Spiroindolones: a new chemotype for the treatment of malaria

The NGBS consortium

Thierry Diagana

MMV stakeholder meeting, Barcelona- March 15th 2010

NOVARTIS

The NGBS consortium

A public-private partnership with multiple stakeholders

Novartis Institute for Tropical Diseases (NITD), Singapore

Team leaders: **Bryan Yeung**, Zou Bin, Christophe Bodenreider

Genomic Institute of the Novartis Research Foundation (GNF)

Team leaders: Arnab Chatterjee, Kelli Kuhen and Elizabeth Winzeler

Biomedical Primates Research Center (BPRC), Rijswijk (NL)

Team leader: Clemens Kocken

Swiss Tropical Public Health Institute (Swiss TPH), Basel (CH)

Team leader: **Matthias Rottmann**

The NGBS consortium

Program Head: Thierry Diagana (NITD), Singapore

wellcome trust

Medicines for Malaria Venture

EDB SINGAPORE

The NGBS consortium

Two major program goals

Drug Discovery with the aim to identify new chemotypes for the development of malaria treatments

1. A one dose cure* for *Plasmodium falciparum* malaria
   - ➢ at least 1 compound selected for Proof-of-Concept in man by end of 2011
2. A curative modality for *Plasmodium vivax* malaria
   - ➢ at least 1 early preclinical development candidate by end of 2011

* This will most likely be a drug combination therapy

Target Product Profile

Project goal: replace the "A" of ACTs while improving compliance

Objectives

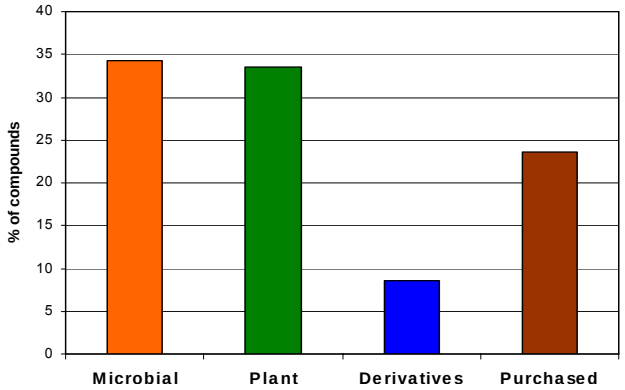
1. Anticipate the threat of artemisinin resistance in SE Asia
2. Improve patient compliance by reducing both pill burden and treatment duration
   - Artemether is fast-acting and potent but it is rapidly eliminated and must be taken twice daily for 3 days
   - Lumefantrine is long-lasting but because of its poor oral bioavailability the total dose is large and the pill burden is high

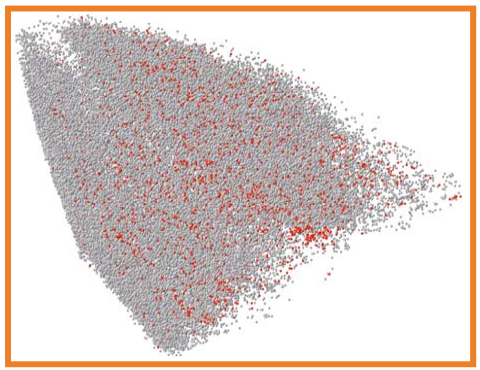
Uncomplicated Malaria TPP	
Properties	**Criteria**
MOA	Non-peroxide, ideally novel chemotype
Antiplasmodial activity	Potently active against blood-stages of all drug resistant parasites
Bioavailability	> 40% orally
Dosing regimen	≤ 3 qd; ideally single dose
Safety	Safety profile not worse than Coartem; ideally safe in pregnant women and infants
CMC	> 3 years shelf-life in endemic countries Low COGS Simple tablet formulation

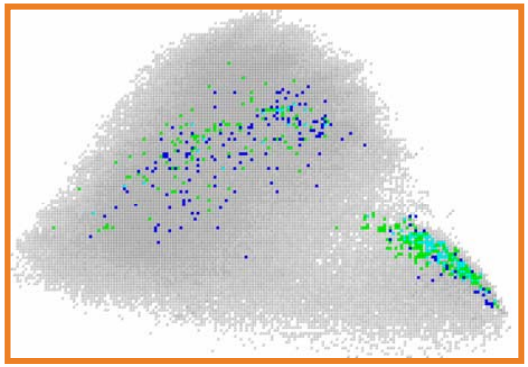
The Novartis Natural Products Library

A highly diverse source of pure and characterized compounds

- A source of pure compounds from various organisms (Plant derived from Shanghai Institute of Materia Medica & Kunming Institute of Botany and microbial from Novartis Natural Product Unit) as well as synthetic compounds with natural product like structural features
- A chemically diverse set of compounds with good drug like properties







NP collection Novartis (red), 170'000 natural products & derivatives from 'dictionary of natural products' (grey)

NP collection Novartis (green), 6'000 drugs (blue); 250'000 organic molecules (grey)

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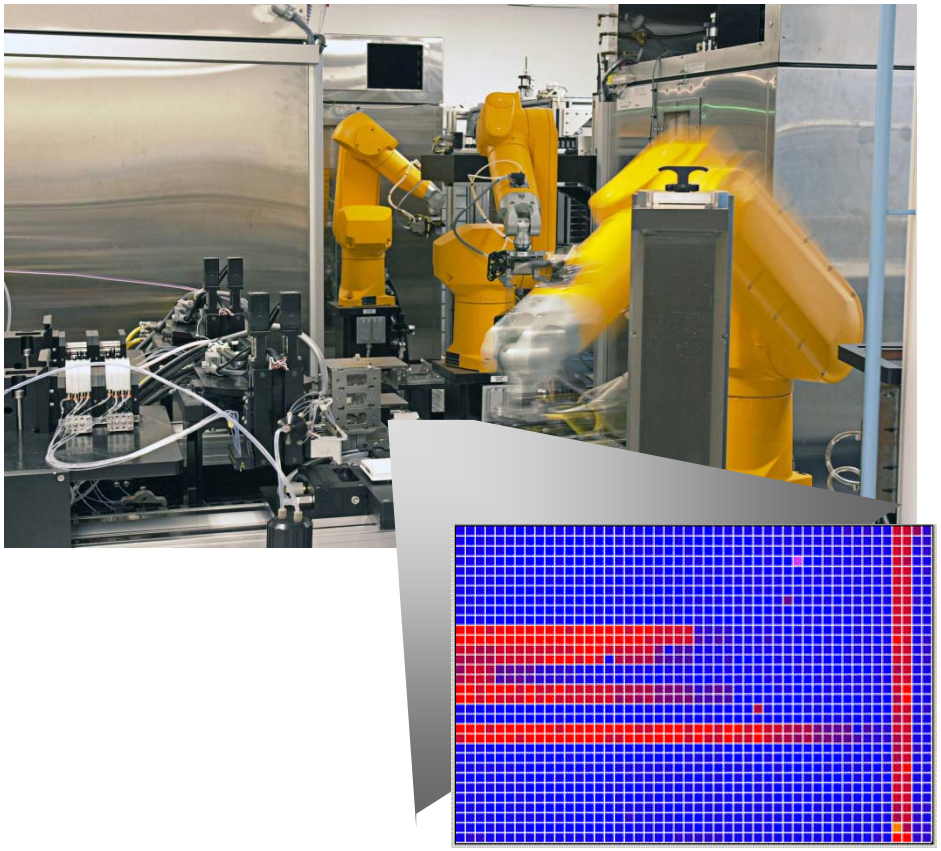
GNF miniaturized a robust HTS cellular assay

Natural products library as a pilot screen for a larger HTS



- GNF optimized and miniaturized a SYBR green Plasmodium proliferation assay for HTS

Plouffe D. et al.,
Proc. Natl. Acad. Sci. 2008 Jul 1;105(26):9059-64

GNF miniaturized a robust HTS cellular assay

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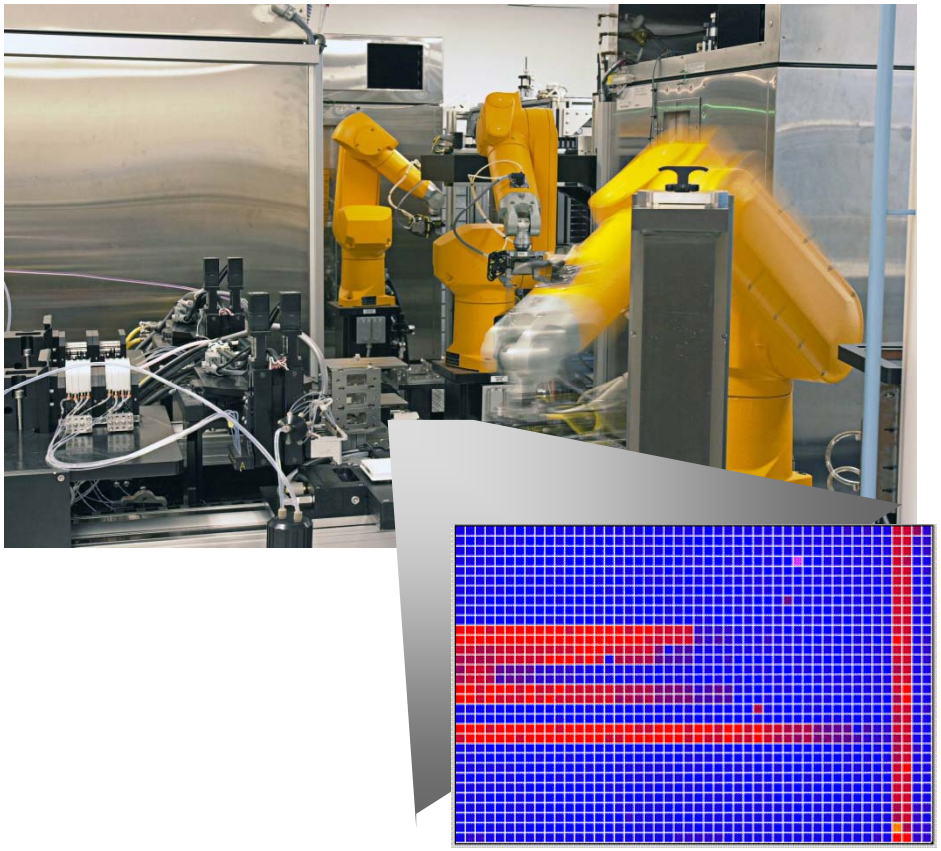

- GNF optimized and miniaturized a SYBR green Plasmodium proliferation assay for HTS
- Following the natural product screen, a large HTS (2.5 million compounds) was carried out

Large amount of chemical diversity (> 6,000 compounds with submicromolar potency) is currently explored at GNF and NITD

Plouffe D. et al.,
Proc. Natl. Acad. Sci. 2008 Jul 1;105(26):9059-64

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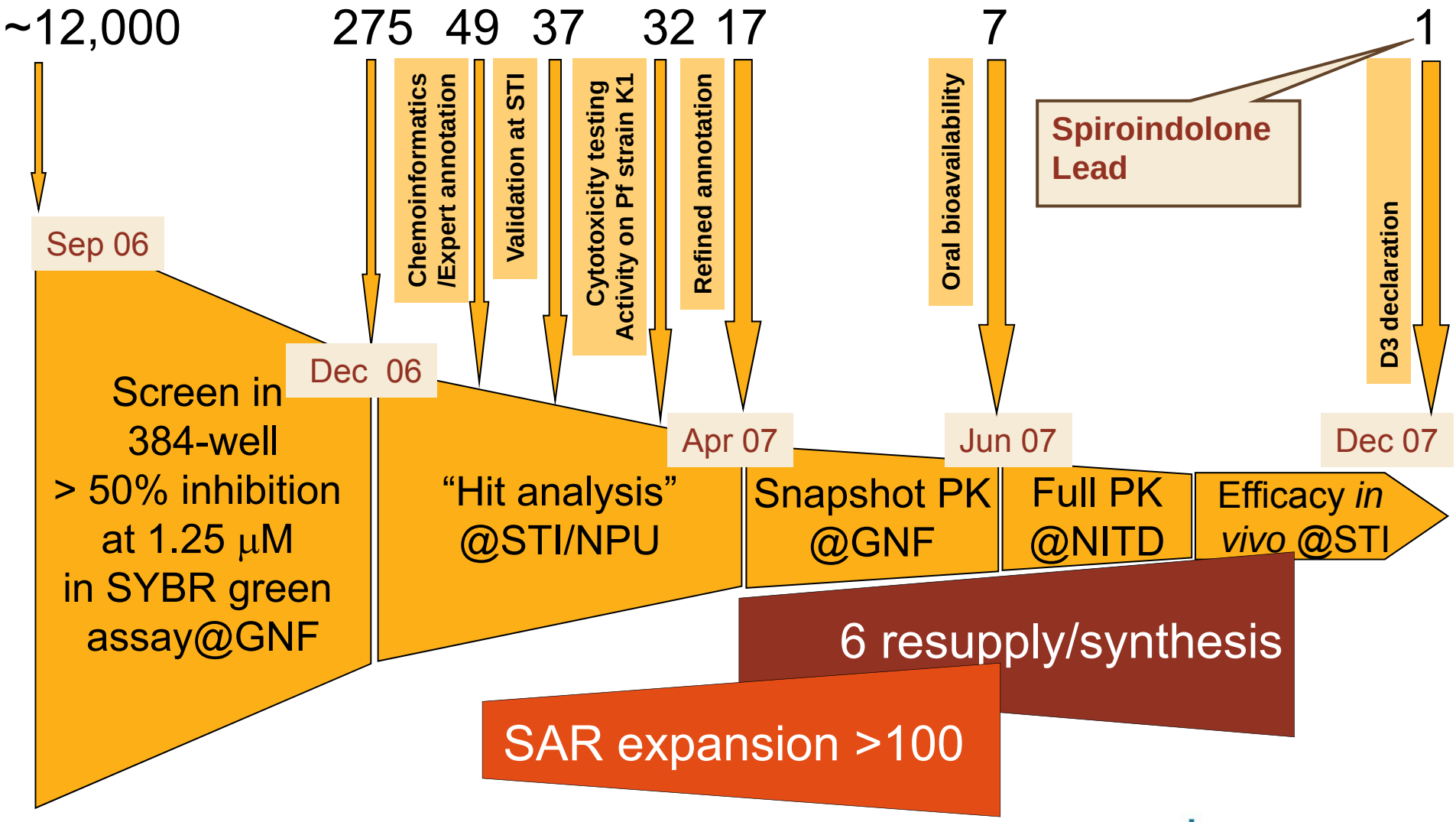
Novartis Natural Products *P. falciparum* screen

Workflow overview and follow-up



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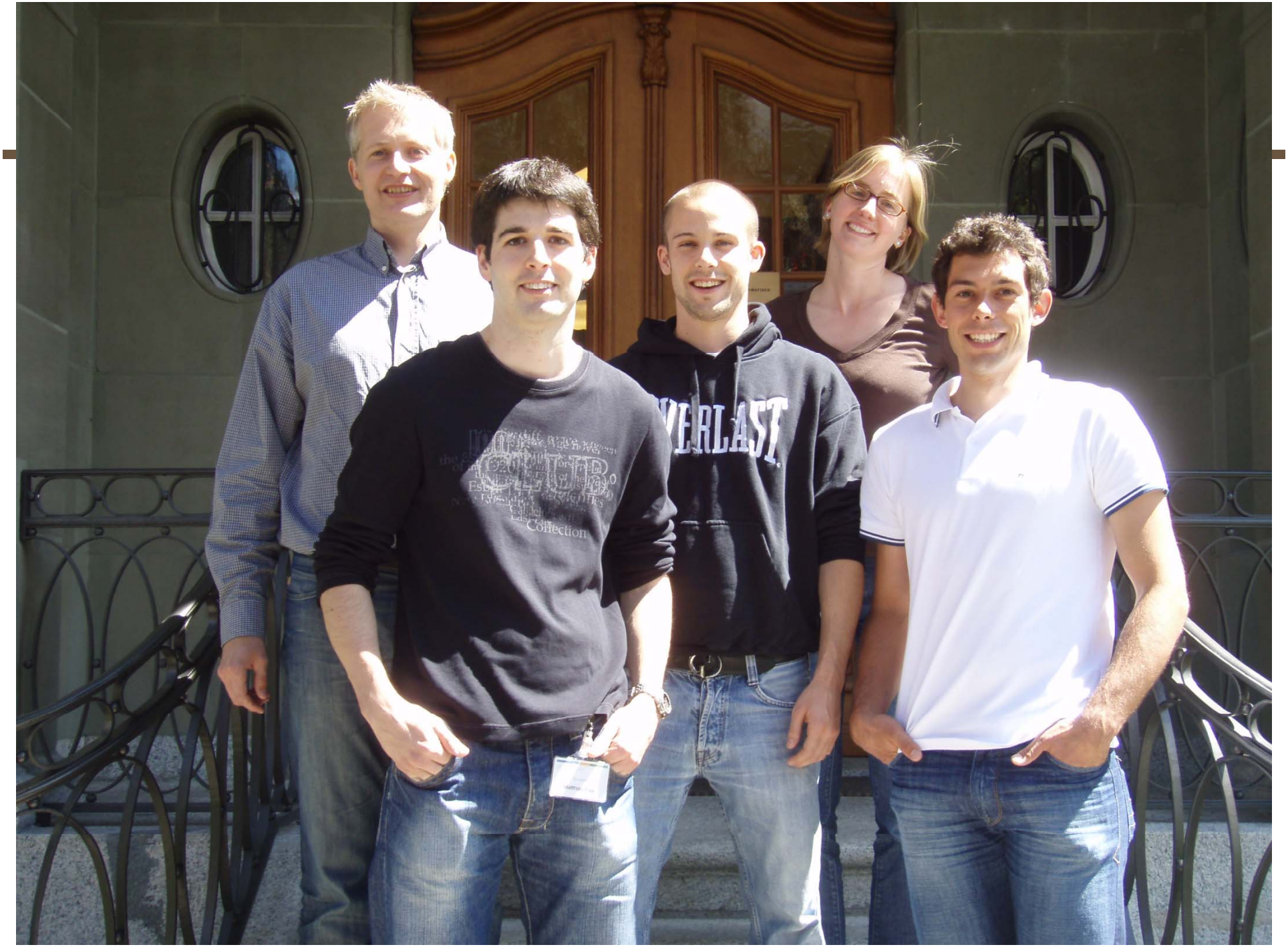
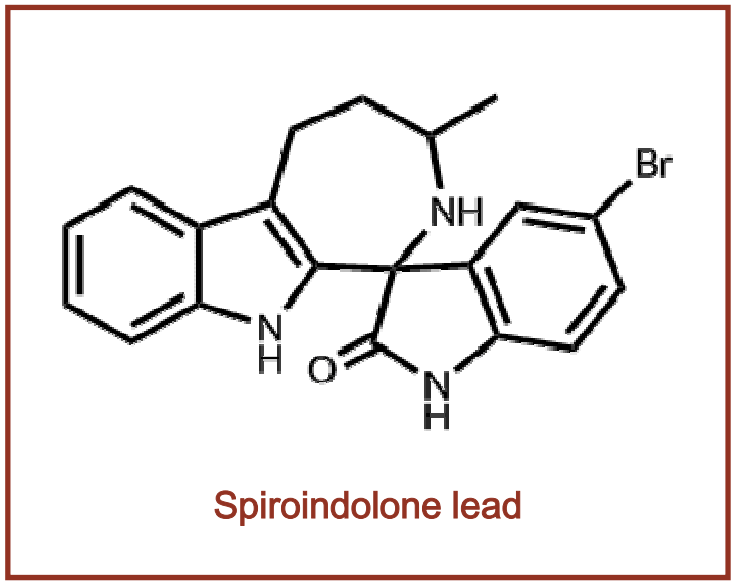

VERLAST

Lead optimization led to drug candidate NITD609

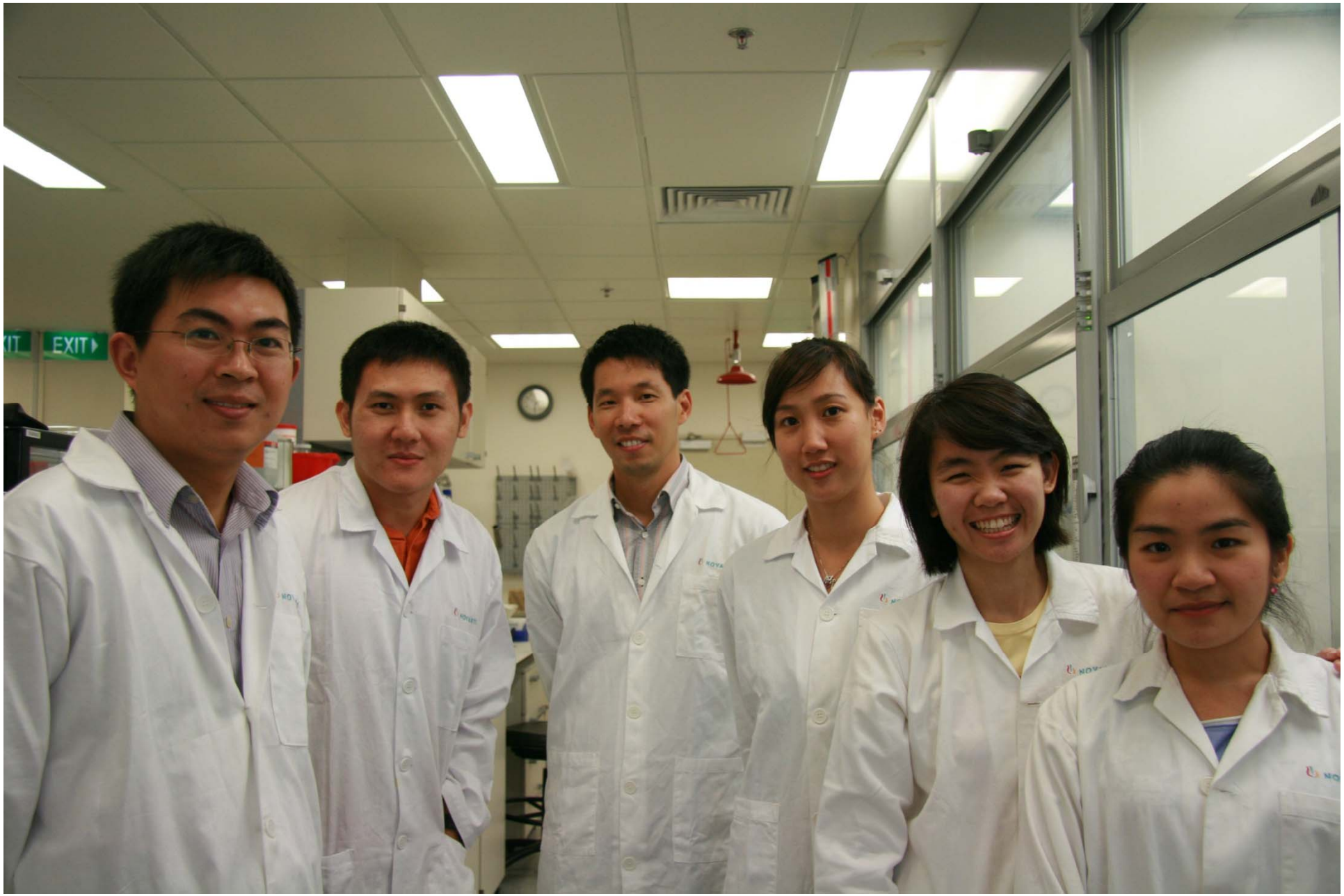
Improving both potency and oral exposure



Spiroindolone lead

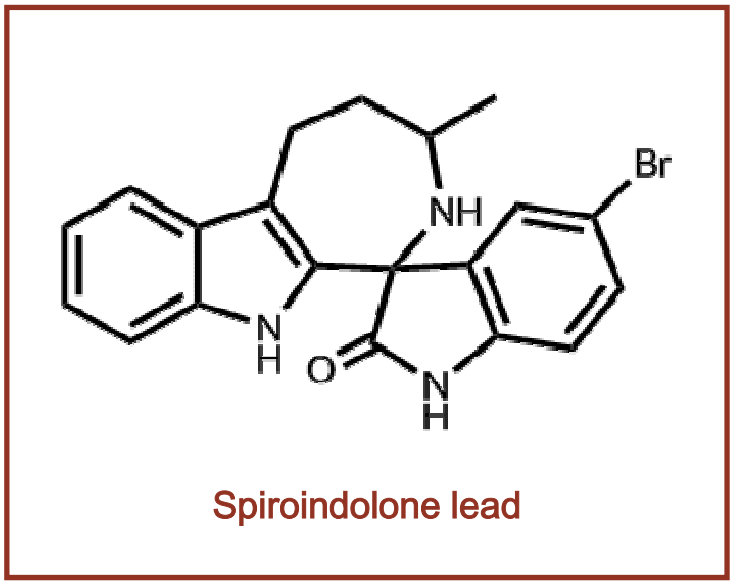
- Moderate potency against NF54 and K1 strains (IC_{50}~80 nM)
- Medium metabolic clearance, CYP450 inhibition liability
- Moderate oral exposure and bioavailability
- Single dose at 100 mg/kg reduced parasitemia by 96% in the *P. berghei* mouse model

NOVARTIS

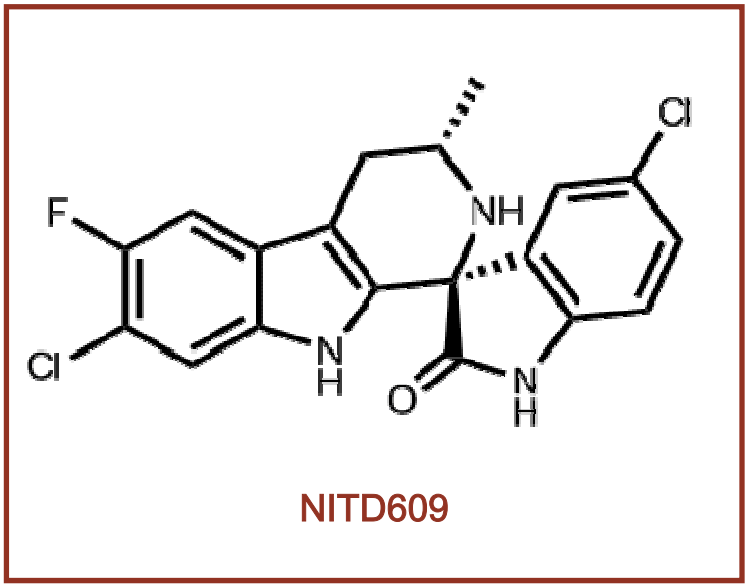

EXIT

Lead optimization led to drug candidate NITD609

Improving both potency and oral exposure



Spiroindolone lead



NITD609

- Moderate potency against NF54 and K1 strains (IC_{50}~80 nM)
- Medium metabolic clearance, CYP450 inhibition liability
- Moderate oral exposure and bioavailability
- Single dose at 100 mg/kg reduced parasitemia by 96% in the *P. berghei* mouse model

- **Improved potency > 80-fold** against NF54 and K1 strains (IC_{50} < 1 nM)
- Low metabolic clearance and no CYP450 liability
- **Oral exposure improved 7 times** and excellent bioavailability
- **Single dose cure at 100 mg/kg** in the *P. berghei* mouse model

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NITD609: pharmacological profile

A new chemotype for the treatment of malaria

- **Pharmacodynamic**
  - Potent and fast-acting blood schizonticidal on both *P. falciparum* and *P. vivax* parasites (IC_{50} ≤ 1 nM)
  - Antimalarial activity superior to all standard antimalarial drugs in a malaria mouse model
  - Low predicted efficacious human dose (< 100 mg)
- **Pharmacokinetic**
  - Excellent oral bioavailability,
  - Low metabolic clearance and moderate to long half-life across all preclinical species
- **Safety**
  - Good selectivity and no significant intrinsic safety liability
    - no cardiotox or genotox potential
  - Tolerated in rats for 14 days daily at multiples of the exposure at the mouse efficacious dose
  - No telemetry or clinical adverse events in single rising dose in dogs at multiples of the exposure at the mouse efficacious dose
- **Technical development**
  - Good bulk stability
  - Simple tablet formulation feasible
  - Synthetic route amenable to kilo-scale

Summary and outlook

Aiming to reach FIH in 2011

- Through high throughput screening with a whole parasite proliferation assay, we have identified in the NPU library the spiroindolone as an antimalarial lead scaffold
- Through medicinal chemistry, the spiroindolone lead was optimized to yield the drug candidate NITD609, selected for proof of concept in March 2010

Outlook

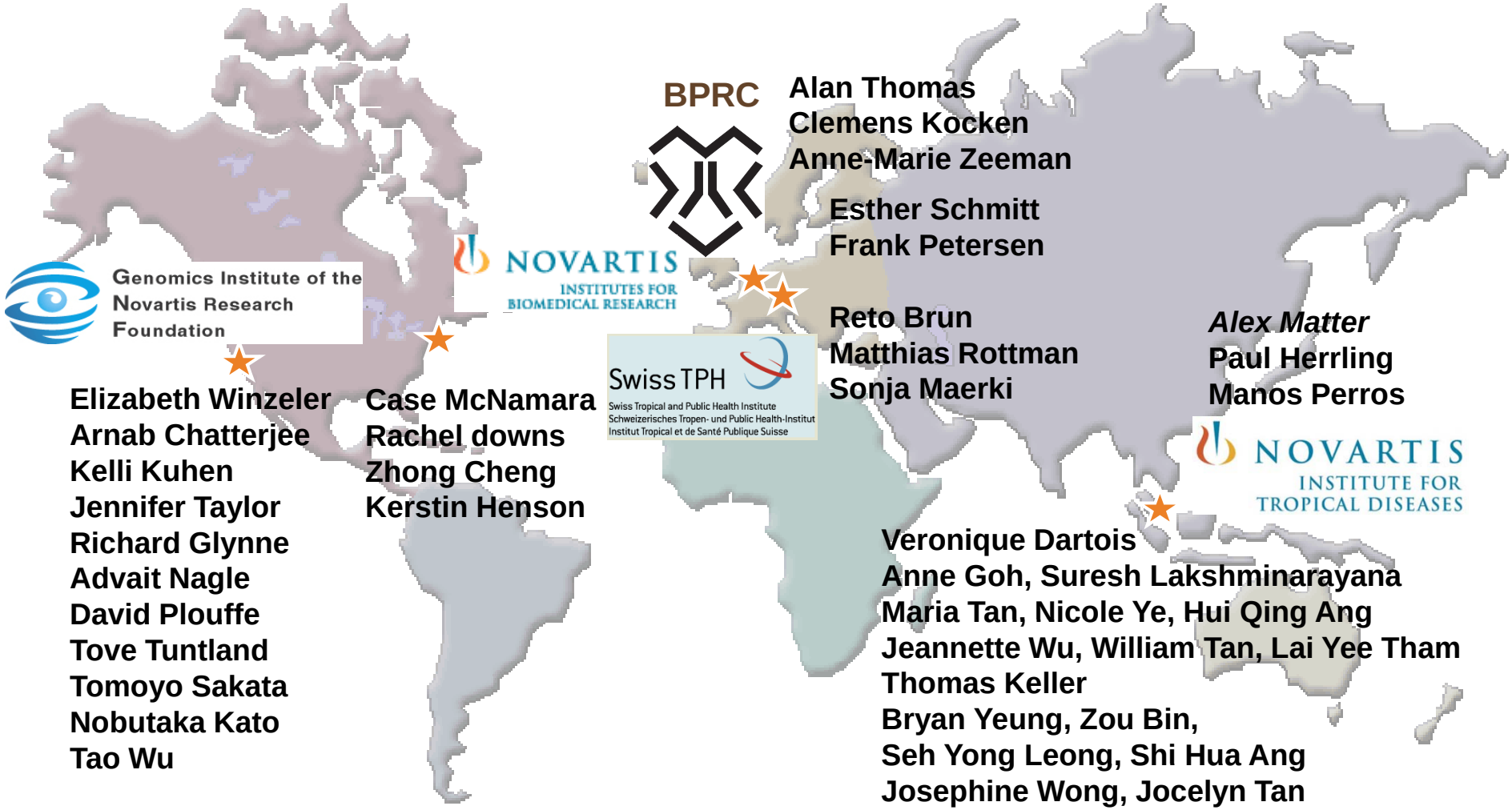
- Completion of all preclinical IND enabling studies and filing of a CTA by the end of 2010
- FIH expected to start in 1st quarter of 2011

The NITD609 Project Team

Research:	Bryan Yeung, Bin Zou, Thomas Keller Matthias Rottmann
DMPK:	Xingmei Han Veronique Dartois, Suresh Lakshminarayana, Anne Goh
Safety:	Margaret Weaver
TRD:	Christine Garrett, Karen Beltz, Rita Ramos, Giancarlo Francese
TM:	Joel Leong

Thank you!

Funders (Wellcome Trust, Singapore EDB and MMV)



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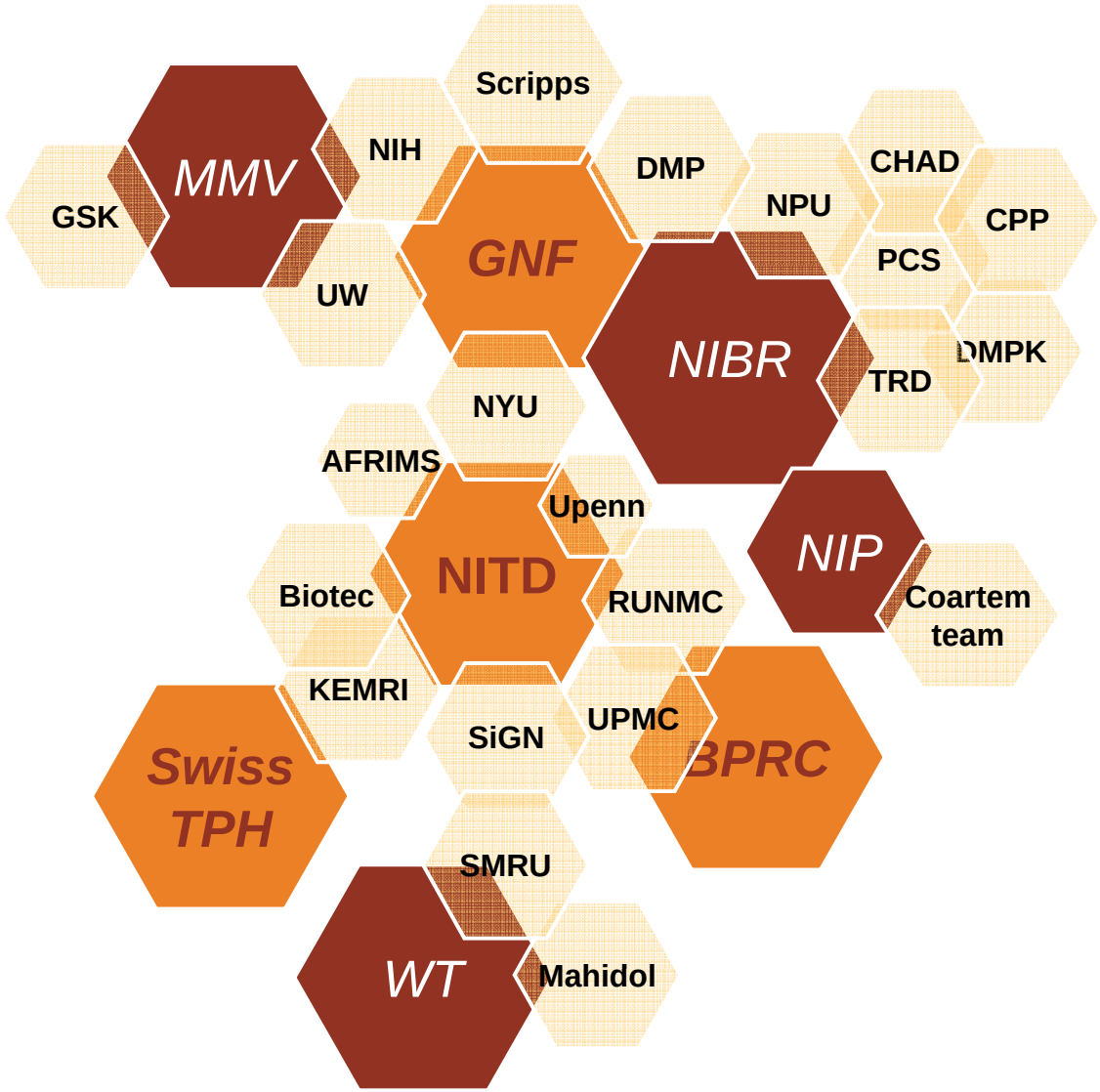
Thank you!

All this would have been impossible without our many collaborators



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