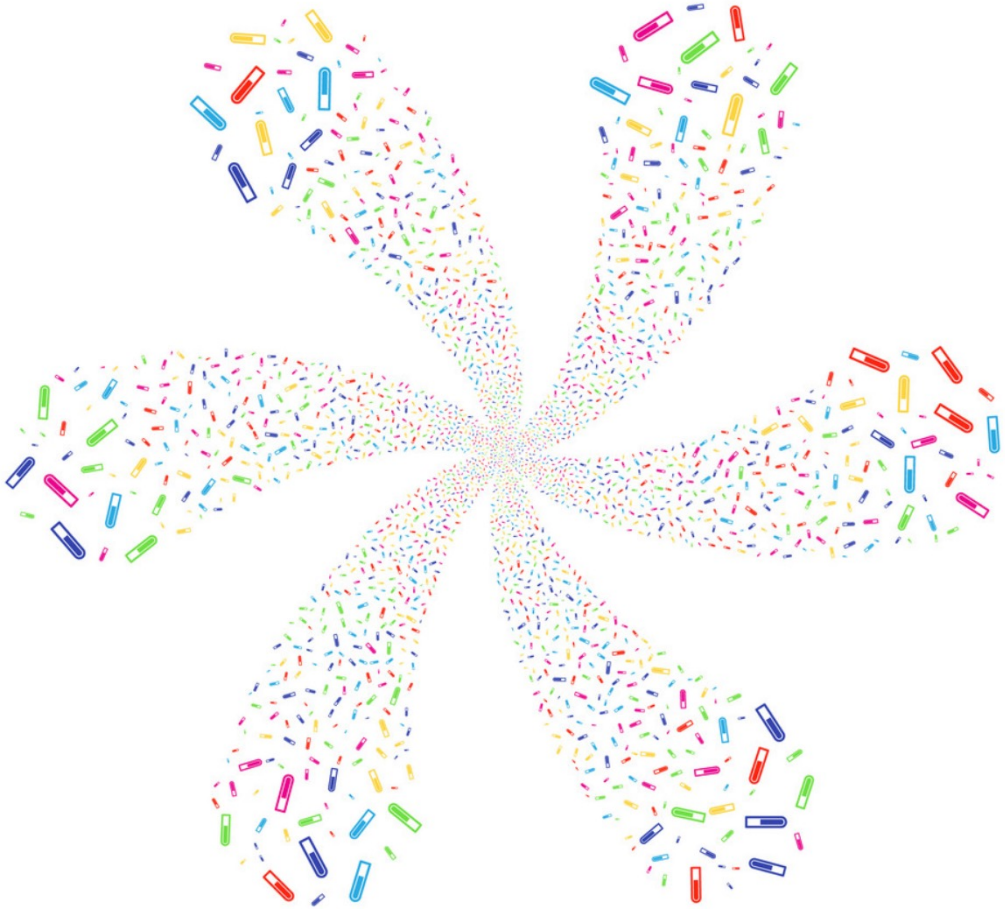
February 23, 2024

Prof. Spencer Knapp
Rutgers University
Department of Chemistry & Chemical Biology

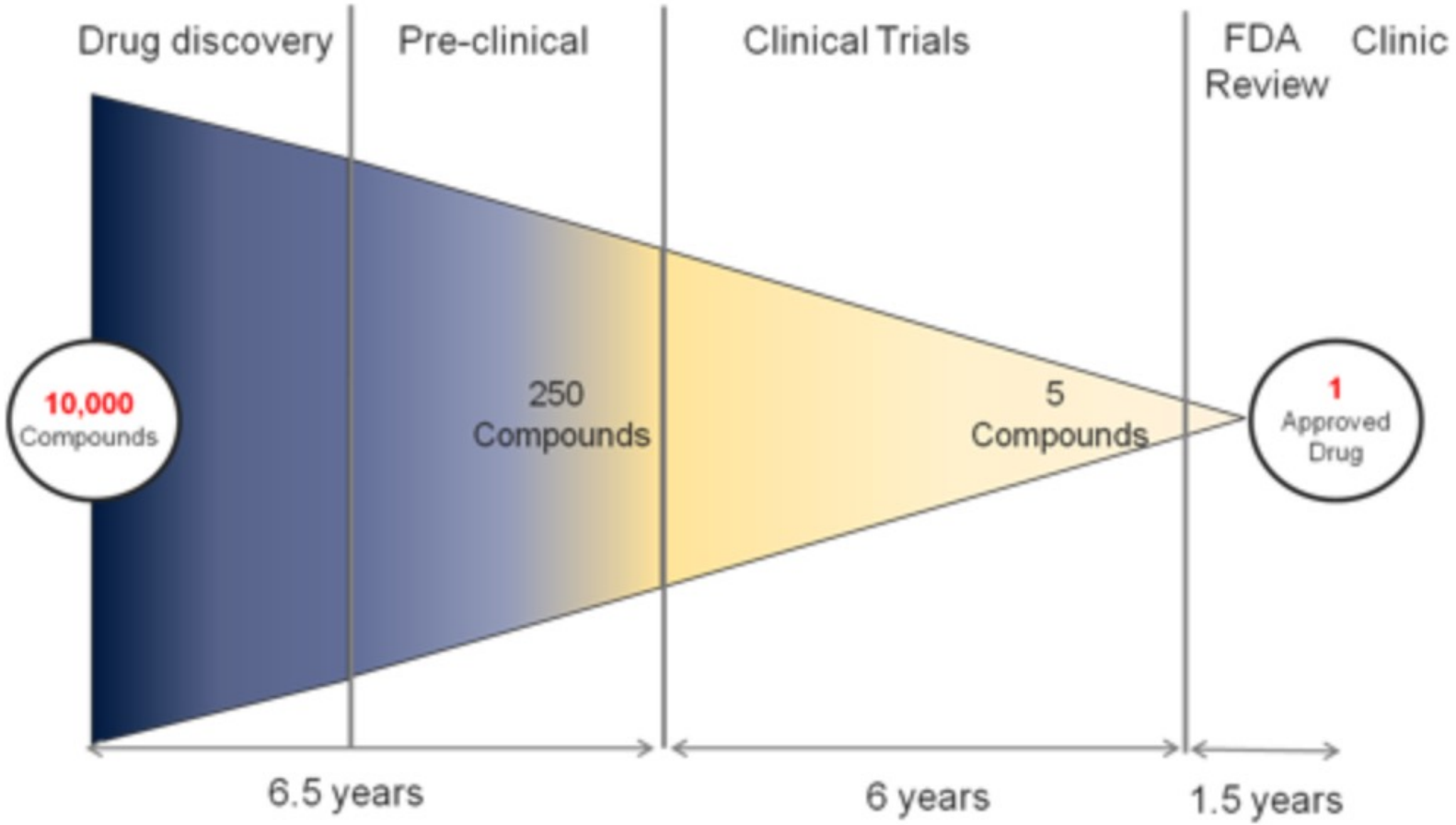
DRUG DEVELOPMENT



WHEN WE SAY "IT'S NOT ROCKET SCIENCE", WE MEAN IT'S SOMETHING FAR MORE COMPLICATED.

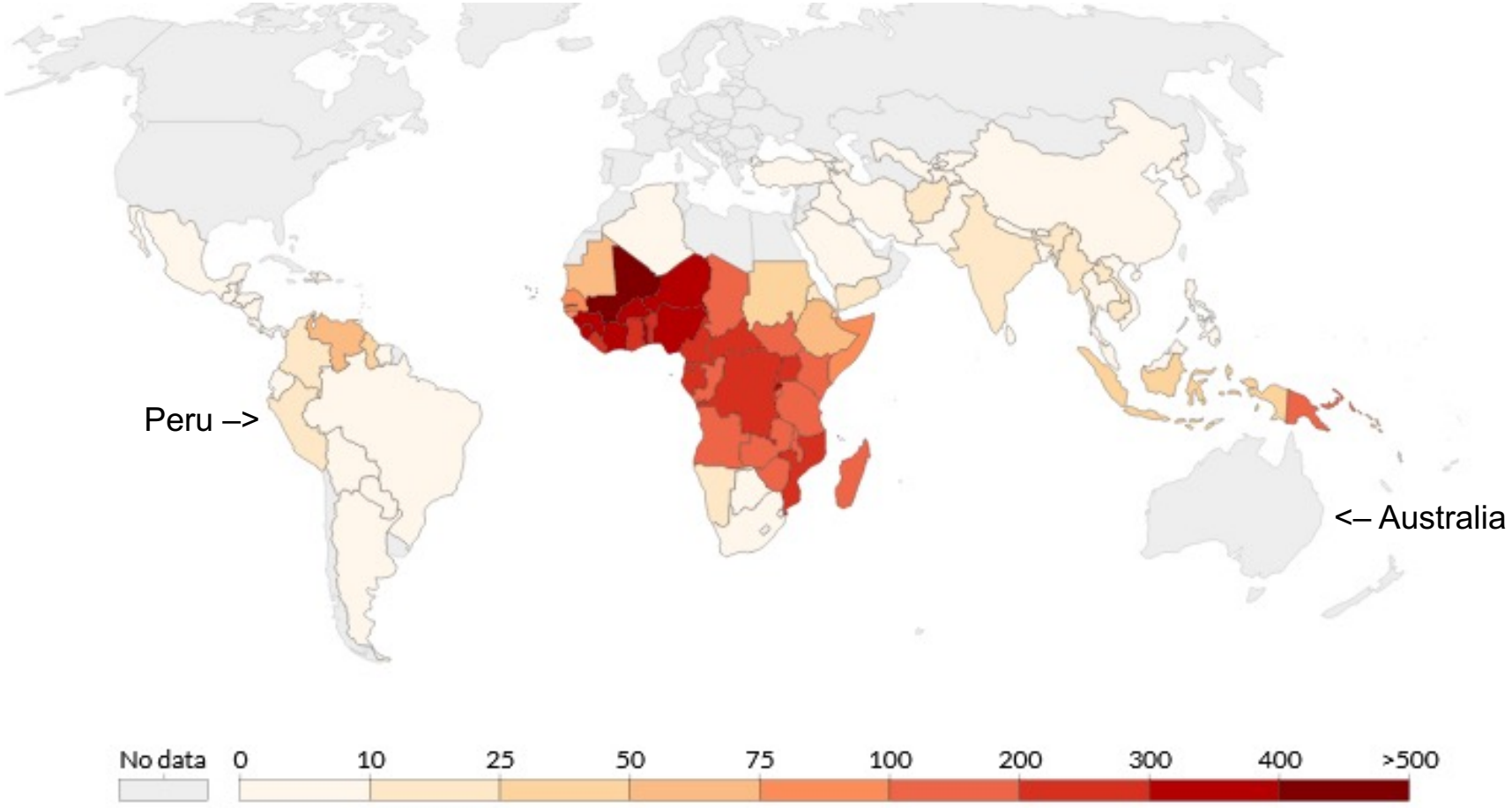


Typical investment for a new drug



Average cost: > 1 $billion

Malaria persists as a wide spread plague



Global malaria deaths per 100K people in 2017 (IHME)

Global malaria burden

- 3 billion people at risk
- ~ 247 million cases per year (WHO, 2021)
- ~ 619,000 annual deaths (WHO, 202)
- 67% of those who die are under the age of 5
- ~20% of child deaths in Africa are caused by malaria
- One child dies every minute

New York Times
November 19, 2018

GLOBAL HEALTH

The Fight Against Malaria Has Reached a Standstill

Deaths from the disease plummeted from 2000 to 2013, but are now stuck at over 400,000 a year. Donor giving is flat, and some countries are not doing enough to protect their citizens.

A mother mourned her six-month-old daughter in Banki, Nigeria, who succumbed to malaria. Nigeria has a quarter of all the world's malaria cases. Jane Hahn for The Washington Post, via Getty Images

By Donald G. McNeil Jr.

Nov. 19, 2018

Progress against malaria has stalled, and the disease remains a significant threat to billions of people despite the expensive, decades-long efforts to contain it, the World Health Organization reported on Monday.

New antimalarials

Coartem® *Dispersible*
Novartis
ARTEMETHER-LUMEFANTRINE

Artesun®
Guilin Pharmaceutical
ARTESUNATE

ASMQ
Cipla
ARTESUNATE-MEFLOQUINE

Krintafel
GlaxoSmithKline
TAFENOQUINE

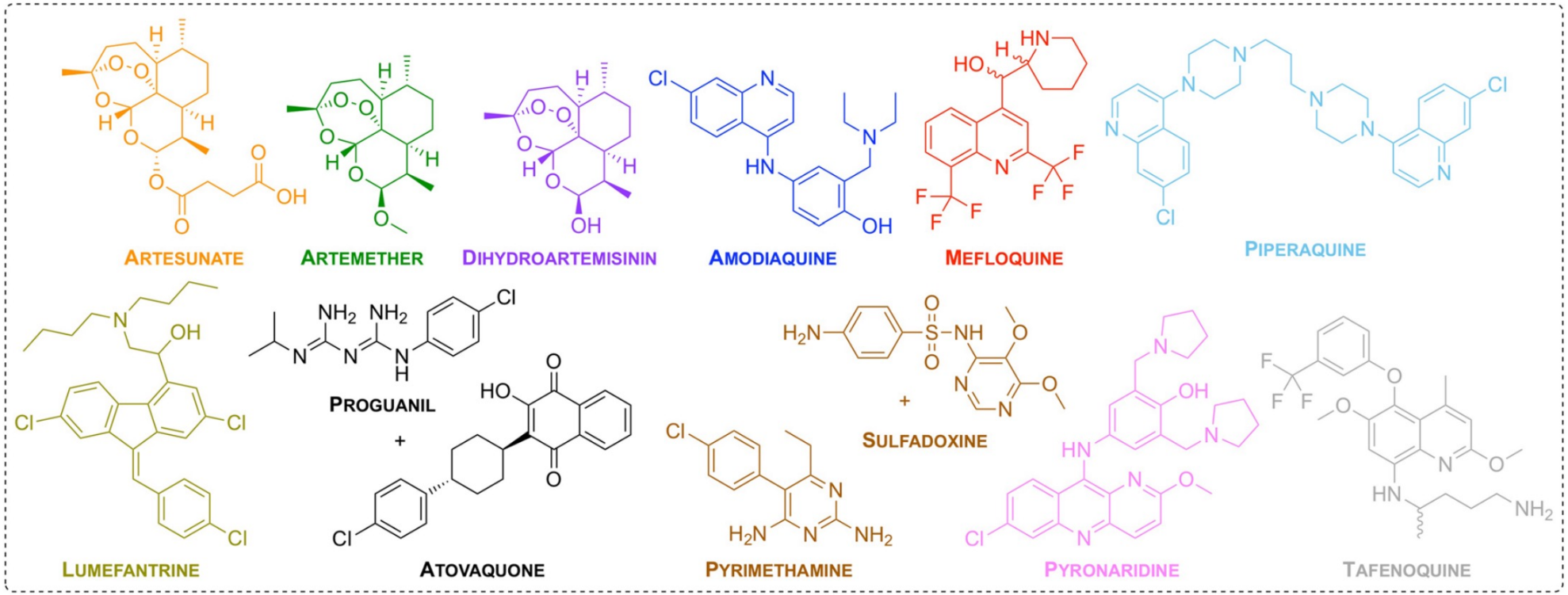
Eurartesim®
Alfasigma/Pierre Fabre
DIHYDROARTEMISININ-PIPERAQUINE

Pyramax® (granules)
Shin Poong
PYRONARIDINE-ARTESUNATE

ASAQ Winthrop®
Sanofi
ARTESUNATE-AMODIAQUINE

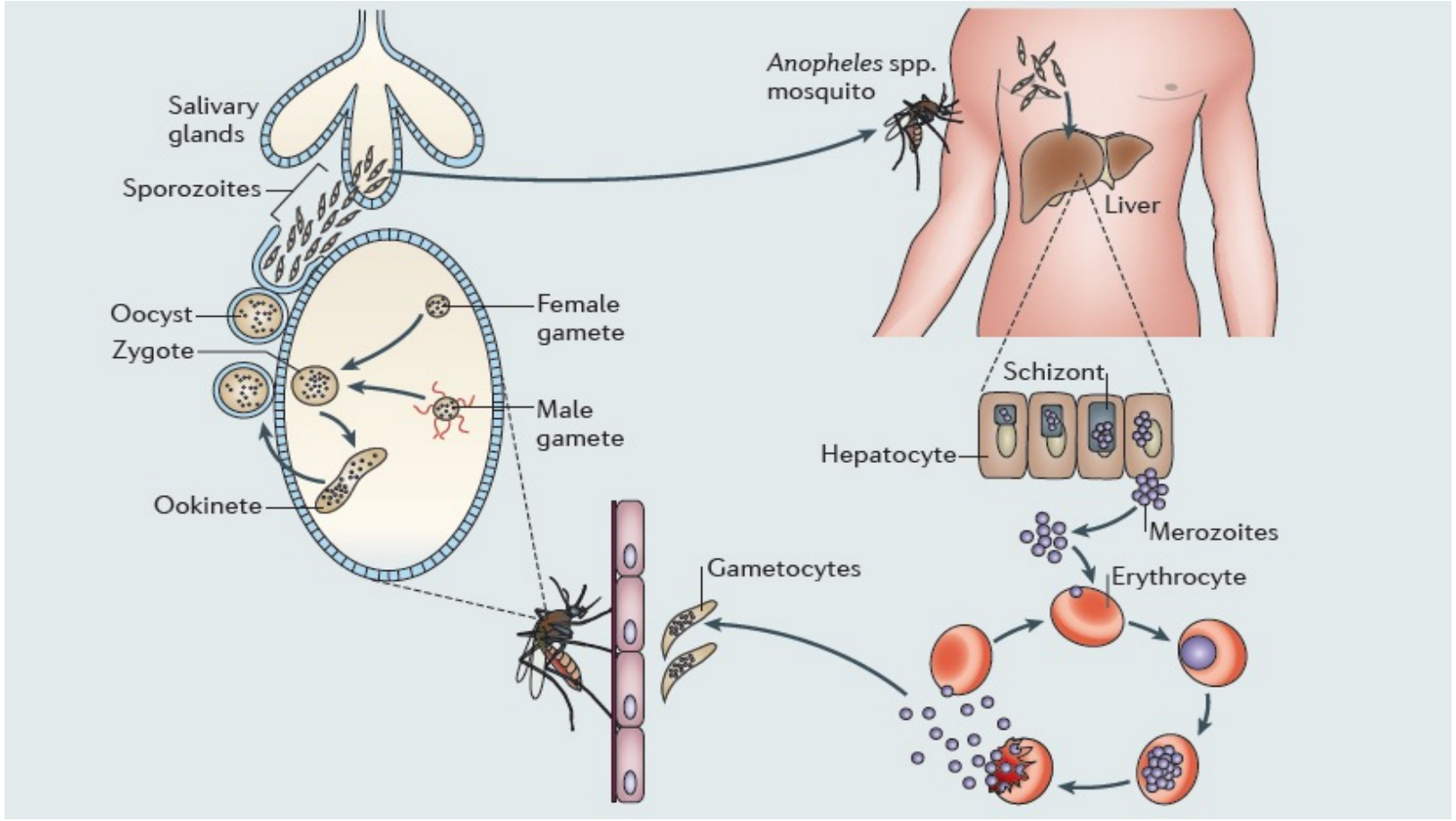
Malarone®
GlaxoSmithKline
ATOVAQUONE/PROGUANIL

SPAQ-CO™
Guilin Pharmaceutical
PYRIMETHAMINE/SULFADOXINE-AMODIAQUINE



Tse et al. *Malaria Journal* (**2019**) 18:93

Malaria pathogen life cycle



Here, we will go after the infected erythrocyte stage (2–16 days post infection), and the gametocyte re-infection process

Planning assumptions

- **You can't do clinical translation in academia**
  - too expensive
  - wrong expertise
  - failure rate too high
- **Translation isn't science, it's engineering**
- **Project management kills creativity**
  - academics don't have incentives to work together
  - managing workflow disturbs academic freedom
  - students don't learn from cookie-cutter procedures
- **One *can* succeed, but …**

… it takes a network!

Kip Guy

SJCRH/UK
Chemistry / pharmacology
Guy Lab

QIMR
Phase 1b
McCarthy Group

UCSF
Malaria biology & genetics
DeRisi Lab

SJCRH
Phase 1a
Gaur Group

Rutgers
Med chem, scale-up
Floyd & Knapp Lab

Bangalore
Contract med chem
Syngene

USF/UGa
Efficacy animal models
EE activity
Kyle Lab

ANU
Target / MOA
Kirk Lab

Madrid
SCID mouse model
GSK

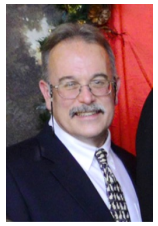
Monash
PK modeling
Charman Lab

Menlo Park
Toxicology &PK
SRI

Geneva
Strategy & positioning
MMV

Andover
IND enabling studies
Eisai

Malaria project personnel



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Sondra Lionetti (UG)
Soomin Jim (UG)

"UG" = undergraduate

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Tom Emge

Swarthmore College

Paul D. Rablen

St. Jude Children's Research Hospital

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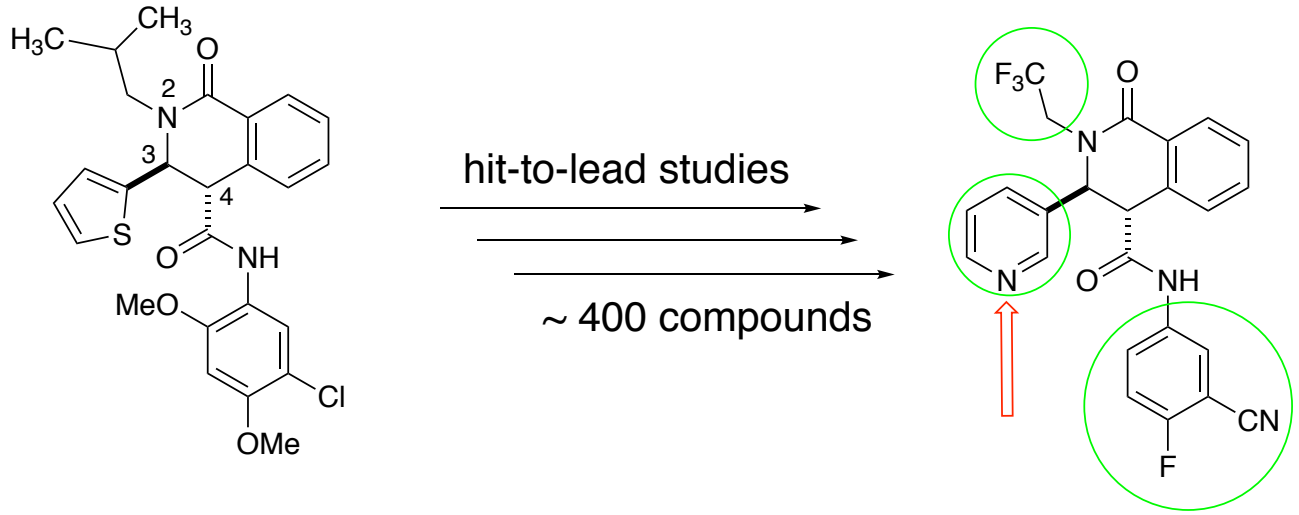
Marisa Martinez
Elena Fernández Álvaro
Sara Viera
Helen Garutixs

Univ. Tenn. Clinical Research Center
Lucinda DelMar
Risa Ramsey
UTCRC staff

SRI International
Jon Mirsalis
Carol Green


work hard
but smart

Hit-to-lead studies at Rutgers, Syngene



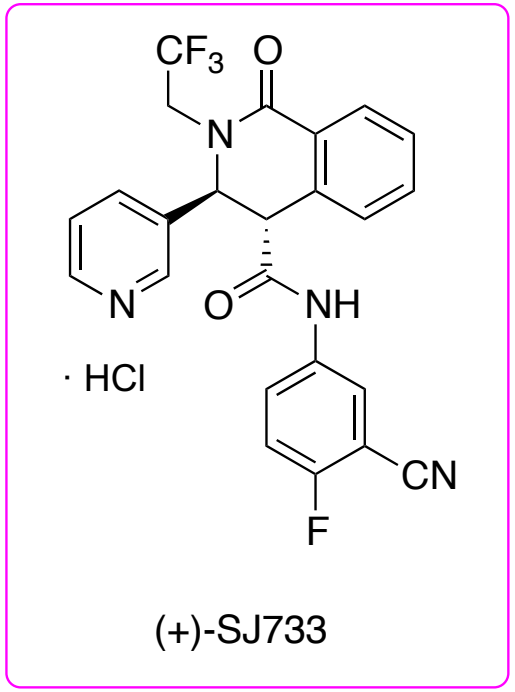
ED_{50} 16 nM	ED_{50} 58 nM	activity: *P. falciparum* in vitro
~ 2 μM	~ 60 μM	water solubility
~ 50% reduction	90% reduction	mouse in vivo *P. Berghei*

Modifications of substituents at N-2, C-3, C-4:

- Improved metabolic stability
- Improved water solubility
- Improved in vivo activity
- No toxicity or carcinogenicity issues
- Possible pyridine oxidation (red arrow)?

David M. Floyd, Philip Stein, Zheng Wang, Jian Liu, Steve Castro, Julie A. Clark, Michele Connelly, Fangyi Zhu, Gloria Holbrook, Amy Matheny, Martina S. Sigal, Jaeki Min, Rajkumar Dhinakaran, Senthil Krishnan, Sridevi Bashyum, Spencer Knapp, and R. Kiplin Guy. "Hit-to-Lead Studies for the Antimalarial Tetrahydroisoquinolone Carboxanilides" *J. Med. Chem.* **2016**, *59*, 7950–7962.

Rutgers scale-up of SJ733 synthesis



(+)-SJ733

80 grams of the final form of **(+)-SJ733·HCl** was made at Rutgers and sent for animal studies

Melting point of HCl salt: 277–279 °C. Both optical and chemical purity are high

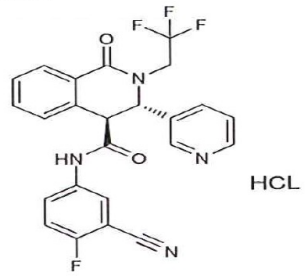
(+)-SJ733 certificate of analysis

SRI INTERNATIONAL
Pharmaceutical Development
Biosciences Division
333 Ravenswood Avenue
Menlo Park, California 94025 USA

Certificate of Analysis
(Revised)
Page 1 of 2

Compound Name: (+)-SJ000557733-26

Structure:



Molecular Formula: $C_{24}H_{16}F_4N_4O_2 \cdot HCl$
Molecular Weight: 504.9

Manufacturer/Supplier: St Jude Children's Hospital, Memphis, TN

Lot No.: ZW-3-90

Test	Test Method	Results
Appearance	Visual	Off white powder
Identification	NMR (SOP 004.221)	Confirms to structure*
Assay (HPLC purity by Normalized Peak Area)	NB 16158, Pages 11 to 19	99.72%
Chiral Purity	NB 16158, Page 7 to 10	> 99.9% of (+) isomer**
Optical Rotation	USP <781> (by Robertson Microlit Method Laboratories)	+146.22
Water Content	Karl Fisher (SOP 004.217)	0.14%

* Based on NMR proton spectrum, two residual solvents were identified and estimated at the level of 0.45% for ethanol and 0.22% for diethyl ether.
** The detection limit of the (-)-isomer was estimated at 0.1%. The (-)-isomer was not detected in the test sample.

US009416124B2

(12) **United States Patent**
Guy et al.

(10) **Patent No.: US 9,416,124 B2**
(45) **Date of Patent: Aug. 16, 2016**

(54) **SUBSTITUTED 2-ALKYL-1-OXO-N-PHENYL-3- HETEROARYL-1,2,3,4-TETRAHYDRO-ISOQUINOLINE-4-CARBOXAMIDES FOR ANTIMALARIAL THERAPIES**

(75) Inventors: **Rodney Kiplin Guy**, Memphis, TN (US); **Fangyi Zhu**, Memphis, TN (US); **Wendyam Armand Guiguemde**, Memphis, TN (US); **David Floyd**, Pennington, NJ (US); **Spencer Knapp**, Skillman, NJ (US); **Philip Stein**, Pennington, NJ (US); **Steve Castro**, East Hannover, NJ (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 12 days.

(21) Appl. No.: **14/240,994**

(22) PCT Filed: **Aug. 24, 2012**

(86) PCT No.: **PCT/IB2012/054305**

§ 371 (c)(1),
(2), (4) Date: **Feb. 25, 2014**

(87) PCT Pub. No.: **WO2013/027196**

PCT Pub. Date: **Feb. 28, 2013**

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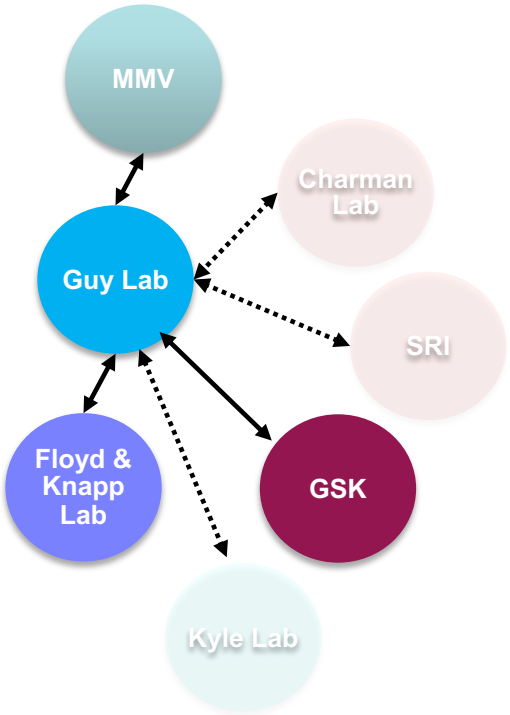
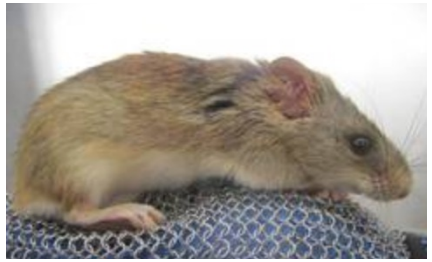
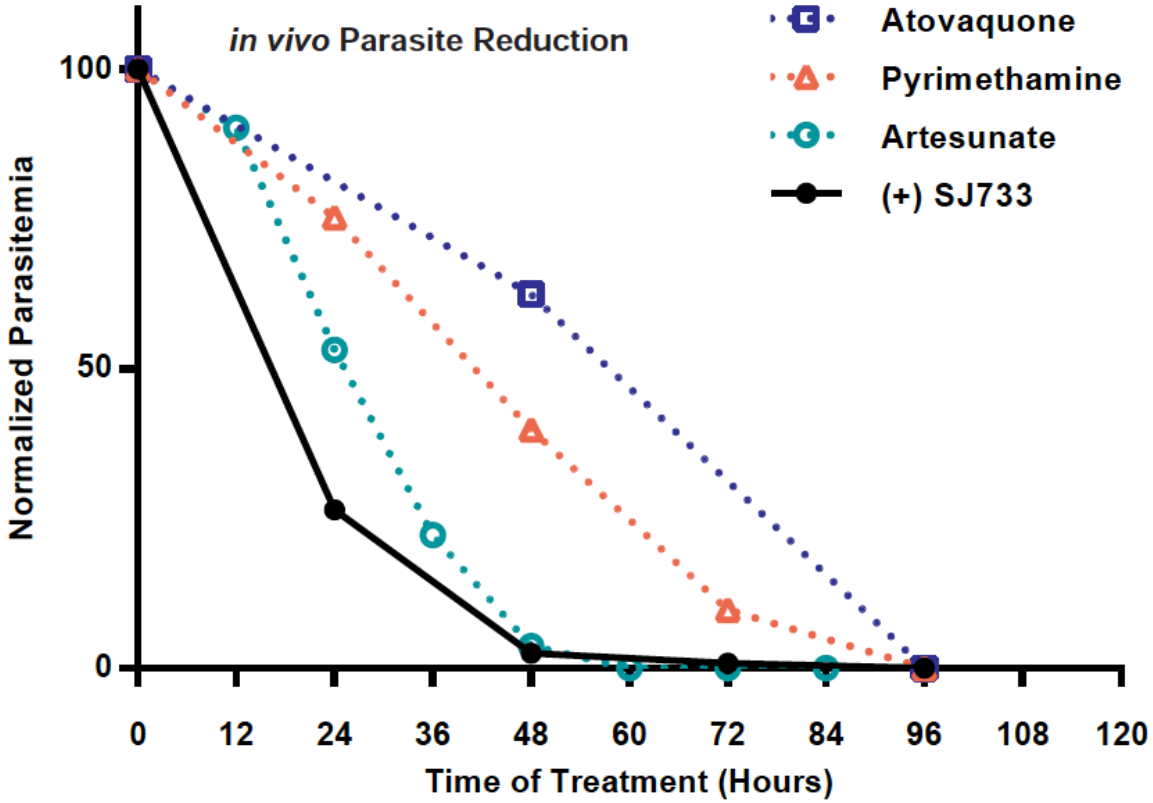
Comparison of (+)-SJ733 with other antimalarials

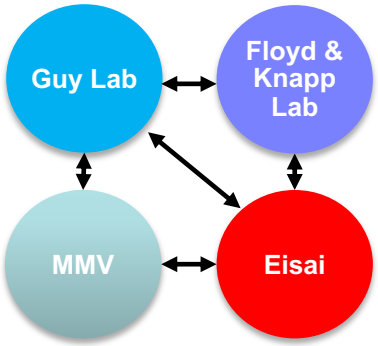




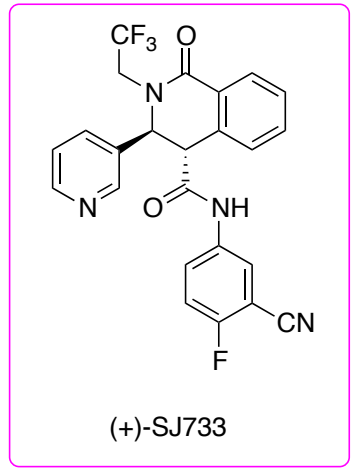


Rapid reduction in parasitemia in a *P. falciparum* humanized mouse model, administered orally

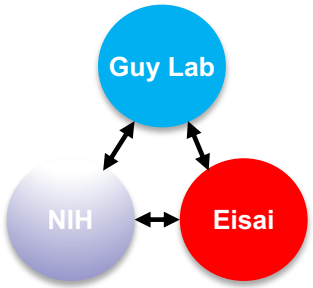
Investigational new drug (IND) enabling studies



- SJ733·HCl was selected as drug substance
- 1 kg GMP synthesis run at Sonas
- 75 mg and 300 mg capsules produced at Catalent

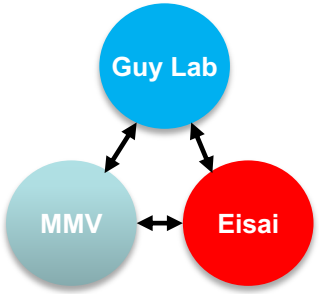


(+)-SJ733



- Rat 7-day toxicity and 7-day reversibility
- Rat respiratory
- Rat functional observational battery

Clean



- Dog 7-day toxicity and 7-day reversibility anemia at 1 g/kg
- Dog cardiovascular elevated methemoglobin at 100 mg/kg

RUTGERS TODAY
Your source for university news
Friday August 11, 2017

NEWS

Promising Malaria Drug Created at Rutgers to Undergo Clinical Trials

The antimalarial compound, first prepared in chemistry professor Spencer Knapp's lab, is to be tested in people

Monday, March 7, 2016

By Todd B. Bates

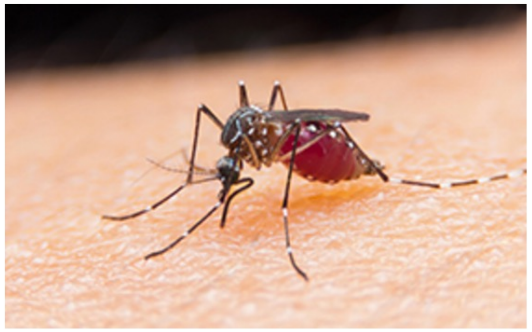


Photo: PlotPhoto
Parasites that infect mosquitoes cause malaria, which has plagued people for millennia

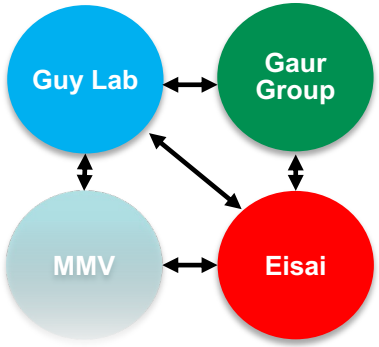
Malaria killed about 440,000 people – mostly young children – last year, but a new drug candidate discovered at Rutgers may help fight the long-dreaded disease.

The compound, which literally blows up malaria parasites in the blood stream, is about to undergo clinical trials, said Spencer Knapp, a chemistry professor in the Department of Chemistry and Chemical Biology at Rutgers University-New Brunswick.

"That's actually a very exciting development," said Knapp, who has been at Rutgers for 38 years and works in the School of Arts and Sciences. "The drugs that are out there are starting to encounter resistance, so this is a new drug candidate just now entering trials. We don't know how effective it will be yet in humans."

"Buzzoff" phase 1a clinical trial in humans

- Leap frog design
  - Safety drives dose escalation decisions
  - Escalation after 7-day safety review
  - Phase 1b is triggered after reaching dose that safely gives the target area-under-curve (AUC) value
- Target exposure $AUC_{0\text{-}24}$: 13000 ng·hr/mL
- PK assay and modeling conducted throughout the study
- Safety assessments include monitoring for methemoglobinemia and hemolysis



Phase 1a summary

75 mg
- No serious adverse events (SAEs) in human volunteers
- Exposure area-under-the-curve (AUC) 2700 µg·h/L

150 mg
- No SAEs
- AUC 4200 µg·h/L

300 mg
- No SAEs
- AUC 10000 µg·h/L

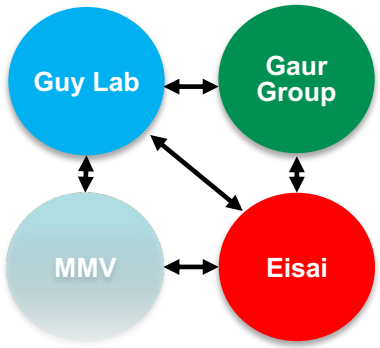
600 mg
- No SAEs
- AUC 25000 µg·h/L
- ALL subjects above 13000 ug·h/L (similar with fed subjects)

600 mg dose gives target exposure AUC

900 mg
- No SAEs
- AUC 17000 µg·h/L

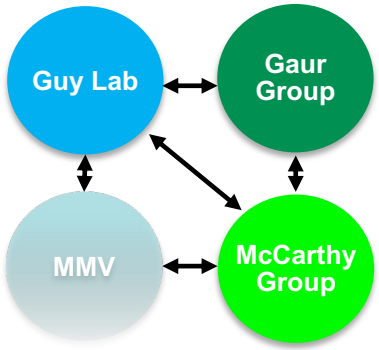
1200 mg
- No SAEs
- AUC 27000 µg·h/L

STOP single ascending dose



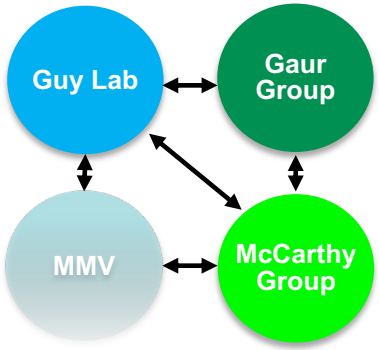
AUC median values shown

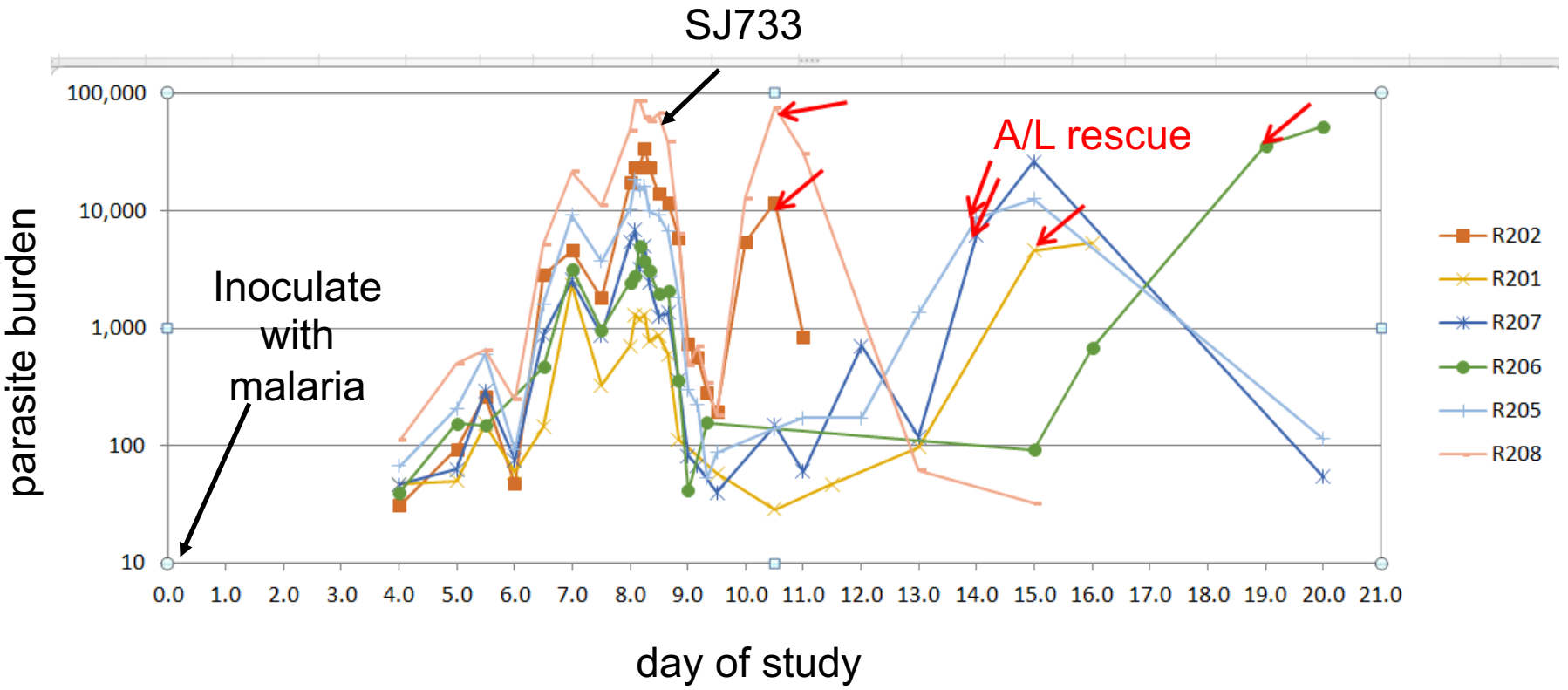
Buzzoff - phase 1b study



- **Human challenge model**
  - Infect healthy volunteers (Australia) with *P. falciparum* 3D7
  - Monitor by qPCR
  - Rescue with Coartem (artemether / lumefantrine) treatment
- **Two cohorts**
  - Safe exposure for MIC – 150 mg
  - Safe exposure for clearance – 600 mg
- **Pharmacokinetics** on day of dosing
- **Pharmacodynamics** throughout study
- **Target $AUC_{0\text{-}24}$**: 13000 ng·hr/mL
- **Safety assessments** include monitoring for methemoglobinemia and hemolysis

Buzzoff phase 1b summary





150 mg

- No SAE's
- Parasite clearance $t_{1/2}$ 6 h
- Transient suppression

→ **600 mg**

- No SAE's
- Parasite clearance $t_{1/2}$ 3.6 h
- Durable suppression (> 30 h)
  - 2/6 recrudesce after 2 days

⇒ **Bonus: suppression of gametocyte formation (blocks transmission)**

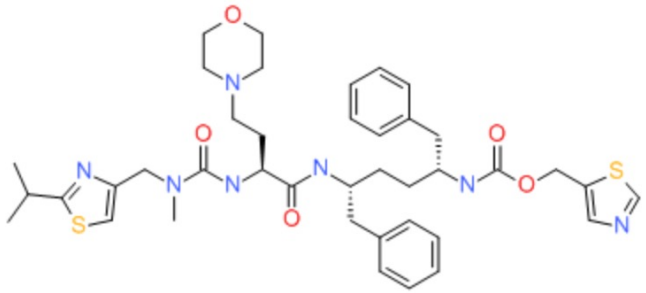
Refined clinical model

- **PK/PD model**
  - **1 day x 600 mg – high risk**
  - **3 day x 600 mg – medium risk**
  - **higher/longer exposure would be better**

- **Refined development path**
  - **explore "pharmacoboost" (CYP 3A4 oxidative metabolism inhibitor cobicistat)**
  - **test initially in 1 day schedule**

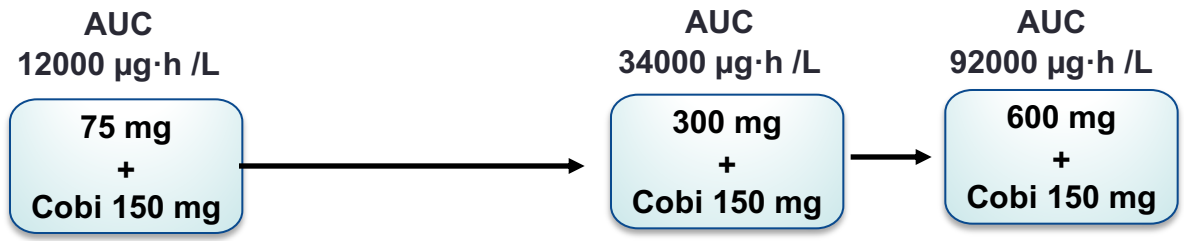
- **Add combination cohorts with SJ733 and cobicistat to Phase 1a study**

cobicistat



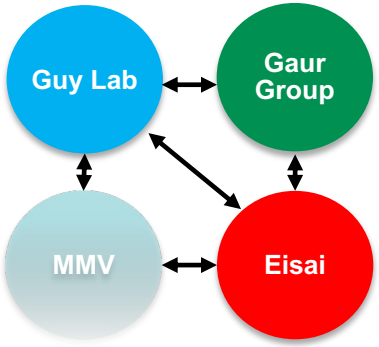
Phase 1a – Summary of Extended Studies

single ascending dose



multiple ascending dose

(AUC median values shown)



Throughout the study:

- **no methemoglobinemia**
- **no clinically significant blood abnormalities**
- **no SAEs**

PK/PD modeling and Phase 1 results

3 x 300 mg SJ733 + 150 mg cobicistat, *or*
3 x 600 mg SJ733:

- Predicted total kill >10^{12}-fold
- Cobicistat boosts SJ733 exposure 4-fold
- Parasitemia suppression > 30 h
- Meets ideal MMV target-candidate-profile-1 (TCP1) for “fast parasite clearance”
- **Phase 1a/b**: “The favourable pharmacokinetic, tolerability, and safety profile of SJ733, and rapid antiparasitic effect support its development as a fast-acting component of combination antimalarial therapy” *Lancet Infect Dis* **2020**; *20*: 964–75

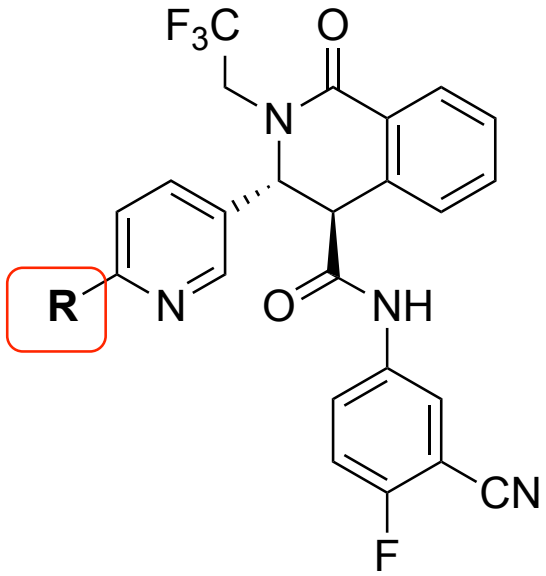
Updated Status (November 2023)

- **Embryo-fetal developmental toxicity studies**
  - SJ733 clean up to 1 g/kg in the rabbit; no evidence of embryotoxicity
  - This result enables Phase 2 in pregnant women

- **Phase 2a field study completed**
  - Target artemisinin resistant *P. vivax* in 20 volunteers in Iquitos Peru
  - 100 mg X 3 d dosing SJ733 with and without cobicistat, then observe to 42 d
  - Parasite clearance (microscopy):16 h (cobi) and 46 h (no cobi)
  - Malaria symptoms recur: 25 d (cobi) and 24 d (no cobi)
  - Complete disappearance of asexual parasites and parasite DNA in 42 d (both)
  - Fast acting and low toxicity aspects of SJ733 confirmed
  - However, oxidative metabolism of SJ733 means further doses required, hence …

Updated Status (continued)

- **New analogues warranted**
  - Further pyridine analogues contracted out by MMV gave oxidation-resistant properties
  - Thus, the cyclopropyloxy analogue (MMV609) holds promise as an improvement on SJ733



	PK parameters (mouse)	PK parameters (rat)
SJ733 (**R** = H)	Cl = 4.2 L/h/Kg $t_{1/2}$ = 1.1 h bioavailability 66%	Cl = 0.8 L/h/Kg $t_{1/2}$ = 7.7 h bioavailability 75%
MMV609 (**R** = *c*-PrO)	Cl = 0.13 L/h/Kg $t_{1/2}$ = 17 h bioavailability 79%	Cl = 0.06 L/h/Kg $t_{1/2}$ = 26 h bioavailability 107%

Funding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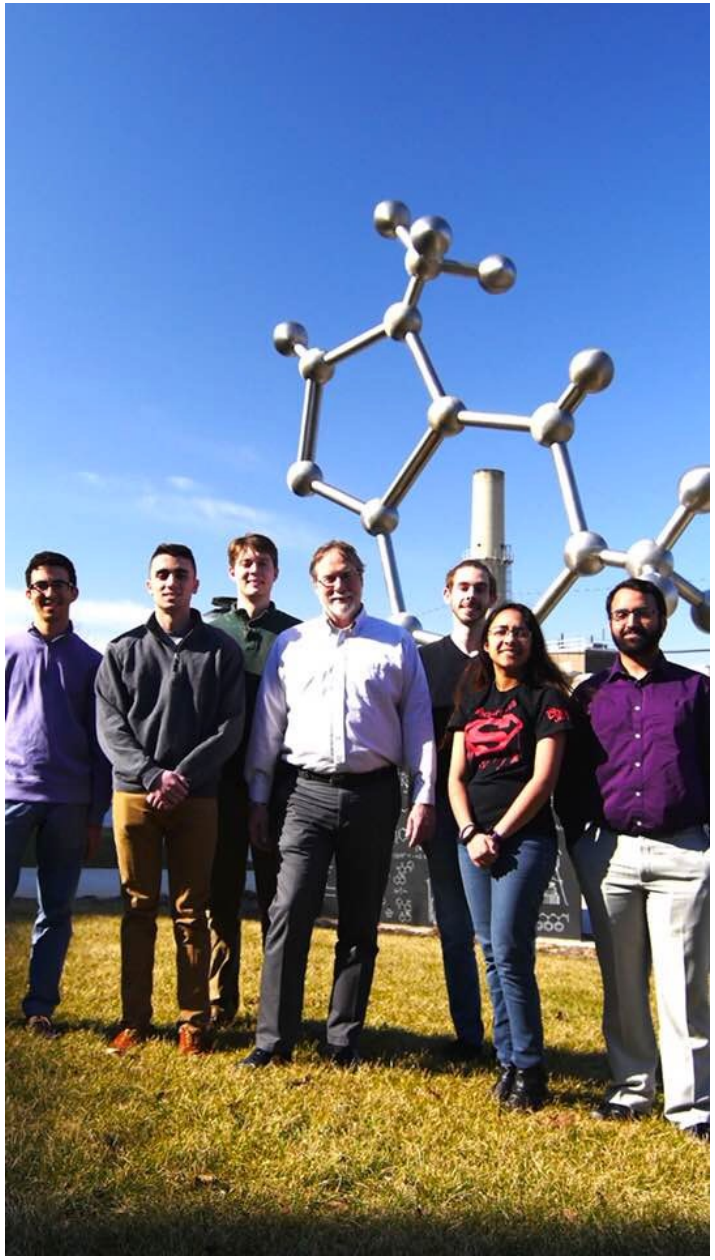
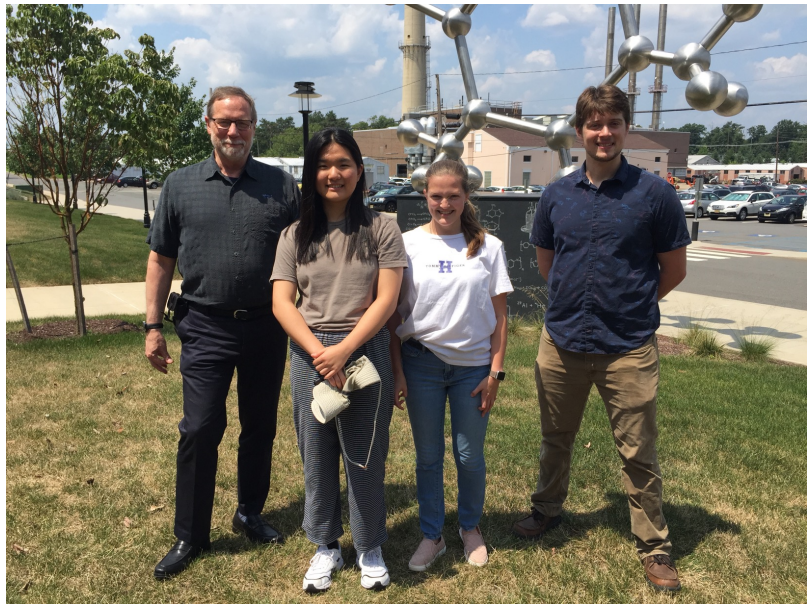
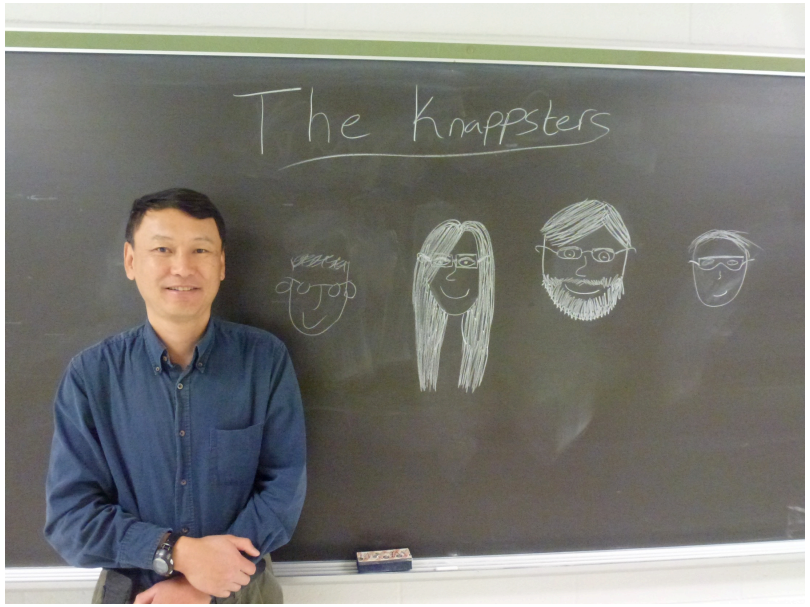
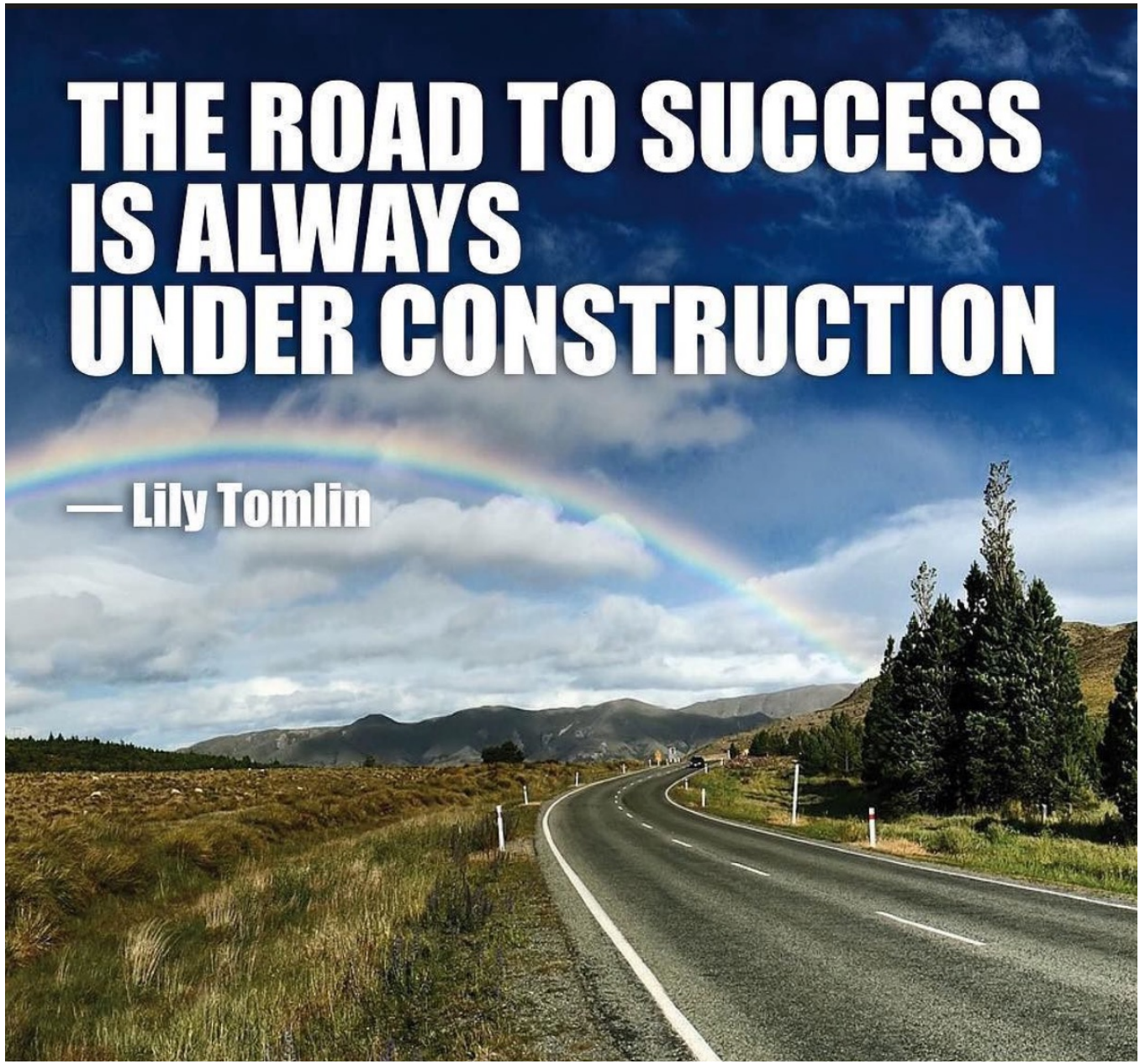
Zakk and Barbaranne Wylde Foundation
Robert Ulrich (Target ex-CEO)
National Institutes of Health
Medicines for Malaria Venture
Global Health Innovative Technology Fund






The knappsters


NMR


THE ROAD TO SUCCESS
IS ALWAYS
UNDER CONSTRUCTION
— Lily Tomlin

Research Projects (2024)

Knapp, Spencer

"Drug Development in the University: Improving the Drug-like Properties of Bioactive Compounds"

- Development of novel structural modifications of bioactive compounds to improve drug like properties
- Investigations into new bio-isosteric replacement of metabolically troublesome functionality (peptides, nucleosides, phenols, anilines)
- Synthesis and evaluation of new small-molecule anti-malarial agents
- Development of new anti-inflammation, anti-epilepsy and anti-cancer compounds

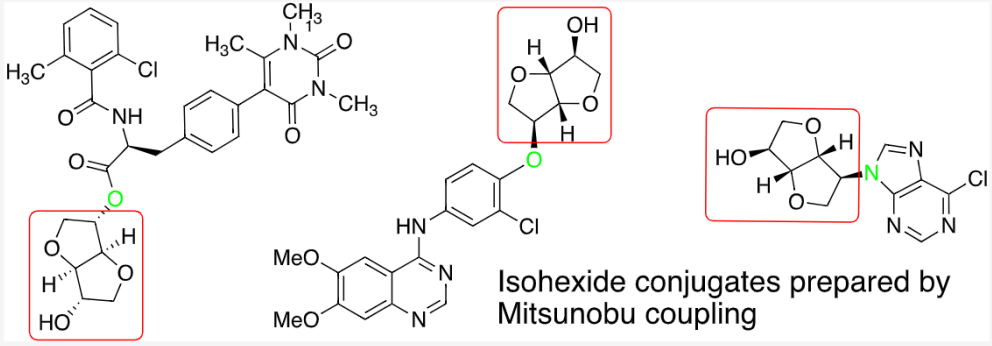
ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett Letter

Incorporation of an Isohexide Subunit Improves the Drug-like Properties of Bioactive Compounds

Achyutharao Sidduri,* Mark J. Dresel, and Spencer Knapp*

Cite This: ACS Med. Chem. Lett. 2023, 14, 176–182 Read Online



ABSTRACT: An enhanced ability to pre-engineer favorable drug-likeness qualities into bioactive molecules would focus and streamline the drug development process. We find that phenols, carboxylic acids, and a purine react with isosorbide ("GRAS" designated) under Mitsunobu coupling conditions to deliver the isoidide conjugates selectively and efficiently. Such conjugates show improved solubility and permeability properties compared with the bare scaffold compounds themselves, and the purine adduct may have applications as a 2′-deoxyadenosine isostere. We anticipate additional benefits, implied by their structures, in metabolic stability and reduced toxicity of the isoidide conjugates as well.

KEYWORDS: *Isosorbide, isoidide, Mitsunobu, solubility, permeability, EGFR, alpha4 integrin, isosteres*

SYNTHESIS ON SCALE

JANUARY 12, 2024

10:00 – 10:10 AM **Welcome – Prof. Jean Baum, Rutgers University, Vice Provost for Life Science**

Opening Remarks – Prof. Lawrence Williams, Chair, Rutgers CCB

10:10 – 11:10 AM **Harshkumar Patel, Bristol-Myers Squibb**
Development of a Sustainable Synthetic Route to BMS-986278

11:10 – 12:10 PM **Kevin Campos, Merck**
Innovations in Synthetic Chemistry at Merck: Striving for the Ideal Commercial Manufacturing Process

12:10 – 1:10 PM **Lunch Buffet – CCB Foyer**

1:10 – 2:10 PM **Chris Senanayake, TCG GreenChem**
Novel Synthetic Approaches toward Complex API Assembly

2:10 – 3:10 PM **Prof. Ken Houk, UCLA**
Pericyclic Reactions in Synthesis and Biosynthesis: Computational Elucidation

2:40 – 2:45 PM **Closing remarks – Prof. Spencer Knapp**, Rutgers CCB, PACS, Symposium Organizer