

Prof. Dr. Frank Petersen

Novartis – Collaboration and Collective Gain

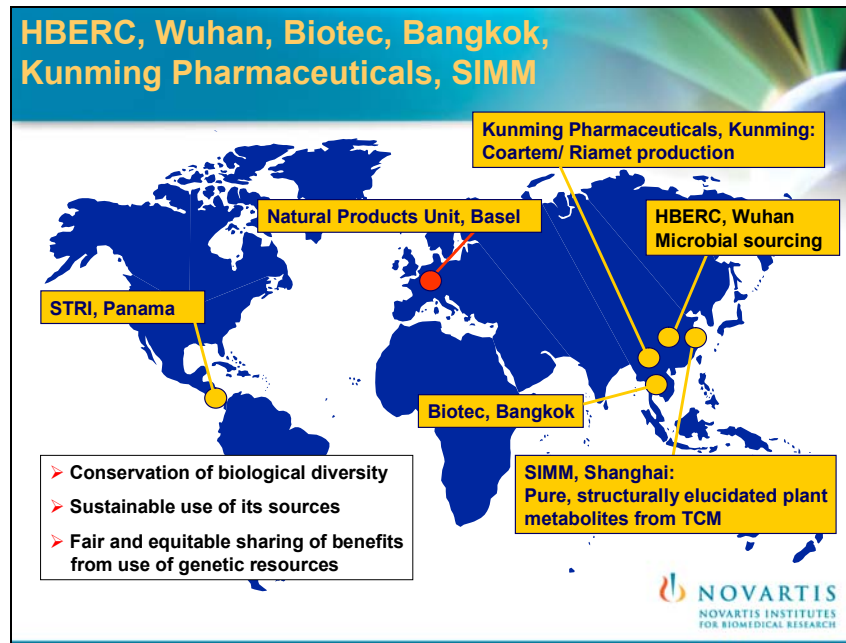
The importance or impact of technologies and research concepts are permanently balanced in industry. The same is true for the natural products programs in the pharmaceutical industry. There are many good reasons to leverage the unusual diversity of evolutionarily selected molecules in drug discovery efforts. On the other hand, the use of those molecules includes intrinsic hurdles or challenges, which some companies may not be willing to take.

Slide 1

Industrial NP Research	
Strengths/ Opportunities	Limitations/ Threats
<ul style="list-style-type: none">▪ Nature a non exhausted source for new pharmacophores▪ NP cover different chemical space compared to synthetics▪ Potential with difficult target proteins▪ Potential with new targets emerging from genomics▪ Pathfinders to new modes of action▪ Proven track record▪ Chance of business build-up with countries of high biological diversity	<ul style="list-style-type: none">▪ NP research in competition eg with CC or in-silico techn.; aggressive expansion of screening libraries leads to "dilution effect" of NPs▪ Complexity of NP major hurdle for derivation follow-up▪ Successful drug discovery activities without NP libraries▪ Bioprospecting collaborations time-consuming and personnel intensive▪ Legal situation in originating countries sometimes unclear (ethnic minorities, traditional/ common knowledge), uncertain outcome of curr. IP disc.

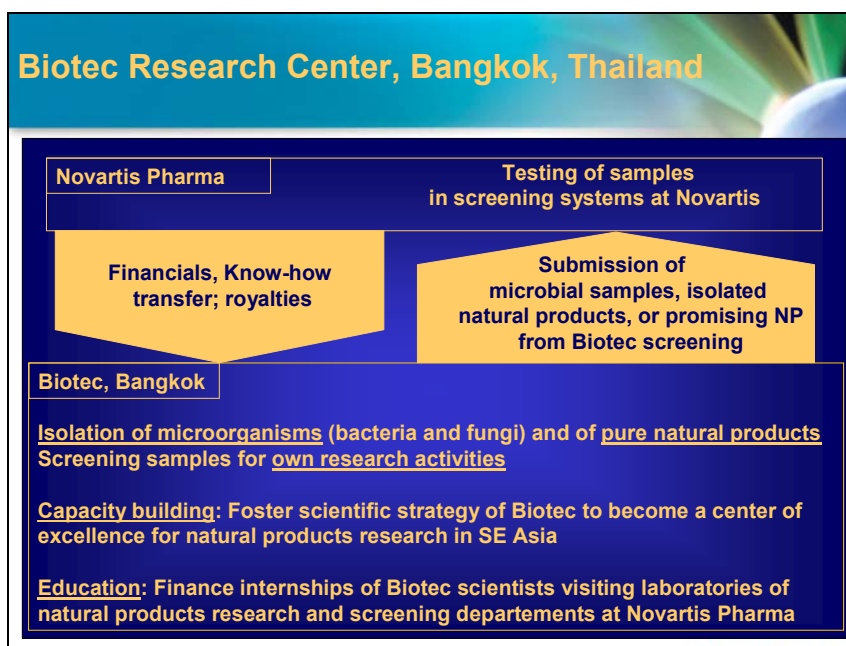
Novartis is strongly committed to natural products based research. A key aspect of this commitment is the creation of external partnerships with countries of high biological diversity. Currently Novartis focuses on collaborations with China and Thailand and in parallel is constantly evaluating other opportunities in order to diversify the access to biological sources.

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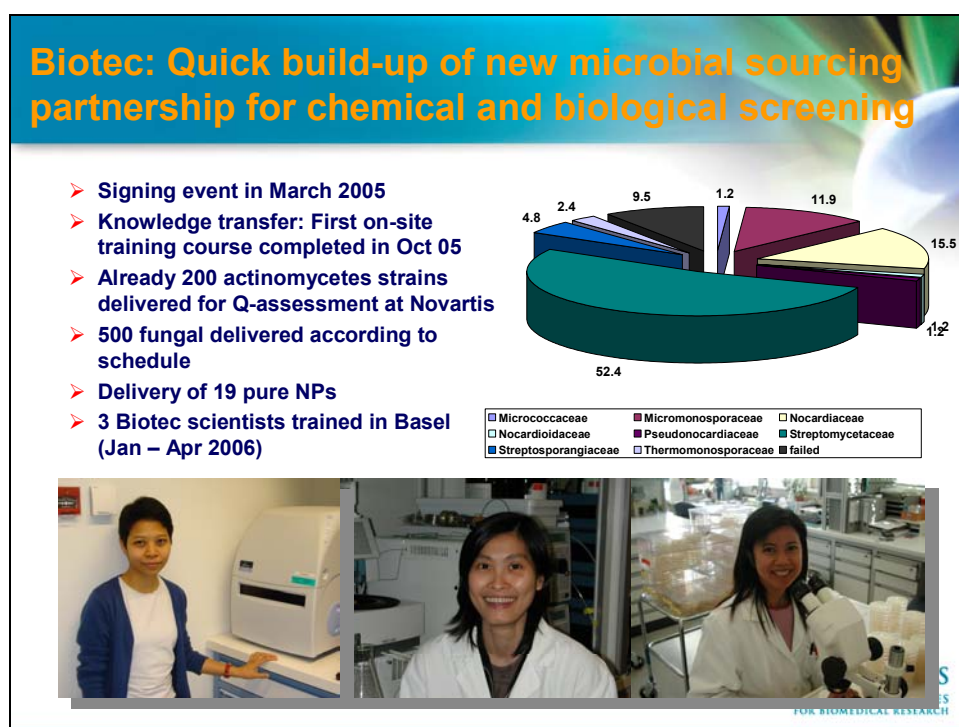
Partner institutes chosen by Novartis are internationally acknowledged specialists in the field of microbial and plant related natural products research. An integral part of current partnership agreements is the exchange of know how by on-site training sessions, the education of scientists in the laboratories of the Novartis Institutes of Biomedical Research and the financing of technology related investments. In the cooperation contracts, success related milestones or royalty payments are also defined.

Slide 3



The project and investment goals are mutually defined in joint steering committee meetings, which are an important instrument to monitor project progress and, if necessary, to redirect collaborations. In the microbial sourcing collaborations, Novartis is responsible for the implementation of specific microbiology skills at the site of partner institutes, guaranteeing the high quality criteria of microbial strains as starting points for Novartis' internal project activities.

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A particularly successful cooperation with the Shanghai Institute of Materia Medica should be mentioned here. Over a period of 6 years, Novartis received more than 1500 isolated molecules from plants of China's traditional medicine from its Chinese partner. From its side, Novartis contributed significantly to the implementation of technological innovations at the Shanghai based institute. There are currently several compounds being considered for closer preclinical investigation at Novartis.

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Shanghai Institute of Materia Medica

Goals

- Drug discovery with purified natural compounds from plants and fungi used in Traditional Chinese Medicine

Time

- Six years collaboration (8. 2001 to 8. 2007); licensing candidates offered by Chinese partners

Project management


- Joint Steering Committee
- Semi-annual meetings in Basel/ Shanghai



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Mutual benefits being shared

- **Know how transfer to SIMM**
 - Newest analytics and prep technologies
 - Scientist and techn training at Novartis and SIMM site
 - NP lectures by Novartis experts for students at SIMM and University of Shanghai
- **Financial Support to SIMM**
 - Equipment and running costs
 - Full training costs, visiting scientists of Novartis labs in Switzerland
 - Milestone payments, royalties
 - Modern electronic database systems
- **Research Progress**
 - Several fold increase of scientific publications since project start
 - Significant number of pure plant metabolites delivered to Novartis for in-house screening
 - First compounds in closer evaluation and development of licensing opportunities



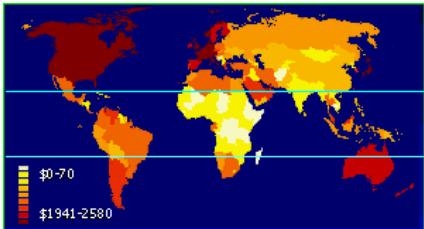
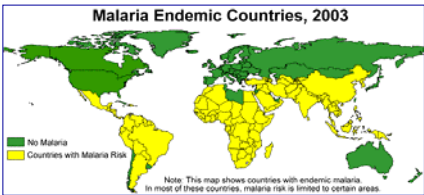

Although the Rio-Convention came into force more than 10 years ago, legal uncertainties regarding entitlement of institutes to start bioprospecting endeavours

with industrial partners remain; undetermined responsibilities and authorities of national government and local administration, lack of official contact points within a country and the much discussed Access and Benefit Sharing framework. However, this issue is by no means an exclusive problem of biodiversity rich countries: the majority of the Western nations also failed to implement suitable modus operandi.

The most advanced Novartis project benefiting from traditional knowledge is related to a traditional Chinese medicine. *Artemisia annua* is a plant, which was used in China against malaria since more than 2000 years.

Slide 7


Malaria – A global health burden of socio-economic relevance



- 40% of the world population live in malaria regions
- 300-500 Mio infections per year (80% in Africa)
- 1,5-2.7 Mio deaths per year (> 90% in Africa; primarily children and pregnant women)
- Increasing emergence of multi drug resistant *Plasmodium falciparum* strains
- Annual financial burden of US\$ 12 bio in African countries

GNP – Per capita (1995)

Source: WHO Roll Back Malaria 2003





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The active ingredient, artemisinin, was isolated in China in 1977 and demonstrated potent and highly selective activity against Plasmodia. The multi drug resistant *Plasmodium falciparum* can be effectively killed with the unusually structured natural product. In a joint development project with Chinese governmental institutes, an artemisinin derivative together with another plasmodicidal drug substance were combined in one tablet and were introduced successfully as Coartem[®]/ Riamet[®] onto the pharmaceutical market in 1999. In 2001, the WHO added the anti-malaria drug to its essential medicines list.

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**Novel therapeutic for malaria:
Multi drug resistant Plasmodia and a NP from TCM**

		
<i>Anopheles sp.</i>	<i>Artemisia annua</i>	Artemisinin

- 340 AD: *Qinghao* (= *Artemisia annua*, Sweet Annie) Traditional treatment of fever described in a Chinese medical handbook
- 1977: Structure elucidation of artemisinin and its identification as the active principle against plasmodia at the Institute for Earth Physics in Shanghai, China
- 1994: Collaboration contract between China and Novartis for the joint development of a combination drug in one tablette with an artemisinin derivative and lumefantrine against multi drug resistant malaria

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In the following years, Novartis implemented the whole supply chain management. Significant investments were made in seed development; horticulture capacity was expanded in Africa and China and manufacturing infrastructure was put in place. Together with Chinese industry partners, the syntheses of the drug substances were developed to production scale and GMP conform processes were established in China.