Access to Medicine: A Novartis Experiment

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Geneva, June 01, 2005
Content

Access to medicines: the problem

A Novartis Experiment:

- Novartis Institute for Tropical Diseases (NITD): discovery in tropical diseases, dengue and tuberculosis.
- Other access to medicine initiatives

Summary
Access to Medicines: multifaceted problems

- Medicines of the rich world are only partly accessible for poorer populations
  - cost
  - distribution
  - literacy-compliance, cultural differences
  - lack of research into diseases endemic in poorer countries
  - ....others

- Pharma Companies traditionally invested only where large markets existed

- Developed societies have evolved to accept some responsibility for the developing world

- Pharma shareholders accept that part of the profits are allocated to alleviate the access to medicine problem
| Access to Medicines in the Developing World: Options for Pharma Companies |
|---|---|
| Money | mostly wasted |
| Existing Drugs at Cost/Free | useful/problematic |
| Discovery of new Drugs * | great need |
| Training of Discovery Scientists | useful |
| Education of patients | necessary |
| Distribution | necessary |
| Medical treatment on site | necessary |

- leveraging modern drug discovery science and technologies for neglected diseases

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Access to medicines: the problem

A Novartis Experiment:

- Novartis Institute for Tropical Diseases (NITD): discovery in tropical diseases, dengue and tuberculosis.
- Other access to medicine initiatives

Summary
Novartis Institute for Tropical Diseases (NITD): Mission

- The Novartis Institute for Tropical Diseases aims to discover novel treatments and prevention methods for major tropical diseases. Initially, Dengue fever and tuberculosis will be addressed.

- In those developing countries where these diseases are endemic, the Novartis Group intends to make treatments readily available and without profit to poor patients.

- The Institute will recruit the best scientific specialists in the world, and as a major center of excellence, will offer exceptional teaching and training opportunities for post-doctoral fellows and graduate students.
Criteria for the Choice of Location of Research Centers

- Access to talent
- Superior research environment: basic sciences and research hospitals, biotech
- **Proximity to patients and their treating doctors**
- Public support for biomedical sciences and political stability
- Acceptable animal experimentation laws
- Acceptable regulation for scientific research (stem cells, etc.)
- Good commercial and regulatory environment for the pharmaceutical industry
- Good intellectual property protection
Novartis Institute for Tropical Diseases

- Location: Singapore
- Operations started January 2003
- Disease Focus: Dengue Fever and Tuberculosis
- Employment: total of ~ 100 FTEs anticipated: 70 scientists and technicians plus 30 students
- 200 million CHF total cost covered by Novartis and Singapore Development Board in a PPP
Novartis Institute for Tropical Diseases (NITD): Employees by Nationalities

By May 2005

- American: 3
- Australian: 4
- Belgian: 1
- British: 4
- Canadian: 1
- Chinese: 6
- Dutch: 1
- Ethiopian: 1
- French: 1
- German: 5
- Indian: 9
- Malaysian: 3
- Burmese: 1
- New Zealand: 1
- Singaporean: 27
- Swiss: 3
- Taiwanese: 1

- Total 72 FTEs, including postdocs
- Plus 6 EDB TAP; 1 PhD Student; 1 Lecturer Attachment
- 38% Singaporean / 62% foreign nationals
Novartis Institute for Tropical Diseases @ Biopolis
Dengue Fever: a Mosquito Borne Viral Disease

- 50 million cases of Dengue each year, 2.5 billion at risk and growing
- Currently, no antiviral treatments for Dengue available
- Mortality in children due to hemorrhagic fever and shock


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Global Distribution of Dengue 2001

Areas infested with *Aedes aegypti*
Areas with *Aedes aegypti* and recent epidemic dengue
Dengue Hemorrhagic Fever and Dengue Shock Syndrome

More severe, potentially lethal variants, following re-infection with different serotypes DEN 1–4:

- Dengue hemorrhagic fever (DHF)
- Dengue shock syndrome (DSS)

DHF is accompanied by hemorrhages, liver enlargement, circulatory failure, patients may then rapidly go into a critical state of DSS

- Currently, there are no specific treatments for Dengue available
- Dengue vaccines are in clinical development but problematic

1. Source: WHO/TDR/STI/Hatz, Image courtesy of the Wellcome Trust

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Dengue Hemorrhagic Fever

Siripen Kalayanarooj, M.D.

Queen Sirikit National Institute of Child Health
(Children’s hospital) Bangkok, Thailand
Target Selection

- Attachment, endocytosis, pH dependent membrane fusion, uncoating (1) **Target**: Host receptor, prevent viral Envelope (E) from pH induced conformational change
- Translation and poly protein processing (5) **Target**: NS3 Protease
- Membrane associated RNA replication in RC (6) **Target**: NS3 helicase, NS5 polymerase, RNA capping activities residing in NS3 and NS5
- Virion morphogenesis, glycoprotein secretion and exocytosis (7) **Target**: host protease?
- Replication involves many viral and host (?) proteins in the cytoplasm. **Target**: Protein interaction sites

Source: Adapted from Lindenbach & Rice, 2001
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Flaviviridae

Tick borne encephalitis

Yellow fever

Japanese encephalitis

Dengue

Pestivirus

Hepatitis C virus
Robert Koch: Discoverer of Mycobacterium tuberculosis

Tuberculosis: Urgent Need for New, Better Drugs

TB incidence rates (WHO Report 2002)

- 9 m new cases p.a.
- 2 m death p.a.
- 50 m infected with drug resistant TB
- 2 bn latently infected
Tuberculosis

- One third of the world population are latently infected with TB bacteria
- The disease is on the increase due to HIV infection, immigration, globalization and increased trade
- There is an alarming increase of drug resistant TB, especially multi drug-resistant TB
- There is an urgent need for development of new anti TB drugs

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New Targets Essential for Growth and Persistence

MDR mutant → mutations → environment

New growth-essential targets

Non-replicator

Novel persistence-essential targets

faster bactericidal action

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PDF as a New Antibacterial Target

- **Conserved** across bacterial species
- **Essential gene** in bacteria (and some parasites)
- **Not required in eukaryotes** (present in mitochondria, not known if hu-PDF is functional)
- **Novel**: distinct from targets of all clinically used antimicrobials
- **Metallo-enzyme**: opportunities for rational design and combichem approaches

Originated in NIBR for upper respiratory tract diseases, bioinformatics show occurrence in M. tuberculosis ➔ NITD takes it up

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# PDF-Degree of Homology Across Related Species, the Value of Bioinformatics

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Source: NITD, Schreiber et al., 2004

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Exploiting Evolution – PDF Target in Multiple Pathogens

TB  Buruli ulcer  Malaria ?  Sleeping sickness ?

PDF  PDF  PDF  PDF
Novartis Institute for Tropical Diseases (NITD): Global Network of Relationships

**Academia** in Singapore (GIS, NUS, NTU, IMCB, etc.) and elsewhere (MPIIB in Berlin, STI in Basel (M. Tanner), NIAID/NIH in Bethesda (C. Barry), TB consortium (D. Young), Dengue consortium)

**Novartis** in
Boston: ID TA, NIBR
La Jolla: GNF
Basel: DT, PP

**Granting agencies, Other PPPs**
Singapore EDB, Global Alliance for TB Drug Development, Bill & Melinda Gates Foundation, WHO, StopTB Partnership Medicines for Malaria Venture (MMV)?
Access to Novartis compound libraries

Annotated proprietary compound libraries are one of the most important elements of a Pharma companies’ competitive strength.

Annotated compound libraries contain about a million compounds, both natural and synthetic.

Compound libraries are repeatedly used against newly emerging therapeutic targets.

Pharma companies do therefore not give external access to their compound libraries.

…but NITD as a member of the Novartis research ‘family’ has free access to the Novartis library and can screen it against all neglected disease targets of interest…this is a unique NITD advantage.
Novartis Global Resources Leverage

Cambridge Mass: Targets Compounds
- Diabetes
- Infectious diseases
- Cardiovascular
- Oncology

United Kingdom: Chronic pain
- Respiratory

Austria: Dermatology

Switzerland: Proteases, HTS
- Autoimmunity & transplantation
- Oncology
- Neuroscience
- Musculoskeletal disease
- Gastrointestinal tract
- Friedrich Miescher Institute (FMI)

California: HTS
- Genomics Institute of the Novartis Research Foundation (GNF)

Japan: Oncology
- Diabetes
- Cardiovascular

Singapore: Novartis Institute for Tropical Diseases (NITD)

3,000 scientists

USD 1 bn / year

Novartis Institutes for Biomedical Research (NIBR)
Novartis Corporate Research Institutes

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Novartis Institute for Tropical Diseases (NITD): Summary Status of Projects

The Drug Discovery Process

Target validation process

D0: Dengue E protein
D1: NS5 polymerase, ICL, NS3 helicase
D2: NS3 protease
D3: PDF-I, Nitroimidazoles, PA-824
Other Novartis Access to Medicine Initiatives

“Improving the health and standard of living of all people is a shared responsibility between the private sector, the public sector and other stakeholders. Novartis actively supports efforts towards the improvement of access to treatment”

- Malaria - partnership with WHO (Coartem)
- Novartis Foundation for Sustainable Development (education+donations)
- Leprosy - partnership with WHO (through Novartis Foundation)
- Tuberculosis - donation of DOTS (Daily Observed Treatment, Short-course)
Summary

- Novartis has established a unique institute in the area of tropical diseases together with Singapore EDB

- Both the developing as well as the developed world will benefit from the new institute

- NITD is well aligned with the Novartis global contribution to minimizing the disease burden of developing nations and will leverage the resources of the entire Novartis research organization.

- NITD will initially work on Dengue and Tuberculosis, but other disease areas might become part of the research portfolio

- Common origins in evolution can be used to plan ‘toolboxes’ addressing whole pathogen families because of common targets.