Overview of NITD TB drug discovery

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NOVARTIS
INSTITUTE FOR
TROPICAL DISEASES

NITD @ Biopolis Singapore Since 2004: Public – Private Partnership

Working on Tuberculosis, Dengue and Malaria

Chromos Bldg

~ 150 people

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NITD's Mission: Drug Discovery for Neglected Infectious Diseases

Discovery and early development up to Proof of Concept in man of novel treatments and prevention methods for major tropical diseases. Main indications are Dengue fever, Tuberculosis and Malaria. Other indications are pursued opportunistically, with partner organizations (platform approaches). The Institute aims at a global leadership position in drug discovery for tropical diseases

In developing countries with endemic disease, treatments will be made available to poor patients, without profit

The Institute recruits the best scientific experts in the world, and as a major center of excellence, offers teaching and training opportunities for post-doctoral fellows, graduate students, undergraduates and trainees

Tuberculosis: Target Product Profile

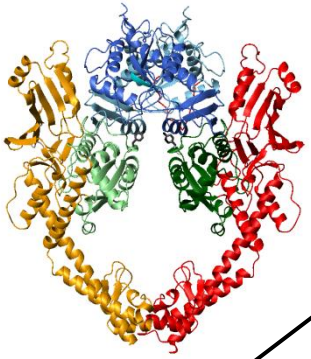
Project goal: Develop novel chemotype actives against MDR and XDR tuberculosis

Therapeutic objectives

1. Enhance cure rate
2. Improve patient compliance by reducing both pill burden and treatment duration
   - Shorten the time of treatment for MDR TB to less than 12 months

Tuberculosis TPP	
Properties	**Criteria**
Antituberculosis activity	Active against MDR and XDR clinical isolates. Cidal against replicating *M. tuberculosis.*
Drug-drug interaction	No Drug-Drug interaction with marketed TB and HIV drugs
Bioavailability	Sufficient for low intra-patient variability
Dosing regimen	Once a day, oral route.
Safety	Safety profile better than marketed TB drugs
CMC	> 3 years shelf-life in endemic countries. Low COGS

TB Drug Discovery Approaches at NITD



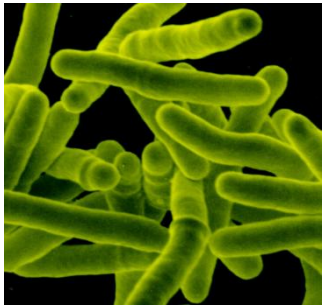
Target-based approach

Lead / Drug finding

Target finding

Cyclomarin; Angew Chem Int Ed Engl. 2011
Lipiarmycin; J Antimicrob Chemother. 2008

3 HTS under different conditions



Cell-based approach

Lead / Drug finding

In vitro – in vivo disconnect (Pyrimidine imidazoles and others)
(target essentiality = f[metabolic/physiological state])

Pethe et al., Nature Communications, 2010

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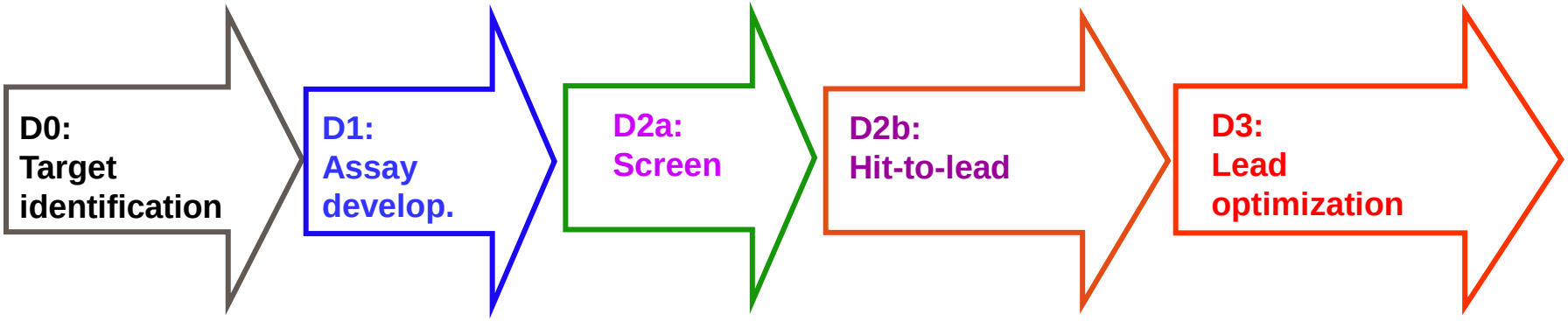
NITD TB Drug Discovery Current Project Portfolio



On-going efforts to identify better/new starting points:
Screen *M. tuberculosis* directly with more diverse set of compounds like

Natural product and NP extracts collection
Library of small and polar compounds etc

- **Scaffold#10 (WCS)**
- **Scaffold #17 (WCS)**

- **Hit to lead activity from phenotypic WCS**
- **Screening "Novartis Rif" analogues active against resistant mutants.**

- **Gyrase screen with Mtb cell active hits**

- **Development of Cell based reporter assays**

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