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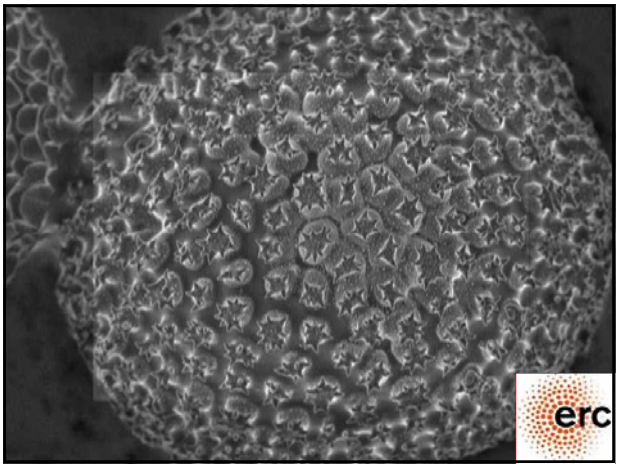
SCHOTT AG – MAINZ
Expertenpanel „Biomaterialien"
Materials Valley Materials Valley

BiomaTICS

Innovative Produkte für die Dental- und Knochenregeneration

Prof. Dr. Werner E.G. MÜLLER
ERC Advanced Grant Investigator
Institute for Physiological Chemistry; Medical Center of the Johannes Gutenberg-University Mainz; Duesbergweg 6; D-55128 Mainz; GERMANY.
E-mail: wmueller@uni-mainz.de

erc



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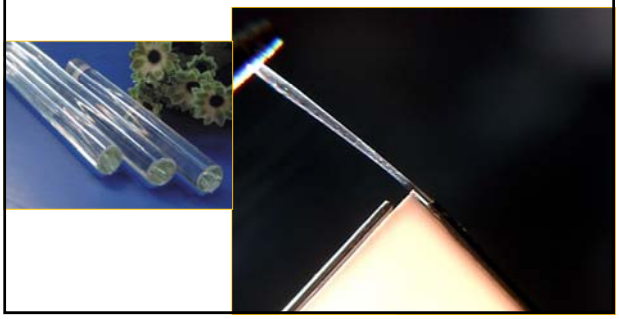
Breaking of glass rods

Schott glass

Chemical synthesis



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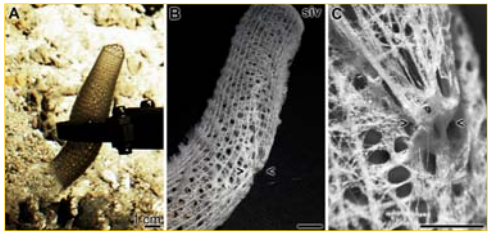
Sponges: Porifera
The interconnected network: spicules



Wang, Schröder, Wang, Müller (2012) Genetic, biological and structural hierarchies during sponge spicule formation: From soft sol-gels to solid 3D silica composite structures. Soft Matter 8:9501–9518.

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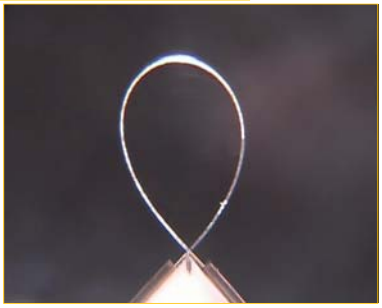
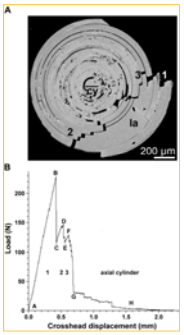
Bio-inspired morphogenesis: Nature

Sponge spicules





Müller, Schröder, Burghard, Pisignano, Wang (2013) Silicateins - A novel paradigm in bioinorganic chemistry: Enzymatic synthesis of inorganic polymeric silica. Chemistry Eur. J. 19:5790-5804.

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Disruptive discoveries

Disruptive innovations

Disruptive technologies

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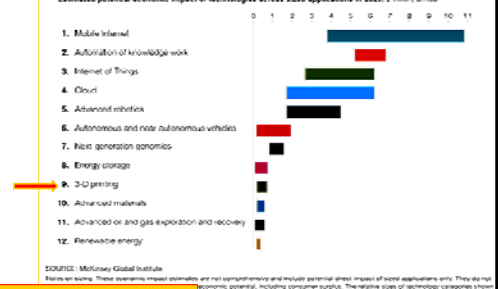
A gallery of **disruptive technologies**



Report McKinsey Global Institute May 2013

Disruptive technologies: Advances that will transform life, business, and the global economy

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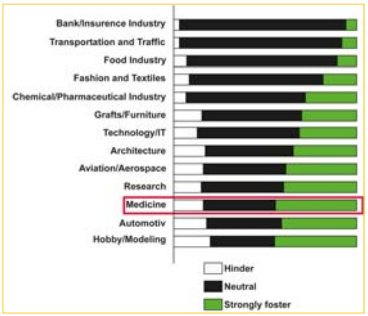
3D printing impact

10-year forecast of additive manufacturing impact per industry



Gartner, Maresch, Fink (2015) The potential of additive manufacturing for technology entrepreneurship: An integrative technology assessment. *Creat Innov Manag* 24: 585-600.

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Johannes Gutenberg "Man of the Millenium"

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Ancient times
Early Modern Age
Present (time)

an Caves Scrolls
408 BCE

r C. Historiae
ı. Vol. 20. Zürich:
1558

Diamond Sutra from Tang Dynasty China, 868 AD

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Question

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Ancient times
Early Modern Age
Present (time)

3D
Printing

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Gutenberg:
Unlimited multiplication of texts

3D printing:
Unlimited multiplication of figures

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HORIZON - the EU Research & Innovation Magazine
is written by independent journalists on behalf of the European Commission's Directorate-General for Research and Innovation.

RESEARCH & INNOVATION
HORIZON
02 April 2014
by Gary Finnegan
Live cells could be used to reconstruct faces

3D-printed bone scaffolding, created by BIO-SCAFFOLDS.
Researchers are developing ways to repair skull fractures – – or reconstruct faces damaged in accidents – by using live cells in 3D-printed implants.

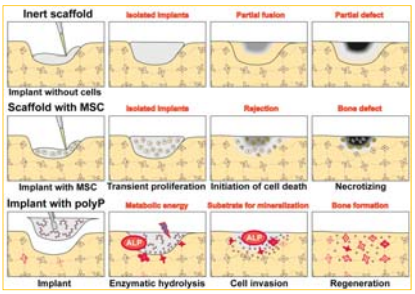
Professor Werner E. G. Müller, coordinator of the EU-funded BIO-SCAFFOLDS project.

RESEARCH & INNOVATION
HORIZON
Live cells could be used to reconstruct faces

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

Do we need cells in the implants??

Implant properties: Inert – with MSC – with polyP



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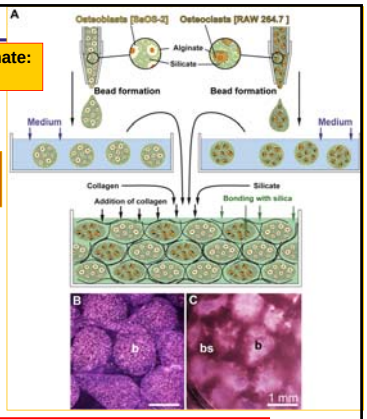
Bio-silica – Bio-polyphosphate: Pre-study

Development of a biomimetically programmable Na-alginate-based hydrogel



Schloßmacher, Schröder, Wang, Feng, Müller (2013) Alginate/silica composite hydrogel as a potential morphogenetically active scaffold for three-dimensional tissue engineering. RSC Advances 3: 11185-11194.

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Lessons learnt

Enzyme-based

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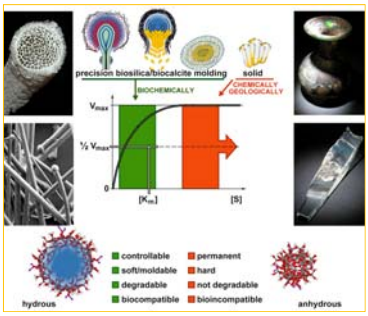
Enzymatic biomineralization

Michaelis-Menten constant



Wang, Schröder, Müller (2014) Enzyme-based biosilica and biocalcite: biomaterials for the future in regenerative medicine. Trends Biotechnol 32: 441-447.

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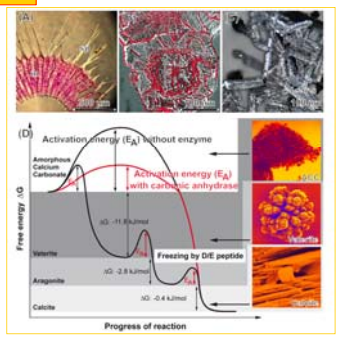
Enzymatic biomineralization

Importance of the activation energy



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"Implant 1.0"

Titanium alloy

"Implant 1.0"

Titanium/ceramics

Towards "Implant 4.0"

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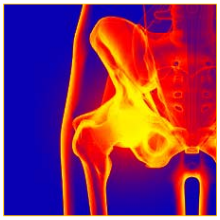
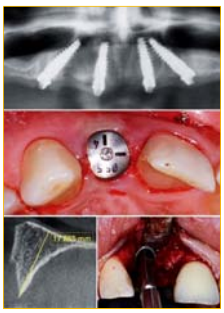
"Implant 1.0"

Bioinert
Not durable
Not regenerative
Risk of infection





Draenert FG, Huetzen D, Neff A, Mueller WEG (2014) Vertical bone augmentation procedures: Basics and techniques in dental implantology. J Biomed Mater Res Part A 102A:1605-1613.

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Nature as a blueprint

Target - enzymes

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Basis of Metazoa:

Sponges: Porifera

Evolution

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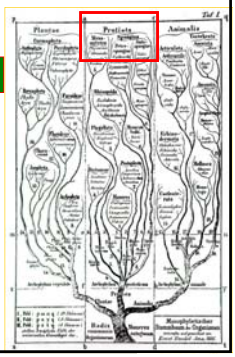
Sponges: Porifera
Evolution

Poriferan molecular toolbox:
:: Evolution

Origin of animals (Metazoa)

Generelle Morphologie der Organismen. Berlin, 1866



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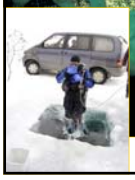
Sponges: Porifera

siliceous skeleton
cellular organization

Sponges: Porifera

Expedition:
Lake Baikal 2006 and 2010
(Siberia)

Icy-cold environment



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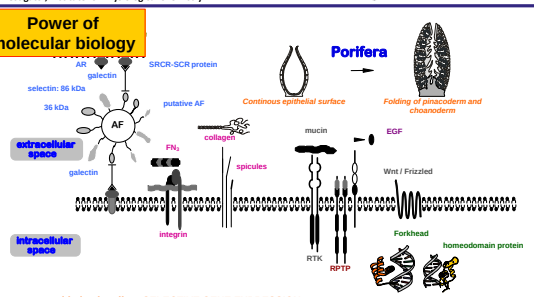
Power of molecular biology



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

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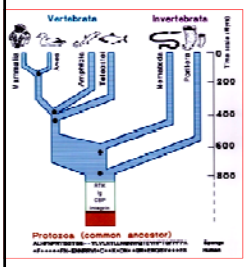
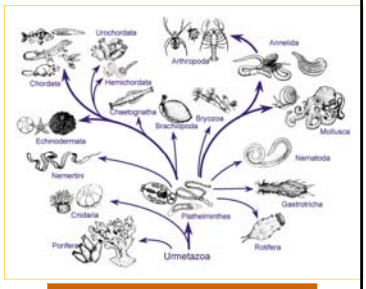
Sponges: Porifera Evolution





Urmetazoa: Monophyly of the animals

Müller WEG (1995) Molecular phylogeny of metazoa [Animals] (1995) Monophyletic origin. Naturwiss. 82: 321-329

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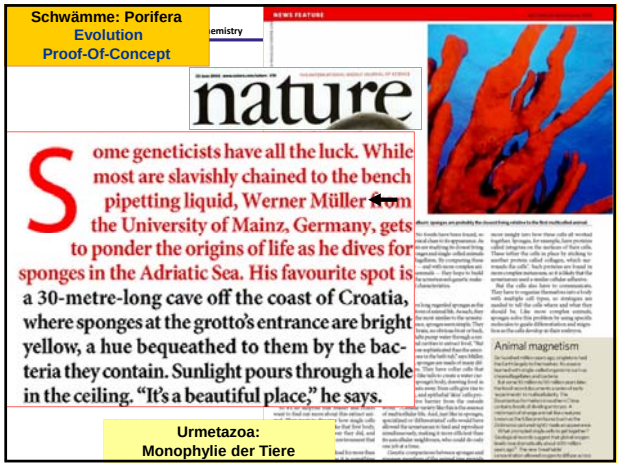
Schwämme: Porifera
Evolution
Proof-Of-Concept



nature

Some geneticists have all the luck. While most are slavishly chained to the bench pipetting liquid, Werner Müller from the University of Mainz, Germany, gets to ponder the origins of life as he dives for sponges in the Adriatic Sea. His favourite spot is a 30-metre-long cave off the coast of Croatia, where sponges at the grotto's entrance are bright yellow, a hue bequeathed to them by the bacteria they contain. Sunlight pours through a hole in the ceiling. "It's a beautiful place," he says.

Animal magnetism

Urmetazoa: Monophylie der Tiere

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Christianity

Christliches Menschenbild und moderne Evolutionstheorien
Botschaft von Johannes Paul II. an die Vollversammlung der Päpstlichen Akademie der Wissenschaften
An die Mitglieder der Päpstlichen Akademie der Wissenschaften anläßlich ihrer Vollversammlung

4. In Anbetracht des wissenschaftlichen Forschungsstandes der Zeit und der Erfordernisse der Theologie betrachtete die Enzyklika *Humani generis* die Lehre vom «Evolutionismus» als ernstzunehmende Hypothese, die es ebenso wie die gegensätzliche Annahme verdiene, genauer untersucht und bedacht zu werden. Pius XII. setzte zwei Bedingungen methodologischer Art hinzu: Man solle diese Ansicht nicht so übernehmen, als ob es sich um eine gesicherte und bewiesene Lehre handelte und als ob man ganz von der

spes, 22). Eben weil sie eine Geistseele hat, besitzt die gesamte menschliche Person einschließlich des Körpers eine solche Würde. Pius XII. hat diesen wesentlichen Punkt betont: Der menschliche Körper hat seinen Ursprung in der belebten Materie, die vor ihm existiert. Die Geistseele hingegen ist unmittelbar von Gott geschaffen: «animas enim a Deo immediate creari catholica fides nos retinere iubet» (Enzyklika *Humani generis*, *AAS* 42 [1950], S. 575).

Mainzer Karl Kardinal Lehmann

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Enigma: Skeleton

How can we understand that an inorganic skeleton is formed at room temperature?

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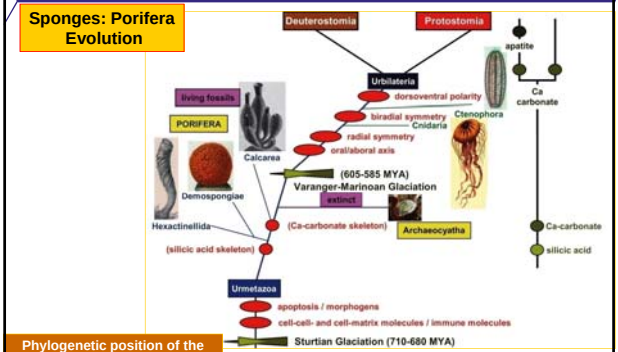
Sponges: Porifera Evolution



Phylogenetic position of the Porifera between the Urmetazoa and the Urbilateria.

Urmetazoa: Monophyly of the animals

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Mineral

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Bio-Mineral

Protein-template
Enzyme-based
Universal

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Biomineralization

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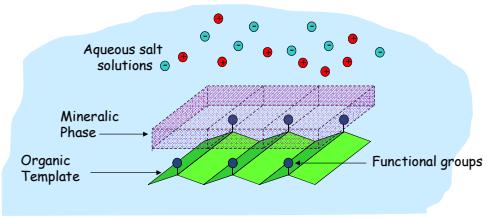
Biomineralization



J. Bill - Stuttgart

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Bio-silica

Importance of:
Bio-silica
Bio-calcite
Enzymes

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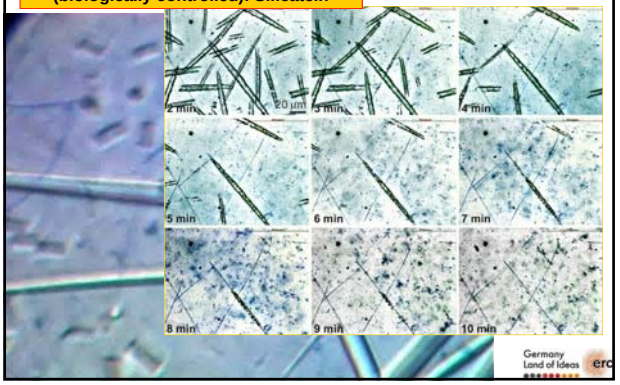
Biomineralization (biologically controlled): Silicatein



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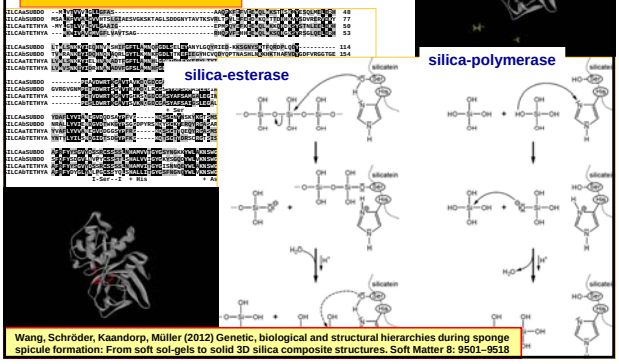
Biomineralization (biologically controlled): Silicatein

Mechanism of silicatein reaction



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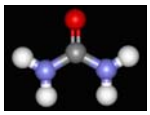
Change of paradigm

Synthesis of urea (Friedrich Wöhler, 1828)

Wöhler synthesis: conversion of ammonium cyanate (inorganic molecule) into urea (organic molecule - biochemistry)



$$NH_4(CNO) \rightarrow NH_2 + HCNO \leftrightarrow (NH_2)_2CO$$

For the first time an organic compound (urea) known to be produced only by biological organisms was produced in the laboratory, using chemical methods, from inorganic reactants.

Breakthrough

Silicatein-catalyzed enzymatic synthesis of silica

Inorganic precursor → Silicatein → Biosilica

For the first time an inorganic material (silica – glass) known to be produced by an inorganic substrate synthesized by enzymes (silicateins) which are only by biological organisms.

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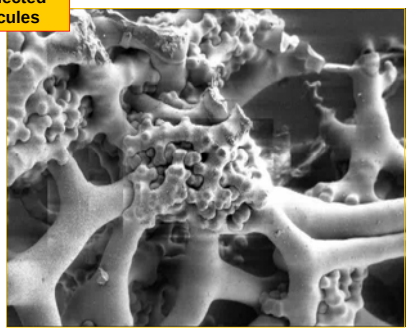
Sponges: Porifera
The interconnected network: spicules



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Biological hierarchy: Nature as a basis

Science AAAS

Flexible Minerals: Self-Assembled Calcite Spicules with Extreme Bending Strength
Filipe Natalio et al.
Science 339, 1298 (2013);
DOI: 10.1126/science.1216260

Flexible Minerals: Self-Assembled Calcite Spicules with Extreme Bending Strength

Natalio, Panthöfer, Müller, Butt, Tremel (2013) Flexible minerals: Self-assembled calcite spicules with extreme bending strength. *Science* 339:1298-1302.

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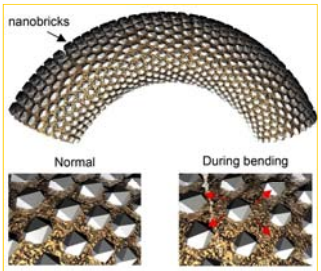
New biomaterials
Flexible minerals



The nanometer size of the calcite bricks facilitates bending of the synthetic spicules. The radius of curvature upon bending is very large compared to the size of the individual particles. This prevents a fracture of the brittle mineral bricks.

Natalio, Panthöfer, Müller, Butt, Tremel (2013) Flexible minerals: Self-assembled calcite spicules with extreme bending strength. *Science* 339:1298-1302.

Biomineralization

Evolution of Biomineralization

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ERC Investigator, Institute for Physiological Chemistry

Human bone formation

Bio-calcite???

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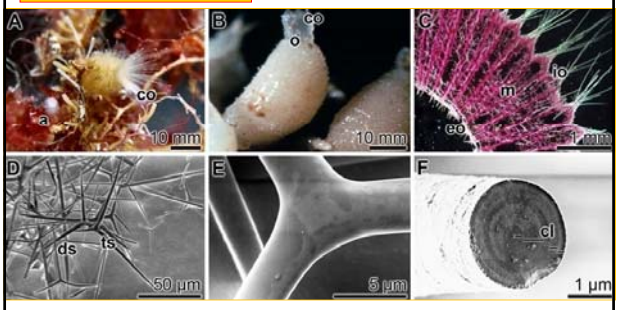
Nature as a Model
Bio-Calcite: Enzymatic
***in vitro* crystal formation**

***S. raphanus* and its calcareous spicules.**



Müller, Schlossmacher, Schröder, Lieberwirth, Glasser, Korzhev, Neufurth, Wang (2014) Enzyme-accelerated and structure-guided crystallization of Ca-carbonate: role of the carbonic anhydrase in the homologous system. Acta Biomaterialia 10: 450-462

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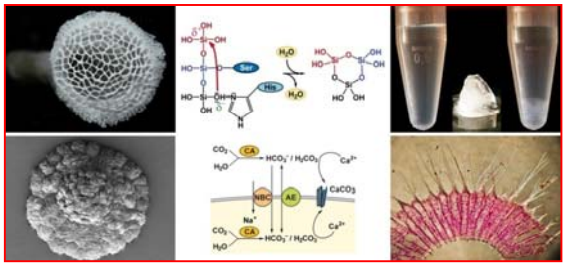
Nature as a Model
Bio-Calcite: Enzymatic
***in vitro* crystal formation**

Carbonic anhydrase



Müller, Schröder, Burghard, Pisignano, Wang (2013) Silicateins - A novel paradigm in bioinorganic chemistry: Enzymatic synthesis of inorganic polymeric silica. Chemistry Eur J 19: 5790-5804.

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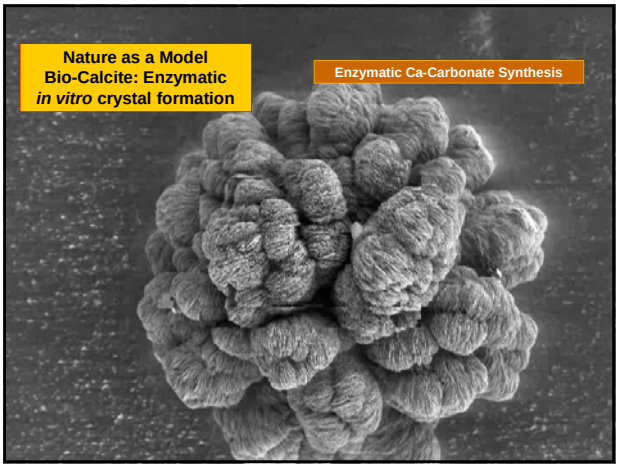
Nature as a Model
Bio-Calcite: Enzymatic
***in vitro* crystal formation**

Enzymatic Ca-Carbonate Synthesis



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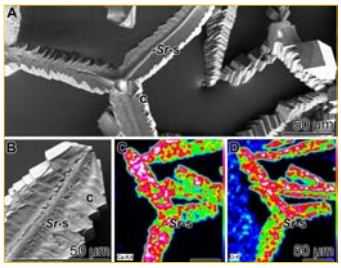
Nature as a Model
Bio-Calcite: Enzymatic
***in vitro* crystal formation**

Element mapping of the surfaces of the rhomboid/rhombohedroid crystals formed in the presence of CA.



Müller, Schlossmacher, Schröder, Lieberwirth, Glasser, Korzhev, Neufurth, Wang (2014) Enzyme-accelerated and structure-guided crystallization of Ca-carbonate: role of the carbonic anhydrase in the homologous system. Acta Biomaterialia 10: 450-462

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Bio-calcite
in human bone

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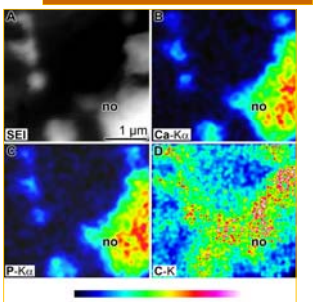
Carbonic anhydrase: Activators – a novel target

Mapping studies for the elements calcium (Ca), phosphorus (P), and carbon (C) around growing nodules (no) onto SaOS-2 cells.



Carbonic anhydrase: Activators – a novel target

Wang, Schröder, Schlossmacher, Neufurth, Feng, Müller (2014) Modulation of the initial mineralization process of SaOS-2 cells by carbonic anhydrase activators and polyphosphate. Calcified Tissue Intern 94: 495–509

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Paradigm shift in bone formation

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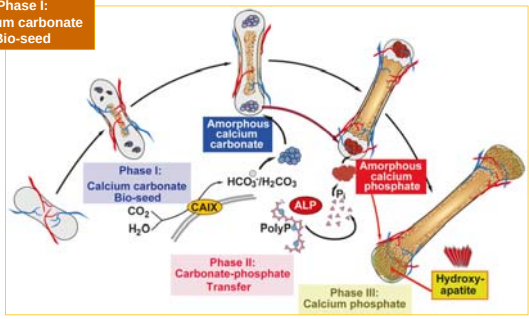
Bio-amorphous Ca-carbonate

Schematic presentation of the process of endochondral ossification and the proposed phases of bone mineral deposition.

Phase I: Calcium carbonate Bio-seed



Tolba, Müller, El-Hady, Neufurth, Wurm, Wang, Schröder, Wang (2015) High biocompatibility and improved osteogenic potential of amorphous calcium carbonate/vaterite. J. Mat. Chem B; in press.

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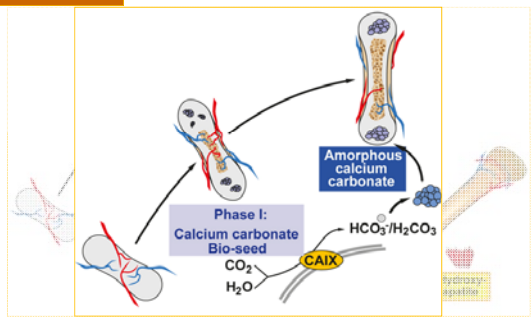

Tolba, Müller, El-Hady, Neufurth, Wurm, Wang, Schröder, Wang (2015) High biocompatibility and improved osteogenic potential of amorphous calcium carbonate/vaterite. J. Mat. Chem B; in press.

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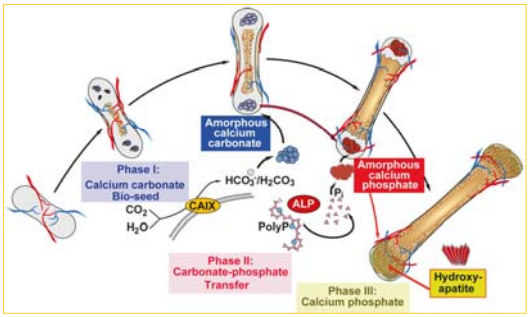

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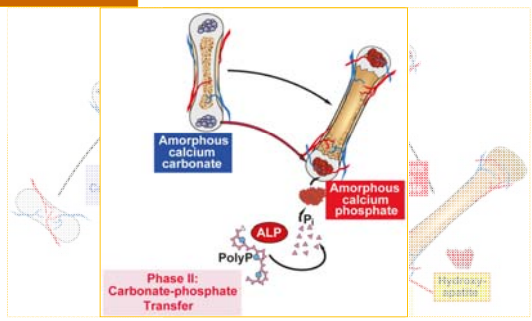
Phase II: Carbonate-phosphate Transfer



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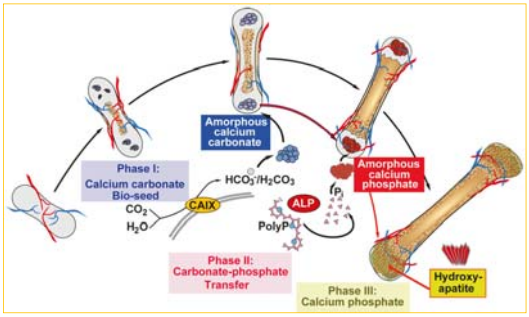
Bio-amorphous Ca-carbonate

Schematic presentation of the process of endochondral ossification and the proposed phases of bone mineral deposition.



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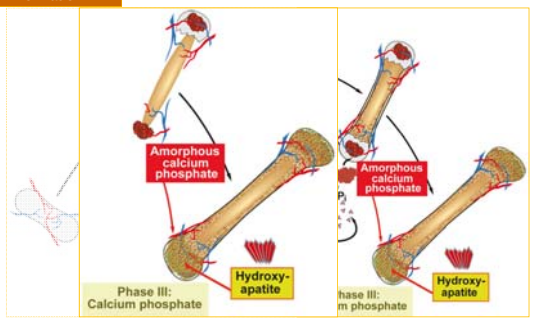
Phase III: Hydroxyapatite Formation



Tolba, Müller, El-Hady, Neufurth, Wurm, Wang, Schröder, Wang (2015) High biocompatibility and improved osteogenic potential of amorphous calcium carbonate/vaterite. J. Mat. Chem B; in press.

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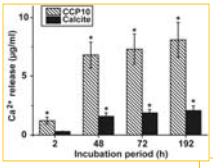
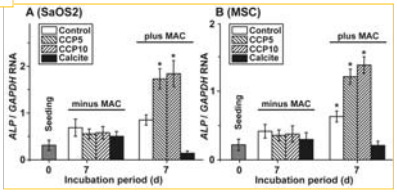


Release of Ca^{2+} from the $CaCO_3$ particles.

Steady-state expression levels of the ALP gene both in (A) SaOS-2 cells and in (B) MSCs.

Amorphous biomaterial



Tolba, Müller, El-Hady, Neufurth, Wurm, Wang, Schröder, Wang (2016) High biocompatibility and improved osteogenic potential of amorphous calcium carbonate/vaterite. J Mat Chem B 4: 376-386.

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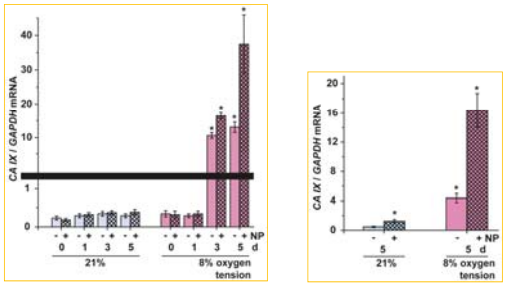
Mineralization under physiological/hypoxic conditions

Alteration of expression of CA IX during hypoxic conditions



Müller WEG, Schröder HC, Tolba E, Diehl-Seifert B, Wang XH (2016) Mineralization of bone-related SaOS-2 cells under physiological hypoxic conditions. FEBS J 283: 74-87

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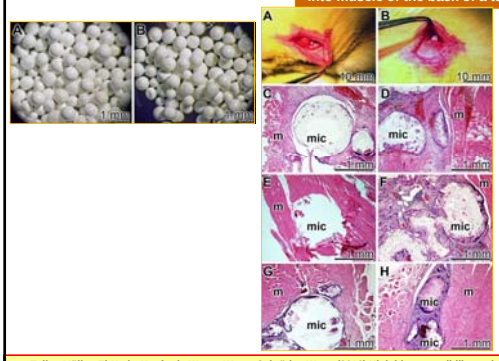
Bio-amorphous Ca-carbonate

Implantation of the implant microspheres into muscle of the back of a test animal.



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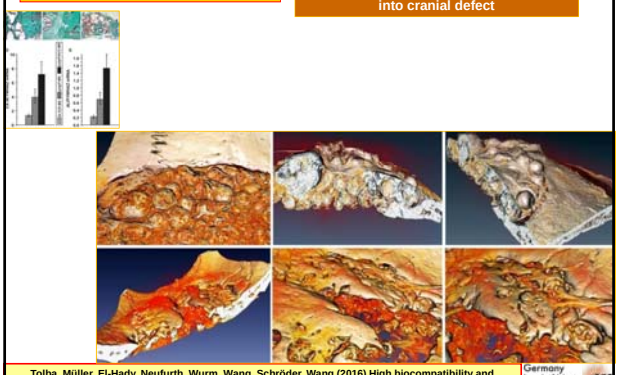
Bio-amorphous Ca-carbonate

Implantation of the implant microspheres into cranial defect



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From ACC to ACP

Bio-phosphate?

Bio-polyphosphate

Metabolic fuel

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What is: Bio-phosphate?

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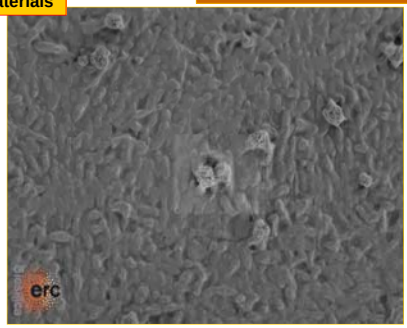
Bio-inspired morphogenesis: New biomaterials

Patch-like hydroxyapatide formation on the surface of SaOS-2 cells



Wiens, Wang, Schloßmacher, Lieberwirth, Glasser, Ushijima, Schröder, Müller (2010) Osteogenic potential of bio-silica on human osteoblast-like (SaOS-2) cells. Calcified Tissue Intern 87: 513–524.

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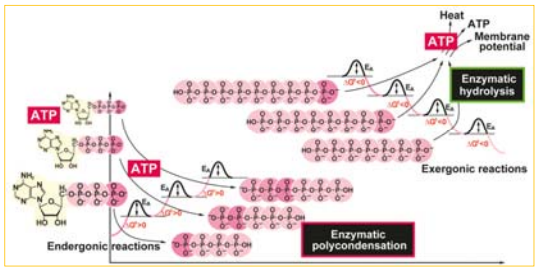
Polyphosphate: Metabolic fuel

Enzymatic synthesis [polycondensation] and enzymatic degradation (hydrolysis) of polyP.



Müller WEG, Tolba E, Schröder HC and Wang XH (2015) Polyphosphate: a morphogenetically active implant material serving as metabolic fuel for bone regeneration. Macromolec Biosci 15: 1182-1197

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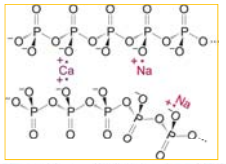
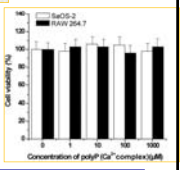
Neues Biomaterial: Polyphosphat



Cells and blood fraction	PolyP class	PolyP content P_i (µM)	PolyP content pmoles/mg protein
Osteoblasts	soluble long chain	394.3 ± 30.6	4331 ± 336
	insoluble long chain	133.8 ± 15.2	1469 ± 167
Gingival cells	soluble long chain	141.3 ± 15.3	1605 ± 174
	insoluble long chain	14.9 ± 5.1	170 ± 58
PBMC	soluble long chain	56.0 ± 2.2	622 ± 24
	insoluble long chain	28.9 ± 7.0	321 ± 78
Erythrocytes	soluble long chain	71.2 ± 14.7	918 ± 190
	insoluble long chain	28.1 ± 4.1	362 ± 53
Plasma	soluble long chain	48.7 ± 7.0	641 ± 92
	insoluble long chain	2.5 ± 1.9	33 ± 25



Polyphosphate: Non-toxic

Müller WEG, Tolba E, Schröder HC and Wang XH (2015) Polyphosphate: a morphogenetically active implant material serving as metabolic fuel for bone regeneration. Macromolec Biosci 15: 1182-1197

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Lieberman, L. (1888) Uber das Nuclein der Hefe und künstliche Darstellung eines Nucleus Eiweiss und Metaphosphatsaure. Ber. Chem-Ges., 21, 598–607.

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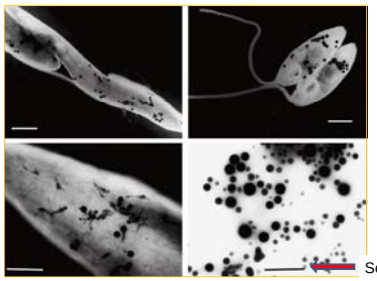
Biomaterial: Polyphosphate Acidocalcisomes

Bioinspired, morphogenetically active microparticles

Morphology of trypanosomatid acidocalcisomes; TEM. Whole cells (a–c) or fractions (d). *Trypanosoma cruzi*; scale bar, 0.5 µm.



Scale bar: 0.5 µm

Docampo R, Ulrich P, Moreno SN (2010) Evolution of acidocalcisomes and their role in polyphosphate storage and osmoregulation in eukaryotic microbes. Philos Trans R Soc Lond B Biol Sci 365: 775-784

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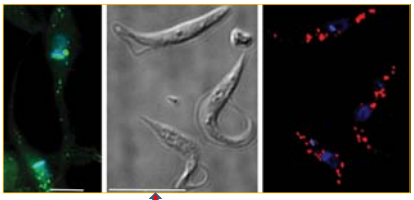
Biomaterial: Polyphosphate Acidocalcisomes

Bioinspired, morphogenetically active microparticles

Acidocalcisomes in trypanosomatids. (a) DAPI staining of epimastigotes of *Trypanosoma cruzi*. Overlay of the green (poly P) and blue (DNA) channels. Acidocalcisomes correspond to the punctate labelling (green).



Scale bar: 5 µm

Docampo R, Ulrich P, Moreno SN (2010) Evolution of acidocalcisomes and their role in polyphosphate storage and osmoregulation in eukaryotic microbes. Philos Trans R Soc Lond B Biol Sci 365: 775-784

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Biomaterial: Polyphosphate Acidocalcisomes

Bioinspired, morphogenetically active microparticles

TEM Pseudomonas putida.

CA-3 cells containing intracellular polyP and PHA granules accumulated from phenylacetic acid. PolyP is visible as small black dots; (inclusions). PHA is visible as large clear/white inclusions

Tobin KM, McGrath JW, Mullan A, Quinn JP, O'Connor KE (2007) Polyphosphate accumulation by *Pseudomonas putida*. Appl Environ Microbiol 73: 1383-1387.

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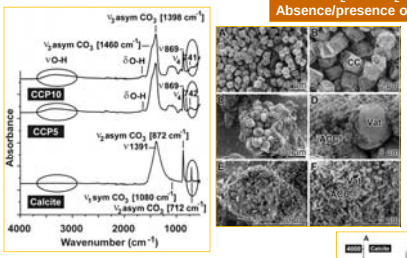
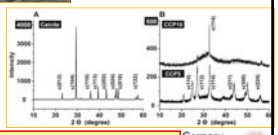
Bio-amorphous Ca-carbonate

Morphology and spectra of the solids formed from $CaCl_2$ and Na_2CO_3; SEM analysis. Absence/presence of polyP.





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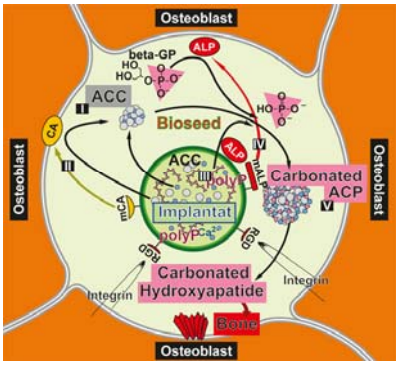

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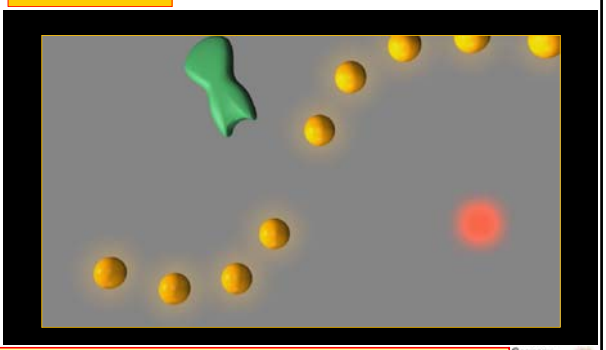
Polyphosphate: Metabolic fuel

Energy and bone mineral substrate



Müller WEG, Tolba E, Schröder HC and Wang XH (2015) Polyphosphate: a morphogenetically active implant material serving as metabolic fuel for bone regeneration. Macromolec Biosci 15:1182-1197

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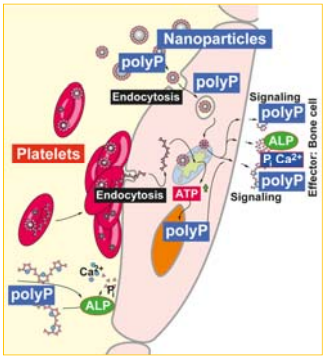
Polyphosphate: Metabolic fuel

Uptake of polyP from platelets and Ca-polyP nanoparticles.



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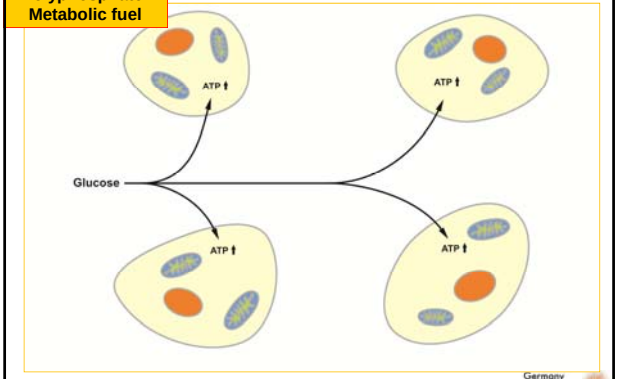
Polyphosphate: Metabolic fuel



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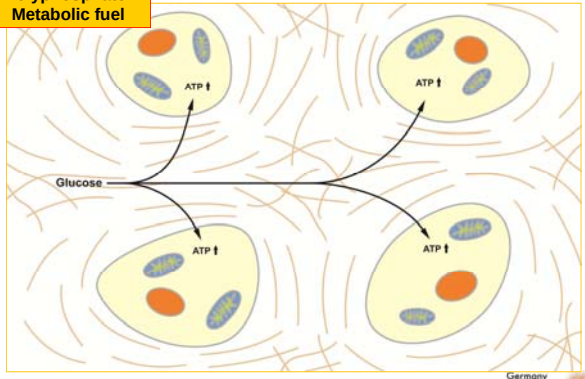
Polyphosphate: Metabolic fuel



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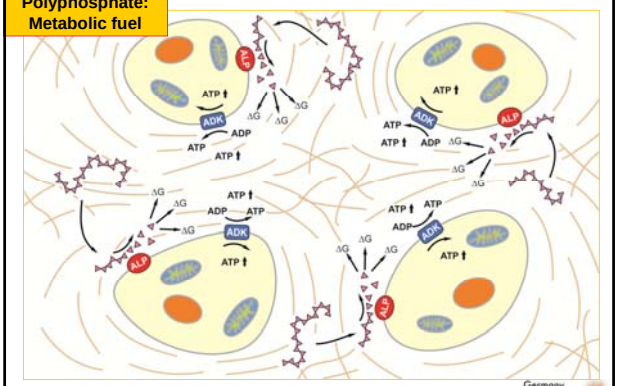
Polyphosphate: Metabolic fuel



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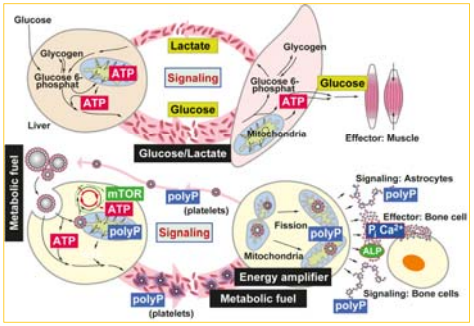
Polyphosphate: Metabolic fuel

Energy transport/signaling role of polyP within the metabolism of an animal/human



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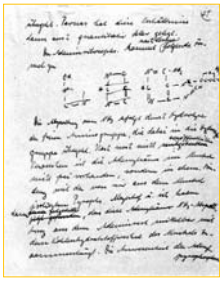
Karl Lohmann chatting with Otto Warburg at the Third Erythrocyte Symposium, November 1960, in the lecture hall of the Institute of Physiological and Biological Chemistry, Humboldt University, Berlin,



Formula of the "Adenosine Ribose Phosphate" from a handwritten manuscript.

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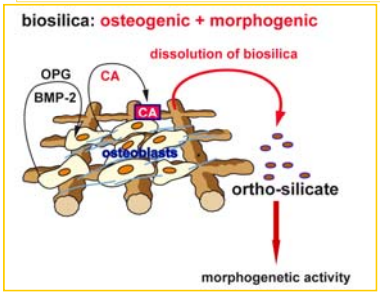
Applied: Biomedicine

Dissolution of biosilica: generation of a morphogenetic potential



Wang, Schröder, Diehl-Seifert, Kropf, Schlossmacher, Wiens, Müller (2013) Dual effect of inorganic polymeric phosphate/polyphosphate on osteoblasts and osteoclasts in vitro. J Tissue Eng Regen Med 7:767-776

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Bio-polyphosphate for bone implants

Hybrid material

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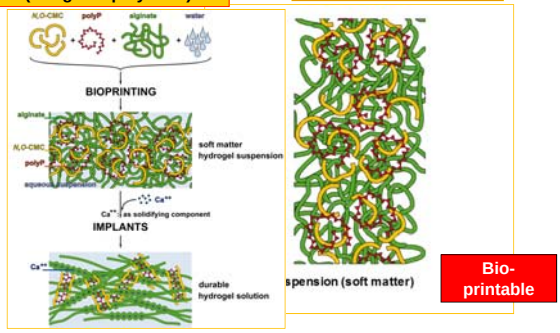
Biocompatible Biomaterial (inorganic polymers)

Natural biopolymers: Self-organizing



Bio-printable

Müller, Tolba, Schröder, Al-Nawas, Wang (2015) A new printable and durable N,O-carboxymethyl chitosan-Ca2+-polyphosphate complex with morphogenetic activity. J Mat Chem B 3: 1722-1730

Germany Land of Ideas erc

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

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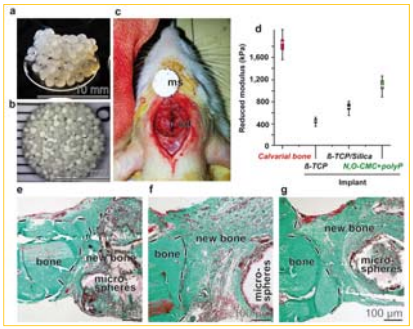
Ca-polyphosphate: Bone implants

In vivo **anabolic activity of the "*N,O*-CMC+polyP" scaffold. Defects had been drilled in cranial bone.**



Müller, Tolba, Schröder, Wang, Al-Nawas, Wang (2015) A new printable and durable *N,O*-carboxymethyl chitosan-Ca^{2+}-polyphosphate complex with morphogenetic activity. J Mat Chem B 3: 1722-1730

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<u>Product:</u>
Dental sealants - Desensitization

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ERC Investigator, Institute for Physiological Chemistry

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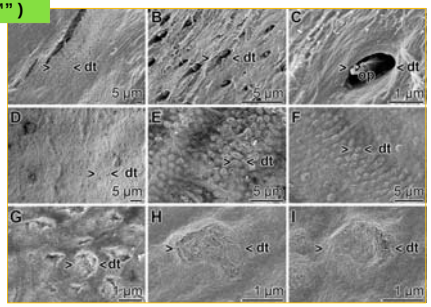
Product: Genuine regenerating toothpaste ("dentoReseal™")

Occlusion of the dentinal tubules by "dRs"-1%; SEM.



<u>Patent application/granted:</u> Müller W.E.G.: METHOD FOR THE PREPARATION OF TEETH COATINGS HAVING MORPHOGENETIC ACTIVITY.. Wordwide (GB) Patent GB1510772.5 (2015)

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Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

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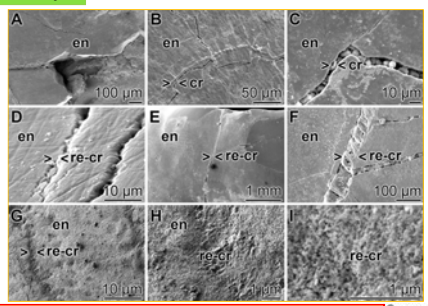
Product: Genuine regenerating toothpaste ("dentoReseal™")

Re-sealing: perfect



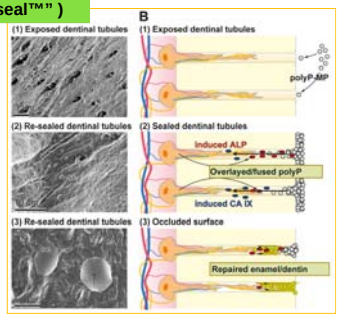
<u>Patent application/granted:</u> Müller W.E.G.: METHOD FOR THE PREPARATION OF TEETH COATINGS HAVING MORPHOGENETIC ACTIVITY.. Wordwide (GB) Patent GB1510772.5 (2015)

Germany Land of Ideas erc

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

Product: Genuine regenerating toothpaste ("dentoReseal™")

Occlusion of the dentinal tubules by the polyP-based and microparticle-formulated "dRs"-1% paste. Occluded by a genuine repair process.

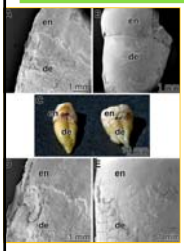


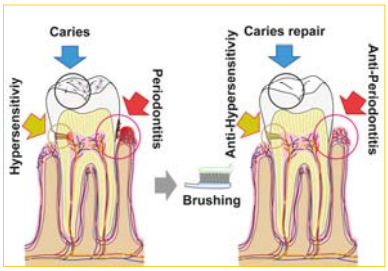
Patent application/granted: Müller W.E.G.: METHOD FOR THE PREPARATION OF TEETH COATINGS HAVING MORPHOGENETIC ACTIVITY.. Wordwide (GB) Patent GB1510772.5 (2015)

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

Product: Genuine regenerating toothpaste ("dentoReseal™")

Three activities:
first, resealing of cracks/fissures within enamel/dentin;
second, filling carious cavities; and
third, remineralization
And:
anti-microbial potential: *Streptococcus mutans*





Patent application/granted: Müller W.E.G.: METHOD FOR THE PREPARATION OF TEETH COATINGS HAVING MORPHOGENETIC ACTIVITY.. Wordwide (GB) Patent GB1510772.5 (2015)

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

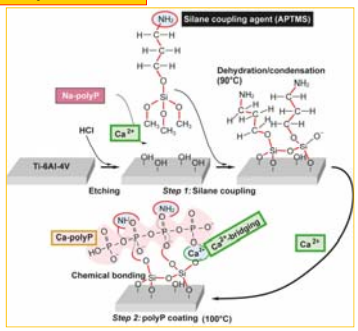
Bio-polyphosphate on titanium implants

Biologization

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

Bio-polyphosphate on titanium implants

Binding of polyP to titanium discs using the silane coupling agent APTMS (scheme).

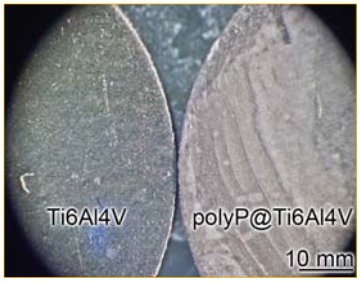


Müller WEG, Tolba E, Schröder HC, Wang S, Glasser G, Diehl-Seifert B, Wang XH (2015) Biologizing titanium alloy implant material with morphogenetically active polyphosphate. RSC Advances 5: 75465-75473

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

Bio-polyphosphate on titanium implants

Comparison between an untreated, dark gray titanium alloy disc (left) and a Ti-Ca-polyP disc (right); light microscopic image.



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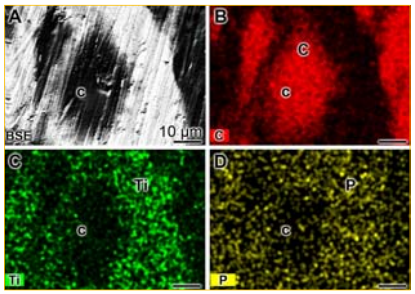
Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

Bio-polyphosphate on titanium implants

Semiquantitative determinations of the elements carbon (C) (B), titanium (Ti) (C) and phosphorus (P) (D) along some cells, growing onto Ti-Ca-polyP discs after a 3 d incubation period.



Müller WEG, Tolba E, Schröder HC, Wang S, Glasser G, Diehl-Seifert B, Wang XH (2015) Biologizing titanium alloy implant material with morphogenetically active polyphosphate. RSC Advances 5: 75465-75473

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

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Implants for knee cartilage

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Implants for knee cartilage

Modelling

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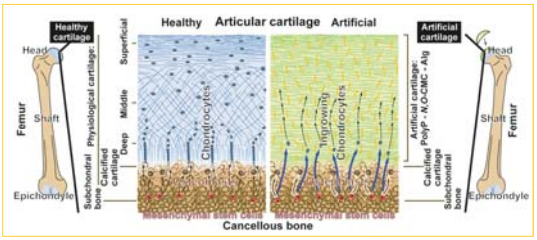
Implants for knee cartilage

Knee cartilage Implant



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Implant 4.0

Implant 4.0

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New Generation in Digital Economy & Society

High Time for:

Bio-Information/Communication (BICT)
And
Cyber-Biophysical Production Systems (CBS)

"Implantology 4.0"

Developing measures to make online communications. Supporting the deployment of a high-quality, digital infrastructure.

Towards "Implant 4.0"

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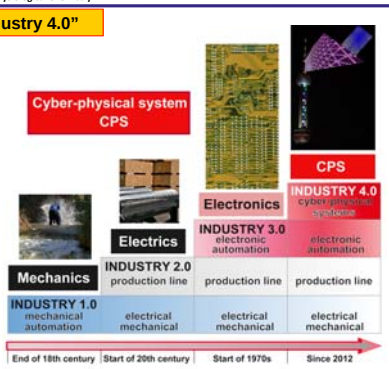
Towards "Industry 4.0"



Towards "Industry 4.0"

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ERC Investigator, Institute for Physiological Chemistry

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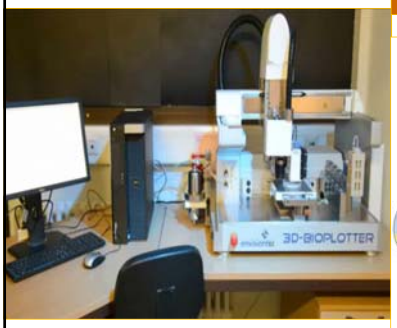
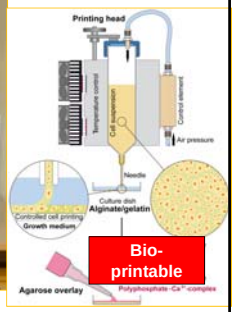
Bio-silica: 3D printing

Cell printing

3D cell printing of scaffolds





Bio-printable

Wang, Schröder, Feng and Müller (2013) The deep-sea natural products, biogenic polyphosphate and biogenic silica, as biomimetic scaffolds for bone tissue engineering. Marine Drugs 11: 718-746.

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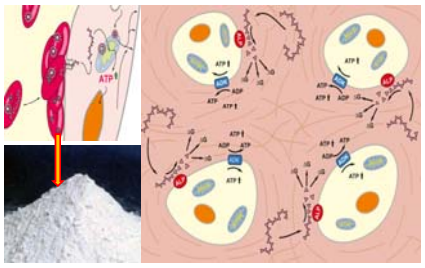
Breakthrough discovery and emerging technology

Amorphous poly-phosphate:
Extracellular ATP - Metabolic fuel - A gold mine for tissue engineering



- Natural – synthetic
- Cheap
- Bio-compatible
- Bio-degradable
- Regeneratively active
- Bio-printable

Müller WEG, Tolba E, Feng Q, Schröder HC, Markl JS, Kokkinopoulou M and Wang XH (2015) Amorphous Ca^{2+} polyphosphate nanoparticles regulate the ATP level in bone-like SaOS-2 cells. *J Cell Sci* 128: 2202-2207;
Müller WEG, Tolba E, Schröder HC and Wang XH (2015) Polyphosphate: a morphogenetically active implant material serving as metabolic fuel for bone regeneration. *Macromolec Biosci* 15:1182-1197.

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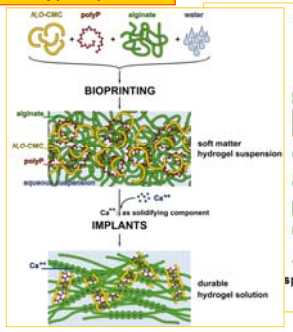
Bone formation: Polyphosphate

Natural biopolymers: Self-organizing



spension (soft matter)

Bio-printable

Müller, Tolba, Schröder, Al-Nawas, Wang (2015) A new printable and durable N,O-carboxymethyl chitosan-Ca2+-polyphosphate complex with morphogenetic activity. J Mat Chem B 3:1722-1730

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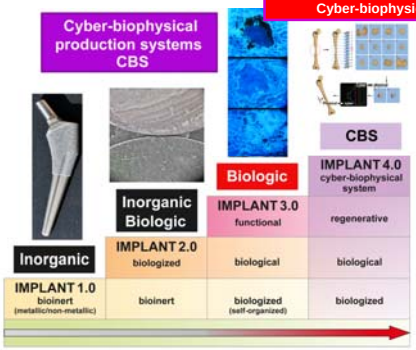
Towards "Implant 4.0"

Ready to cross the final frontier to Cyber-biophysical/chemical systems

Cyber-biophysical production systems CBS



Towards "Implant 4.0"

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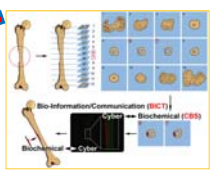
Towards "Implant 4.0"

Nature as blueprint

Towards "Implant 4.0"

Bio-Information/Communication (BICT)



Towards "Implant 4.0"

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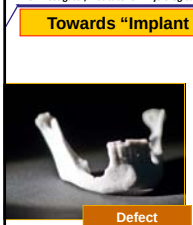
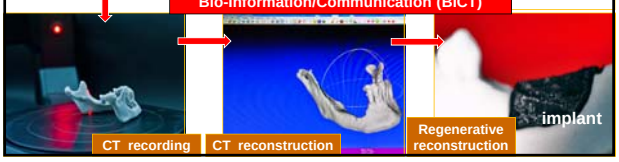
Towards "Implant 4.0"



Defect

Bio-Information/Communication (BICT)



CT recording

CT reconstruction

Regenerative reconstruction

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Bio-Information/Communication (BICT)

Proton and Heavy Ion Hospital in Shanghai (China)
↓
University Medical Center Mainz (Germany)
↓
Tsinghua University Beijing (China)

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ERC Investigator, Institute for Physiological Chemistry

Towards "Implant 4.0"

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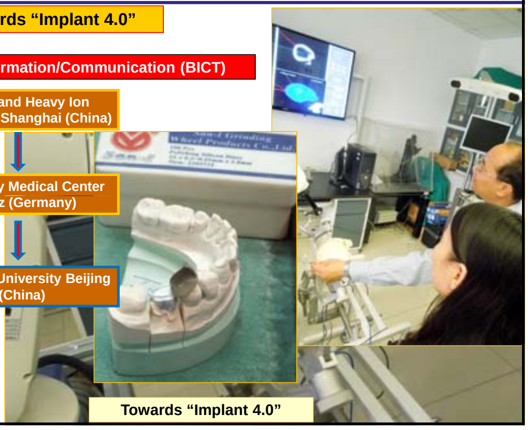

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Bio-Information/Communication (BICT)

Ruder Boskovic Institute (Croatia)
↓
University Medical Center Mainz (Germany)
↓
National Research Centre (NRC) (Egypt)

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Bio-Information/Communication (BICT)

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University Medical Center Mainz (Germany)
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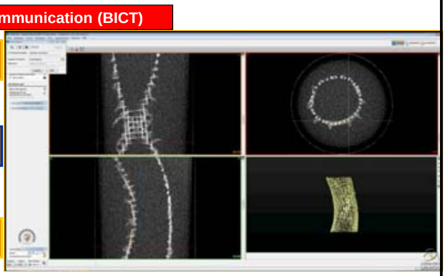
National Research Centre (NRC) (Egypt)



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Towards "Implant 4.0"

Bio-Information/Communication (BICT)

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Towards “Implant 4.0”

Bio-Information/Communication (BICT)

Ruder Boskovic Institute (Croatia)

↓

University Medical Center Mainz (Germany)

↓

National Research Centre (NRC) (Egypt)

President – NRC
Prof. Dr. Ashraf Shaalan

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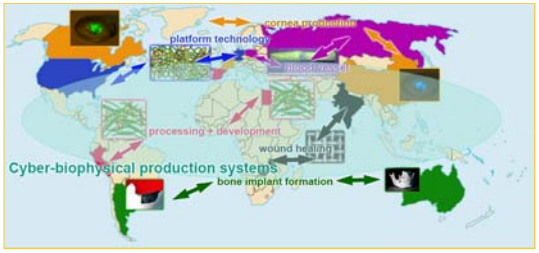
Towards “Implant 4.0”

Bio-Information/Communication (BICT)



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ERC Investigator, Institute for Physiological Chemistry

Financial support

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ERC Investigator, Institute for Physiological Chemistry

WACKER

novozymes Rethink Tomorrow

SCHÜTZ DENTAL GROUP

Kooperationsvertrag: Chemische Fabrik Budenheim

erc

Research fundings

Deutsche Forschungsgemeinschaft DFG

VolkswagenStiftung

Bundesministerium für Bildung und Forschung

Boehringer Ingelheim Stiftung

PTJ Projektträger Jülich Forschungszentrum Jülich

Stiftung Rheinland-Pfalz für Innovation

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ERC Investigator, Institute for Physiological Chemistry

Two important EU grants

SEVENTH FRAMEWORK PROGRAMME

BlueGenics

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

ERC Advanced Investigators Grant

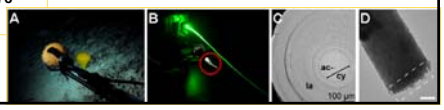
erc European Research Council

European Research Council
ERC Advanced Grant 2010

Proposal Full Title:
From gene to biomineral: Biosynthesis and application of sponge biosilica

PROPOSAL ACRONYM: **BIOSILICA**

Proposals ERC-2010-AdG – Proposal n° 268476 BIOSILICA



Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

ERC Proof of Concept Grant

European Research Council

Bringing Great Ideas to Life

PROPOSAL 324564 - SILICA-BASED NANOBIOMEDICAL APPROACHES FOR TREATMENT OF BONE DISEASES: PROOF-OF-CONCEPT

APPLICANT - WERNER E. G. MÜLLER

Silicatein is a unique enzyme from siliceous sponges that is able to catalyze the formation of an inorganic material, silica or "biosilica" which forms the inorganic skeleton of these sponges. Another exceptional property of this protein is its dual function: silicatein both (i) acts as an enzyme (biosilica formation) and (ii) exhibits structure-forming/guiding activity.

Even more important with regard to the biomedical application of silicatein: the product of the enzymatic reaction, biosilica, is osteogenic and biocompatible and allows the formation of a moldable material – the ideal basis for the potential application in bone healing. Moreover, we demonstrated that biosilica not only increases the expression of bone morphogenic protein 2 (BMP-2) involved in bone formation, but also modulates the ratio of expression of two proteins, osteoprotegerin and RANKL, that are crucial in pathogenesis of osteoporosis.

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

ERC Proof of Concept Grant-2: 2015

Press release

5 February 2015

Bringing research to the market: ERC funds 59 innovative projects

A simple blood test to diagnose breast cancer, a forensic device to trace the origin of tropical timber, and artificial veins inspired by marine sponges; these are some of the inventions to be developed by 5 of 'Proof of Concept' Grants fron

Artificial blood vessels inspired by marine sponges

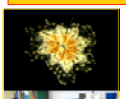
Prosthetic vascular grafts are the tiny synthetic channels used to redirect blood flow during surgery. In the course of his ERC-funded research into potential new biomaterials, Prof. Werner E.G. Müller unexpectedly found that certain polymers have potential to make a new generation of narrow vascular grafts based on the minute biosilica structures found in marine sponges.

With a 'Proof of Concept' Grant, he plans to build on these findings to introduce innovative, extra narrow vascular grafts on the market. The materials currently used work well for grafting large-diameter vessels but are inappropriate for small-diameter vessels required for coronary artery bypass grafting, for example. The new artificial vessels, designed by Prof. Müller, improve existing options because they can be better adapted to the needs of individual patients, are able to prevent thrombosis, have adjustable degradation rates, and can be easily fabricated. The 'Proof of Concept' Grant will support the team in safety standardisation, market analysis, preparation of a business plan, and in their efforts to scale-up the production process prior to clinical studies. This is the second 'Proof of Concept' Grant awarded to Prof. Werner E.G. Müller following his research into biomaterials, the first being obtained in 2012 to support production of biosilica-based scaffolds for bone regeneration.

ERC grantee: **Prof. Werner E.G. Müller**
Host institution: Mainz University, Germany

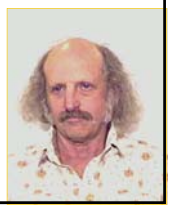
Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

Invertebrate Immunology



Baruch Rinkevich
National Institute of Oceanography, Haifa

Eric Davidson
Caltech USA



Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

27-10-2013: Reception in Frankfurt

President European Commission
José Manuel Barroso

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Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

The Order of Merit of the Federal Republic of Germany

Our federal president: Schloss Bellevue
Joachim Gauck

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Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

25-06-2013: Reception in Berlin

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

Univ.-Prof. Dr. Werner E.G. MÜLLER
ERC Investigator, Institute for Physiological Chemistry

Univ.-Prof. Dr. Werner E.G. MÜLLER
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