NITD609: a novel and potent drug candidate for the treatment of uncomplicated malaria

Thierry Diagana, Novartis Institute for Tropical Diseases
New Delhi, November 7th 2012 – MMV stakeholders meeting
Drug resistance to artemisinin in SE Asia

“L’histoire se répète?”

History of antimalarial drug resistance

Emergence of artemisinin-resistant in SE Asia

Phyo et al., Lancet 6736(12), 60484 (2012)  

We need novel MOA to anticipate drug resistance – How?
HTS phenotypic screening at GNF

Game-changing for infectious neglected diseases drug discovery?

GNF successfully optimized and miniaturized assays enabling HTS for neglected diseases (e.g. Chagas, Sleeping sickness, Malaria, Leishmaniosis and Tuberculosis)

(1) Rapid route to drug candidates for neglected diseases
(2) Provide opportunities to discover and validate new targets
Global Phenotypic Screening for Antimalarials

The *P. falciparum* druggable genome?

Guiguemde et al., Chemistry & Biology - (Vol. 19, Issue 1, pp. 116-129)
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

- **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 investigational safety/efficacy have not been established
NITD609 a novel antimalarial drug candidate
*From HTS to POC trials in 5 years*

Rottmann et al., *Science*  VOL 329 SEPTEMBER 2010

*NITD609 investigational safety/efficacy have not been established*
Positive POC trials in Thailand

- Multicenter, open-label, non-comparative study
- Two cohorts of 10 patients each with *P. vivax* and *P. falciparum*
- NITD609 administered 30 mg daily for 3 days followed by standard of care started on Day 5

NITD609 investigational safety/efficacy have not been established
NITD609 may inhibit a non-SERCA P-type ATPase
From phenotypic screening back to a putative molecular target

- Lab-evolved drug resistant mutants display non synonymous SNPs in a putative non-SERCA P-type ATPase (*PfATP4*) localized to the plasma membrane
- Spiroindolones disrupt Na\(^+\) (but not Ca\(^{2+}\)) and pH homeostasis in the parasite

Data from Natalie Spillman and Kiaran Kirk, Australia National University

NITD609 investigational safety/efficacy have not been established
Discovered novel antimalarial chemotypes targeting several key plasmodium life-cycle stages

- NITD609 POC trials outcome declared positive → targets sexual and asexual blood-stages
- GNF156 phase I clinical trials completed → targets sexual and asexual blood-stages as well as liver schizonts
- Targeting the elusive *P. vivax* hypnozoite? Novel chemical series are being optimized

Annotated malaria box (5,698 compounds) available for malaria research community → toolbox for the discovery of novel drug targets

NITD609 and GNF156 investigational safety/efficacy have not been established
Thank you!

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