Spiroindolones: a new chemotype for the treatment of malaria

The NGBS consortium
Thierry Diagana
MMV stakeholder meeting, Barcelona- March 15th 2010
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
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

<table>
<thead>
<tr>
<th>Properties</th>
<th>Criteria</th>
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<tr>
<td>MOA</td>
<td>Non-peroxide, ideally novel chemotype</td>
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<tr>
<td>Antiplasmodial activity</td>
<td>Potently active against blood-stages of all drug resistant parasites</td>
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<td>Bioavailability</td>
<td>&gt; 40% orally</td>
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<td>Dosing regimen</td>
<td>≤ 3 qd; ideally single dose</td>
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<td>Safety</td>
<td>Safety profile not worse than Coartem; ideally safe in pregnant women and infants</td>
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<td>CMC</td>
<td>&gt; 3 years shelf-life in endemic countries</td>
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<td>Low COGS</td>
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<td>Simple tablet formulation</td>
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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).
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.,
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
- 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.,
Novartis Natural Products *P. falciparum* screen

*Workflow overview and follow-up*

- ~12,000
- 275 49 37 32 17
- 7

**Screen in 384-well**
- >50% inhibition at 1.25 µM in SYBR green assay

**Dec 06**
- “Hit analysis” @STI/NPU

**Apr 07**
- Cytotoxicity testing on Pf strain K1
- Refined annotation

**Jun 07**
- Snapshot PK @GNF
- Full PK @NITD
- Efficacy *in vivo* @STI

**Dec 07**
- 1

**Sep 06**
- Cheminformatics/Expert annotation
- Validation at STI
- Oral bioavailability
- Spiroindolone Lead
- SAR expansion >100
- 6 resupply/synthesis

**9 | Spiroindolone_MMV project of the year 2010 | T. Diagana | March 15th 2010 |**
Lead optimization led to drug candidate NITD609

Improving both potency and oral exposure

- 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
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

- **NITD609**
  - **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
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

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<tr>
<th>Role</th>
<th>Team Members</th>
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<tbody>
<tr>
<td><strong>Research:</strong></td>
<td>Bryan Yeung, Bin Zou, Thomas Keller, Matthias Rottmann</td>
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<tr>
<td><strong>DMPK:</strong></td>
<td>Xingmei Han, Veronique Dartois, Suresh Lakshminarayana, Anne Goh</td>
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<td><strong>Safety:</strong></td>
<td>Margaret Weaver</td>
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<td><strong>TRD:</strong></td>
<td>Christine Garrett, Karen Beltz, Rita Ramos, Giancarlo Francese</td>
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<td><strong>TM:</strong></td>
<td>Joel Leong</td>
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Thank you!

Funders (Wellcome Trust, Singapore EDB and MMV)
Thank you!

All this would have been impossible without our many collaborators