

Natural Products Unit

# Accessing microorganisms as genetic resources for natural products in drug discovery

**Frank Petersen**

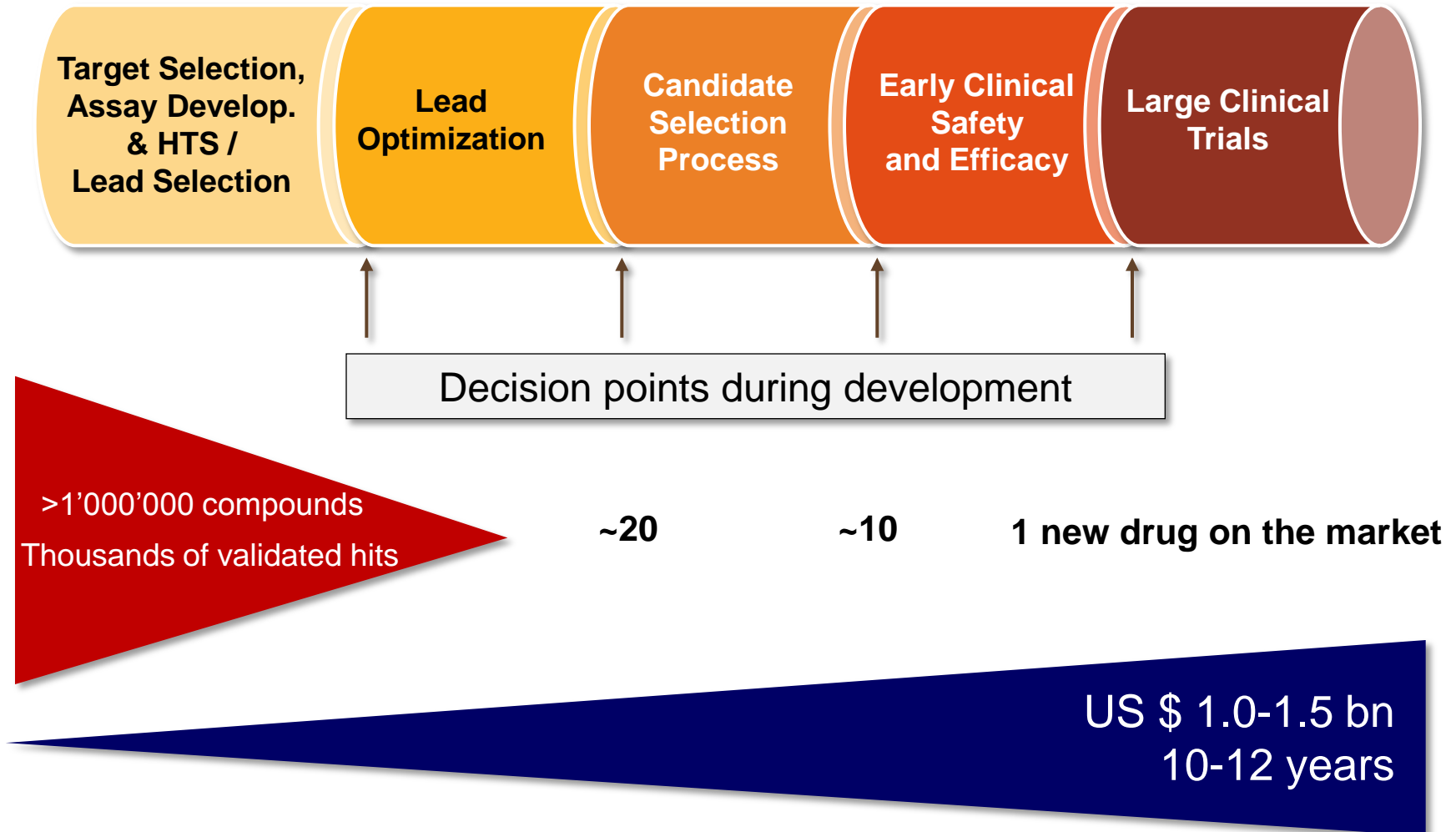
**Natural Products Unit, Novartis Pharma AG**

Feb 5, 2013, IFPMA Side event, WIPO IGC 23



# Success rate vs investments in drug development

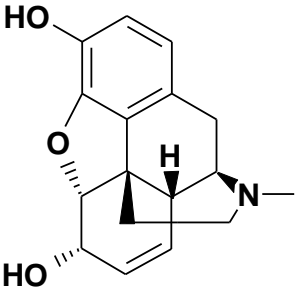
*An estimate*



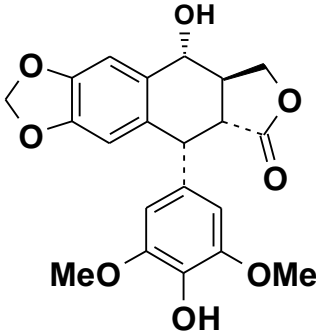
(Kola & Landis, Nat Rev Drug Disc, 2004)

|Leveraging Genetic Resources in Pharma R&D| Frank Petersen

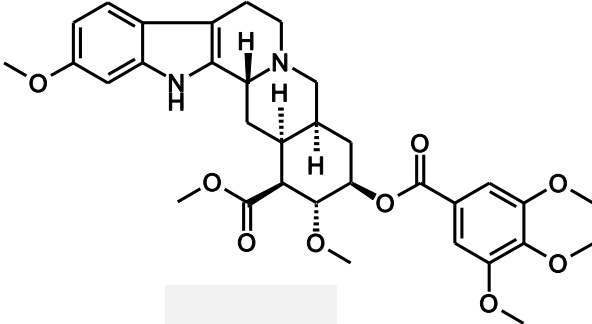
# Natural products from the traditional medicine stood at the cradle of the pharmaceutical industry



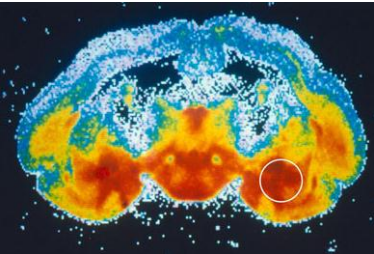
Morphium



Podophyllotoxin

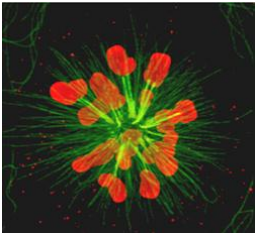


Reserpine

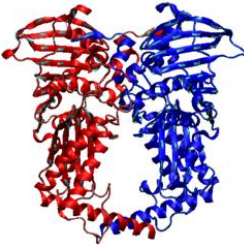


Opiate receptor

## Pain



Spindle formation



topoisomerase II

## Cancer



Dopamine-biochemistry

## Morbus Parkinson

# Dimension of biological diversity

## Terrestrial ecosystems

- **Mega-diversity regions:**  
E.g. S. America, Australia, Indonesia
- **Hotspots of diversity:**  
Tropical rainforests: 4 % of the land surface with 50 % of all species on Earth

➤ ~ 150'000 natural products

## Marine ecosystems

- **Highest degree of biodiversity**
- **90 % of all organisms classes**

➤ ~ 15'000 natural products

# Natural products classes and their introduction in human therapy

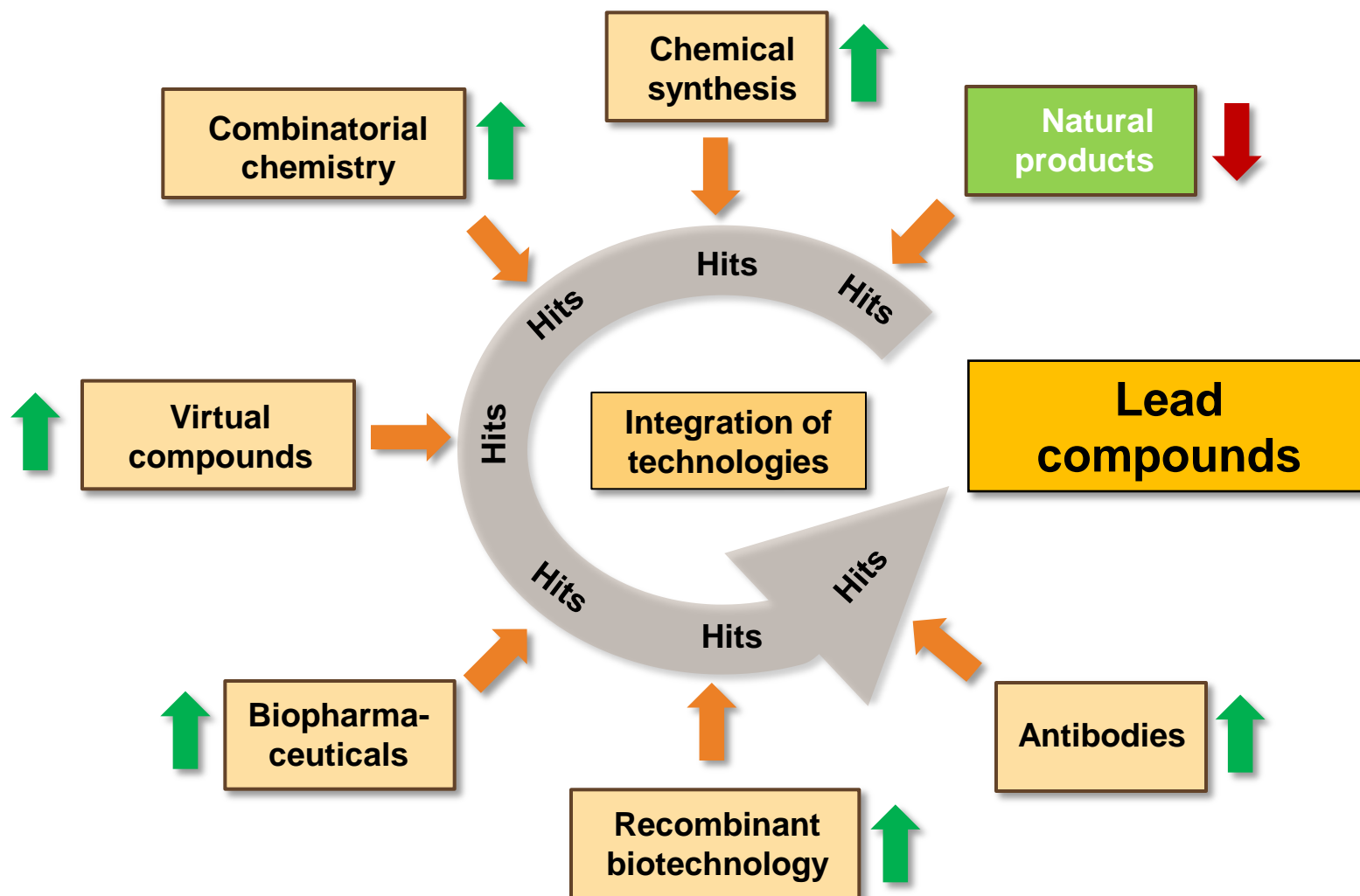
Microbial Group	Published Natural products	Approved NP-classes (1981- 06/2010)*
<i>Actinomycetes</i> (einschl. anderer Bakteriengruppen)	12'959	14
<i>Myxobacteria</i>	595	1
Fungi	13'416	5
Plantae	~130'000	5

\*Only NPs considered, indentified after 1970

Antibase, 2010  
Ganessan.: Cur. Opinion Chem Biol: 12; 306 (2008)  
Hughes: Nature Rev, 2008, 2009, 2010

# Sources for new pharmaceuticals

*Natural products are not the only substance library any more*



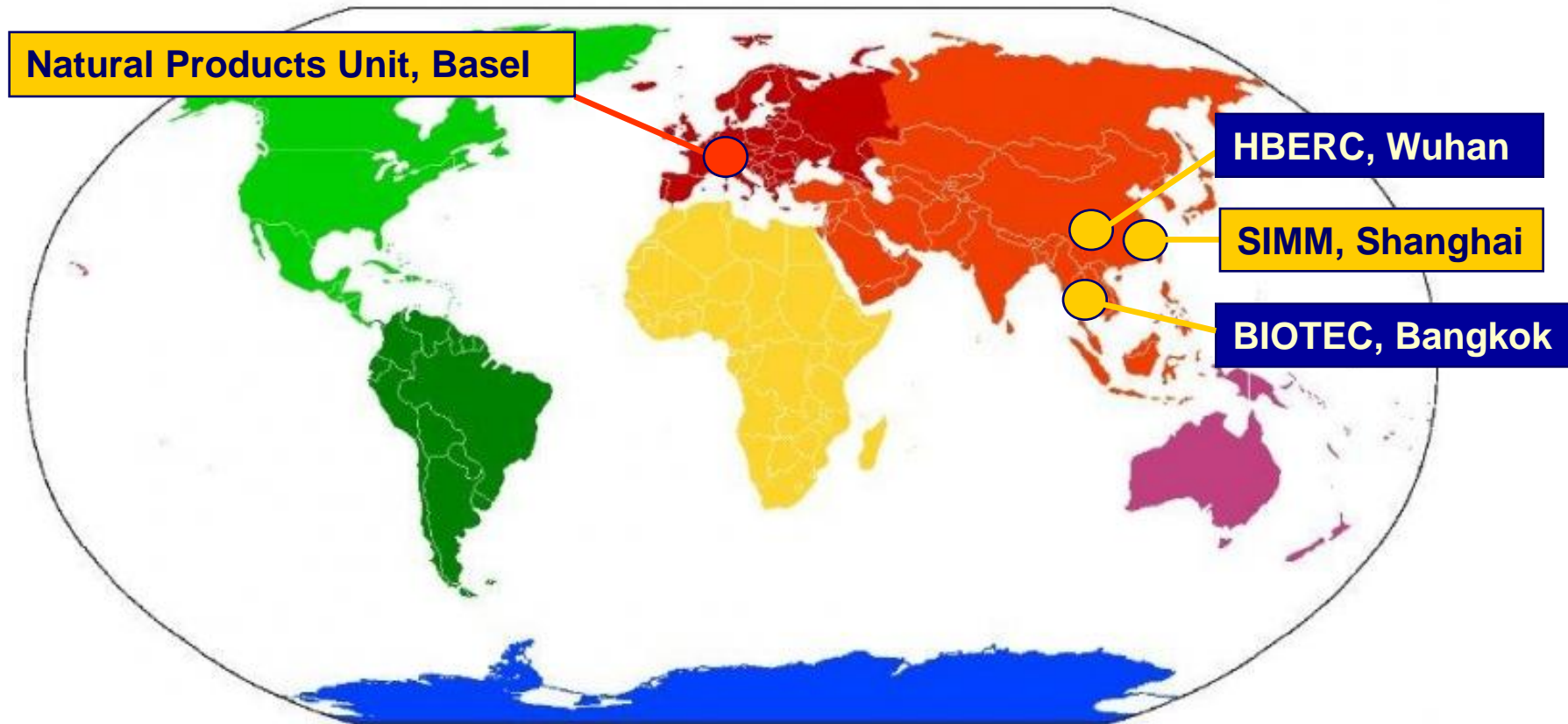
# Termination or reduction of pharmaceutical natural products research during the last two decades

- Reduction of antibiotics research and focus on new drug discovery technologies
- No compatibility with high throughput screening concepts
- Competition with synthetically derived substance libraries
- Legal uncertainties (eg IP) and ABS obligations in the CBD context
- Novartis AG is one of the last big pharmaceutical companies conducting bioprospection

<b>BMS</b>	<b>(US)</b>
<b>Abbott</b>	<b>(US)</b>
<b>Merck</b>	<b>(US)</b>
<b>Monsanto</b>	<b>(US)</b>
<b>Lilly</b>	<b>(US)</b>
<b>Schering-Plough</b>	<b>(US)</b>
<b>Glaxo SmithKline</b>	<b>(UK)</b>
<b>Bayer</b>	<b>(D)</b>
<b>B. Mannheim</b>	<b>(D)</b>
<b>B. Ingelheim</b>	<b>(D)</b>
<b>Novo Nordisk</b>	<b>(DK)</b>
<b>Roche</b>	<b>(CH)</b>
<b>Syngenta</b>	<b>(CH)</b>
<b>Sanofi-Aventis</b>	<b>(F)</b>

<b>Pfizer</b>	<b>(US)</b>
<b>Novartis</b>	<b>(CH)</b>
<b>Astellas</b>	<b>(J)</b>
<b>Takeda</b>	<b>(J)</b>
<b>Kirin Breweries</b>	<b>(J)</b>
<b>Ajinomoto</b>	<b>(J)</b>
<b>Kyowa Hakko</b>	<b>(J)</b>
<b>Taisho</b>	<b>(J)</b>
<b>Eisai</b>	<b>(J)</b>

# Overview of recent bioprospection partnerships



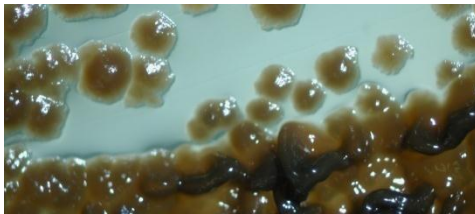
- **Protection of biological diversity**
- **Sustainable use of leveraged genetic resources**
- **Fair and equitable sharing of benefits**



# Overview sourcing collaborations

*The past 15 years*

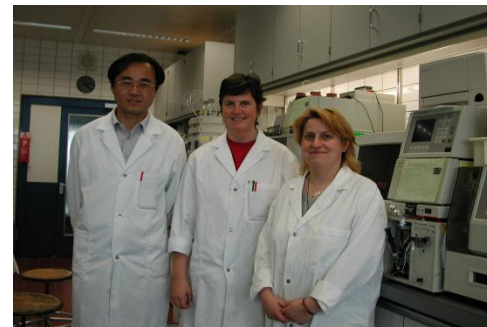
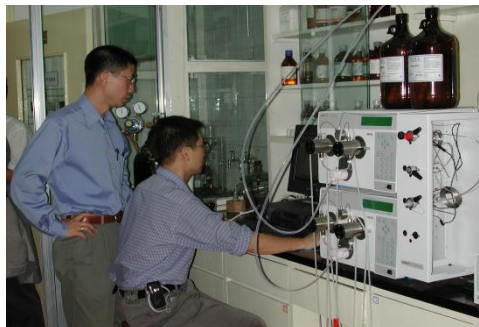
- 1999: Microbial sourcing project with Hubei Biopesticide Engineering Research Centre, Wuhan
  - Capacity build-up by technology transfer, training, supply of equipment and scientific advice
  - In 2006, Chinese partner received significant financial support from Chinese government
  - In the meantime, new co-operations with other companies based on implemented technologies and know-how
  - 2009: One compound in late pre-clinical research at Novartis



# Overview sourcing collaborations

*The past 15 years*

- 2001: Plant natural products project with Shanghai Institute of Materia Medica
  - Drug discovery with purified natural compounds from plants and fungi used in Traditional Chinese Medicine
  - Transfer and training in newest analytical and preparative technologies (investments exceeded in-house figures at that time)
  - 8 visiting scientists trained at Novartis Basel; full cost coverage
  - Significant number of pure natural products from medicinal plants delivered to Novartis for in-house screening



# Overview sourcing collaborations

*The past 15 years*



- 2005: Microbial sourcing collaboration with Biotec Institute, Thailand
  - Case study
- 2006: Plant natural products project with Kunming Institute of Botany
  - Intensified drug discovery efforts with purified natural compounds from plants and fungi used in Traditional Chinese Medicine



# Case study Biotec, Thailand

## Overview

- Contract signed in 2005 by H.E. Korn Thapparansi, Ministry of Science and Technology, Prof. Morakot Tanticharoen, Director Biotec, and Dr. Daniel Vasella, CEO Novartis
- First term started June 2005
- Third term until 2014
- Main goals:
  - Support BIOTEC to become center of excellence in South-East Asia
  - Include Thai biodiversity in modern drug discovery



# Case study Biotec, Thailand

## Structure of Partnership

**Novartis AG**

Testing of samples  
in screening systems at Novartis

Financials, Know-how  
transfer; royalties

Submission of  
microbial samples, isolated  
natural products, or promising NP  
from Biotec screening

**Biotec, Bangkok**

Isolation of microorganisms (bacteria and fungi) and of pure natural products  
Screening samples for own research activities

Capacity building: Foster scientific strategy of Biotec to become a center of  
excellence for natural products research in SE Asia

Education: Finance internships of Biotec scientists visiting laboratories of  
natural products research and screening departments at Novartis Pharma

# Case study Biotec, Thailand

*Knowledge transfer: On site training at BIOTEC*

- Seminars by 3 Novartis experts for drug discovery in infectious diseases coming from USA, SP and CH in May 2005
- 2 courses à 4 weeks each at BIOTEC to transfer knowledge for the isolation of actinomycetes bacteria – the most important source of natural antibiotics



# Case study Biotec, Thailand

*Knowledge transfer: Visiting scientists in Novartis laboratories in Basel*

- So far 8 Biotec scientists trained in chemistry, microbiology, High Through-put drug and animal pathogen screening at Novartis in Switzerland – totaling in 23 months of training
  - Capacity build up in microbiology, chemical profiling, and biological screening at BIOTEC
  - Dissemination of specific microbiology know-how to scientists from other SE Asian countries
  - Advice in new strategy and introduction of new research concepts at BIOTEC



# Case study Biotec, Thailand

## *Overview of achievements*

- > 7'200 microorganisms received for drug discovery
  - BIOTEC is owner of strains
  - Novartis receives time-limited, exclusive user right
  - BIOTEC conducts own research programs with same strains



- Constantly increasing number of natural products from Thailand investigated in HTS at Novartis
  - 2006: 10 % of all isolated NPs at Novartis from BIOTEC strains
  - In 2009: 30 % of all isolated NPs at Novartis from BIOTEC strains
- So far no development candidate identified





# Tracking the source of genetic resources

*Reliable database and clear SOPs ensure transparency*

## Registration of genetic sources/ material in databases

**Strain or plant extract**



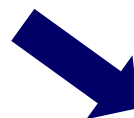
**Barcode or unique name**  
e.g. 1000851036



Sample	Results	Sample details	Result details
sample details			
Name	Type	Class	Medium
1000851036	STRAIN	FUNG	
Method			
Prompt	Value	Unit	
Species	BEAUVERIA FELINA		
Taxonomic level 2	SORDARIOMYCETES		
Taxonomic level 1	ASCOMYCOTA		
Sample origin	REU		
Sample supplier	BTR		
Lab journal Nbr	E-31479		
Sequence region	ITS1F-ITS4		

**Registration in NP db NICE incl. country of origin & supplier**

Sample	Results	Sample details	Result details
Selected result details			
Name	Medium		
VN36978-A001	MP10-00.00		
Method			
MAINCULT			
Prompt	Value	Unit	
Cultivation temperature	24		
Cultivation duration	6.0		
Cultivation flask	F52		
Media group	A		
Effective harvest date	19-08-2002		
Cultivation start date	13-08-2002		
Cultivation media volume	50.00		



**Cultivation and Extraction:**  
**Data stored in NP db NICE**

# Tracking the source of genetic resources

*Reliable database and clear SOPs ensure transparency*

## Connection of biological results to genetic sources in databases

**Isolation of pure compounds**



**Unique compound code**



**Registration in central chemical db WITCH, incl. reference to source and in NP db NICE**

Batch 1 (NVP-AST069-NX-1)

Batch Date:  Initial Amount:

Building Block Information (local storage, not for central BB Archive)

Available	Amount:	Lab Location:
1 <input type="checkbox"/>	<input type="text"/> g	<input type="text"/>
2 <input type="checkbox"/>	<input type="text"/> g	<input type="text"/>

Purity:

Rand. Screen Box:

Programme:	Code	TA	Name
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Supplier:

To Be Tested On:

Prescr. of Solubility:

Batch Comment:



**Biological activities of compound stored in db Pharon/Avalon**

# Conditions for a successful use of genetic resources in NP-research under CBD regulation

## Legal certainty

- **National legislation with regulation of access rights necessary**  
(-> Art. 6 Nagoya Protocol)
- **Governmental entitlement of partner institute to negotiate sourcing contract**
- **Inclusion of indigenous groups by collaboration partner or governments**  
(-> Art. 6 &13 Nagoya Protocol)

## Exclusivity/ Transparency

- **No exclusive access to biological resources of a country necessary;**  
however time-restricted exclusivity important for research cooperation
- **Transferability of biological material to the laboratories of the industry partner**
- **Implementation of transparency instruments to cover origin and location of genetic resources at industry partner**

## Prior informed consent

- **Flexible definition of PIC terms due to complexity of drug discovery process and long time horizon**  
**Coverage of broader range of research and development activities**  
(-> Art. 5.1 Nagoya Protocol “mutually agreed terms”)

# Conditions for a successful use of genetic resources in NP-research under CBD regulation

## Fair and Equitable

- **Open and flexible negotiations according to needs; mutual definition of CBD-benefits by contract parties (significant differences of scientific expertises and know-how)**
- **Mechanisms to ensure equitable sharing of short-, mid and long-term benefits with respect to risks and success rates (-> Art. 5 and annex of Nagoya Protocol)**

## Education

- **THE key for sustainable capacity building; one of the main motivations to contact Novartis' NP group**
- **Definition by collaboration partners and adapted to specific needs and capabilities on site**

## IP and financial compensation

- **Transparent regulation of ownership of inventions; resulting patents filed according to international patent law**
- **Licence and royalty payments**