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

Target Selection, Assay Develop. & HTS / Lead Selection

Lead Optimization

Candidate Selection Process

Early Clinical Safety and Efficacy

Large Clinical Trials

Decision points during development

>1’000’000 compounds
Thousands of validated hits

~20
~10
1 new drug on the market

US $ 1.0-1.5 bn
10-12 years

(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.

Opiate receptor: Morphium

Spindle formation: Podophyllotoxin

Topoisomerase II: Reserpine

Pain

Cancer

Morbus Parkinson

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

| Morphium | Podophyllotoxin | Reserpine |

| Opiate receptor | Spindle formation | topoisomerase II |

| Morbus Parkinson |

| Pain |

| Cancer |
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

Marine ecosystems
- Highest degree of biodiversity
- 90% of all organisms classes

- ~ 150’000 natural products
- ~ 15’000 natural products
Natural products classes and their introduction in human therapy

<table>
<thead>
<tr>
<th>Microbial Group</th>
<th>Published Natural products</th>
<th>Approved NP-classes (1981-06/2010)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Actinomycetes</em> (einschl. anderer Bakteriengruppen)</td>
<td>12‘959</td>
<td>14</td>
</tr>
<tr>
<td><em>Myxobacteria</em></td>
<td>595</td>
<td>1</td>
</tr>
<tr>
<td>Fungi</td>
<td>13‘416</td>
<td>5</td>
</tr>
<tr>
<td>Plantae</td>
<td>~130‘000</td>
<td>5</td>
</tr>
</tbody>
</table>

*Only NPs considered, indentified after 1970

Antibase, 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

<table>
<thead>
<tr>
<th>Company</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>(US)</td>
</tr>
<tr>
<td>Abbott</td>
<td>(US)</td>
</tr>
<tr>
<td>Merck</td>
<td>(US)</td>
</tr>
<tr>
<td>Monsanto</td>
<td>(US)</td>
</tr>
<tr>
<td>Lilly</td>
<td>(US)</td>
</tr>
<tr>
<td>Schering-Plough</td>
<td>(US)</td>
</tr>
<tr>
<td>Glaxo SmithKline</td>
<td>(UK)</td>
</tr>
<tr>
<td>Bayer</td>
<td>(D)</td>
</tr>
<tr>
<td>B. Mannheim</td>
<td>(D)</td>
</tr>
<tr>
<td>B. Ingelheim</td>
<td>(D)</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>(DK)</td>
</tr>
<tr>
<td>Roche</td>
<td>(CH)</td>
</tr>
<tr>
<td>Syngenta</td>
<td>(CH)</td>
</tr>
<tr>
<td>Sanofi-Aventis</td>
<td>(F)</td>
</tr>
<tr>
<td>Pfizer</td>
<td>(US)</td>
</tr>
<tr>
<td>Novartis</td>
<td>(CH)</td>
</tr>
<tr>
<td>Astellas</td>
<td>(J)</td>
</tr>
<tr>
<td>Takeda</td>
<td>(J)</td>
</tr>
<tr>
<td>Kirin Breweries</td>
<td>(J)</td>
</tr>
<tr>
<td>Ajinomoto</td>
<td>(J)</td>
</tr>
<tr>
<td>Kyowa Hakko</td>
<td>(J)</td>
</tr>
<tr>
<td>Taisho</td>
<td>(J)</td>
</tr>
<tr>
<td>Eisai</td>
<td>(J)</td>
</tr>
</tbody>
</table>
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

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 départements 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 BIOTECH
  - Dissemination of specific microbiology know-how to scientists from other SE Asian countries
  - Advice in new strategy and introduction of new research concepts at BIOTECH
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

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

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

Biological activities of compound stored in db Pharon/Avalon
Conditions for a successful use of genetic resources in NP-research under CBD regulation

- 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)
- 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
- 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”)

Legal certainty

Exclusivity/Transparency

Prior informed consent
Conditions for a successful use of genetic resources in NP-research under CBD regulation

- 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
  \(\Rightarrow\) Art. 5 and annex of Nagoya Protocol
- 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
- Transparent regulation of ownership of inventions; resulting patents filed according to international patent law
- Licence and royalty payments