A Technological Revolution is underway...

- Gene Expression Profiles
- Laser Scanning Cytometry
- Proteomics
- and, and, and...
- Structural biology - high throughput docking - Virtual Screens
- Rational Drug Design
- Non-invasive Imaging

2 A. Matter, EPFL, Dec 3, 2007
Cutting-Edge Chemistry – Novel Chemistry Space
Scott Biller, Head of Global Discovery Chemistry, NIBR – Novartis Preclin Research Day, May 2005

Smart Combinatorial Libraries
- Gene-family oriented
- Diversity oriented

In silico screening

Fragment-based screening

Rational approaches to difficult targets

Traditional Medicinal Chemistry

Natural Products

Traditional Medicinal Chemistry
However, R&D Productivity is of concern....

- In 2005 20 drugs registered, in 2006 17!
- R&D productivity increases not proportional to cost increases
- Pricing pressures (consumer and payor concerns, criticism of public opinion), and...
- Increased safety constraints (black box labelings, post-marketing surveillance, withdrawals, etc) result in pressure on margins
- Risk of return on investment (ROI) on R&D becoming negative

**Conclusion**: R&D must become more cost-effective!
The Chokepoints of R&D Productivity

Rate Limiting Steps in the Drug Discovery Process

- The right target
- Good leads
- Predictive quality of biological screens
- High quality drug candidates
- The right patients
- Predictive early clinical endpoints – meaningful biomarkers
- Smart dose-finding
- Smart clinical trial strategy including (smaller) lead indications
- Clinical trial design in line with regulatory strategy
Target Selection – Three Ingredients

For successful drug discovery we need

- A well-defined target, i.e. a biochemically well-defined substrate of drug action
- Knowledge of the molecular epidemiology of the target, in representative sample sizes
- Demonstration of the “essentiality” of the target in the disease process and “non-essentiality” for the host, as the basis of the conceptual approach
- A clear understanding of “drugability” hurdles
Targeted Drugs

- A targeted drug addresses one or more well-defined targets, usually in the context of deregulated signal transduction pathways.
- A targeted drug is expected to offer significantly enhanced safety because of its selectivity.
- A targeted drug addresses homogeneous patient populations with regard to the target; this requires effective molecular diagnostics for patient selection.
- The effect of a drug on the target should yield a readout that is measurable rapidly in patients = biomarkers.
Classical case of target concept

Signal transduction pathway after somatic mutation of one element (e.g. ras) Possible intervention at the site of the mutated target or downstream

Gain of function mutation

Growth
Quiescence
Differentiation
Senescence
Apoptosis
Complication: redundancy

Signal transduction pathways after somatic mutation of two elements
Effective interventions must address both pathways

- Loss of function mutation

Additional complications:
- Crosstalk and Multitasking
Pathways are really parts of networks...

A kinase-phosphatase network...

arrows point from bait to hit
- kinase
- phosphatase
kinase
phosphatase
other
arrows point from bait to hit
Gleevec® as an example of a targeted drug

Gleevec inhibits three related tyrosine kinases:

- Abl kinase
- c-Kit receptor tyrosine kinase
- PDGF-Rα as well as PDGF-Rβ tyrosine kinases
# Chronic Myelogenous Leukaemia (CML): Clinical course of disease in pre-imatinib era

<table>
<thead>
<tr>
<th>Chronic Phase</th>
<th>Advanced Phases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accelerated Phase</td>
</tr>
<tr>
<td><strong>Median 4–6 years stabilisation</strong></td>
<td><strong>Median duration up to 1 year</strong></td>
</tr>
<tr>
<td>Relatively asymptomatic: fatigue; weight loss; elevated white blood cells; enlarged spleen</td>
<td>Impaired differentiation of myeloid precursors. Blast cells &gt; 15% in PB</td>
</tr>
</tbody>
</table>

**Disease Progression**

- Normal Haematopoiesis
- CML
14% of CML patients possess p210 BCR-ABL chromosome translocation

- BCR-ABL gene encodes protein in which Abl kinase is constitutively activated
- This activated tyrosine kinase activates multiple intracellular signalling pathways
- Philadelphia chromosome is responsible for CML and Glivec normalises haematological parameters in CML patients

Nowell & Hungerford, Science 1960;142:1497
Bcr-Abl tyrosine kinase activates multiple pathways

Bcr-Abl

- Cytoskeletal proteins
- Decreased adhesion
- Enhanced mobility

SRC
- C-Cbl
- Gab2
- PI3K
- AKT
- BAD

Shc
- Grb2
- Stat5
- Raf
- MEK1/2
- MAP kinase cascade

Survival
- Proliferation
- Differentiation

Bcr-Abl tyrosine kinase activates multiple pathways: decreased adhesion and enhanced mobility.
Gleevec® in Chronic Myelogenous Leukemia (CML)

- In Phase I trials efficacy at 500 mg seen after one month in late-stage patients, well-tolerated

In Phase II/III trials in early-diagnosed CML patients:
- Three-fold better cytogenetic response (84% vs 30% compared to best available therapy); complete haematologic responses (96%)
- Over 18 months less than 3% patients progress

Druker et al. 2001, NEJM 344, 1031
Progression-free survival of chronic phase CML patients according to 12 month response to imatinib

- CCyR with >=3 log reduction: 97%
- CCyR with <3 log reduction: 89%
- No CCyR: 72%

Estimated rate at 54 month:
- CCyR with >=3 log reduction: 97% (p=0.017)
- CCyR with <3 log reduction: 89% (p<0.001)
- No CCyR: 72%

Months since randomization:
0 6 12 18 24 30 36 42 48 54 60

% without progression:
0 10 20 30 40 50 60 70 80 90 100
Let’s remember – Gleevec can do more than just inhibit Bcr-Abl kinase!

Gleevec inhibits three related tyrosine kinases:

- Abl and Bcr-Abl kinase
- c-Kit receptor tyrosine kinase
- PDGF-Rα as well as PDGF-Rβ tyrosine kinases
Gastro-Intestinal Stromal Tumor (GIST): c-Kit Signaling – activating mutations of c-Kit
Patient with a gastro-intestinal stromal tumor, GIST, treated with Glivec for one month shows dramatic shutdown of metabolic activity of the tumor which is predictive for clinical response.
CT Scan Results - Pre/Post Glivec

27 Jun 2000

4 Oct 2000
Tumor Biopsy Before STI571

Living GIST cells

Ki-67 antigen

CD117 (c-KIT) antigen

Tumor Biopsy After STI571

Few GIST cells remain, in background of degenerated cells
A growing tree of more than 10 indications...

**Glivec/Imatinib inhibiting Bcr-Abl, c-Kit and PDGF-Rs**

**Bcr-Abl inhibition:**
- Chronic Myeloid Leukemia (CML)
- Ph1+ Acute Lymphocytic Leukemia (ALL)
- Abl inhibition; inhibition of the pathogenesis of pox viruses

**c-Kit inhibition:**
- Gastro-intestinal stromal tumor (GIST)
- c-Kit+ Acute Myeloid Leukemias (AML)

**PDGF-R inhibition:**
- Rα: Hypereosinophilic syndrome (HES) and 5% of all GIST
- Rβ: Chronic Myelomonocytic Leukemia (CMML), Langerhans cell histiocytosis (LCH) and Chordoma
- PDGF ligand: Dermatofibrosarcoma protuberans (DFSP)

**Fibrosis, Asthma**
North – South
Neglected Diseases

- Group of about 20 communicable diseases, primarily occurring in developing countries
- These diseases represent major unmet medical needs in terms of morbidity, disability, mortality
- These needs are underserved by health authorities, funding agencies and the pharmaceutical industry for lack of funds, and lack of commercial incentives
- Rapidly changing landscape
  - Growing awareness in the northern hemisphere of globalization of diseases
  - New sources of private and gov't funding
  - New organizations, NGOs, PPPs
Disease Burden Distribution by Select World Bank Region, 2001

Percent

<table>
<thead>
<tr>
<th>Region</th>
<th>Communicable, maternal, perinatal, and nutritional conditions</th>
<th>Noncommunicable diseases</th>
<th>Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asia</td>
<td>44</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>70</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>High-income countries</td>
<td>87</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>World</td>
<td>37</td>
<td>53</td>
<td>11</td>
</tr>
</tbody>
</table>

Note: Numbers are rounded.

Source: Disease Control Priorities in Developing Countries, second edition, 2006, Table 4.1
Medicines of the rich world are only partially accessible in developing countries

World Pharma Market (Billion US$)

Developing Countries (ex Africa)

Africa

Developed Countries

Spectrum, Pharmaceutical Industry Dynamics, April 2002
Number of working hours to pay for full treatment courses (average worldwide price)

**Source:** WHO/CHD, CTD, DAP, EMC, GTB
Major health problems in the developing world

Three major killer diseases in Tropical Countries have been identified to be

- HIV/AIDS (32 million infected, approx. 3 million dying/year)
- Malaria (about 500 million infected annually, more than 1 million dying/year, mostly children)
- Tuberculosis (2 billion latently infected, 9 million new cases/year, 1.75 million dying/year)

These diseases – as many others - are neglected by the established pharma industry due to the real/perceived lack of sufficient commercial potential (90% of resources devoted to 10% of diseases)
Resistance is affecting nearly all global infectious diseases - but prevalence varies greatly

Acute Respiratory Infections (ARI) and bacterial meningitis
- 12 - 55 % penicillin resistance in *S. pneumoniae*

Diarrhea: shigellosis
- 10-90+ % amp, 5-95% TMP/SMZ resistance

Malaria
- chloroquine resistance in 81/92 countries

Sexually Transmitted Infections /STIs: gonorrhoea
- 5 - 98 % penicillin resistance in *N. gonorrhoeae*

Tuberculosis
- 2 - 40 % primary drug resistance

Source: WHO/CHD, CTD, DAP, EMC, GTB
The Novartis Institute for Tropical Diseases (NITD)
NITD @ Biopolis in Singapore

Surface: 4'900 m² (four top floors of the Chromos Building)
Fully operational BSL-2 and BSL-3 facilities including animal facility
Drug discovery disciplines: Medicinal chemistry, Analytics, Screening, Pharmacology, Dengue and TB biology
Mission of NITD

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
Research & Development Cycle / Activities of NITD within drug optimization cycles

NITD NGOs, Govt’s, CROs

Clinical Need

Clinical Drug Candidate

Product (Drug)

Academic Research

Basic Research Clinical Research Epidemiology

Drug Discovery

Academic Research

Dengue and TB Research Biology:
- Concepts
- Assays

Screens In Vitro

Pharmacology
- PK, Biomarkers, Efficacy models

Medicinal Chemistry

NITD Singapore

NITD/Novartis PHARMA

Pre-clinical Development

Synthesis/Upscaling Formulation Physico-chemical Parameters Toxicology

Development Candidate

Clinical Trials

Clinical Trials

Clinical Trials

Clinical Trials

Clinical Trials
New Tools are Needed

- New and well-validated drug targets with documented essentiality, epidemiology, drugability
- Predictive preclinical models – imaging technologies
- New Diagnostics: fast, reliable, cheap
- Biomarkers: capable to measure accurately via non-invasive technologies pharmacodynamic endpoints in early clinical trials
- New clinical trial methodologies based on state-of-the-art technologies
- New Drugs / new drug candidates / new drug combinations
Some constraints for the development of drugs for the developing world

Drugs for the developing world must have certain qualities:

- Potent (active at relatively low dosages)
- Easy to make – low cost of goods
- Stable under severe conditions (heat, humidity)
- Very well-tolerated (based on their selectivity)
- Orally bioavailable
- Absence of drug-drug interactions, for anti-TB drugs no interactions with antiretroviral drugs
Lead finding is critical....the classical approach
unfortunately not very successful!

Use High throughput screening, smart libraries, virtual approaches, fragment-based screens for hit discovery

There are very few validated targets
There are even fewer validated targets that are drugable

Source: Graphic adapted from Scott Biller (NIBR)
Lead finding via unbiased approaches in complex, cellular systems...*no free lunch!*

- Libraries
  - Chemicals
  - siRNAs
  - Nat Products
  - Mab’s

- Microbial cultures or infected cells; wt or sensitized through mutations, siRNAs, metabolic conditions such as low O₂, low nutrients

- “Hit ID”

- Target deconvolution through whole genome sequencing

- Hit ID

- New Medicine
Dengue Fever
Dengue Fever: Symptoms – Spread

- Mosquito-transmitted, viral infection
  
  \textit{(Aedes aegypti, Aedes albopictus)}

- Dengue fever is characterized by:
  - Sudden onset of fever
  - Lethargy
  - Painful headaches
  - Nausea and vomiting
  - Eye, joint, muscle pain, rash ("breakbone-fever")

- Dengue is believed to be spread through:
  - Rapid urbanization
  - Increased travel and trade
  - The lack of effective mosquito control efforts
Severe Dengue: Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS)

More severe, potentially lethal variants of DF, often following re-infection with different serotypes DEN 1-4 are:

- 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.

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

source: www.intercanalum.com.br/saude/dengue.html
Dengue Research Strategy at NITD - Potential interventions: virus or host

Mosquito bite

Onset of symptoms: high fever etc. 2-10 days after bite

Incubation period

Febrile phase

Fever typically lasts 3-4 days

Convalescence phase

2-3%

DHF/DSS

Reduce viral load
Target: virus

Prevent or treat DHF
Target: host factors

(Slow) Recovery 5 - 7 days after onset of symptoms
Target approach 1: Dengue virus life cycle

Viral targets
- E protein and viral enzymes

Host targets
- α-glucosidases, furin etc
- unprejudiced search using systems biology approaches
RNA genome and polyprotein

- 5'UTR
- + strand RNA genome
- 3'UTR

Translation

- NH₂
- COOH
- Furin
- prM
- C
- E
- NS1
- 2A
- 2B
- NS3
- 4A
- 4B
- NS5

Protease
Helicase
NTPase
5'ter RNAPase
Polymerase
Methyltransferase
Guanylyl transferase

N2B/NS3 protease
Signalase

Capsid
Membrane protein
Lipid bilayer
Envelope
RNA

Shi, 2002 Current Opinion in Investigational Drugs 3, 1567

Zhang et al., 2003

45 A. Matter, EPFL, Dec 3, 2007
NS5 polymerase: Multifunctional enzyme

- NS5 is a multifunctional protein
  - Methyl transferase (MTase) uses S-adenosyl methionine (Adomet) for methylation of 5’ Cap; also contains a guanylyl transferase function to add GTP cap
  - Interdomain region with nuclear localisation signal (NLS) and NS3 helicase binding site
  - Polymerase (Pol) domain containing conserved motifs found in all RNA dependent RNA polymerases (RdRp)
  - NS5 MTase and NS5 Polymerase are (highly) drugable targets
**NS5 Polymerase**

*Multifunctional enzyme*

- S-adenosyl-L-methionine Methyl Transferase
- RNA-dependent RNA polymerase
- Right-handed fold

Egloff et al., 2007

Yap et al., 2007

(+)-RNA → RdRp → Copy (-) RNA → Viral proteins

(−)-RNA → RdRp → Copy (+) RNA → Viral progeny
A mouse model for testing dengue drugs

Mouse model for Dengue infection validated at NITD
IP injection of tissue culture produced virus.
In Level 3 Biosafety Laboratory.
Reducing Dengue viremia with antiviral treatment

Nucleoside analogue, NS5 polymerase inhibitor.

In-vitro active against HCV and Dengue virus (EC50 17 µM)

Good oral availability and PK in-vivo.

Dengue viremia on day 3 post-infection after nucleoside inhibitor treatment

Vehicle low dose high dose

p=0.004

Low dose: 5 mg/kg
High dose: 50 mg/kg
Oral dosing twice daily

Schul et al, JID 2007
Tuberculosis
Mycobacterium tuberculosis

Cole et al. 1998, Nature 393, 537
Tuberculosis epidemiology

TB incidence rates (WHO Report 2002)

- ~2 billion people latently infected
- Annually 9 mio new cases with 1.75 mio deaths/year worldwide
- 50 mio with drug-resistant TB
- Disease on the increase due to HIV infection, immigration, globalization and increased trade
Why Tuberculosis?

- There is an urgent need for development of new anti TB-drugs.
- No new drugs developed in 30 years.
- Diagnostics based on 19th century technology.

Mycobacterium tuberculosis

pictures from: www.anapath.necker
Tuberculosis research strategy: major goals

Development of oral anti-mycobacterial drugs with new mode of action that fulfill at least one of the following criteria:

- active against Multi Drug Resistance (MDR) TB and the recently identified extremely resistant (XDR) TB
- active in immunosuppressed/AIDS patients
- improved ‘sterilizing’ activity, i.e. shorter (‘2 month’) and more effective treatment of active and / or latent TB
Tuberculosis: Concepts, Targets, Compounds

Drug resistant mutant bacillus

Drug resistant non-replicating wild type bacillus

Growth-essential targets (e.g. DHFR, DHPS, Pantothenate kinase)

Survival-essential targets (GCGH targets)

Growth- and survival-essential targets (PA824 back-up)
Malaria
Restarting Malaria Research....

- Pioneering antimalarial drug discovery in the context of an international public-private consortium
- Output of high-quality drug candidates
- Scientific Advances
- Funders: Wellcome Trust, Medicines for Malaria Venture, EDB, Novartis (in kind)
- Program Grant for 5 years, 20 mio USD
- Research done in a global consortium of 10 collaborating institutions
The Malaria Global Health Burden

- Infects approximately 500 million people each year
- >1 million infected people (mostly children) die each year
- Drug resistance to most common antimalarials is increasing
Malaria Life Cycle
Two Major Program Goals

- Drug Discovery for malaria based on novel drug targets, with the aim to find
- a one dose cure* for *Plasmodium falciparum*, and
- a curative modality* for *Plasmodium vivax*

- These goals have been set jointly by MMV, Wellcome Trust and NITD, and have been approved by the boards of MMV and the Wellcome Trust

* This can be a single compound, but more likely is a drug combination
Nine Projects / Targets that were set in 2006

- Novel drug targets in the liver stages (hypnozoites) of *P. vivax*: *Challenges!*
- Chemogenomics of *P. falciparum* with novel compound libraries, including a large (pure) Natural Product library – *very successful*
- Folate metabolism – Cyclohydrolase: *Assay being developed*
- Transcription – Helicases: *NoGo*
- Malarial Signal Peptide Peptidase (mSPP): *good progress*
- Anaerobic glycolysis – Hexose Transporter: *NoGo*
- Signal Transduction – pfCDPK1 kinase Inhibitors: *difficult*
- Redox metabolism – Thioredoxin Reductase: *NoGo*
- Artemisinin analogs: *very successful*
- New DHFR inhibitor: *very successful*
There are about 20 tropical diseases that are largely neglected by Western medicine due to lack of commercial incentives (10/90 gap).

Burden of disease is particularly high for respiratory tract infections, HIV/AIDS, malaria and tuberculosis.

New tools are urgently needed:
- Diagnostics
- Vaccines
- Drugs
- Microbicides
- Insectizides
These diseases are scientifically/technically highly approachable (with the possible exception of vaccines)

Technical solutions must be adapted to the particular needs of patients in tropical countries

Adoption of these solutions is by no means guaranteed; requires active participation of researchers, health authorities and civil society of the developing country

But: Relatively modest investments can make a big difference

There is a huge potential to innovate!
Thank you!