Biodiversity and natural products based therapeutics in medicine

Frank Petersen

Head Natural Products Unit, Novartis Switzerland

Swiss Biodiversity Forum

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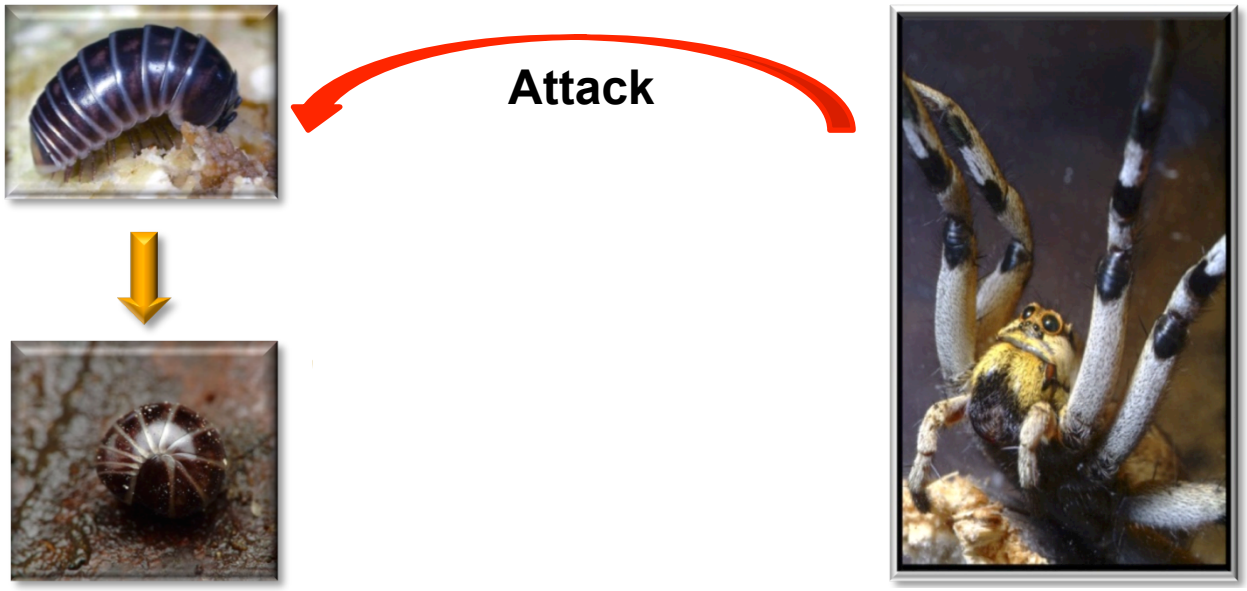
Natural Products – Fitness factors

How to survive in nature

- **European millipede *Glomeris marginata* is a prey of *Lycosa sp.* wolf spiders (“tarantula”)**



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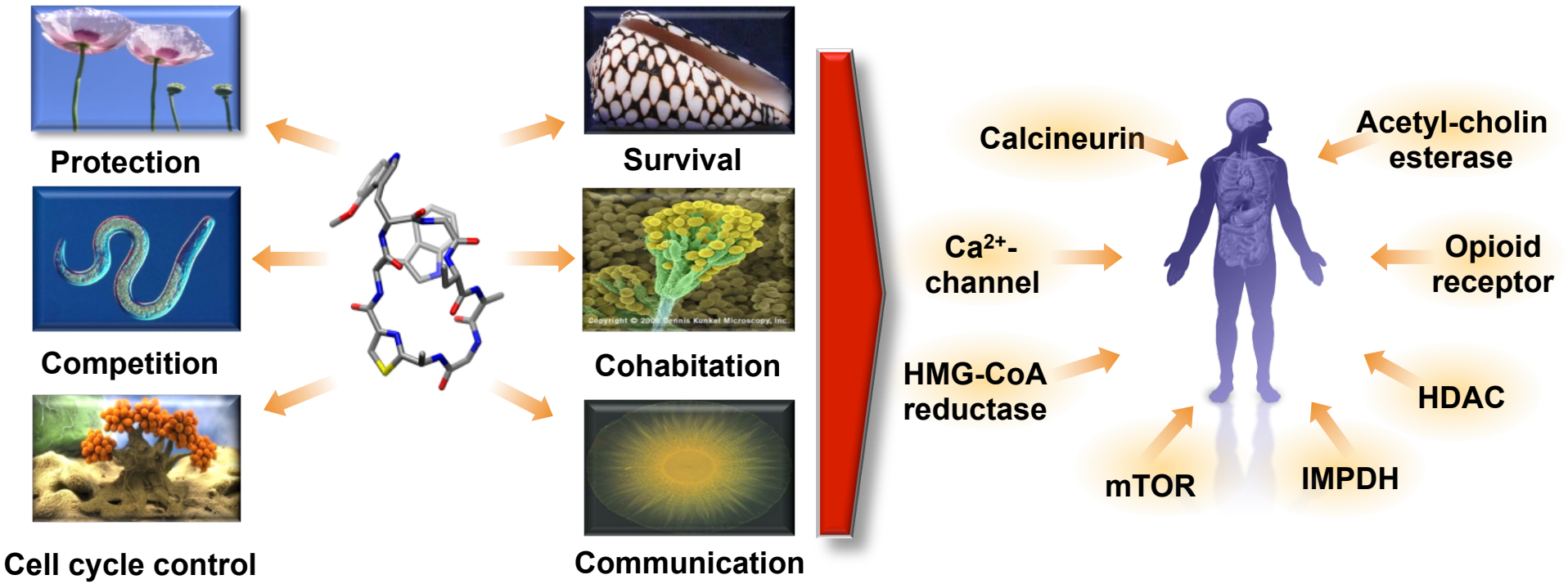
Natural Products provide paths to new therapies

Targets of NP in nature are also involved in human pathophysiologies



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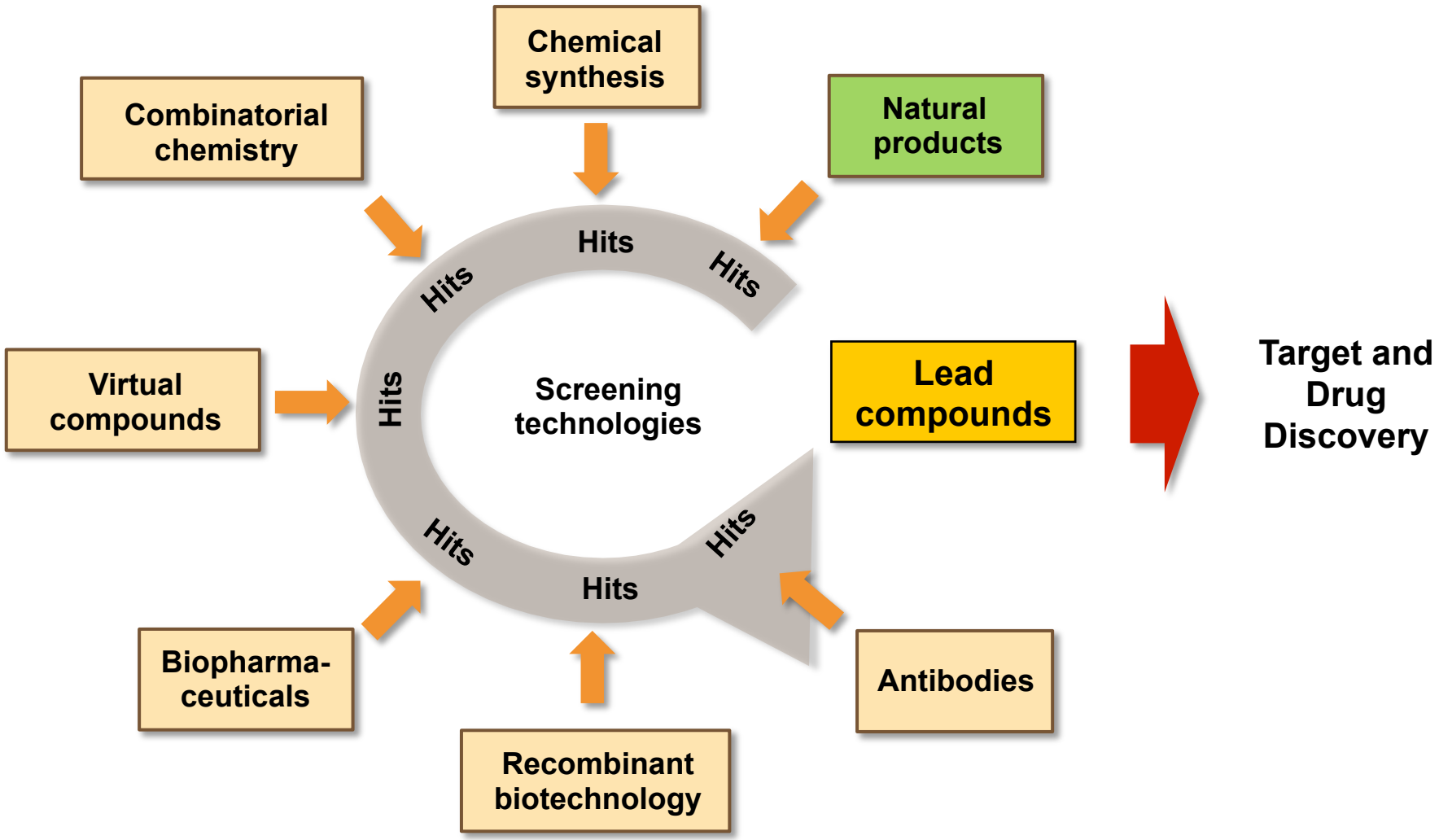
Sources for new pharmaceuticals

Natural products as a compound source for complementary drug discovery concepts



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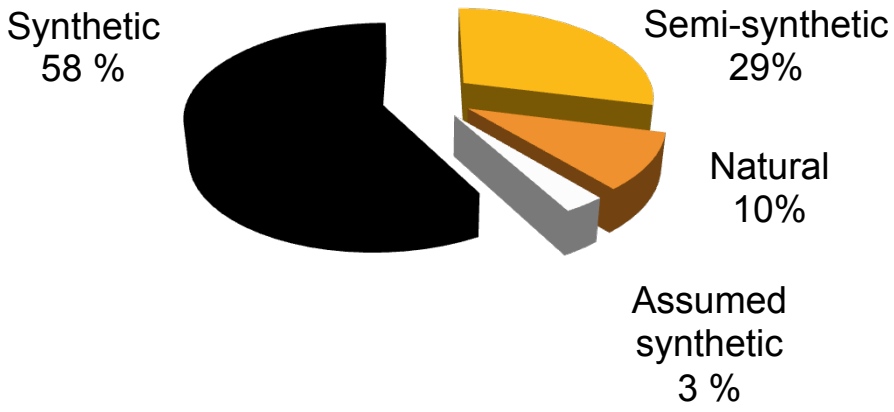
Natural Products provide paths to new drugs

The therapeutic perspective

- **Natural products based compounds for therapeutic innovation**
  - Account for 39% of 1000 marketed drugs (2010)
- **Majority of NP classes, approved between 1981- 03/2015**

Analysis of 1000 marketed drugs: Origin of compounds



Bade et al., European J. of. Med. Chem. ***2010****, 5646-5662*

Approved NP classes and semi-synthetics between 1981- 03/2015

Microbial Group	Published Natural Products	Approved NP-classes (1981-3/ 2015)	Drug approvals of related derivatives (1981-3/2015
Actinomycetes (incl other bacterial taxa	12'959	17	29
Myxobacteria	595	1	1
Fungi	13'416	5	17
Plantae	~130'000	11	12

*Only NPs classes considered, identified **after** 1970

Antibase, ***2010****; Ganessan:. Cur. Opinion Chem Biol: 12; 306 (****2008****)*
*Hughes, Mullard: Nature Rev****, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015***
Drugs.com 2015

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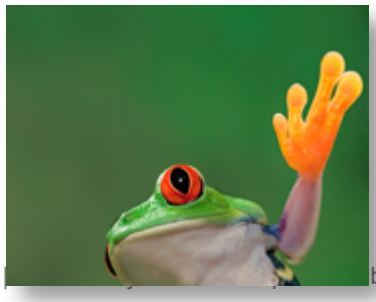
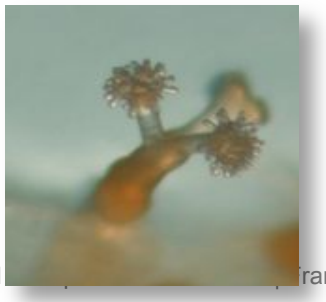
Biodiversity regions and described natural products

- **Terrestrial**
  - Mega-diversity regions: E.g. S. America, Australia, Indonesia
  - Hotspots of diversity: Tropical rainforests: 4 % of the land surface with 50 % of global diversity
  - ~160'000 natural products described

- **Marine**
  - Highest degree of biodiversity
  - 90 % of all organisms classes
  - ~ 15'000 natural products described

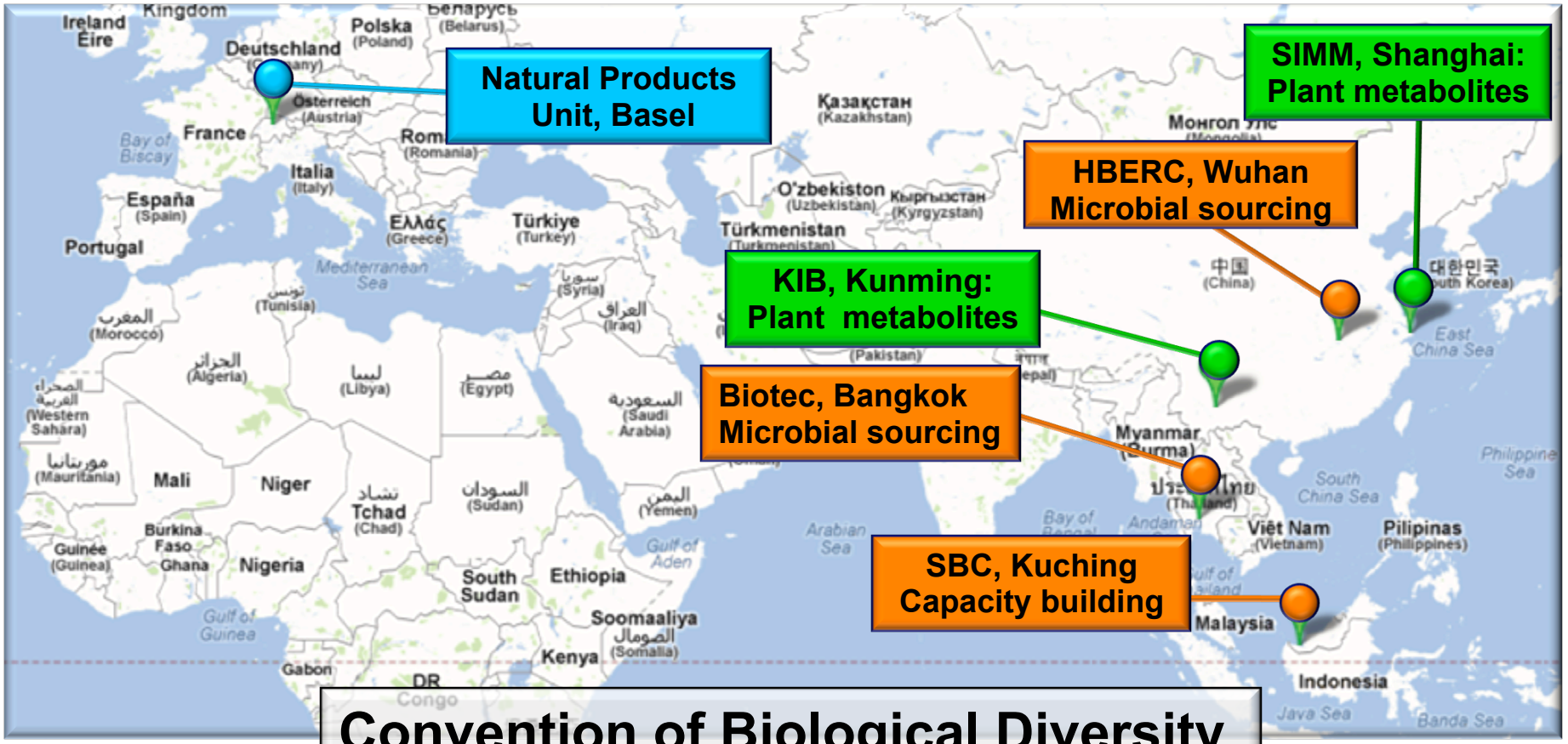
- **Totally known natural products**
  - ~ 175'000 natural products (2014)

based rank P

Access to biodiversity

Bioprospection and Convention of Biological Diversity



Convention of Biological Diversity

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

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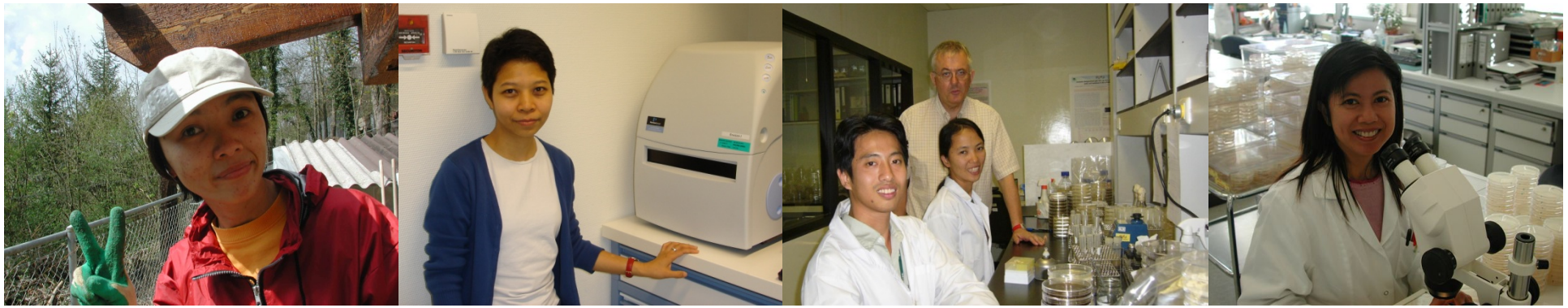
Case study Biotec, Thailand

Knowledge transfer: On-site and in Novartis laboratories in Basel

- 12 Biotec scientists trained in chemistry, microbiology, High-through-put drug at Novartis Switzerland and US– totaling in 35 months of training
- Drug discovery seminars/ lectures by Novartis experts in infectious diseases and natural products research coming from USA, SP and CH
- Courses à 4 weeks each at BIOTEC to transfer knowledge for the isolation of targeted microorganisms classes
- Dissemination of specific microbiology know-how to scientists from other SE Asian countries



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Case study Biotec, Thailand

Overview of achievements

- > 9'000 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

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Leveraging plant diversity in medicine

From antique phytotherapy to pharmaceutical industry

Experience

17000 BC: First Shamans on paintings

(Lascaux cave painting; 17000 BC)

Documentation

3rd millenium: Earliest written plant medications in Mesopotamia

Clay tablet, Nippur, Sumeric, 2100 BC

75 AD: Dioscorides wrote "*De Materia Medica*" with 813 plants and 102 minerals for 4740 indications

Vienna Dioskurides, 512 AD

Transformation

1823/ 27: Birth of the pharmaceutical industry - commercialisation of morphium and of quinine

1898: Aspirin – mass production of a synthetic, natural product based drug

Biodiversity and herbal remedies as therapeutics

- Majority of plant derived drugs via ethnobotanical leads
  - 75 % of approx. 140 single entity drugs
- Untapped chemical potential of plant metabolites
  - 140 drugs developed from approx. 100 out of 250.000 species
  - < 10 % of all plant species phytochemically investigated
- 30’000 plant species in China (10% of plant diversity)
  - 12’000 plant species used in TCM
  - 100’000 TCM recipes
- TCM plant diversity with underexplored therapeutic potential to discover new medications

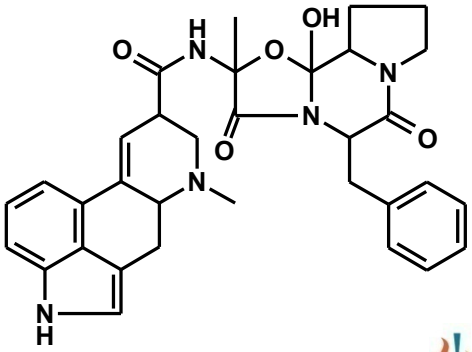
Farnsworth, 1985
*Ganessan:. Cur. Opinion Chem Biol: 12; 306 (**2008**)*
*Hughes, Mullard: Nature Rev**, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015***
Drugs.com 2015; Lin, 2001

Traditional medicine as sources for new therapeutics: Ergot

The begin of the pharmaceutical research (at Sandoz)

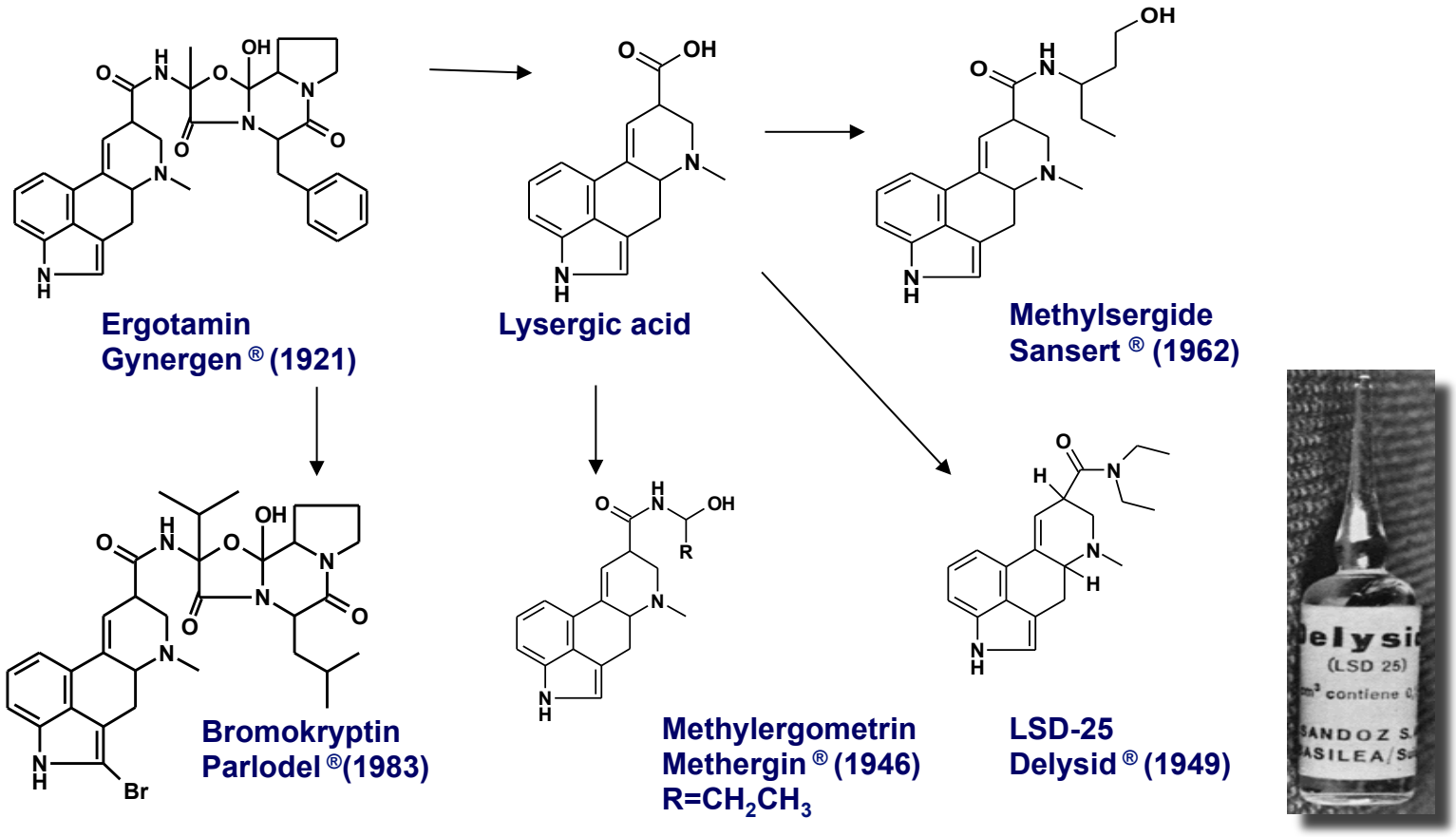
- Hippokrates noted substantial increase of aborts during humid summers
- Adam Lonicerus: First documentation of the benefit of an aqueous ergot extract for parturition and for post-partum bleeding control in Europe (1582)
- Instable administration and varying concentration of active components in decoction biggest problems
- 1918: Isolation of ergotamine for post partum bleeding control at Sandoz

Arthur Stoll
1887-1971



Ergot alkaloid research at Sandoz

Targeting 5-HT, dopamine, and α-adrenergic receptors



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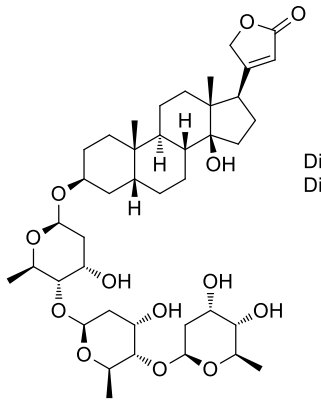
Plants as sources for new therapeutics: Heart glycosides

Glycosides from Asperagales, Lamiales: treatments of heart insufficiency

- Papyrus Ebers, 1550 v. Chr:
  Sea squill for the treatment of weak puls and dropsy
- *De historia stripium*, 1542:
  Foxglove for the treatment of dropsy and epilepsy
- Engl. physician William Withering (1741-1799): First systematic research on therapeutic and side effects of a medication: Digitalis treatment with 158 Patienten (1785)
- Isolation of heart glycosides from *Digitalis lanata* at Sandoz AG allowed more reliable administration



Digitoxin
Digitalis purpurea

Urinea maritima

Leonhart Fuchs, *De historia stirpium*
Basel, 1542

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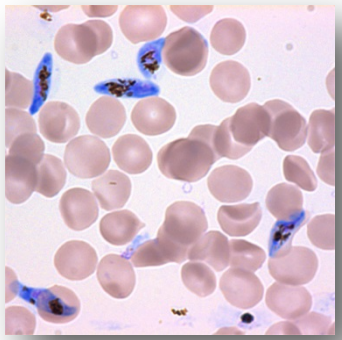
Plants as sources for new therapeutics: Artemsinin

First line treatment against malaria

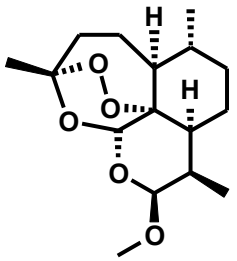
- 340 AD: *Qinghao* (= *Artemisia annua*, Sweet Annie): Traditional treatment of malaria described in a Chinese medical handbook
- 1977: Structure elucidation of artemisinin and its identification as the active principle against plasmodia
- 1994: Collaboration between China and Novartis for the joint development of a combination drug with an artemisinin derivative and lumefantrin against malaria
- 1998: Coartem® /Riamet® approval

Anopheles sp



P. falciparum

Artemisia annua



Artemisinin

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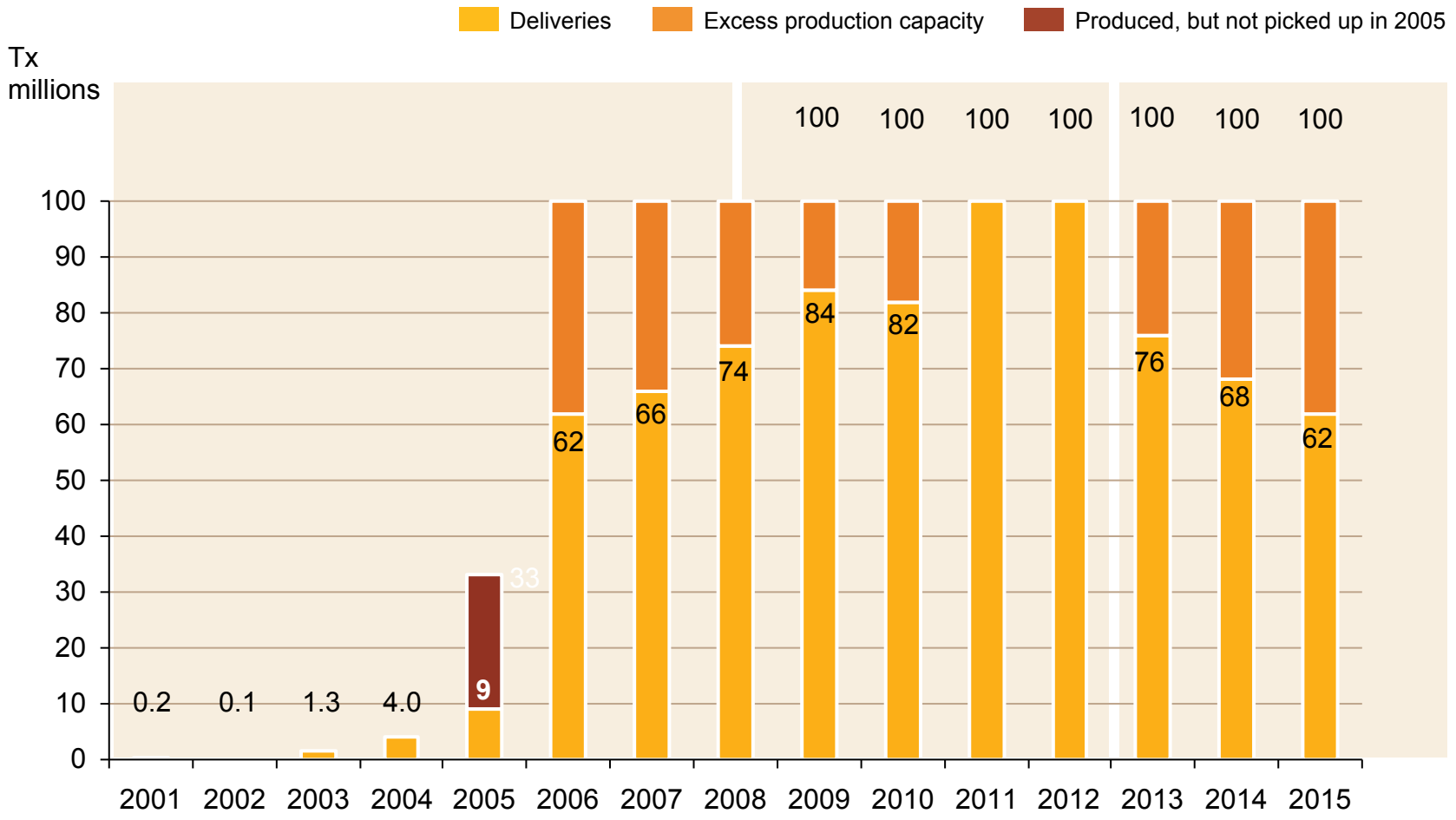
More than 800 Mio malaria patients treated with Coartem® until end of 2015

Approx. > 1.5 Mio lives could be safed



Hans Rietveld, 2016

Th. Kuhn und Y. Wang in *Natural Compounds as Drugs Vol. II*; Progress in Drug Research (66) eds F. Petersen & R. Amstutz, Birkhäuser Verlag (2008)

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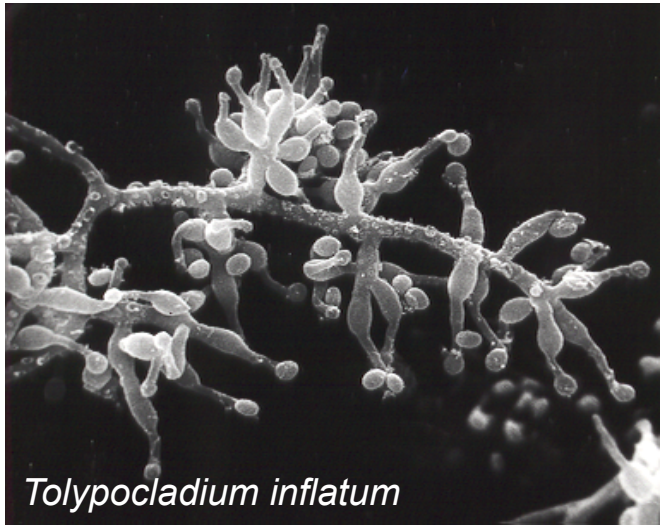
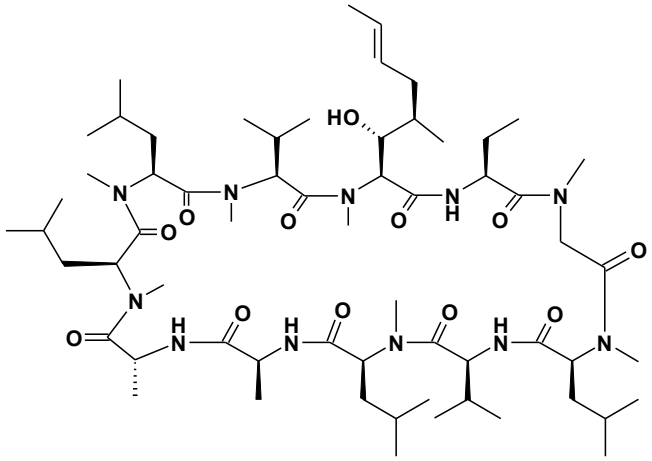
Fungi as sources for new therapeutics: Cyclosporine

Opening up a new medical field: Transplantation medicine

- Cyclosporin (Neoral/Sandimmun®)
- Natural product of filamentous fungus *Tolypocladium inflatum*
- Cyclic peptide 11 amino acids
- Immunosuppressive activity
- Cyclosporine binding to cyclophilin inhibits the calcineurin function and thereby the T-cell mediated immune response
- Launched 1982 in transplatation medicine and serious form of inflammatory diseases (eg in psoriasis)





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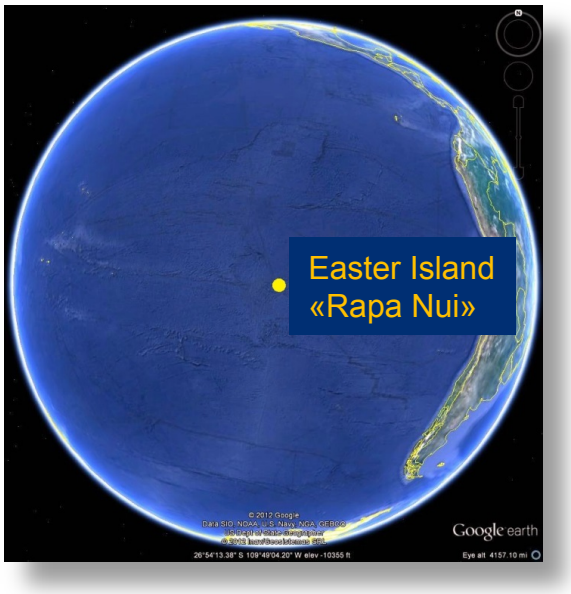
Bacteria as sources for new therapeutics: Rapamycin

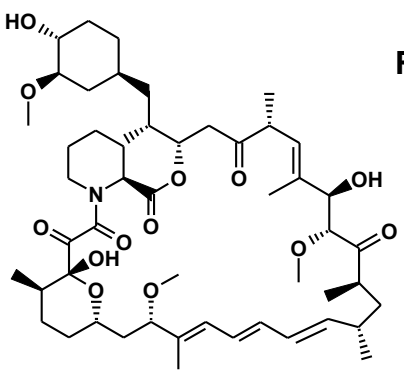
Actinomycetes and a new therapeutics class for transplantation medicine and oncology

- Bacteria of the class *Actinomycetes* responsible for the production of 60 % of all approx 27'000 microbially derived natural products (Antibase, 2010)

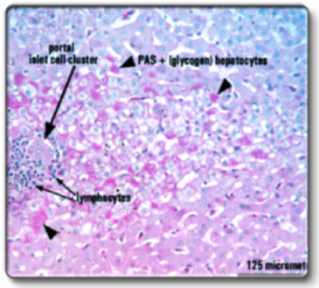
1964



1975



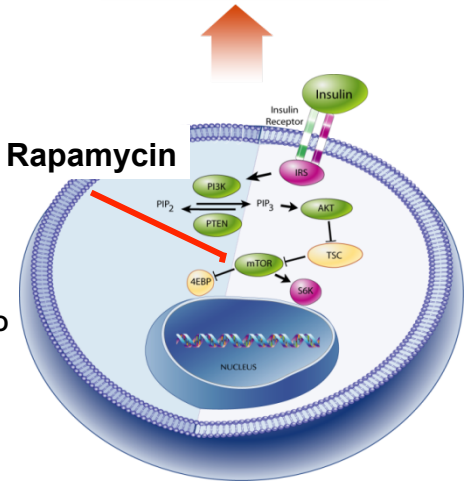
Rapamycin



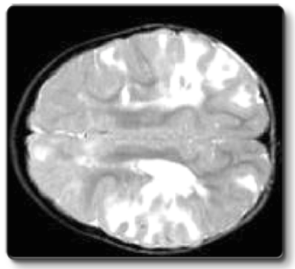
Transplantation medicine

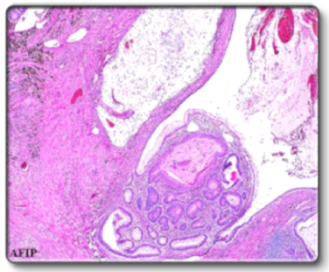
CERTICAN everolimus

2003



Tuberous sclerosis 2011





Cancer

NEW AFINITOR® (everolimus) tablets

2009

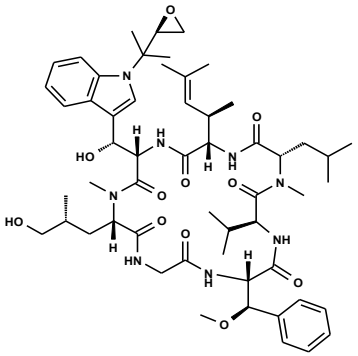
J. Mannick et al.: mTOR inhibition improves immune function in the elderly. Sci Transl Med; 24 December 6, 268, 268 (2014)

Bacteria as sources for new tools: Cyclomarine

Identification of new druggable target in M. tuberculosis

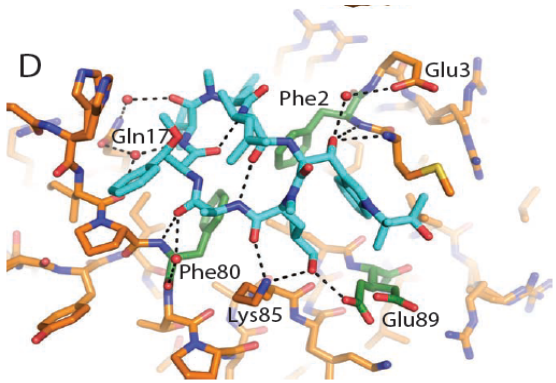
- Mycobacterium tuberculosis infection:
  - 14 Mio tuberculosis cases; 1.7 Mio deaths (2009)
- New targets urgently needed
- Discovery of cyclomarin as potent *M.tub.* inhibitor
- Proteomics investigations with Myco*bacterium* lysates reveal ClpC1 as responsible target
- ClpC is a regulatory unit of Clp protease; cyclomarin binding leads to uncontrolled proteolysis

NOVARTIS INSTITUTE FOR TROPICAL DISEASES



Cyclomarin A

MIC_{50} = 0.04 - 0.11 uM



Spangers et al, PNAS, 102, 16678 (2005)
Schmitt, EK et al., Angew Chem Int. Ed, 2011, 50, 1-4
World TB Day, 2011
Dileep V. et al., *J. Biol. Chem. 2013 288: 30883-30891*

Summary

- Natural products account for a considerable part of today‘s medicines
- Biodiversity driven access to natural products resources is key to ensure a broad chemical diversity for subsequent drug discovery efforts
- Nagoya protocol and the Convention of Biological Diversity regulate bioprospection partnerships and provide improved legal clarity
- Natural products displaying a complementary chemical diversity to synthetically derived substances can function as „pathfinders“ to new biological targets and as springboards to uncharted areas of the chemospace
- Recent introductions of natural products in human therapy underpin their important role in the discovery of innovative treatment options