MARINE BOARD

3rd MARINE BOARD FORUM

NEW TECHNOLOGIES FOR A BLUE FUTURE

18 April 2012

Royal Flemish Academy for Sciences and the Arts, Hertogsstraat 1, 1000 Brussels

Molecular Marine Biotechnology: From genes to bioactive products

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Vice-President IMBA
[International Marine Biotechnology Association]

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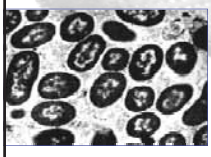
Sponges: Porifera
Deep sea organisms

Sponges: Porifera
Source of drugs

Sponges: filter feeder

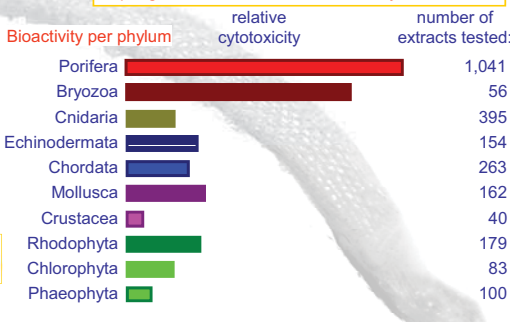


tons of water/day

Bioprospecting: Sponges

Porifera: bioprospecting

Sponges: richest source for secondary metabolites



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erc

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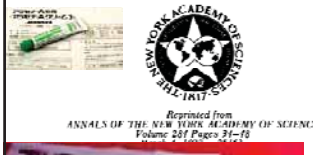
Drug development:
SUCCESS - araA

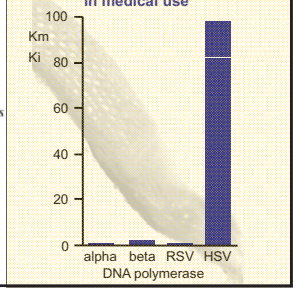
INHIBITION OF HERPESVIRUS DNA SYNTHESIS BY 9 β D ARABINOFURANOSYLADENINE IN CELLULAR AND CELL-FREE SYSTEMS*

W. E. G. Müller, R. K. Zahn, K. Dittlingmaier, and D. Falke



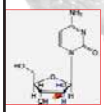
Reprinted from ANNALS OF THE NEW YORK ACADEMY OF SCIENCES Volume 284 Pages 34–48

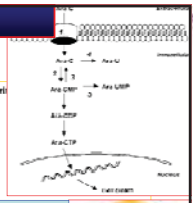
araA
Vidarabin
↓
1975:
first drug
in medical use



Drug development:
Anti-leukemic drug: araC

Our studies





araC:
Polymerase inhibitor

Europ. J. Cancer Vol. 8, pp. 421–428. Pergamon Press 1972. Printed in Great Bri

Action of
1-β-D-Arabinofuranosylcytosine on
Mammalian Tumor Cells—2.

Kani Medail

Inhibition of Mammalian and Oncogenic V
Polymerases

WERNER E. G. MÜLLER, ZEN-I. YAMAZAKI, HEINZ H. SÖGTROP and RUDOLF K. ZAHN

Institut für Physiologische Chemie, Johannes Gutenberg Universität, 65 Mainz, Johann Joachim Becher Weg 13, West Germany

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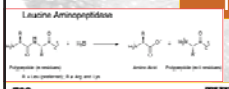
Müller W, Yamazaki Z, Sögtrop HH, Zahn RK (1972) Action of 1-ß-D-arabinofuranosylcytosine on mammalian tumor cells. 2. Inhibition of mammalian and oncogenic viral polymerases. Europ J Cancer 8: 421-428.

Drug development:
Bestatin

Leucine aminopeptidase:
Target enzyme for immunostimulants

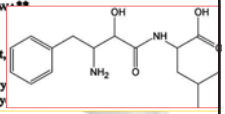


728 THE JOURNAL OF ANTIBIOTICS JUNE 1983

IMMUNOCHEMICAL IDENTIFICATION OF THE CELL SURFACE BOUND LEUCINE AMINOPEPTIDASE, THE TARGET ENZYME FOR THE IMMUNOSTIMULANT BESTATIN

GABRIELE LEYHAUSEN*, MONIKA GRAMZOW*, RUDOLF K. ZAHN*, RENATE STEFFEN*, HAMAO UMEZAW** and WERNER E. G. MÜLLER*

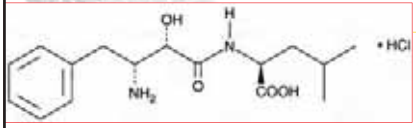
*Institut für Physiologische Chemie, Universität, 6500 Mainz, West Germany
**Institute of Microbial Chemistry 3-14-23, Kamiosaki, Shinagawa-ku, Toky



Leyhausen G, Gramzow M, Zahn RK, Steffen R, Umezawa H, Müller WEG (1983) Immunochemical identification of the cell surface bound leucine aminopeptidase, the target enzyme for the immunostimulant bestatin. J Antibiotics 36: 728-734.

Drug development:
Bestatin

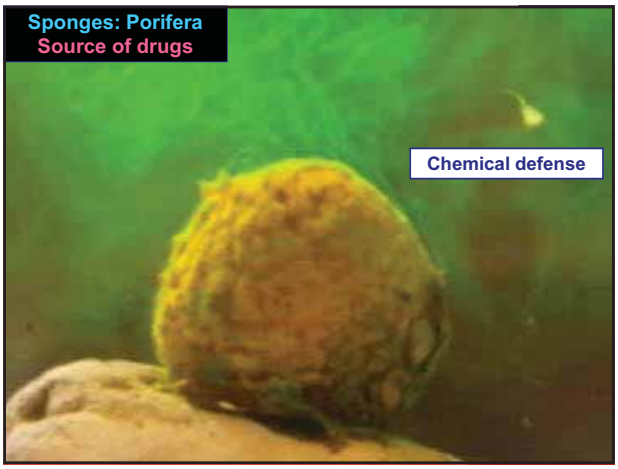
Bestatin:
Immunomodulator

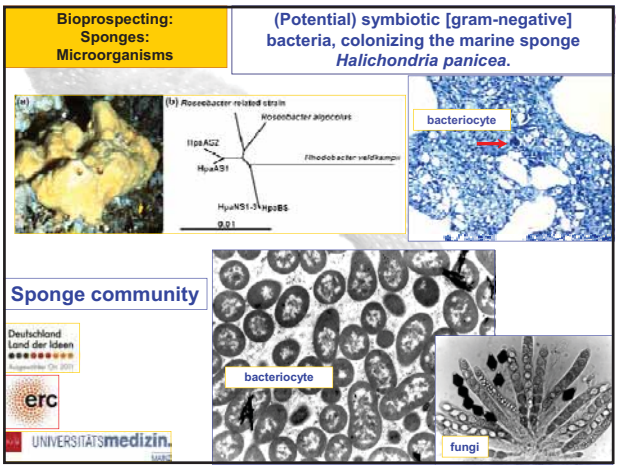


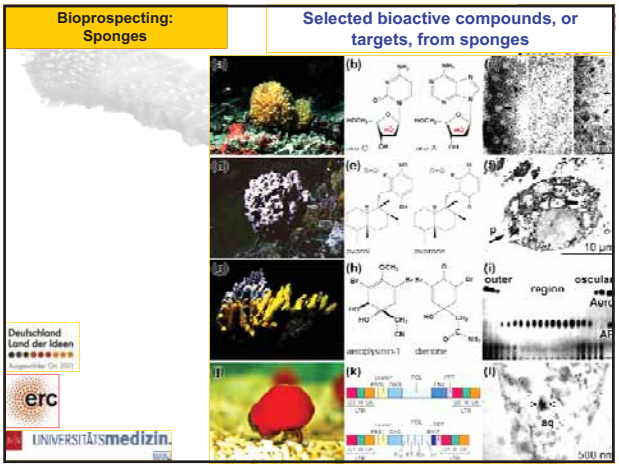
Induction of DNA Polymerase α and Terminal Deoxynucleotidyl Transferase in the Human Lymphoblastoid Cell Line Molt-4 by the Immunomodulator Bestatin

Gabriele Leyhausen[1], Wolfgang Dippold[2], Rudolf K. Zahn[1], Karl-H. Meyer zum Büschenfelde[2], Hamao Umezawa[3] and Werner E. G. Müller[1,*]

Leyhausen G, Dippold W, Zahn RK, Meyer zum Büschenfelde KH, Umezawa H, Müller WEG (1984) Induction of DNA polymerase α and terminal deoxynucleotidyl transferase in the human lymphoblastoid cell line Molt-4 by the immunomodulator Bestatin. Immunopharmaco l 7: 151-157.


Sponges: Porifera
Source of drugs
Chemical defense


Bioprospecting:
Sponges:
Microorganisms
(Potential) symbiotic [gram-negative] bacteria, colonizing the marine sponge *Halichondria panicea*.
bacteriocyte
Sponge community
bacteriocyte
fungi
Deutschland Land der Ideen
erc
UNIVERSITÄTSmedizin.


Bioprospecting:
Sponges
Selected bioactive compounds, or targets, from sponges
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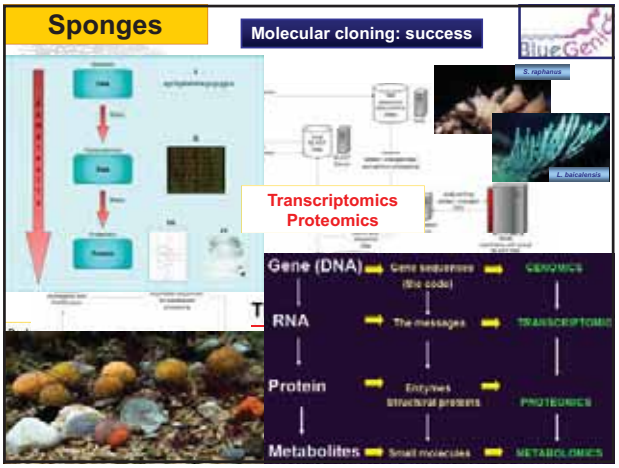
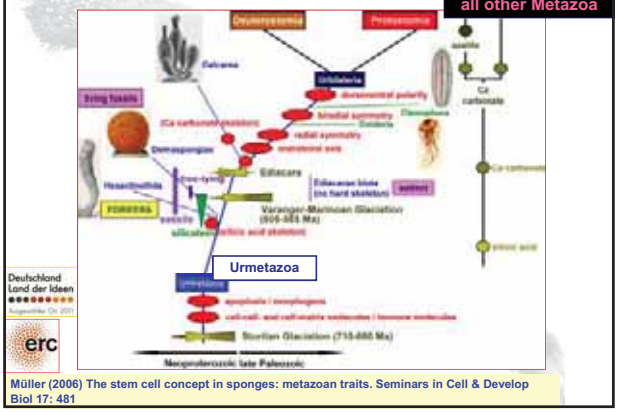

Sponges
Molecular cloning: success
BlueGenic
Transcriptomics
Proteomics
Gene (DNA)
RNA
Protein
Metabolites
GENOMICS
TRANSCRIPTOMICS
PROTEOMICS
METABOLOMICS

Evolution

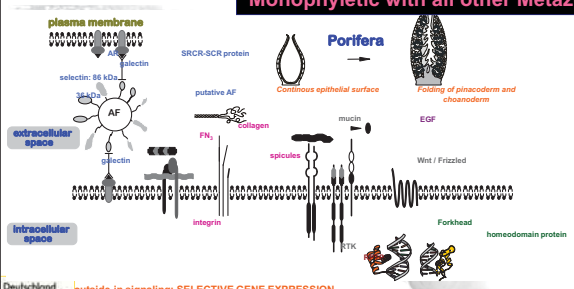
Sponges: Porifera
Monophyletic with all other Metazoa



Müller (2006) The stem cell concept in sponges: metazoan traits. Seminars in Cell & Develop Biol 17: 481

Building blocks

Sponges: Porifera
Monophyletic with all other Metazoa



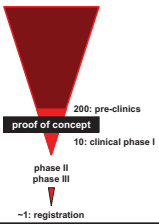
outside-in signaling: SELECTIVE GENE EXPRESSION
cell-cell adhesion: CELL ASSOCIATION
cell-matrix adhesion: TISSUE / SKELETON FORMATION
cell proliferation and differentiation: GROWTH
soluble factors: MORPHOGENS
secreted molecules: AXIS FORMATION
transcription factors: AXIS FORMATION

Drug development: Chemical synthesis

Chemical „Blind Cow“ Game: combinatorial chemistry

3 years	**Activity trials – synthesis – screening** 5.000 to 10.000 substances ✓
3 years	**Activity screening – synthesis – screening** ~ 200 substances ✓
2 years	**Clinical phase I** 10 substances
3 years	**Clinical phase II** 8 substances

Combinatorial chemistry
[5 - 10,000 chemicals synthesized]



Drug development: Biological selection

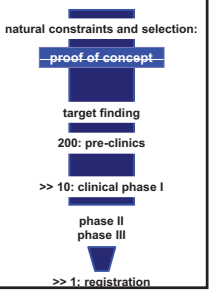
Biological Selection

Natural selection and optimization
5.000 to 10.000 substances

Activity of biomedical interest
5.000 to 10.000 hits

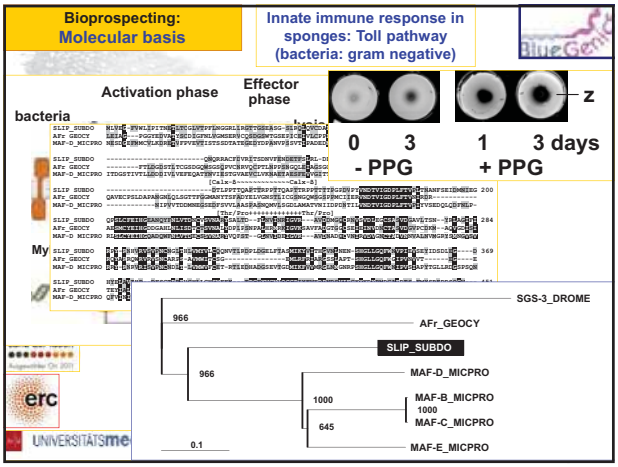
Challenge:
discovery of the hits

Evochemistry
[200 secondary metabolites]



Bioprospecting:
Molecular basis

Innate immune response in sponges: Toll pathway (bacteria: gram negative)



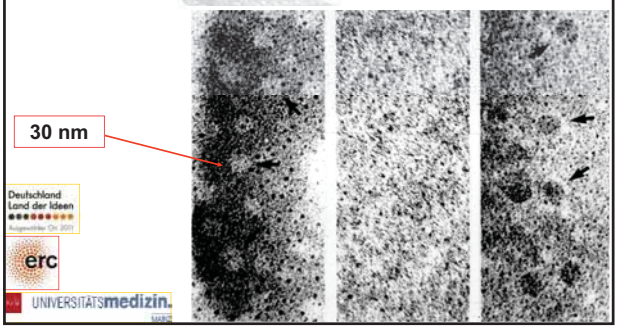
Bioprospecting:
Sponges

Killing of pathogens

Membrane attack complex, lysis

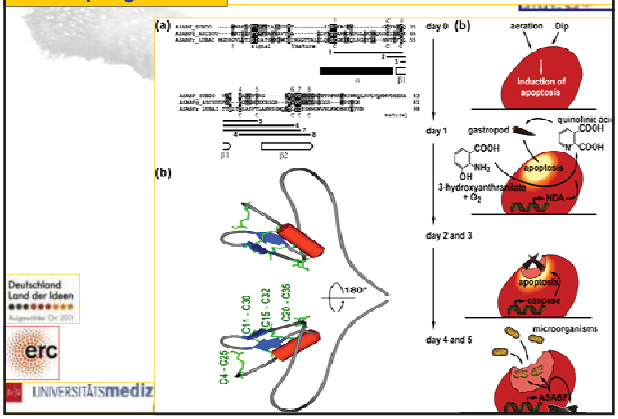
Tethya hemolysin

streptolysin O



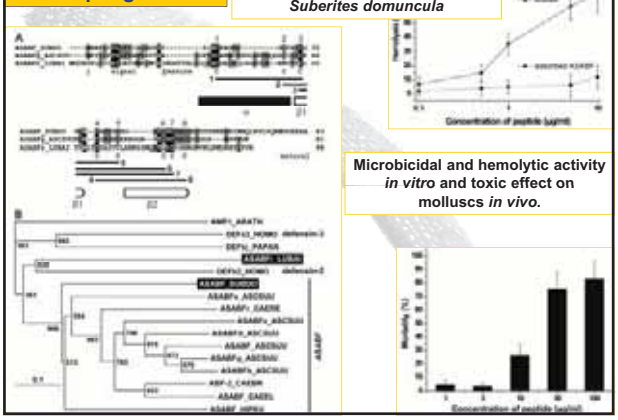
Bioprospecting:
Sponges

Inducible ASABF-type antimicrobial peptide from *Suberites domuncula*



Bioprospecting:
Sponges

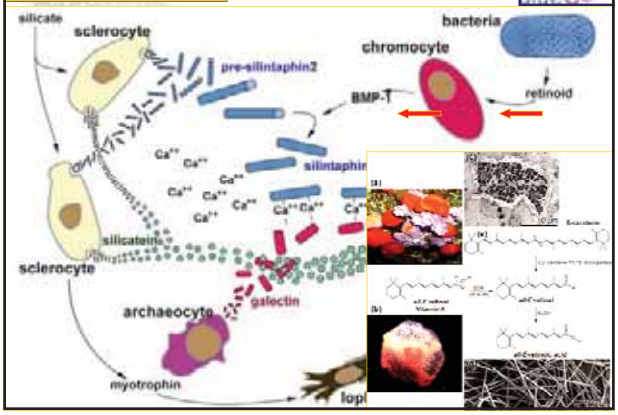
Inducible ASABF-type antimicrobial peptide from *Suberites domuncula*



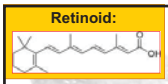
Microbicidal and hemolytic activity *in vitro* and toxic effect on molluscs *in vivo*.

Bioprospecting:
Sponges

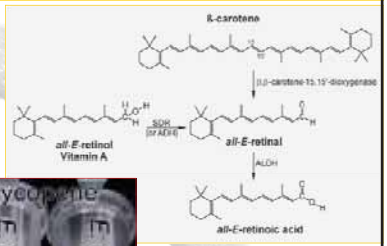
Formation of retinoids/retinoic acid in *S. domuncula*



Retinoid:

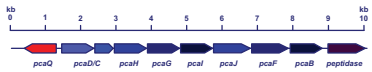


Main steps of the retinoic acid formation via the ß,ß-carotene 9',10'-dioxygenase and the retinol dehydrogenase (SDR/ADH) / retinal dehydrogenase



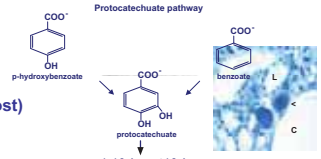
Bioprospecting:
Sponges

bacterial gene cluster: protocatechuate/polyketide cluster

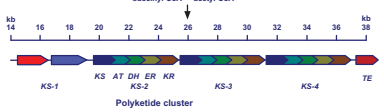


microorganisms

Protocatechuate pathway



interaction: tyrosinase (host) - protocatechuate (bacterium)



Polyketide cluster

increased synthesis of polyketides

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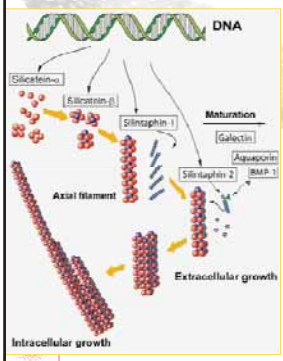
Breter
Müller
Batel

Bioprospecting:
Sponges

Hexactinellida
Euplectella aspergillum

the JAGO-team

Genetic hierarchy:
Soft matter formation



Genetic hierarchy:
enzymatic machinery for soft matter formation

Proposed hierarchical genetic model controlling the synthesis of the siliceous spicules

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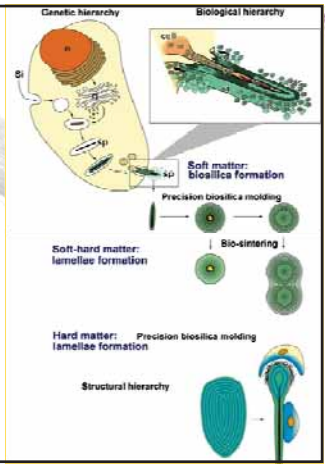
Biological hierarchy:
Soft matter formation

Different levels of hierarchy during spicule formation



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Bio-inspired morphogenesis:
Nature: application

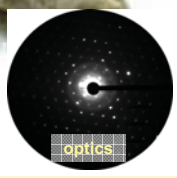
Hybrid material

skeleton

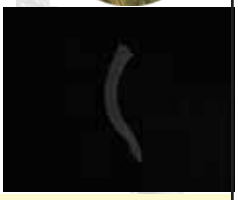
sieves
catalysts

nanowires

enzymatic
biosilica:
medicine



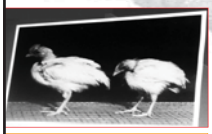
optics



Müller, Wang, Cui, Jochum, Tremel, Bill, Schröder, Wiens (2009) Sponge spicules as blueprints for the biofabrication of inorganic-organic composites and biomaterials. Appl Microbiol Biotechnol 83: 397

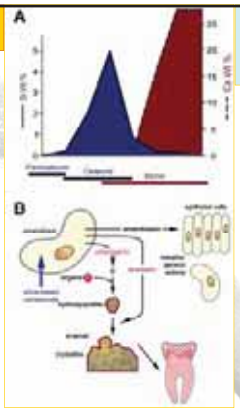
Bio-inspired morphogenesis:
Nature: application

New biomaterials



Carlisle 1988 (Sci Total Environm)

Silicon accumulation during early stages of bone formation
Differential gene expression



Silicatein:
Application in dentistry and bone reconstitution

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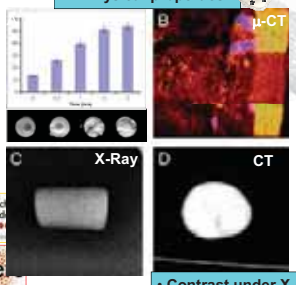
erc

Müller WEG, Boreiko A, Wang X, Krasko A, Geurtsen W, Custódio MR, Winkler T, Lukić-Bilela L, Link T, Schröder HC (2007) Calcif Tissue Int 81:382-393

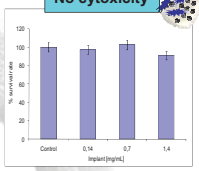
New Biomaterials:
Bone reconstitution

Development of 2-component functional implant
– component 2: moldable functional implant

Physical properties



No cytoxicity



Next:

- Contrast under X-ray and CT
- Bone regenerative evaluation
- Availability of X-ray and CT

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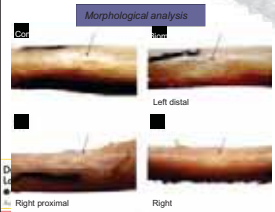
New Biomaterials:
Bone reconstitution

Development of 2-component functional implant
– component 2: moldable functional implant

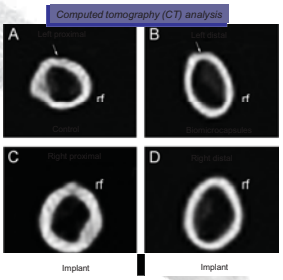
Implant experiments *in vivo – 9 weeks*

Morphological analysis



Photographic images of the rabbit femur's surface after 9 weeks of implantation. The positions and correspondent "implants" material are displayed. Arrows show the location of 3 mm hole.

Computed tomography (CT) analysis



X-ray computed tomography (CT) images of the rabbit femur (*rf*) implanted with different materials after 9 weeks.

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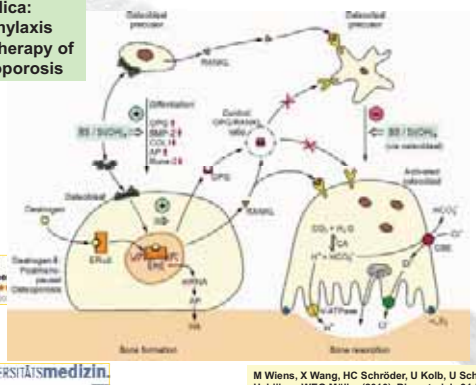
New Biomaterials:
Biosilica

Biosilica: Prophylaxis and therapy of osteoporosis



M Wiens, X Wang, HC Schröder, U Kolb, U Schloßmacher, H Ushijima, WEG Müller (2010). Biomaterials 31:7716-7725

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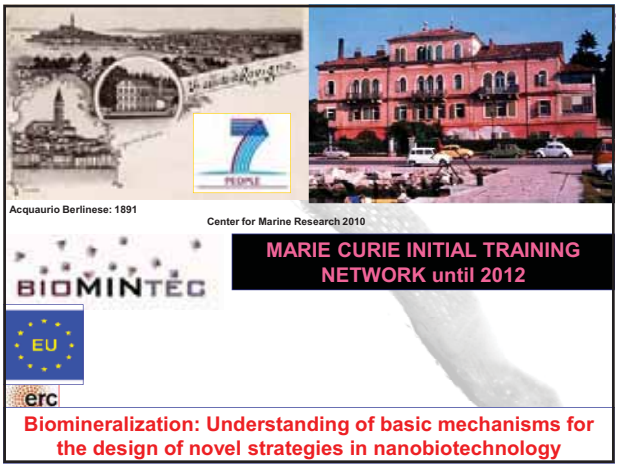
Renato Batel:
Summer school in Rovinj

Mainz: Partner university with Zagreb


Acquaurio Berlinese: 1891
Center for Marine Research 2010
BIOMINTEC
MARIE CURIE INITIAL TRAINING NETWORK until 2012
EU
erc
Biomineralization: Understanding of basic mechanisms for the design of novel strategies in nanobiotechnology


The program: 2010-2015
Joint Lab: Nano-Bio-Composites
Meeting in Beijing:
14th October 2010
Sino-European Workshop on Marine Bio-Nano-Technology
WORKSHOP
Deutschland Land der Ideen
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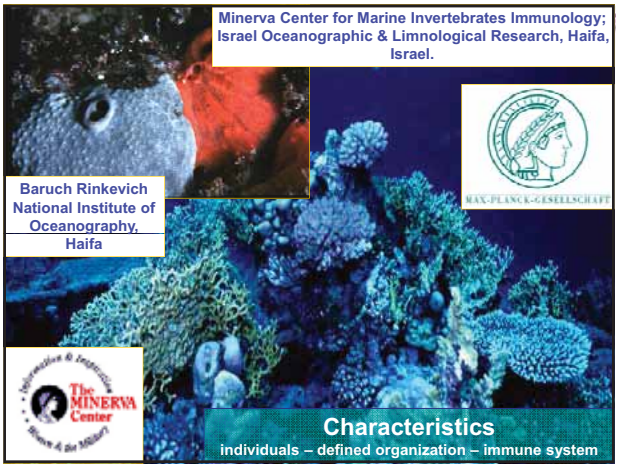
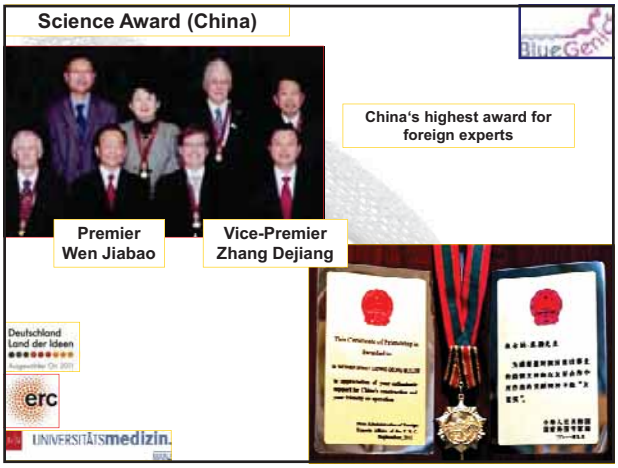
The program: 2010-2015
Joint Lab: Nano-Bio-Composites
Meeting in Beijing:
14th October 2010
The partners
WORKSHOP


HFSP
Grant International Human Frontier Science Program (RG-333/96-M)
20 YEARS IN PURSUIT OF EXCELLENCE
Invertebrate Immunology
Baruch Rinkevich National Institute of Oceanography, Haifa
Eric Davidson Caltech USA


Minerva Center for Marine Invertebrates Immunology; Israel Oceanographic & Limnological Research, Haifa, Israel.
Baruch Rinkevich National Institute of Oceanography, Haifa
MAX-PLANCK-GESELLSCHAFT
The MINERVA Center
Characteristics
individuals – defined organization – immune system


Mainz named 2011: City of Science
Urkunde
Ausgewählter Ort 2011
Minister-President Kurt Beck
STADT DER WISSENSCHAFT 2011
... ist Mainz!


Science Award (China)
BlueGenic
China's highest award for foreign experts
Premier Wen Jiabao
Vice-Premier Zhang Dejiang
Deutschland Land der Ideen
erc
UNIVERSITÄTSmedizin.


12-01-2012:
Premier WEN Jiabao meets foreign experts
Thanks for outstanding contributions for China
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PORIFERA
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European Research Council
ERC Advanced Grant 2010
Until 2016
Proposal Full Title:
From gene to biomineral: Biosynthesis and application of sponge biosilica
PROPOSAL ACRONYM: BIOSILICA
Proposals ERC-2010-AdG – Proposal No. 268476
BIOSILICA
ERC Advanced Investigators Grant
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