Biomaterials – the merger of devices with biologicals

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University of Pennsylvania
Philadelphia, PA

Society for Biomaterials, Founders Award Lecture, Charlotte, NC, April 2015

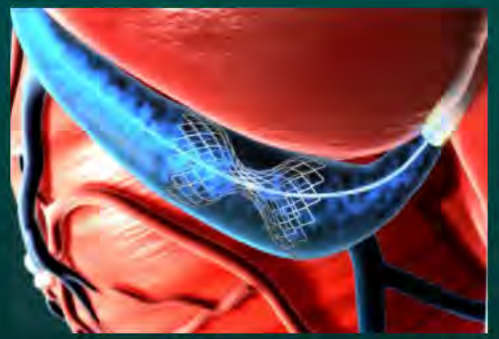
Human identity related to identity of language

Eric Zenmour

In : Mélancolie Française, March 2010

Science being an activity of man,
let us use this unique identifier of the mind
and ask the question how do we interpret the word
"biomaterials"

“Eventually, large device companies will look more like Amgen, as we will need to have biologicals in our devices”



drug coated stents
(rapamycin)

Stephen Oesterle, MD
Senior Vice President of Medicine and Technology
Medtronic
In : Genetic Engineering and News, August 1, 2008

Previously, orthopaedic implants were designed simply as mechanical devices; the biological aspects of the implant were a byproduct of stable internal/external fixation of the device to the surrounding bone or soft tissue. *More recently, biologic coatings have been incorporated into orthopaedic implants in order to modulate the surrounding biological environment*..... While many of these coatings are still in the preclinical testing stage, bioengineers, material scientists and surgeons continue to explore surface coatings as a means *of improving clinical outcome of patients undergoing orthopaedic surgery.*

Stuart Goodman, et al.
The future of biologic coatings for orthopaedic implants
Biomaterials, p. 3174 (2013)

Biomaterials are hybrid materials

The illustration of bioceramics

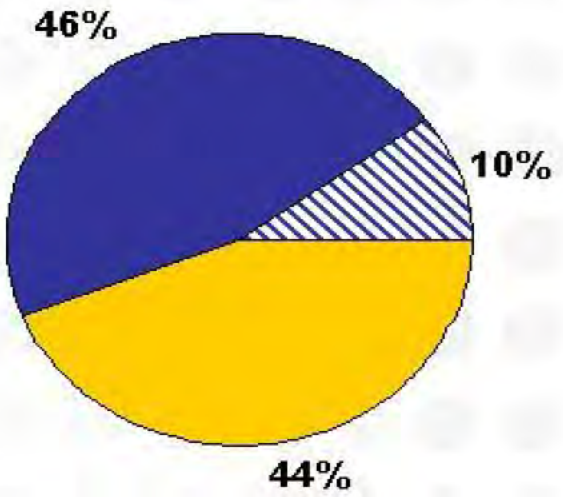
- ***Bioactive ceramics***
  Biologically reactive ceramics and glasses that enhance bone formation and stimulate tissue regeneration
- **Inorganic controlled release materials, *including sol gel glasses***
- **(Inert ceramics for wear resistance)**

Problem: Bone Formation

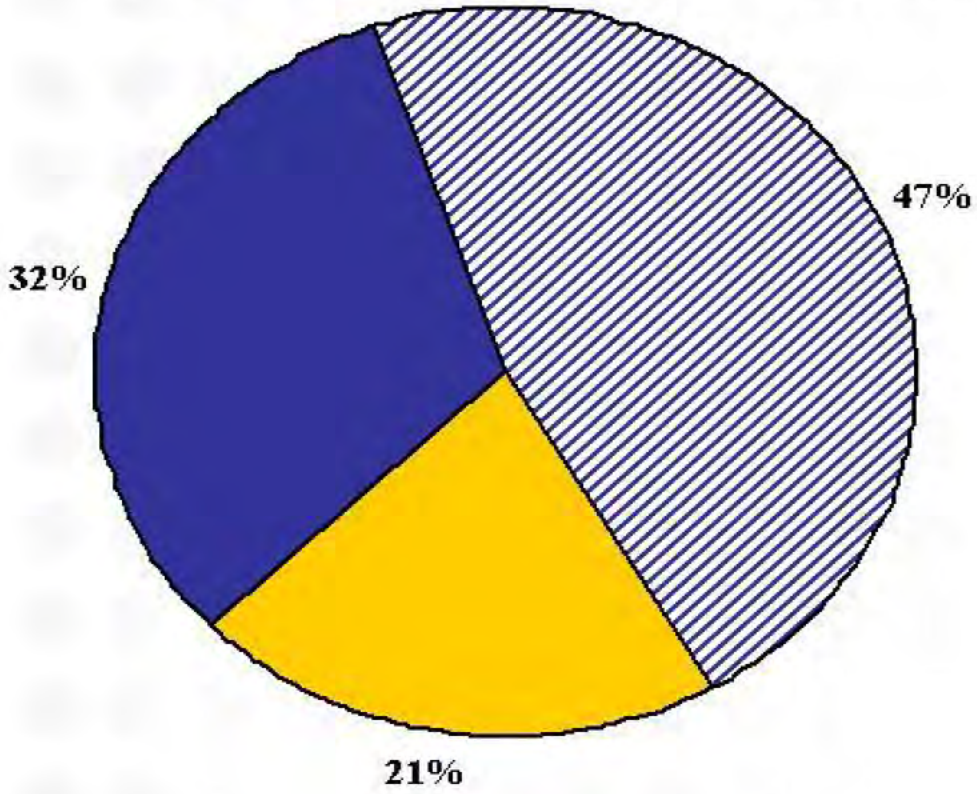
- Biological Grafts
  - » Autografts
    - Donor site morbidity
    - Limited donor bone supply
    - Anatomical and structural mismatch
  - » Allografts
    - Immunological response
    - Disease transmission
- Synthetic grafts (Biocompatible ceramics and glasses)
  - » Hydroxyapatite (HA)
  - » Tricalcium Phosphate (TCP)
  - » Bioactive glass (BG 45S5, …)
- Tissue Engineering
  - » Scaffolds
  - » Molecules (growth factorsBMP-2, OP-1,…)
  - » Cells

Non-Structural Bone Graft U.S.
Market Overview

2001 $360 MM Market



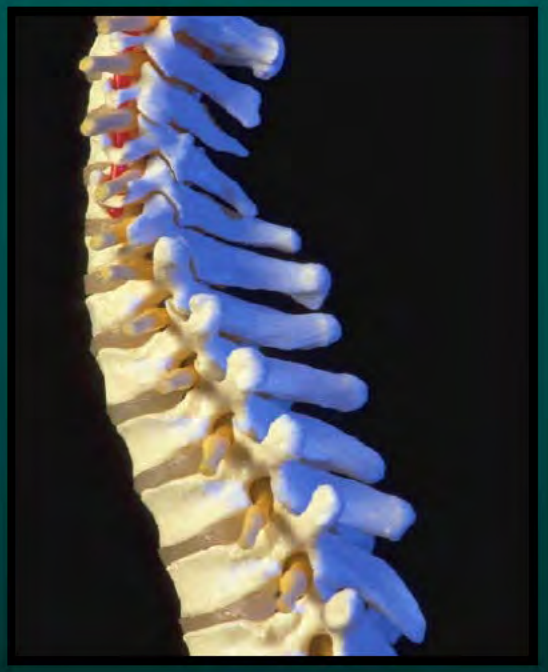
2007 $1,000 MM Market

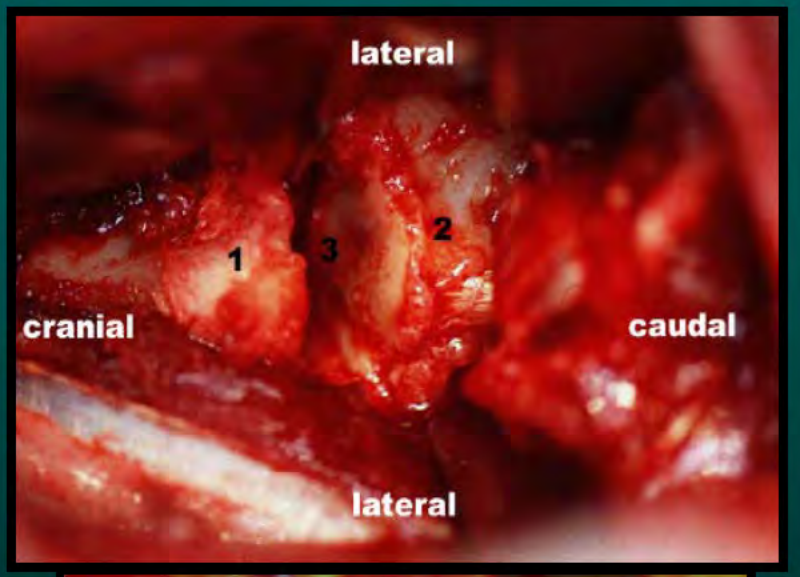


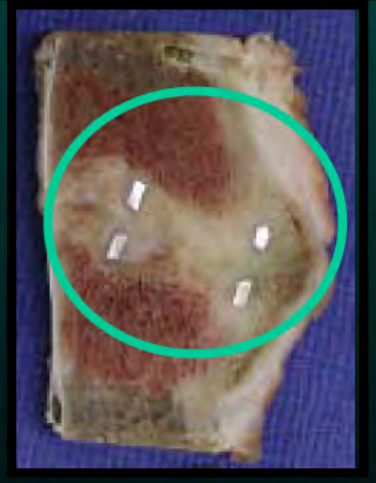
- Autograft
- Non-structural Allograft / DBM
- Synthetic Scaffolds & Cells
- Synthetic Scaffolds, Cells & Signals

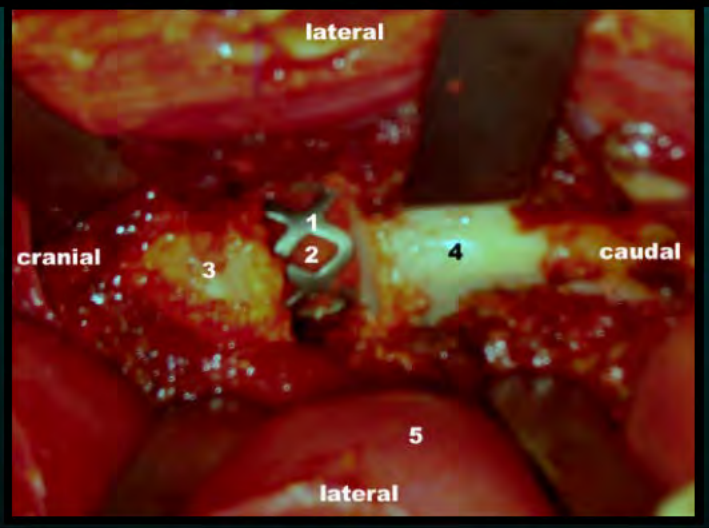
Source: Data Monitor; Market Dynamics: Bone Substitutes and Growth Factors, December 2002

Spinal fusion

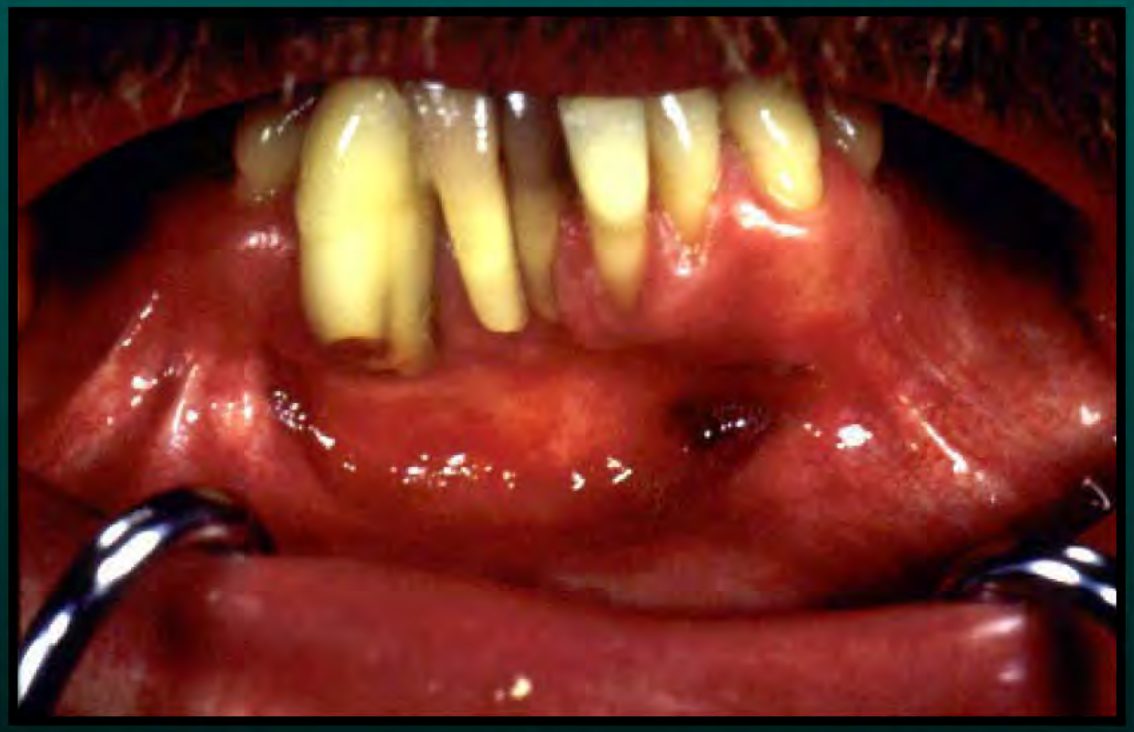








Bony defect resulting from tumor surgery



Bioactive ceramics and glasses
Key references

Hench et al., 1972

Aoki, 1972

Jarcho et al., 1976

De Groot, 1980

Ducheyne et al., 1980

Kokubo, Yamamuro, et al., 1985

The effect of hydroxyapatite impregnation on skeletal bonding of porous coated implants

Statistically significant differences

- at 2 weeks: $p < 0.01$
- at 4 weeks: $p < 0.001$

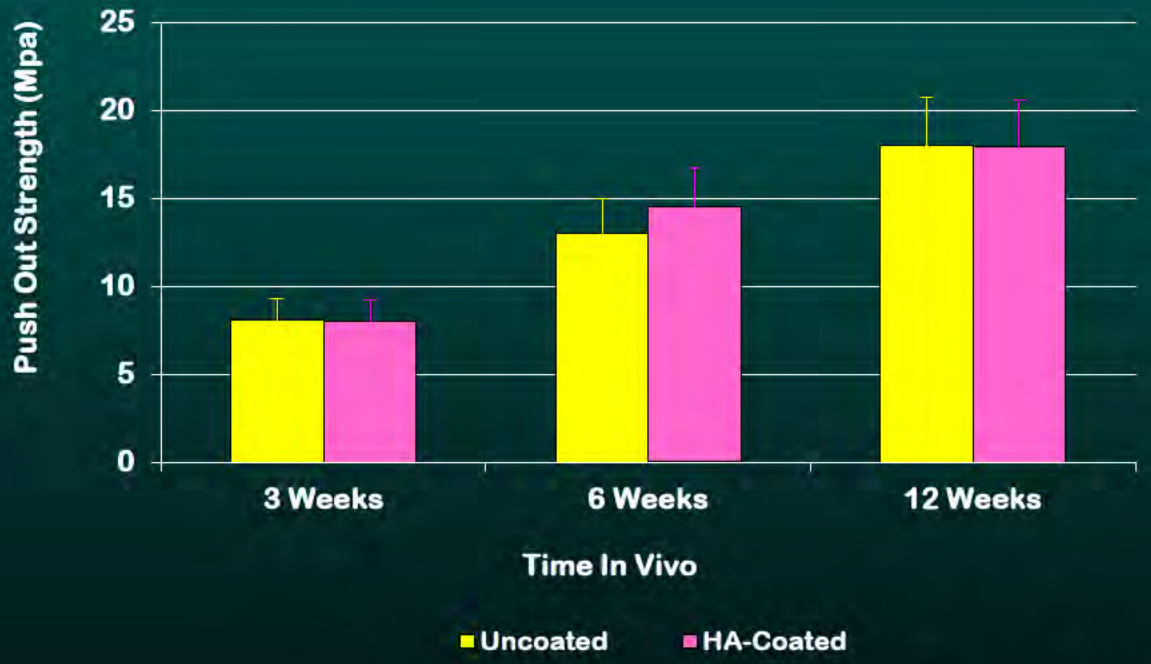
No meaningful difference

- at 12 weeks: $p < 0.5$

P. Ducheyne et al., J. Biomed. Mater. Res., 14, 225 (1980)

Effect of PS-HA on Ti

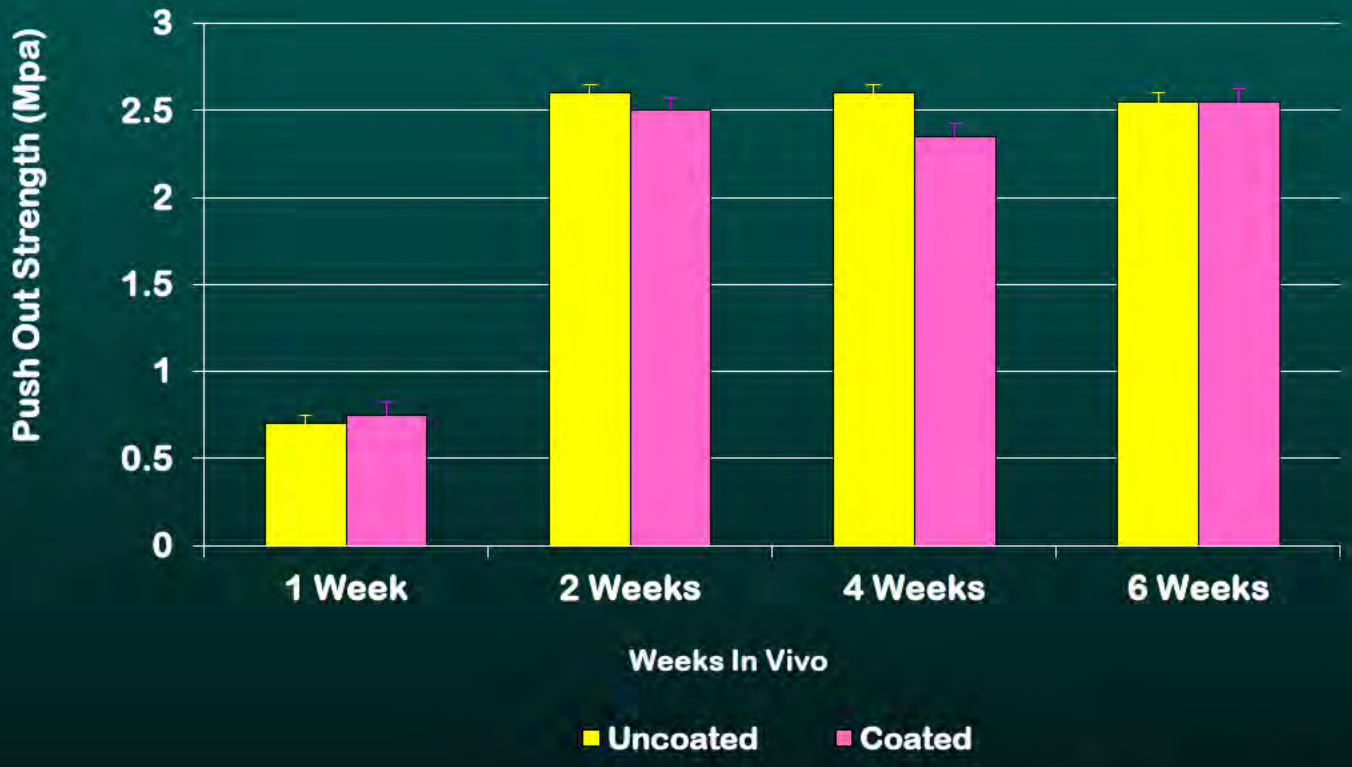
Canine Push-Out Testing



(Cook et al., 1988)

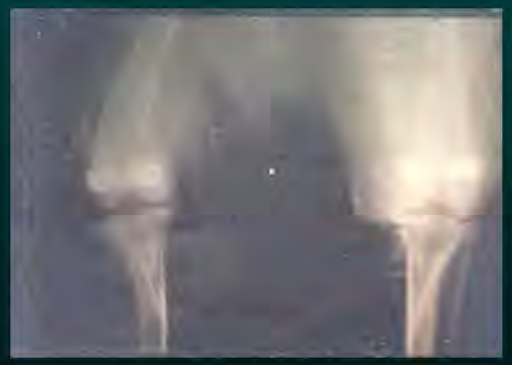
HA Coated Fibermetal Mesh

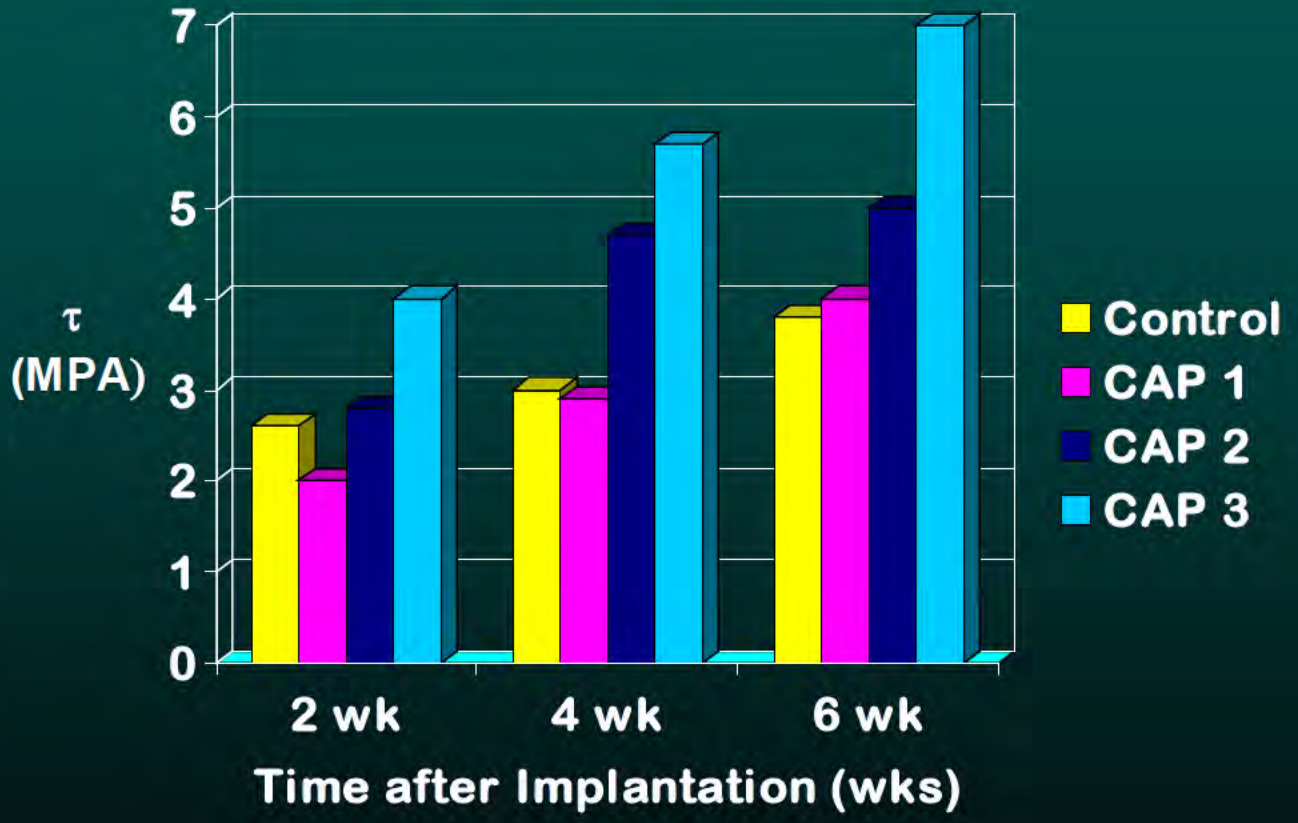
Pull Out Shear Strength



(Rivero et al., 1988)

The effect of calcium phosphate coating characteristics on early postoperative bone tissue ingrowth





Ducheyne et al., Biomaterials 11, 531 (1990)

The effect of calcium phosphate coating characteristics on early postoperative bone tissue ingrowth

Statistically significant differences

(CAP 3 vs. control)

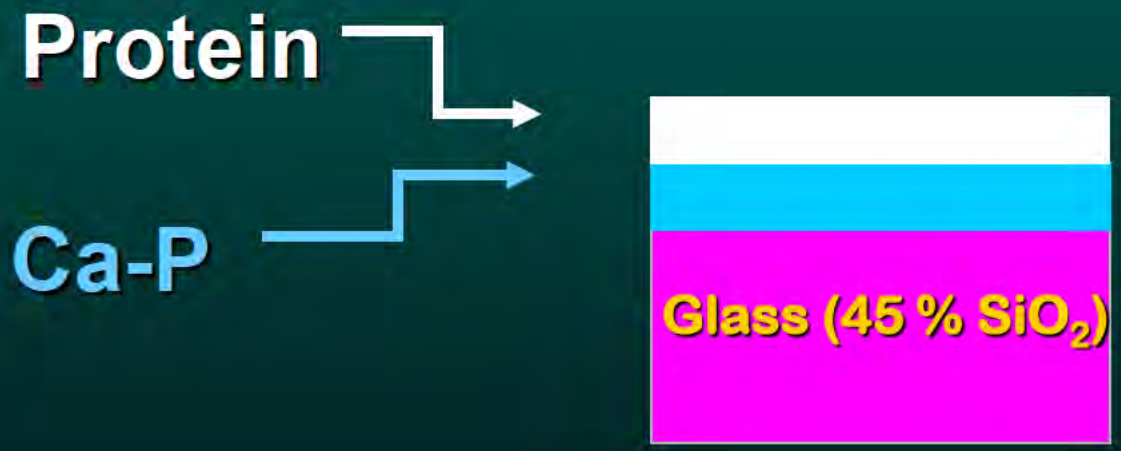
- at 2 weeks: $p < 0.005$
- at 4 weeks: $p < 0.01$
- at 6 weeks: $p < 0.001$

Ducheyne et al., Biomaterials 11, 531 (1990)

Mechanisms of bioactivity

- surface reactivity
  - » Ca – P layer formation
  - » preferential Fn adsorption
  - » Fn binding effect
  - » growth factor adsorption
- solution effect
  - » ionic dissolution product
  - » cell produced osteogenic factors
- porosity effect

Bioactive Glass (BG) Surface Modification



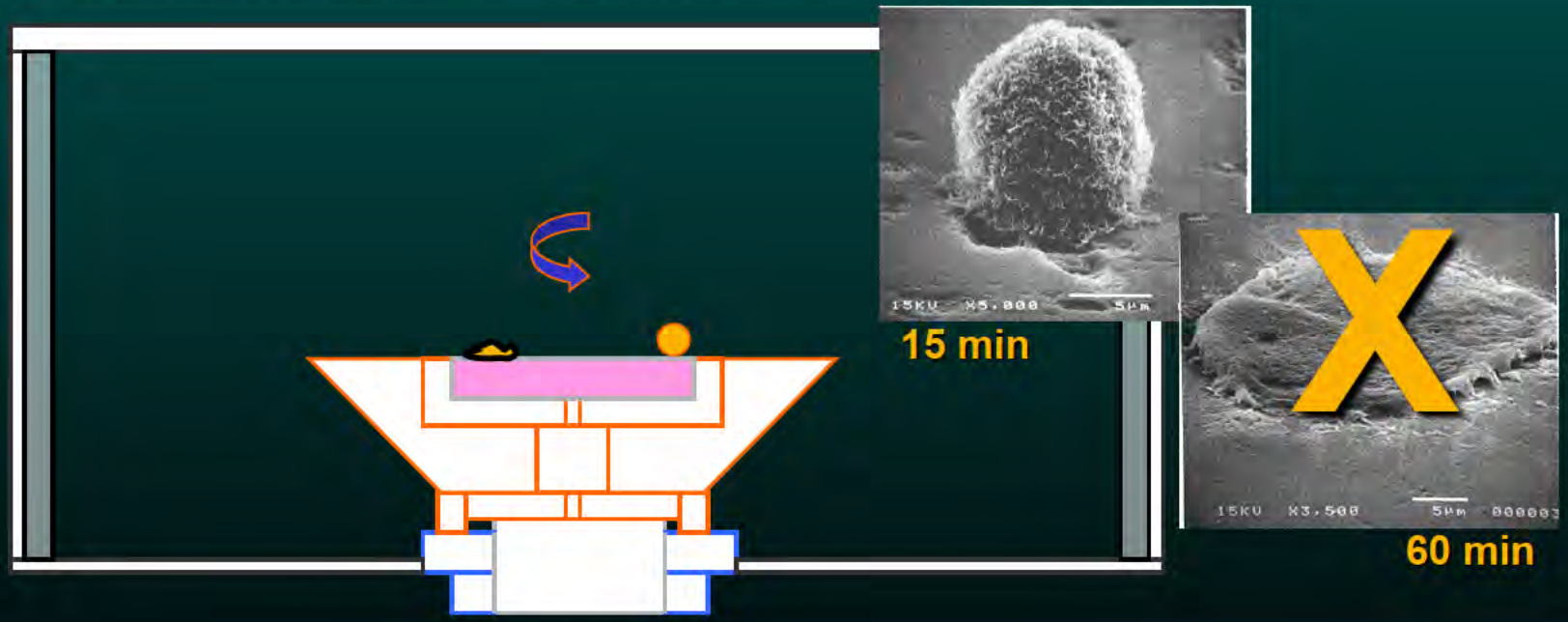
Cell Detachment Apparatus (CDA)

Spinning disk in an infinite fluid:

- linear range of shear stresses to attached cells

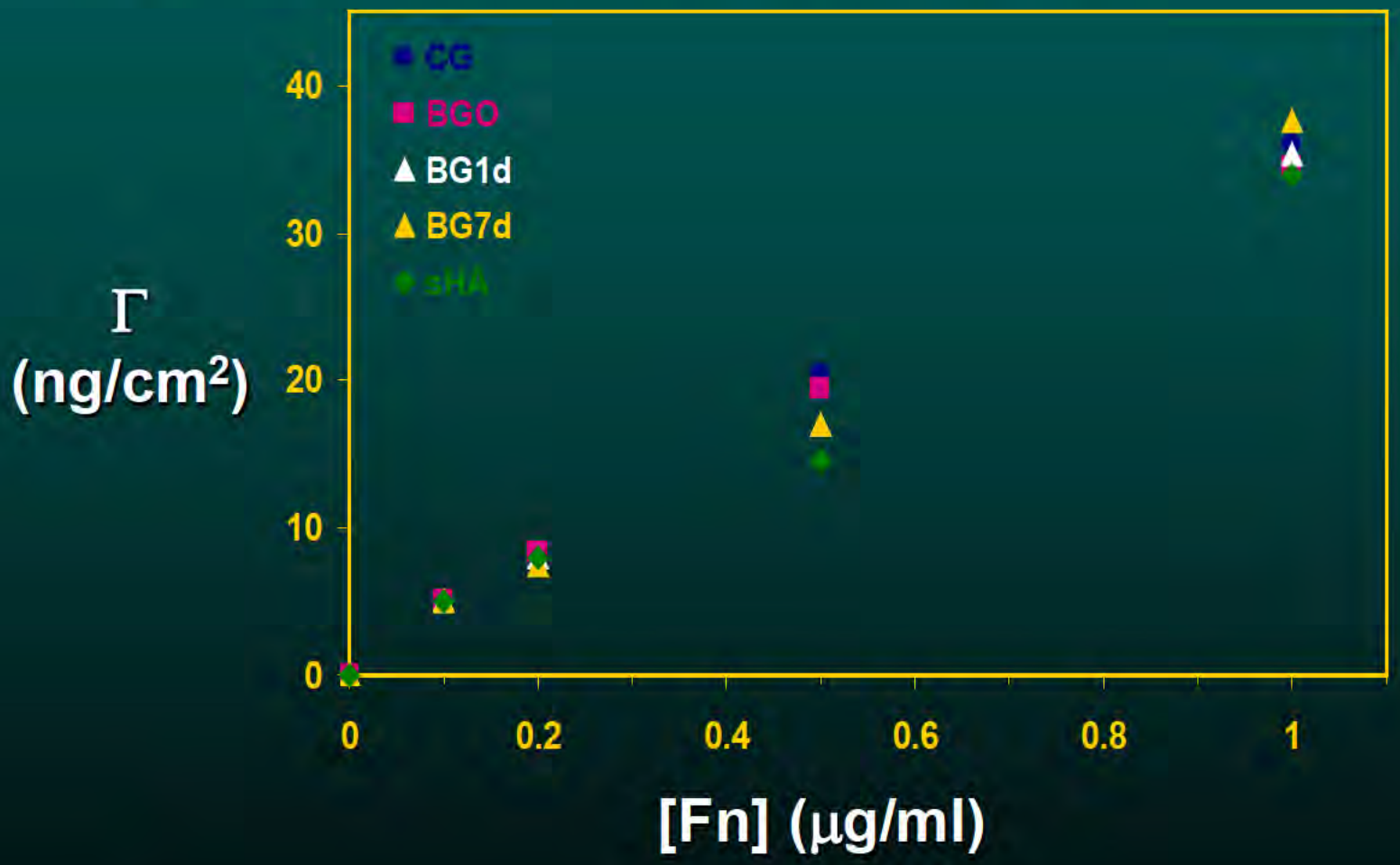
$$\tau = 0.8r\sqrt{\rho\mu\omega^3}$$

- uniform chemical environment at the surface



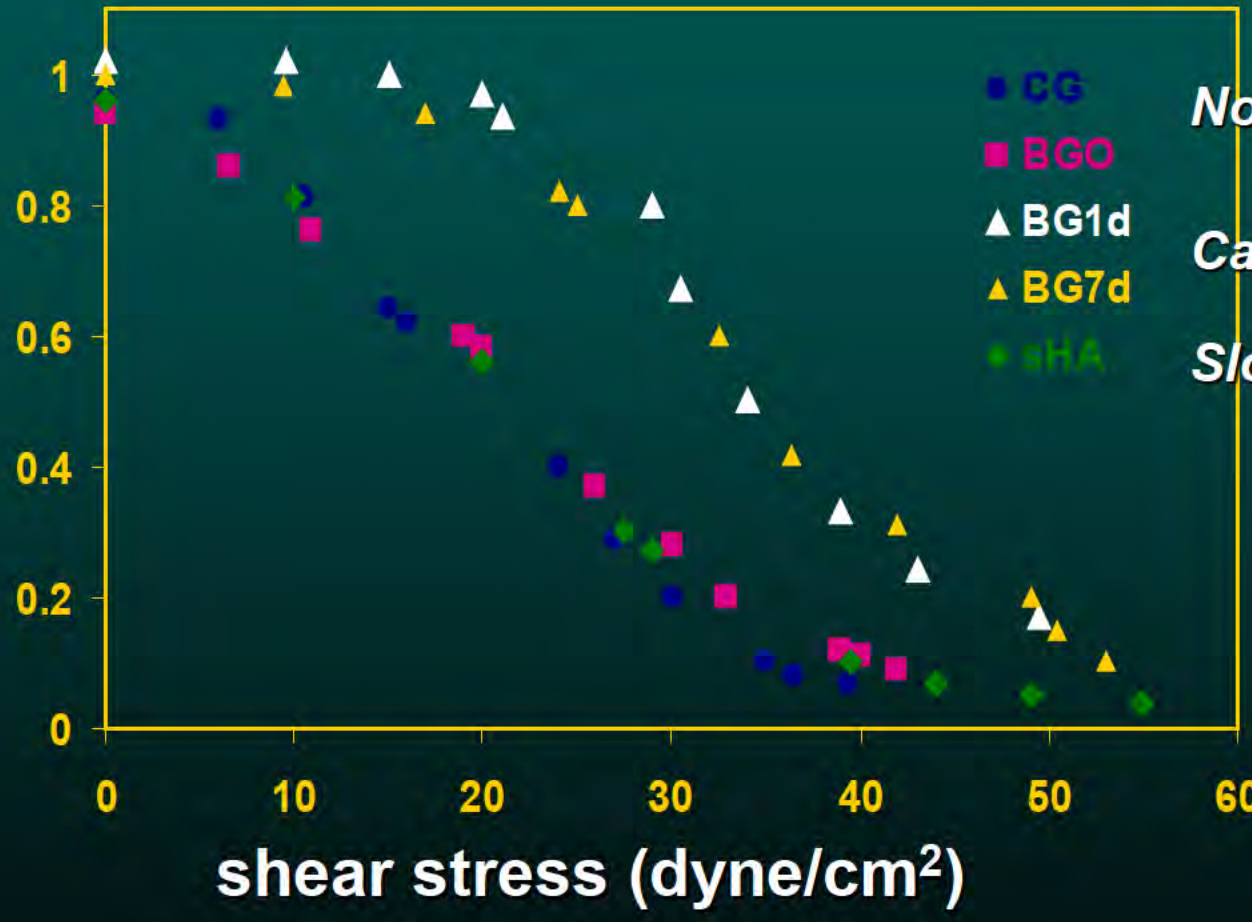
A. Garcia et al., J. Biomed. Mater. Res. (1998)

Fibronectin Adsorption



Cell detachment experiments

Profiles for substrates coated with 0.1 μg/ml Fn

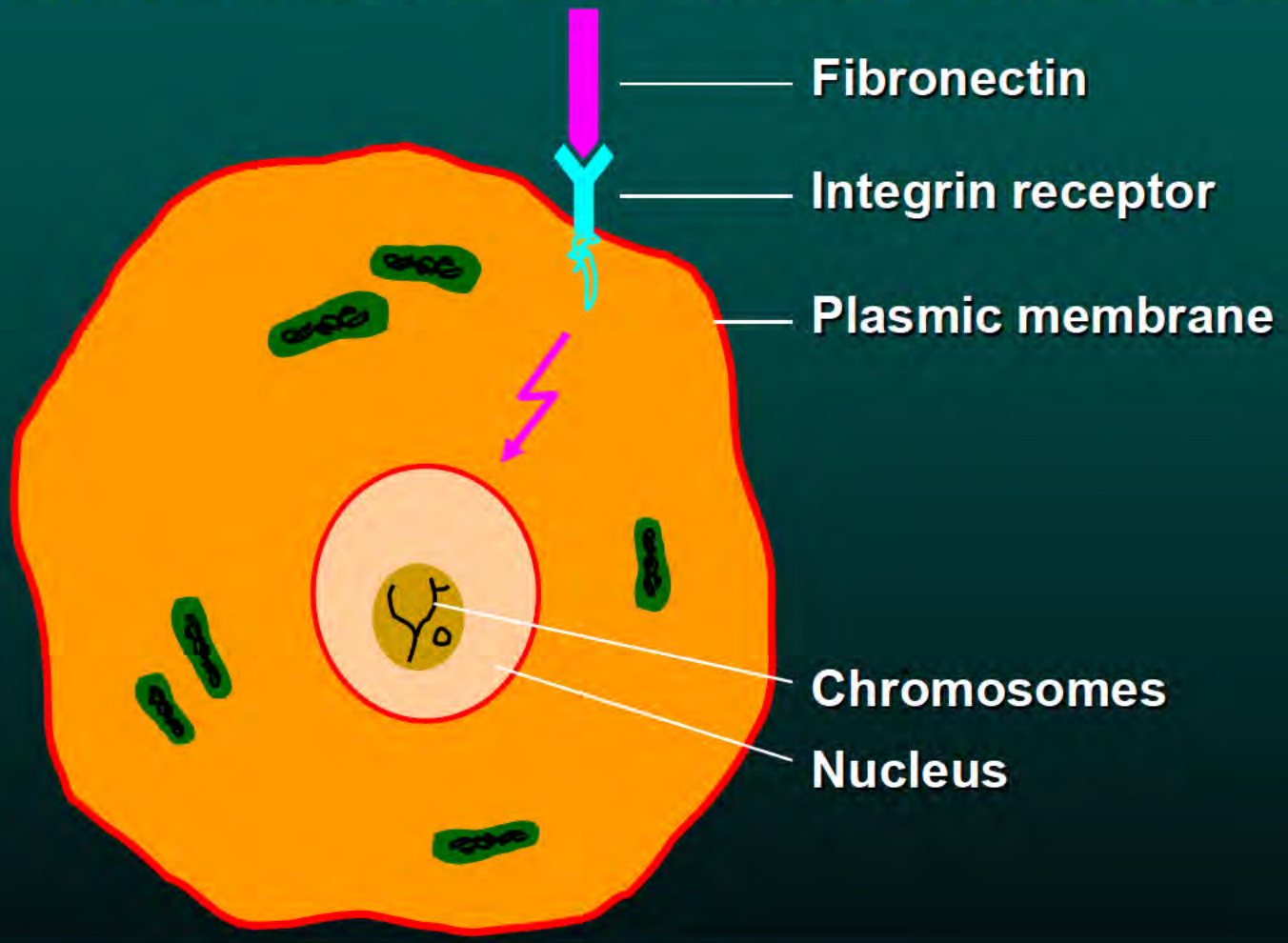


No CaP present

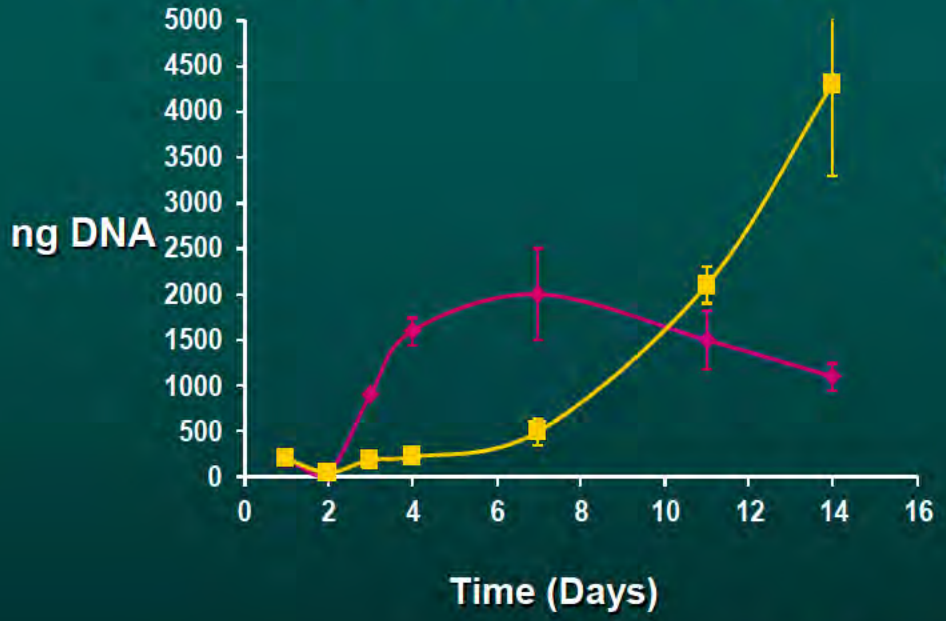
CaP formed on BG

Slowly reacting CaP

Intracellular component of the activated integrin receptor participates in the cell signaling cascade



Proliferation



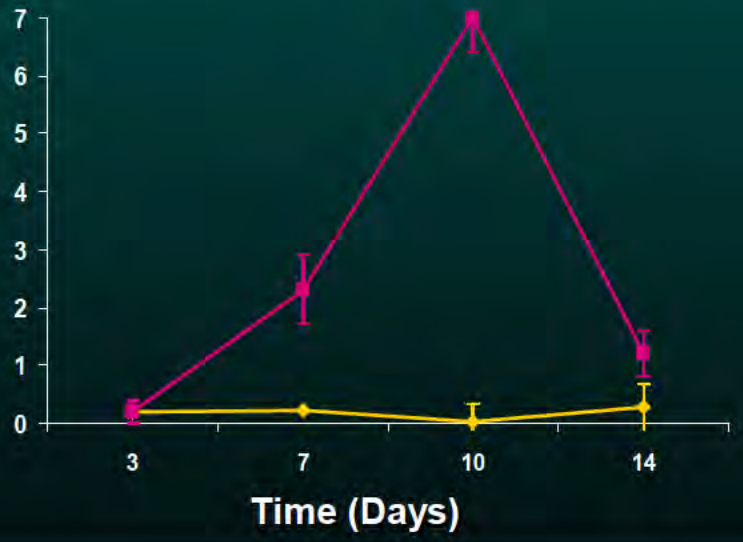
Cells on SM-BG *5

Cells on HA *5

Differentiation

AP activity

nMole/min/μg DNA



A. El-Ghannam et al., J. Orthop. Res. (1999)

Mechanisms of bioactivity

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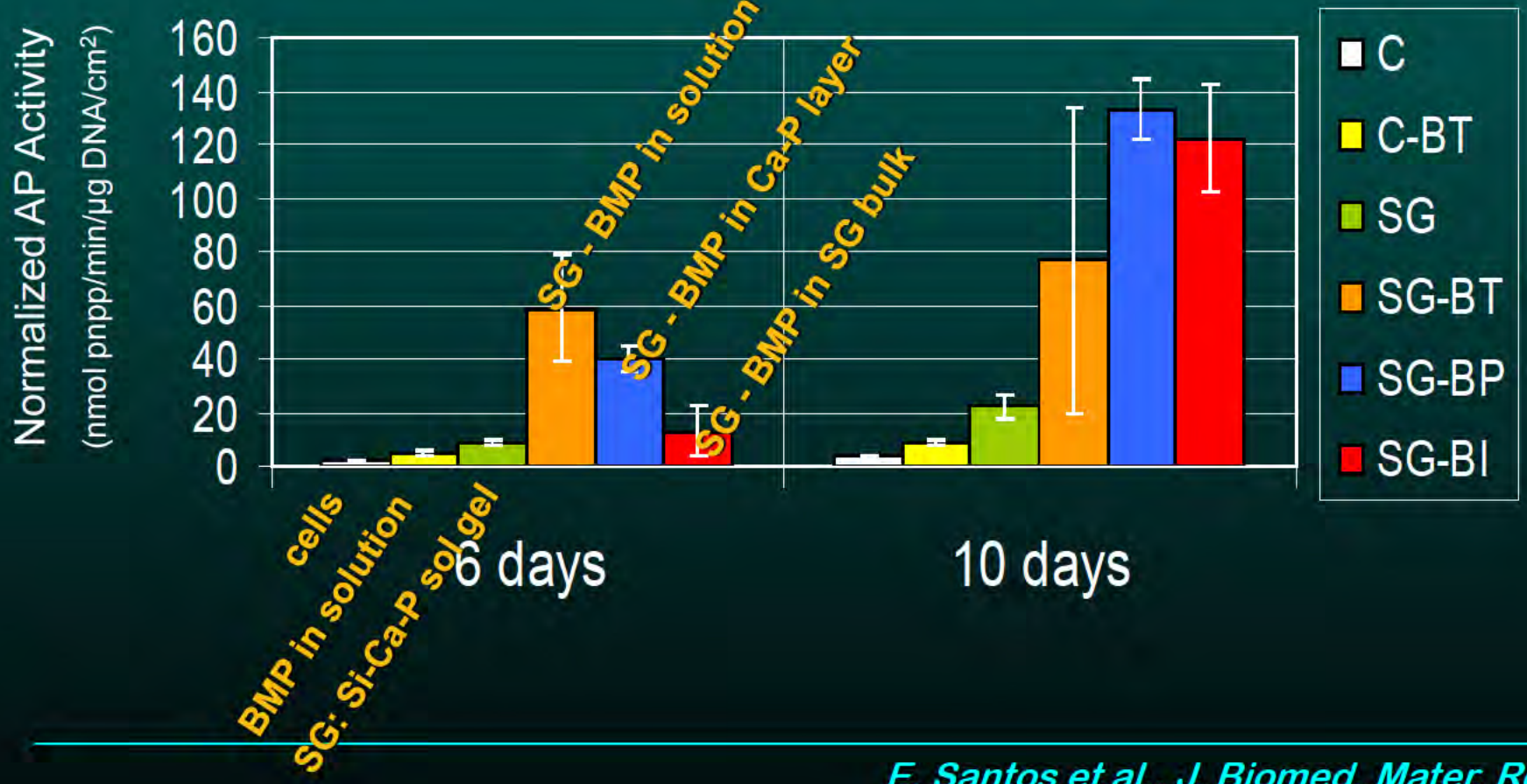
  - » preferential Fn adsorption
  - » Fn binding effect
  - **» growth factor adsorption**
- solution effect
  - » ionic dissolution product
  - » cell produced osteogenic factors
- porosity effect

Bioassay with Stromal Marrow Cells

Alkaline Phosphatase Activity



E. Santos et al., J. Biomed. Mater. Res., 1998

Mechanisms of bioactivity

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Differentiation of osteoprogenitor cells

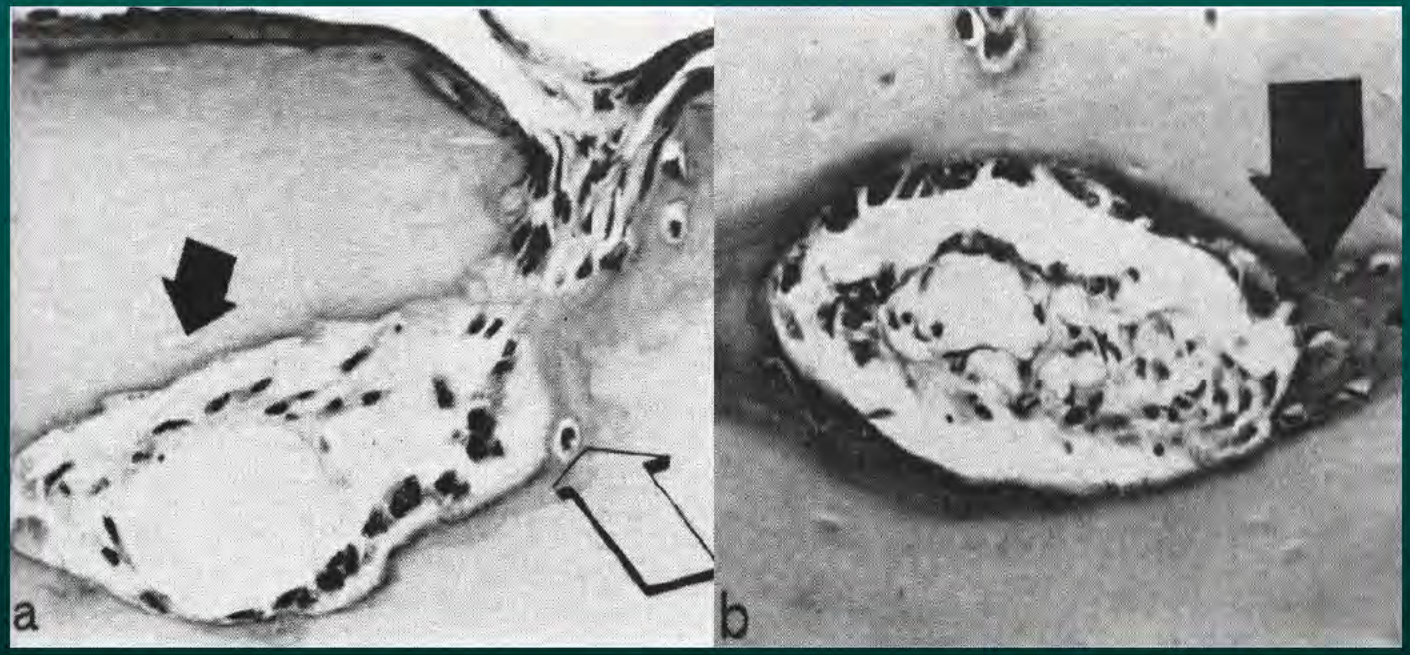
3 months implantation in the dog mandible

- bioactive glass granules of narrow size range cause differentiation of osteoprogenitor cells to bone forming cells (osteoblasts)
- unique finding for a synthetic bone graft material
- each granule acts as a nucleus for new bone formation

Schepers et al., 1991

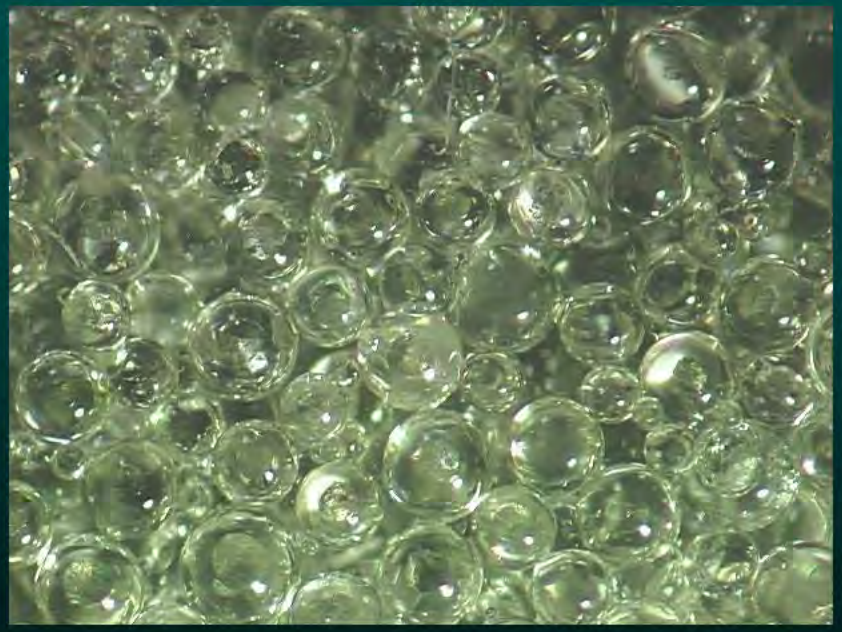
Urist, "Bone: Formation by Autoinduction"

Science (1965)



"....New bone was deposited in pockets or excavation chambers filled with proliferating osteoprogenitor cells. The process began within a few weeks and was complete in a few months. How much new bone could be attributed to the osteoconduction of cells growing in from the walls of the host bone, and how much could be accounted for by osteogenic induction, was not apparent from experiment on normal, healthy bones...."

Non-bioactive and bioactive materials with constant pore structure
Microsphere-based discs



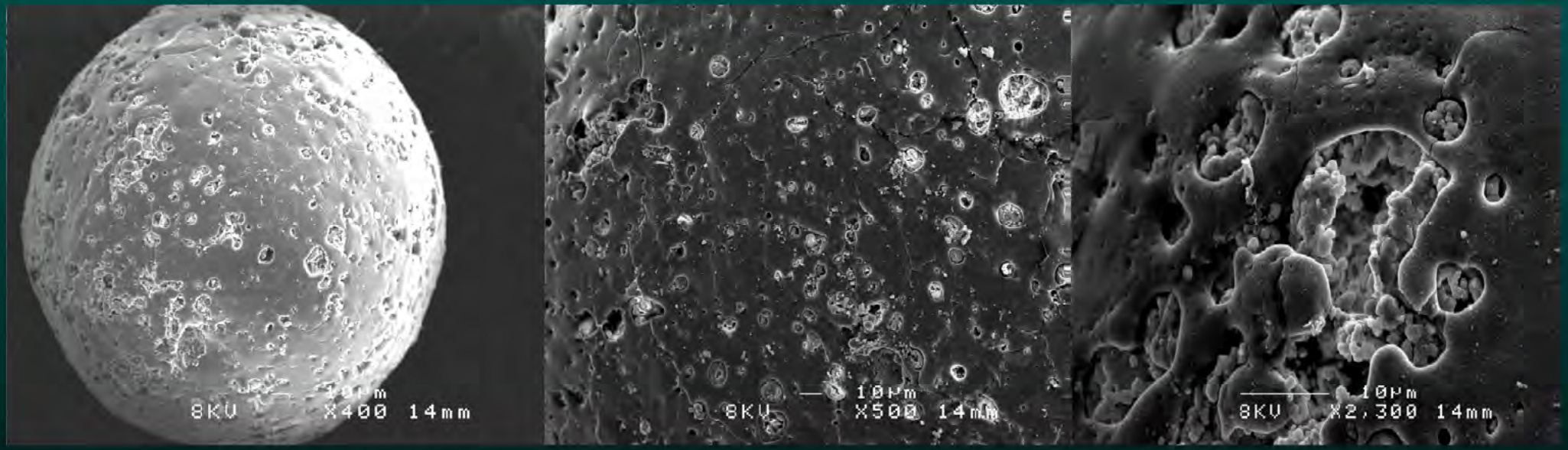
PLGA

PLGA-30%BG

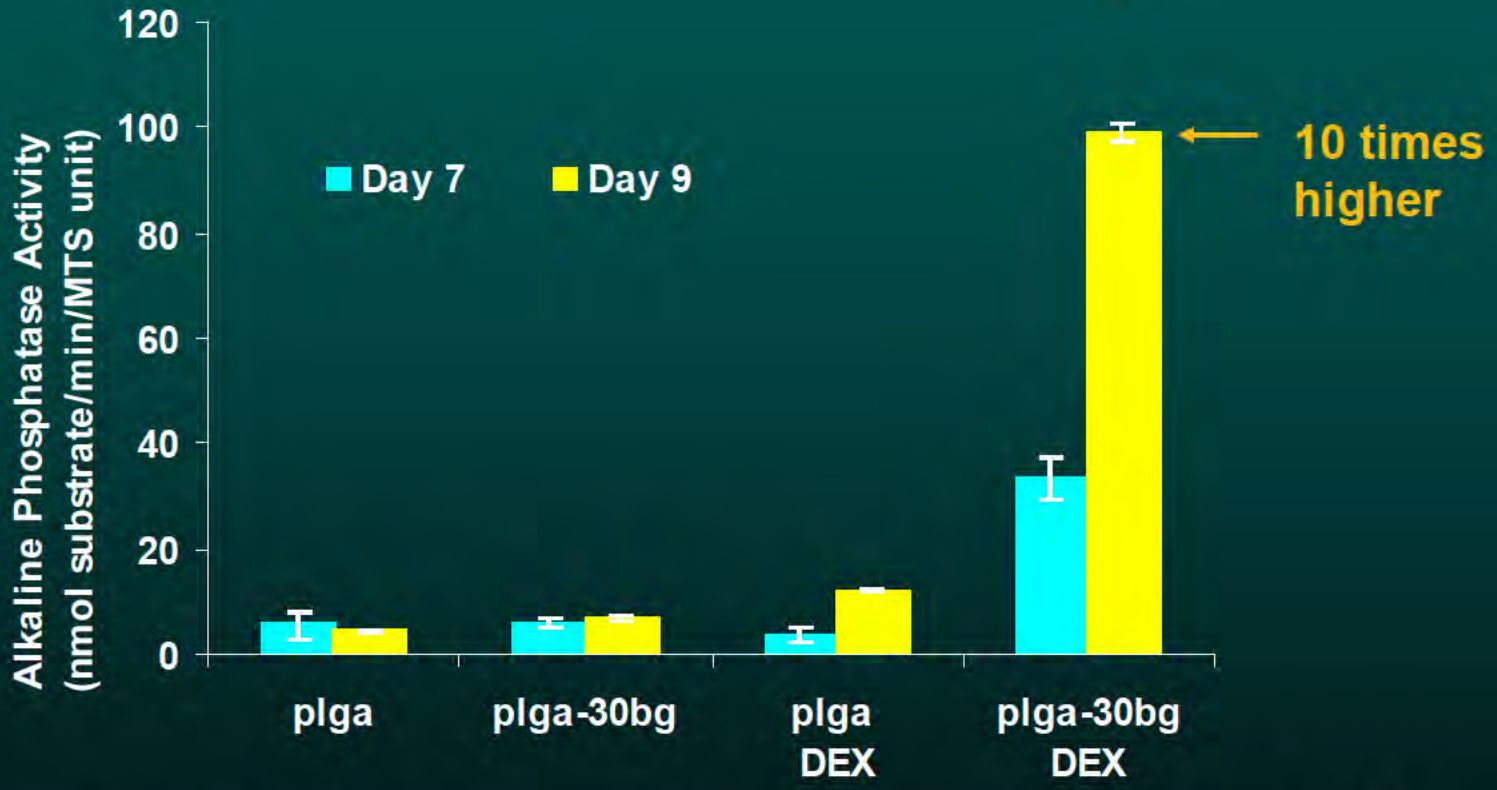
J. Yao et al., Biomaterials 2004; J. Yao et al., J. Biomed. Mater. Res., 2005

Formation of Ca-P layer - SEM

PLGA-30%BG composite: 14 days of immersion in TE



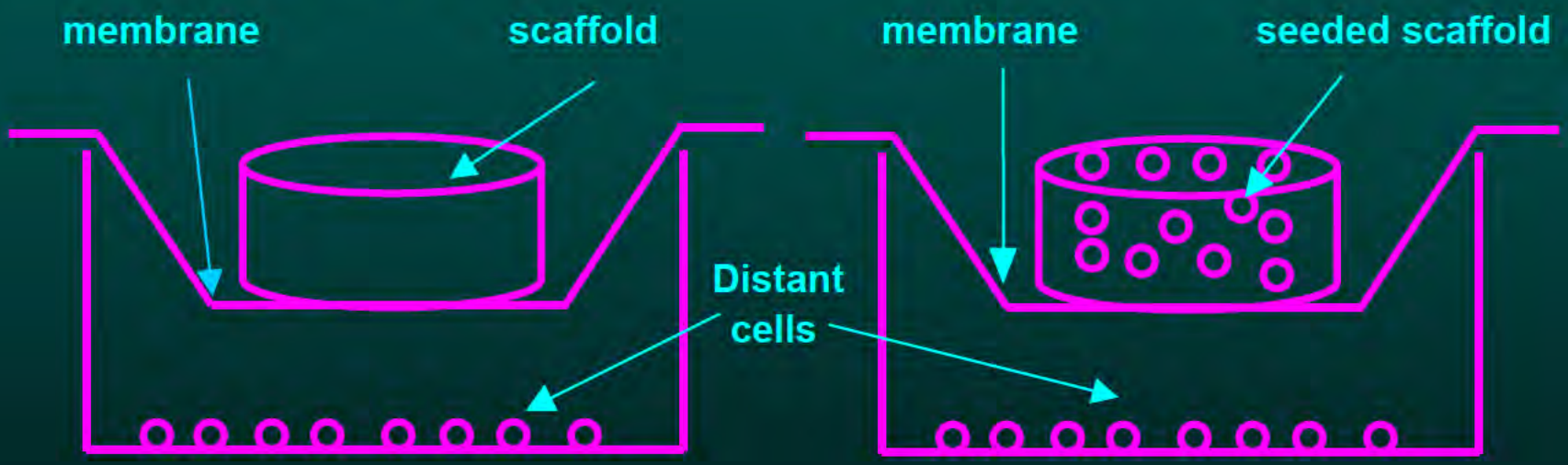
Osteogenesis of rat marrow stromal cells
In vitro evaluation - AP activity



Osteogenesis of rat marrow stromal cells cultured on porous PLGA scaffold or PLGA-30%BG scaffold for 7 and 9 days. Dex = 10 nM

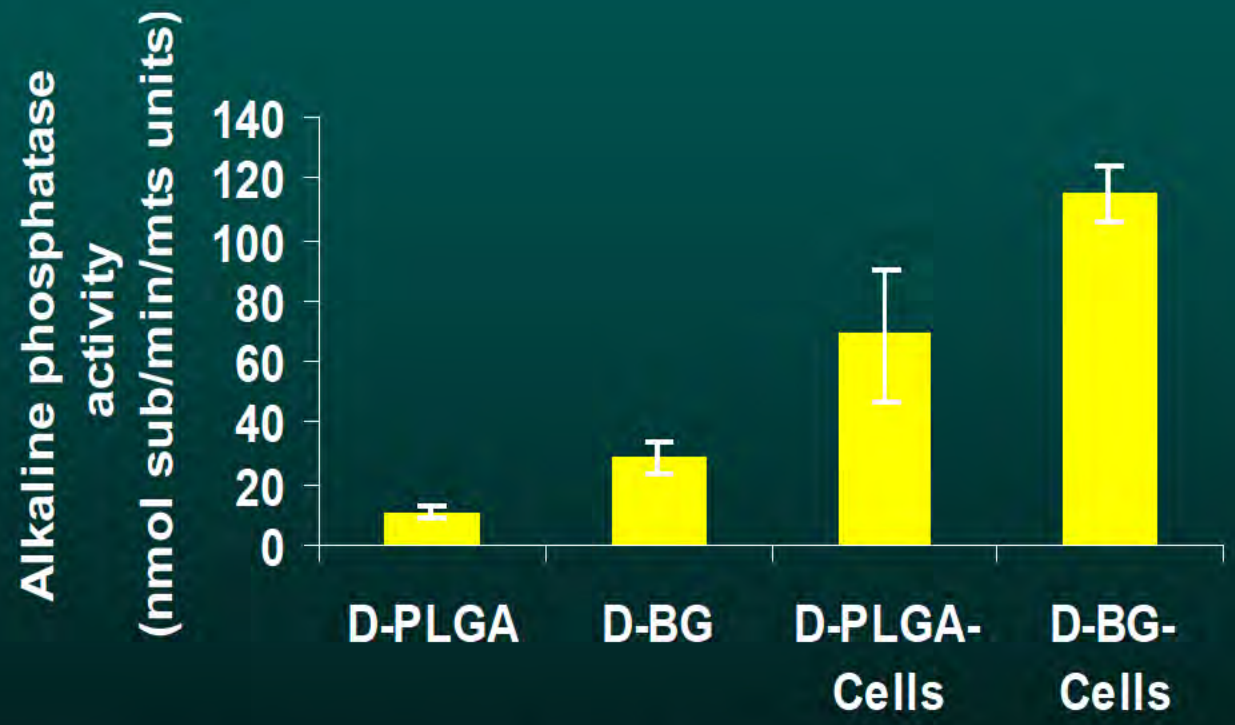
Solution mediated effect

Cell culture system



Cells were physically separated from scaffolds, which were either not seeded or seeded with cells
(exclude the effect of direct contact with scaffold)

Osteogenesis of rat marrow stromal cells
In vitro evaluation - AP activity



Osteogenesis of rat marrow stromal cells on plastic wells for 9 days. Cells were separated from scaffolds by membranes. D: distant cells

Biomaterials are hybrid materials

The illustration of bioceramics

- ***Bioactive ceramics***
  Biologically reactive ceramics and glasses that enhance bone formation and stimulate tissue regeneration
- **Inorganic controlled release materials, *including sol gel glasses***
- **(Inert ceramics for wear resistance)**

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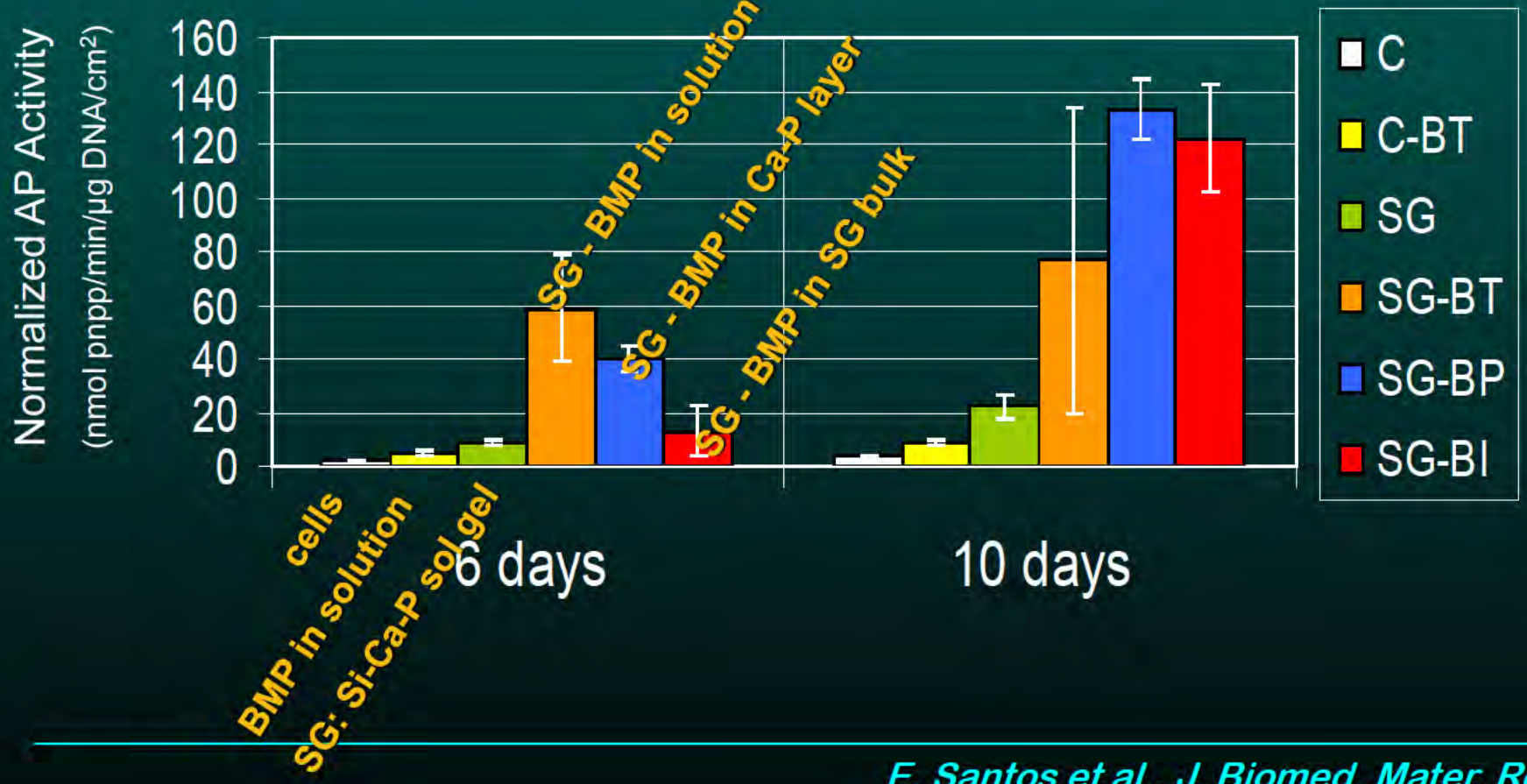


E. Santos et al., J. Biomed. Mater. Res., 1998

Tissue Repair and Regeneration

with delivery from

Silica xerogels (Silica sol-gels)

Room-temperature process

- Highly porous materials – porosity at the nanoscale
- Release properties controlled by the nanostructure

Sol-gel processing steps

Hydrolysis

$\equiv$Si-OR + H_2O $\rightleftharpoons$ $\equiv$Si-OH + ROH

Organosilane

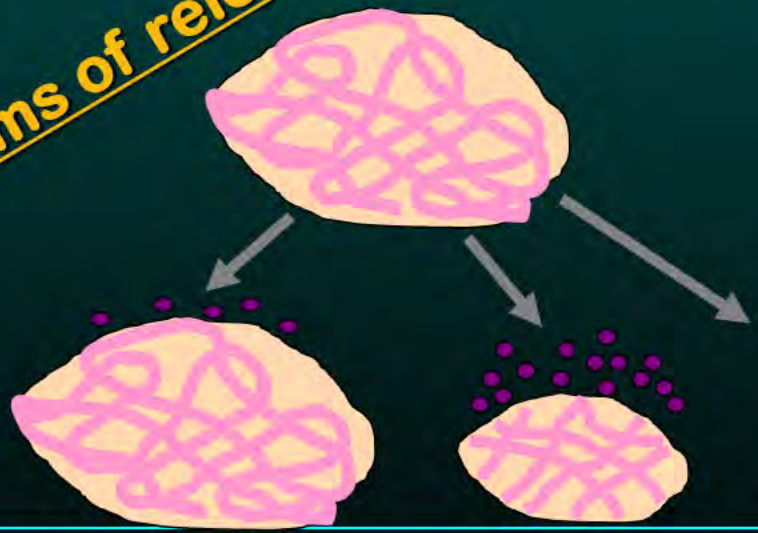
Condensation

$\equiv$Si-OH + HO-Si$\equiv$ $\rightleftharpoons$ $\equiv$Si-O-Si $\equiv$ + H_2O

$\equiv$Si-OR + HO-Si $\equiv$ $\rightleftharpoons$ $\equiv$Si-O-Si $\equiv$ + ROH

Silicon Oxide

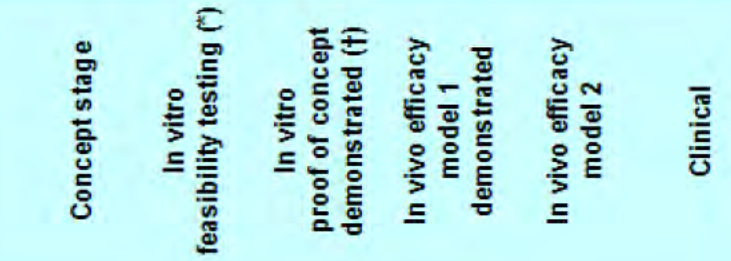
Mechanisms of release



First references

- Nicoll et al., *Biomaterials*, 1997
- Bottcher et al., *J. Sol Gel Science & Technology*, 1997
- Sieminska et al., *J. Sol Gel Science & Technology*, 1997
- Santos et al., *J. Biomed. Mater. Res.*, 1998
- Falaize et al., *J. Am. Ceramic Soc.*, 1999
- Kortesuo et al., *J. Biomed. Mater. Res.*, 1999

pipeline



Infection treatment and control (I)

- Thin films on fracture fixation material for the controlled release of antibiotics
- Bactericidal thin films on percutaneous external fixator pins
- Thin films on joint prostheses for the treatment of joint arthroplasty revisions
- MRSA treatments

Pain treatment and control (P)

- Post-surgical pain
- Abuse resistant controlled delivery of opioids
- Wound dressings for the delivery of analgesics

Controlled release of biological molecules (BM)

- Controlled release of BMP-2
- Controlled release of TGF-ß
- Controlled release of monoclonal antibodies
- Treatment of compartment syndrome

Delivery of anti-proliferative drugs

- Controlled release of antiproliferative agents (Rapamycin)
- Thin films for drug eluting stents

Combination treatments

- Combined delivery of antibiotics and growth factors for the treatment of oral pathologies (I, BM)
- Wound dressings for pain and infection control (I, P)

Scaffolds for tissue engineering

- Large volume bone tissue engineering

Benefits of silica xerogels (sol-gels)

- excellent film to substrate adherence (for fundamental reasons)
- upon release, therapeutic efficacy maintained
- control of release of molecules varying in size from small (<1 kDA) to large (>70 kDa)
- burst release avoided by virtue of processing flexibility
- release can be controlled for a duration ranging from hours up to one year
- Poorly soluble molecules can be delivered

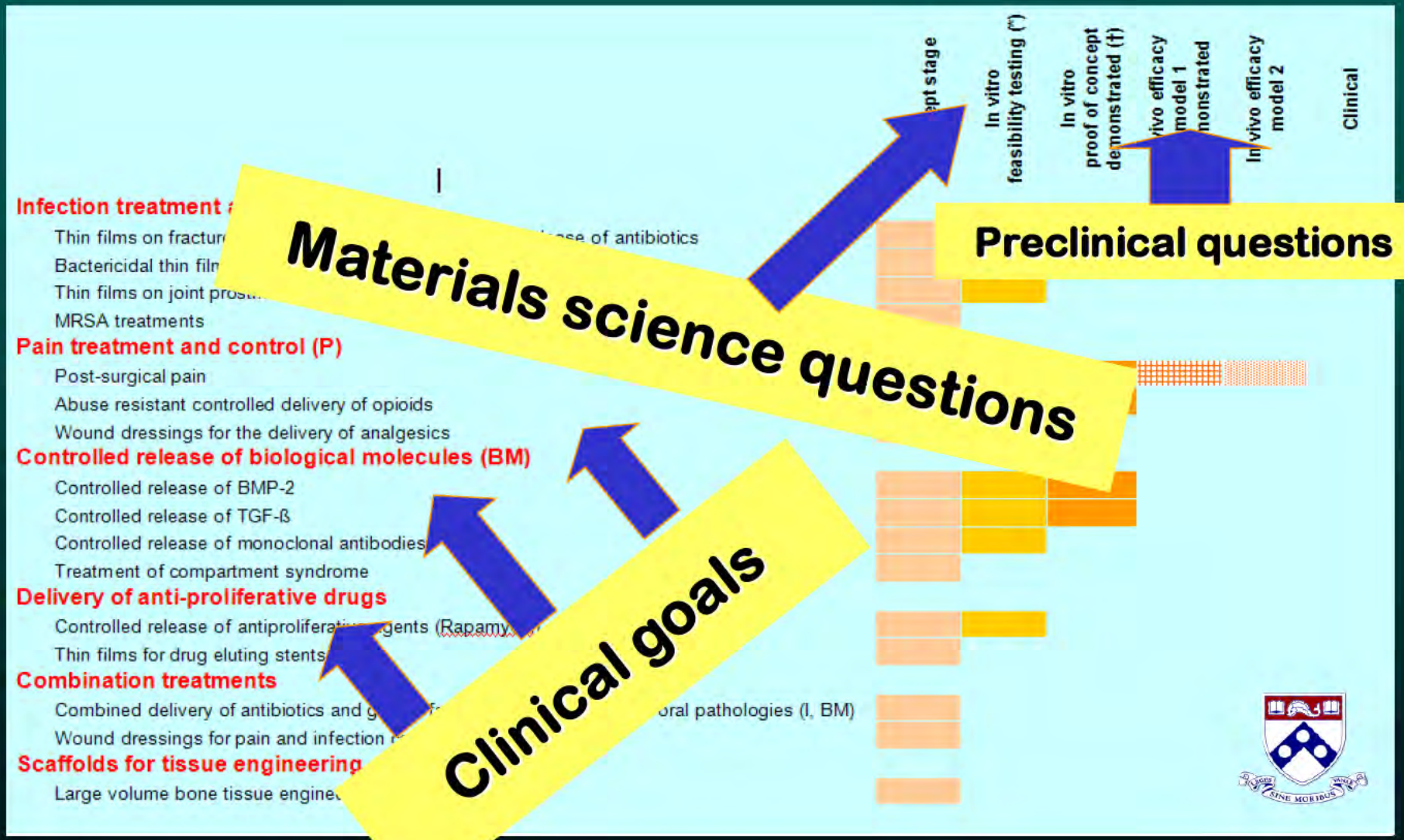
Nicoll et al. (1998), Falaize et al. (1998), Santos et al. (1999), Radin et al. (2002)

Benefits of silica xerogels (sol-gels), cont…

- molecules are protected while in the sol gel (compare to the *in vivo* half life – e.g PDGF: 2 minutes)
- various molecules can be delivered simultaneously
- substantially full release of therapeutic agents
- resorbable
- biocompatible
- room temperature processing

Nicoll et al. (1998), Falaize et al. (1998), Santos et al. (1999), Radin et al. (2002)

pipeline


In vitro feasibility testing (*)
In vitro proof of concept demonstrated (†)
In vivo efficacy model 1 demonstrated
In vivo efficacy model 2
Clinical
Infection treatment
Thin films on fractur
ase of antibiotics
Bactericidal thin fil
Thin films on joint pros
MRSA treatments
Pain treatment and control (P)
Post-surgical pain
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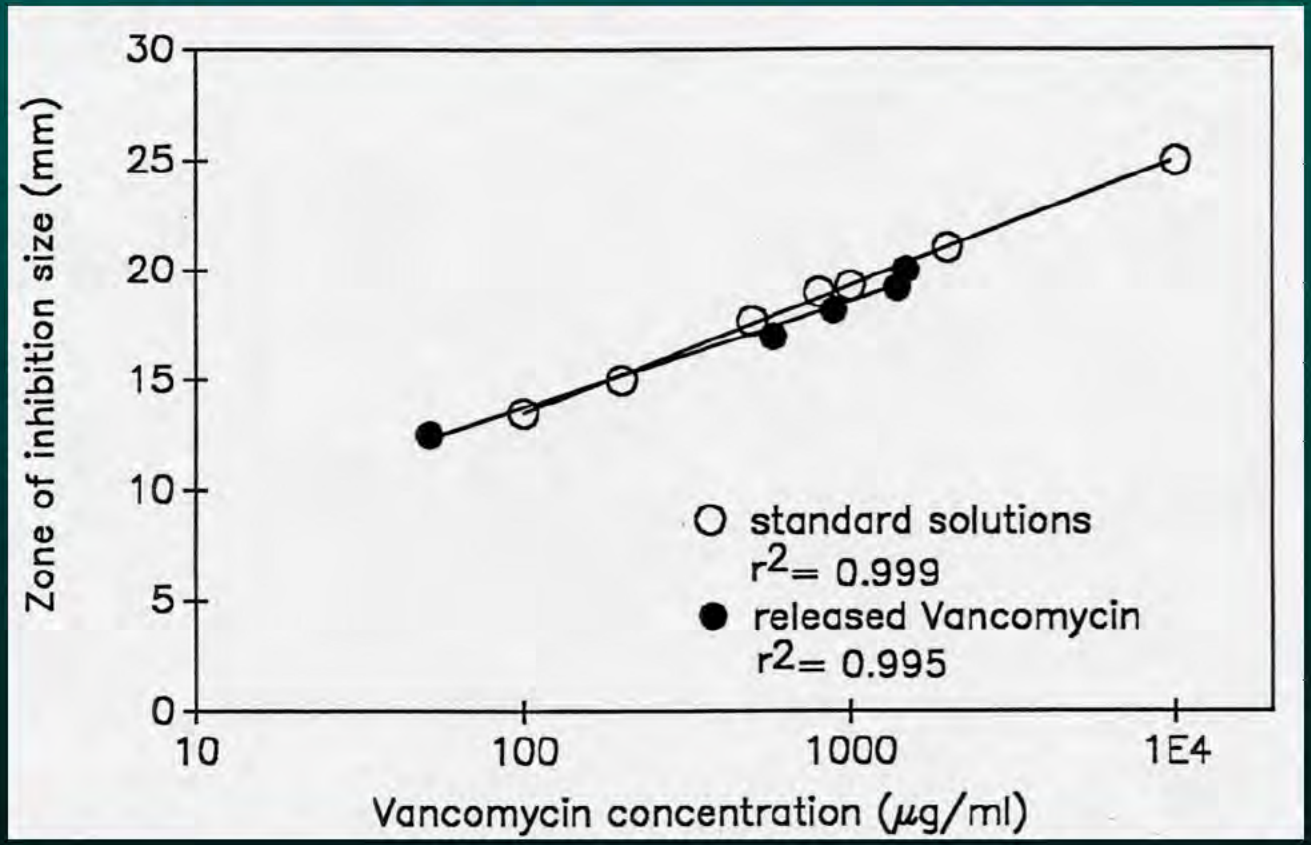
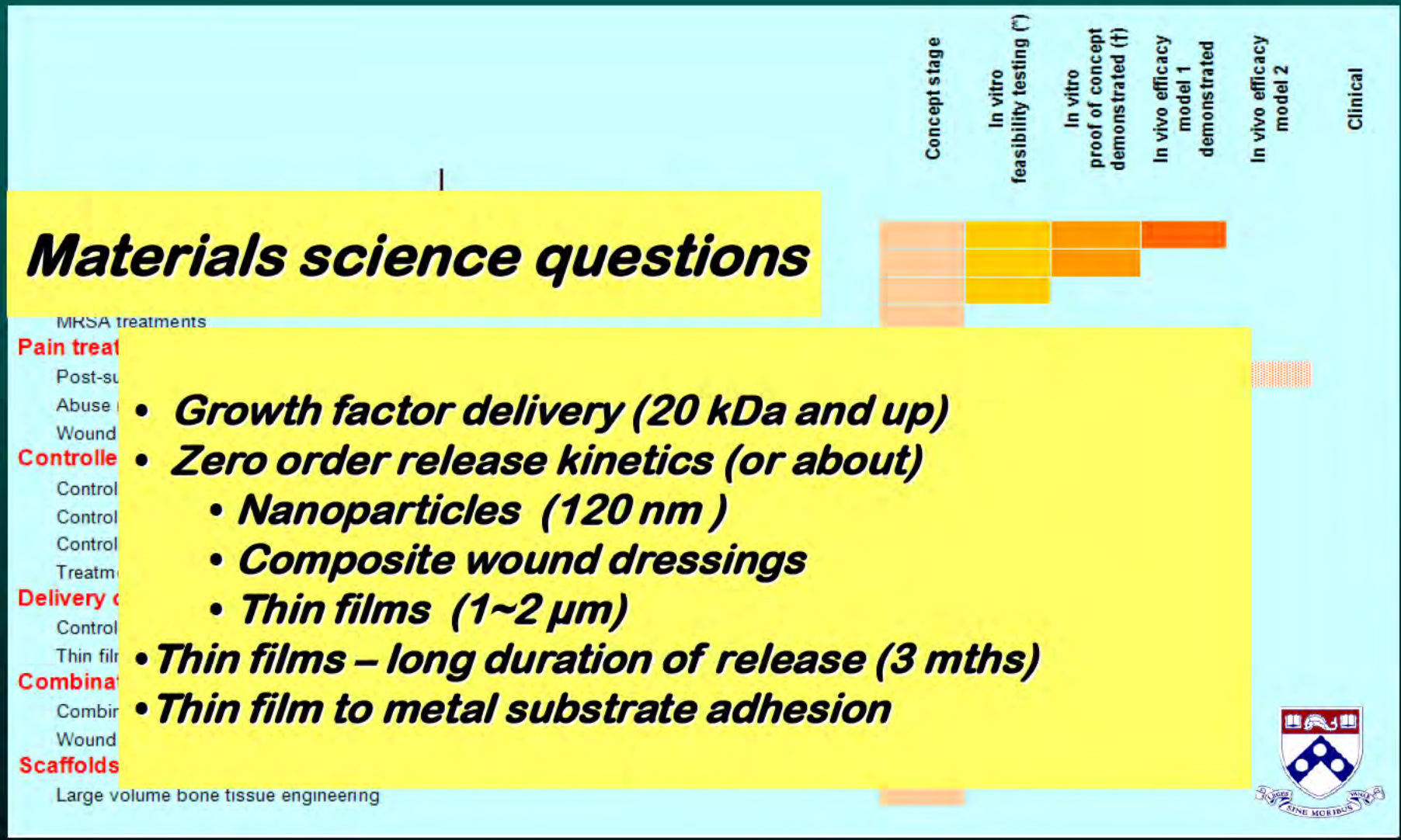
Scaffolds for tissue engineering
Large volume bone tissue engine
Materials science questions
Preclinical questions
Clinical goals

Dose response curve
Vancomycin release



S. Radin et al., J. Biomed. Mater. Res., 2001

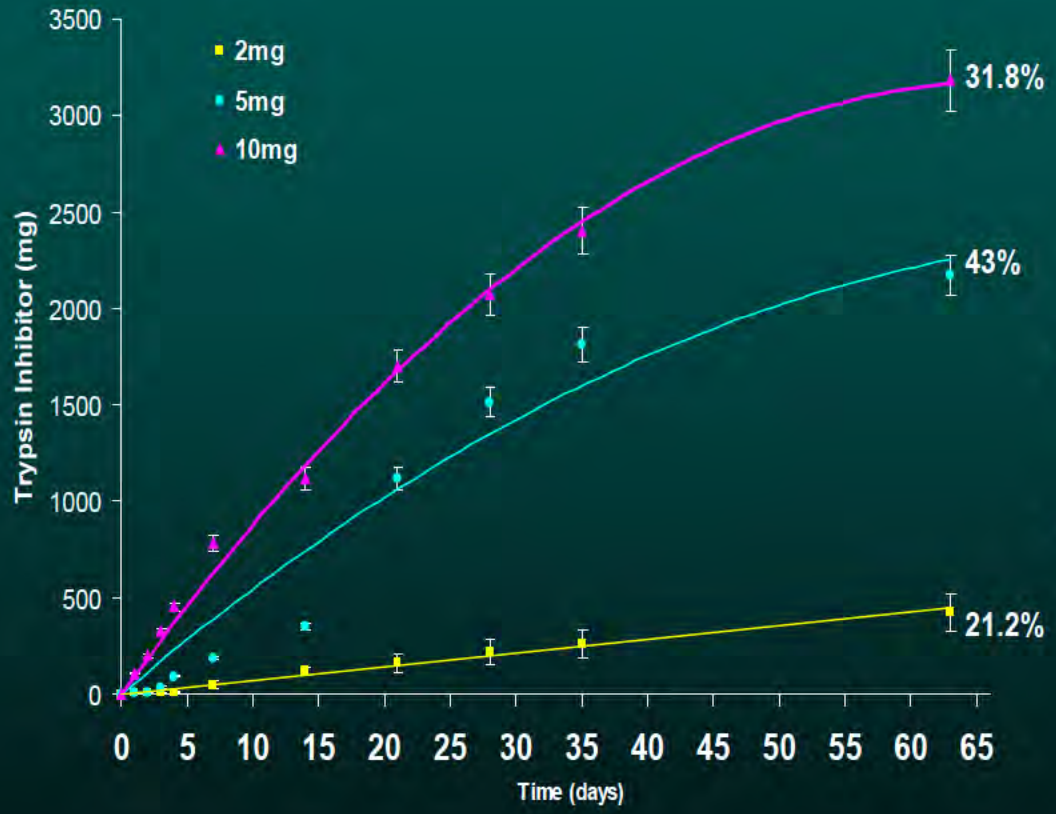
pipeline



Materials science questions

- *Growth factor delivery (20 kDa and up)*
- *Zero order release kinetics (or about)*
  - *Nanoparticles (120 nm)*
  - *Composite wound dressings*
  - *Thin films (1~2 μm)*
- *Thin films – long duration of release (3 mths)*
- *Thin film to metal substrate adhesion*

Cumulative Trypsin Inhibitor (20 kDa) release
TMOS-derived xerogel



- Time- and load-dependent release
- 20 % released by 9 weeks

Santos et al. (1999)

Macromolecules – Release kinetics

Nanostructural control

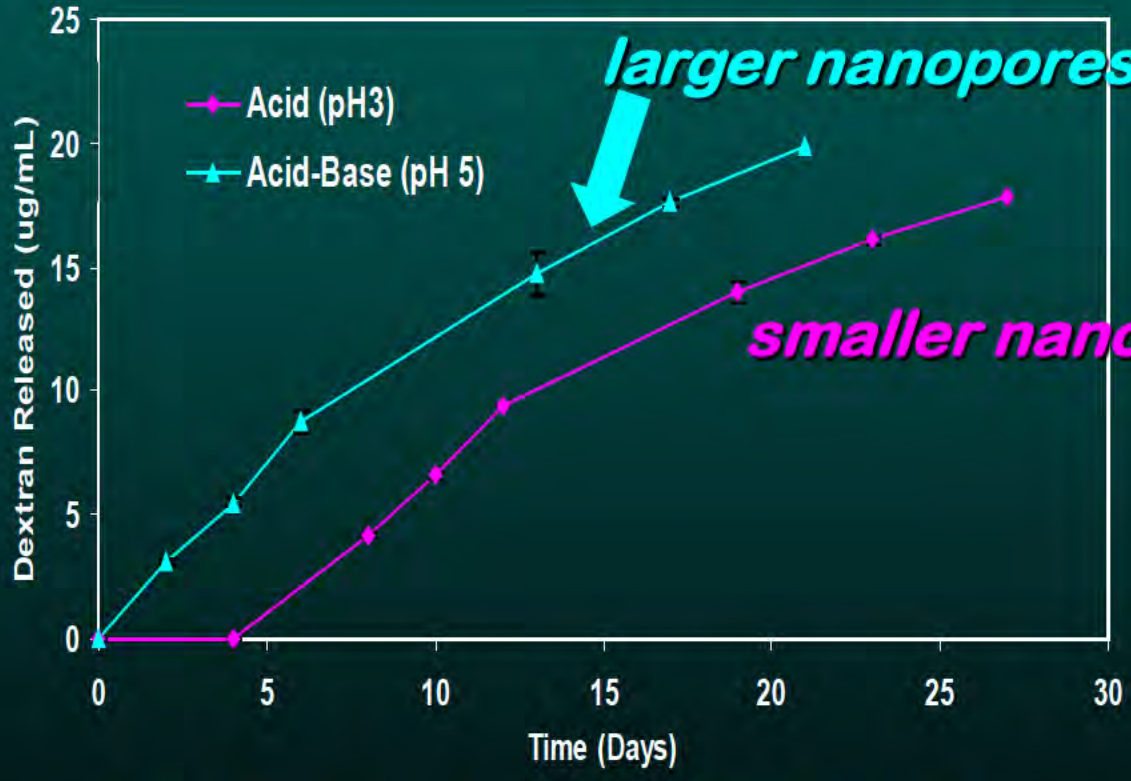
Modeling experiments

- dextran, a hydrophilic polysaccharide, is used as a model molecule having different sizes
- molecular weight can vary from 3 to 500 kDa
- this eliminates the effect of molecule chemistry on
  - » sol gel processing
  - » release properties
- molecular weight used: 10, 40 and 70 kDa

Radin et al., Acta Biomaterialia (2013)

Effect of nanopore size -

Variation of catalysis pH



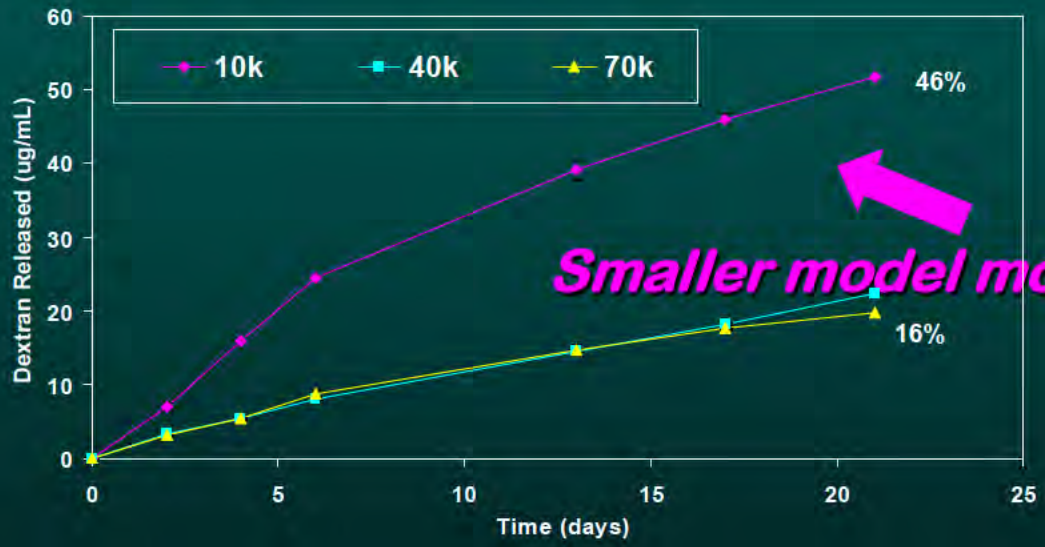
larger nanopores (3.5 nm)

smaller nanopores (1.8 nm)

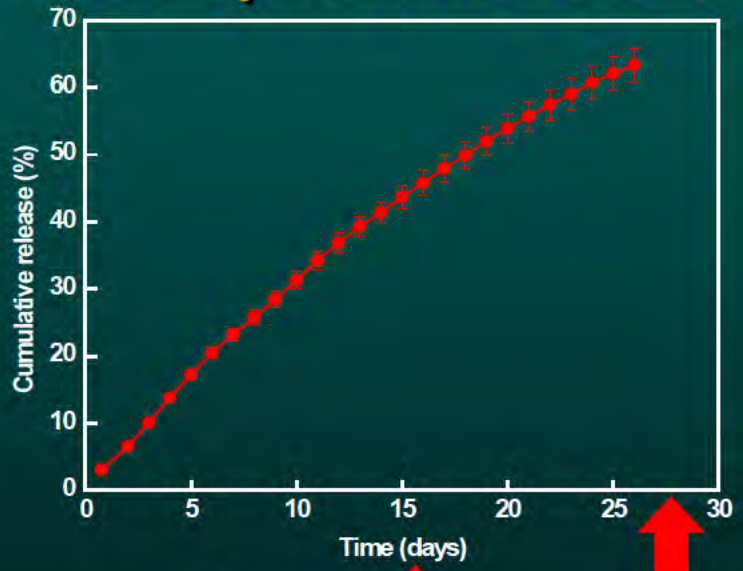
One dextran weight used: 70 kDa

Effect of molecular weight

Larger nanopores used (acid-base catalysis at pH 5)



Cumulative Trypsin Inhibitor (TI) Release from PEG-coated Mesoporous Silica Nanoparticles (MSN)



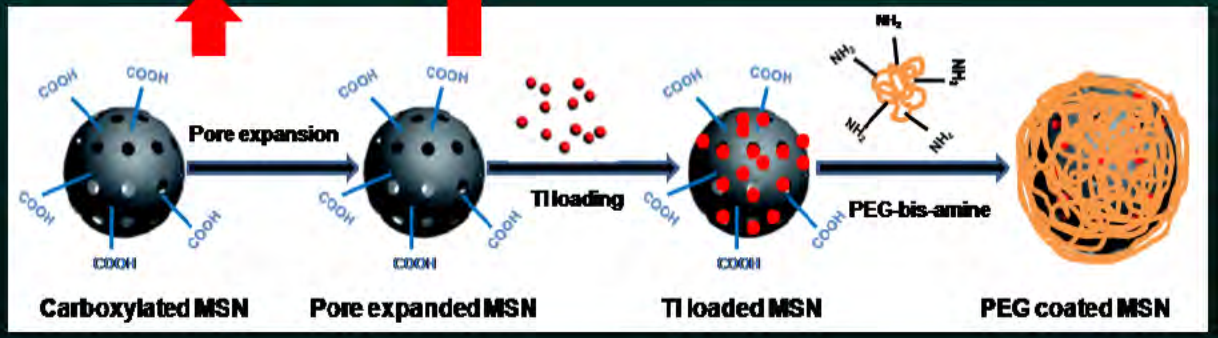
Properties

120 nm average diameter

3.5 nm average pore size

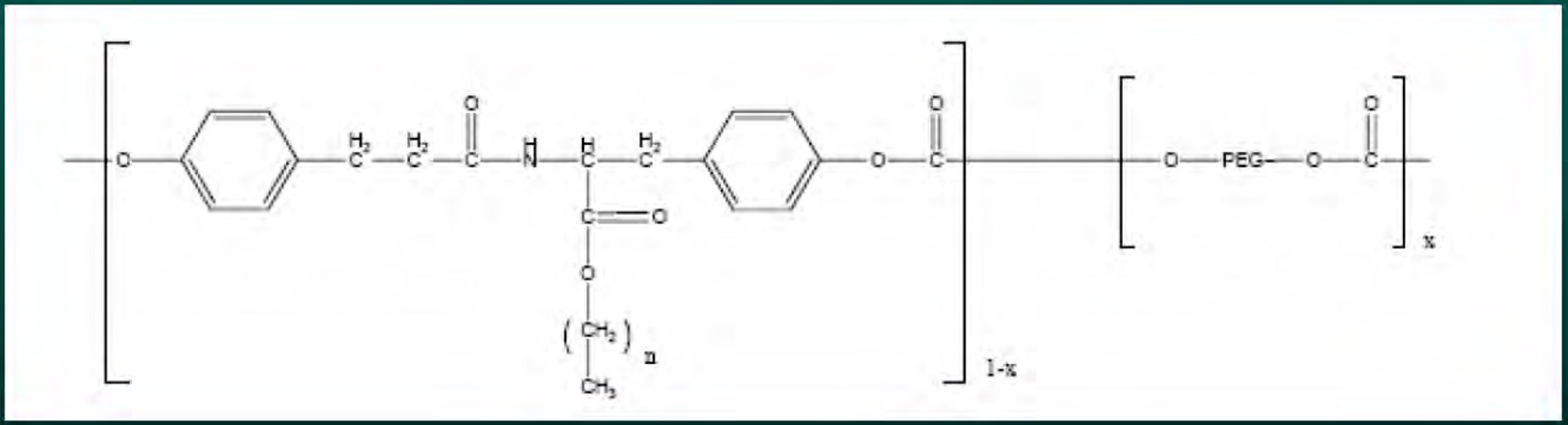
Results

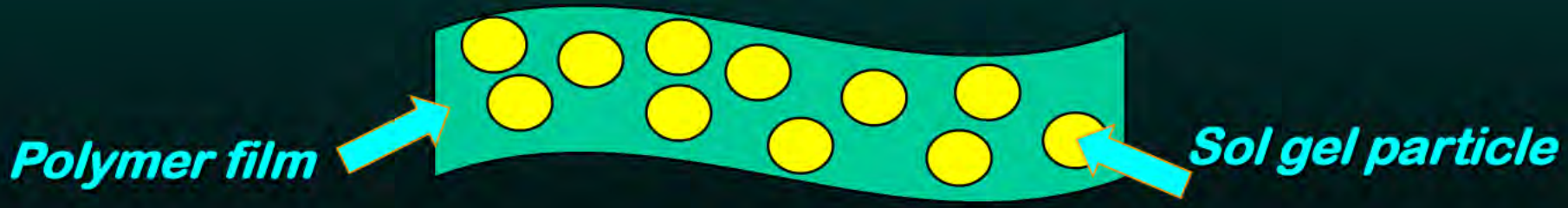
- the absence of an initial burst
- sustained near zero order release over 4 weeks



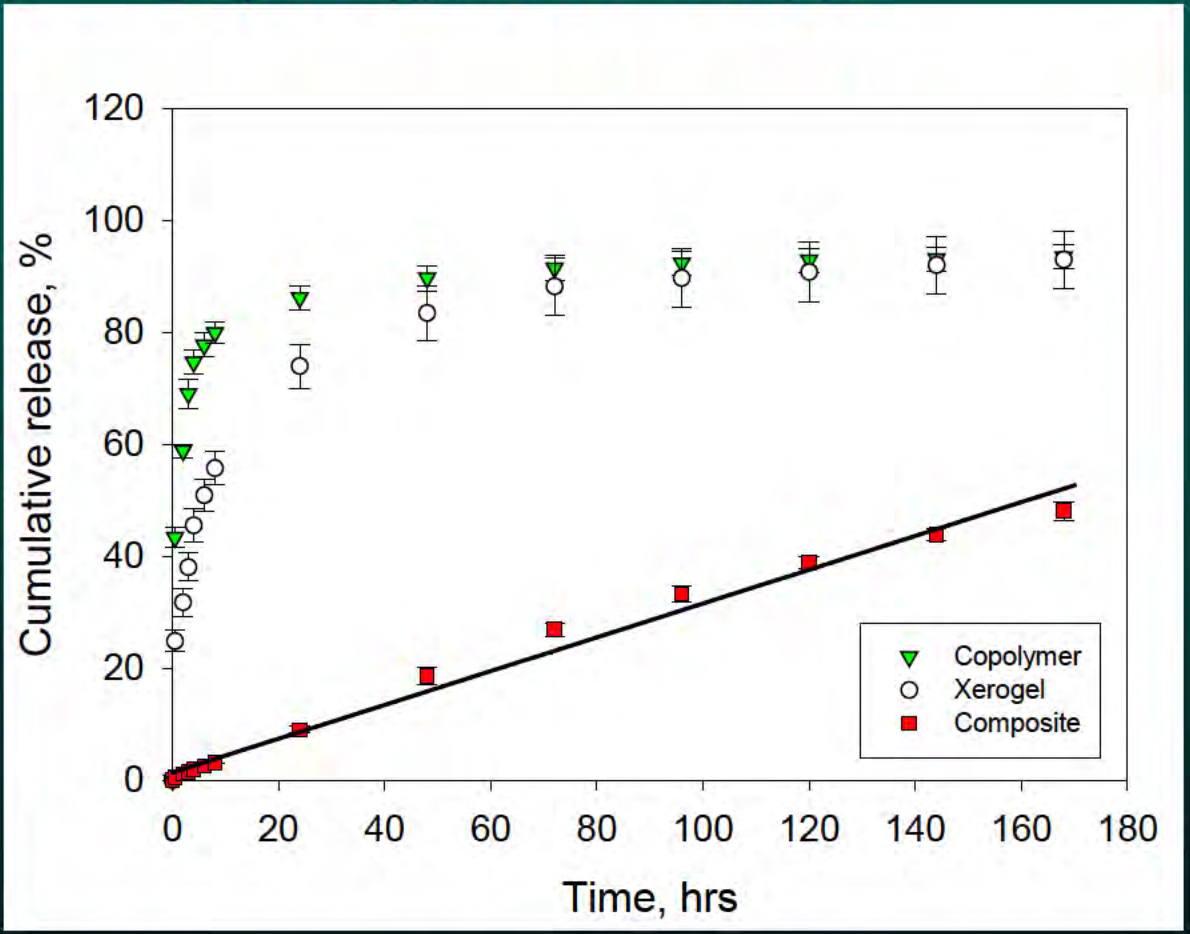
Bhattacharyya et al., Acta Biomaterialia (2012)

Composite Xerogel-Copolymer Wound Dressings





Composites enable controlled, zero-order release of Bupivacaine for 1 week

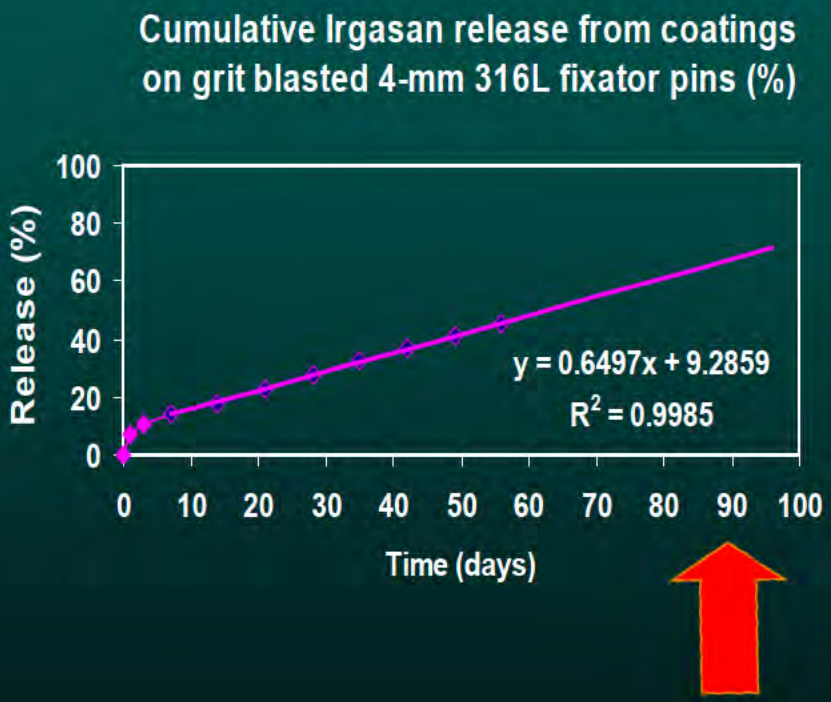


Release rates controlled by:

- Tyrosine-based monomer hydrophilicity and PEG content
- Xerogel porosity, particle size and drug loading

Costache et al., Biomaterials (2010)

In vitro release
Coatings on fixation pins



Release from coatings composed of 5 layers with 10% triclosan (<300 Da)

- long-term release, up to 60 days
- Initially: first order release (up to 7 days)
- followed by sustained, near zero-order release
- Extrapolation:
  - » release continues beyond 90 days (3 months)

Qu et al. (2015)

Mechanical properties of thin sol-gel films

	Crack onset strain (%)	Crack saturation strain (%)	Critical cracking stress (GPa)	Interfacial shear strength (MPa)	Fi... fractu... energy (J/m^2)	Interfacial fracture energy (J/m^2)
Polished Metallic surface	10	10	6.10	519.72	688.59	61.02
Sandblasted (0.28 MPa) Metallic surface	5	16	3.05	153.37	112.43	156.21

H. Qu et al., 2015

Preclinical and clinical questions

Infection treatment and control (I)

- Thin films on fracture fixation material for the controlled release of antibiotics
- Bactericidal thin films on percutaneous external fixator pins
- Thin films on joint prostheses for the treatment of joint arthroplasty revisions
- MRSA treatments

Pain treatment and control (P)

- Post-surgical pain
- Abuse resistant controlled delivery of opioids
- Wound dressings for the delivery of analgesics

Controlled release of biological molecules (BM)

- Controlled release of BMP-2
- Controlled release of TGF-ß
- Controlled release of monoclona
- Treatment of compartment synd

Delivery of anti-proliferative

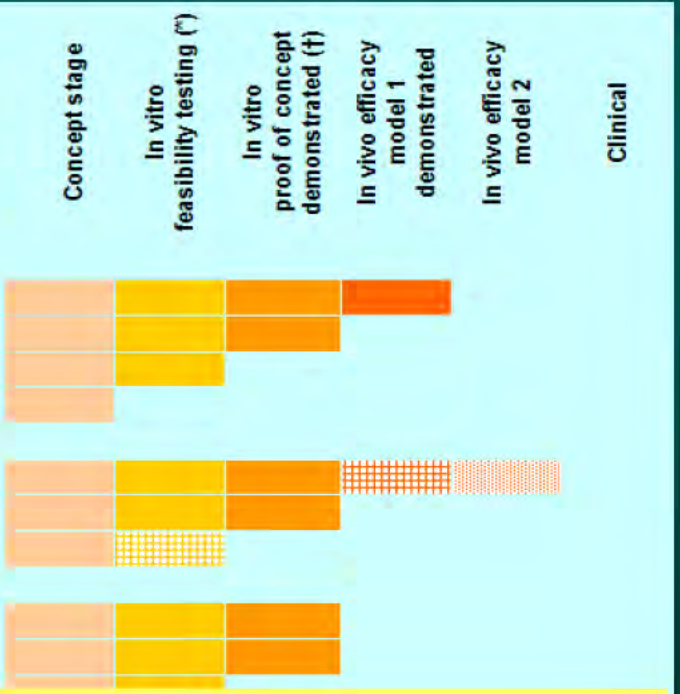
- Controlled release of antiprolifer
- Thin films for drug eluting stents

Combination treatments

- Combined delivery of antibiotics
- Wound dressings for pain and in

Scaffolds for tissue engineer

- Large volume bone tissue engin



- ***Infection treatment and control***
  - ***Internal fracture fixation***
  - ***Percutaneous pins***

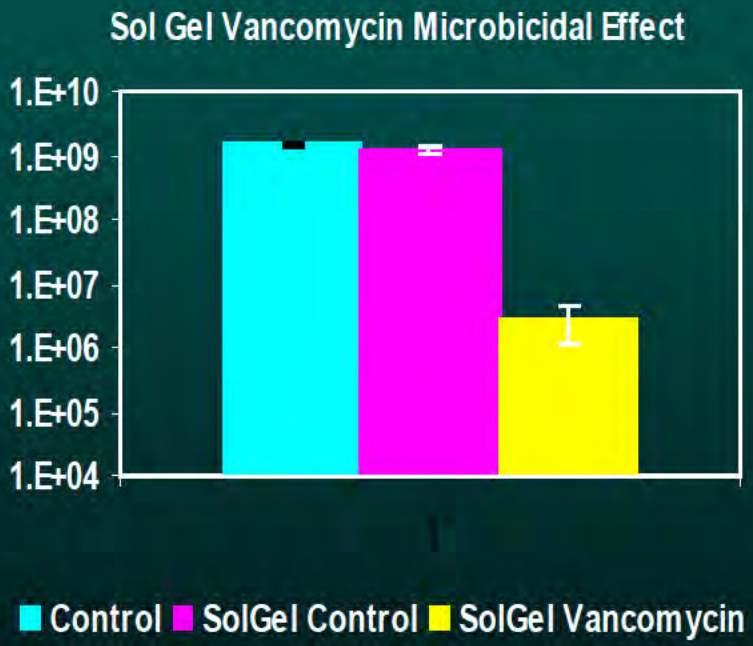
Bone infections
The clinical issue

- Risk of infection is considerable in open fractures
- Prevention is challenging when fracture fixation material is used
- *Bacteria adhere to internal fixation nails and form a biofilm*
- High resistance of the biofilm to systemic antibiotic treatment may require further surgical procedures

In vitro bactericidal activity

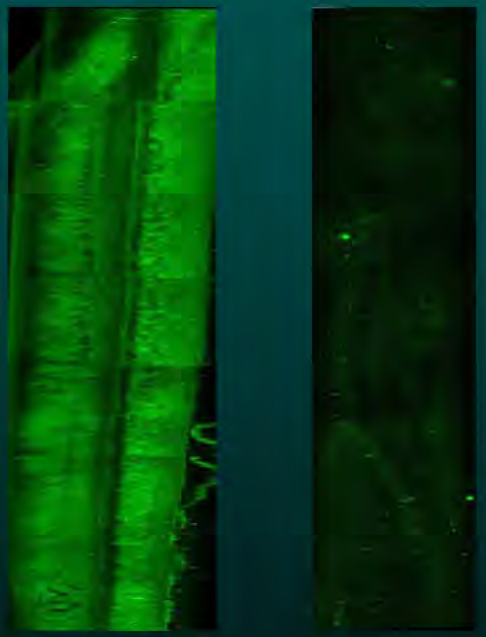
- Samples
  - Controls
    - » IM nails (metallic surface)
    - » Sol-gel coated IM nails without vancomycin
  - Treatment
    - » Sol-gel coated IM nails with vancomycin
- Staphylococcus aureus cultures
  - » 1 x10^3 cfu, 37^{0}C, 24h
- Evaluation
  - » bacterial counts
  - » live/dead staining - confocal laser microscopy

In vitro bactericidal effect



In comparison to controls, number of S. aureus colonies were reduced by three orders of magnitude on sol-gel / vancomycin films

In vitro bacterial inhibition
Confocal microscopy



- Uncoated samples (left)
  - » viable bacteria adhere and proliferate
- Sol-gel/vancomycin coated (right)
  - » bacterial adhesion is prevented

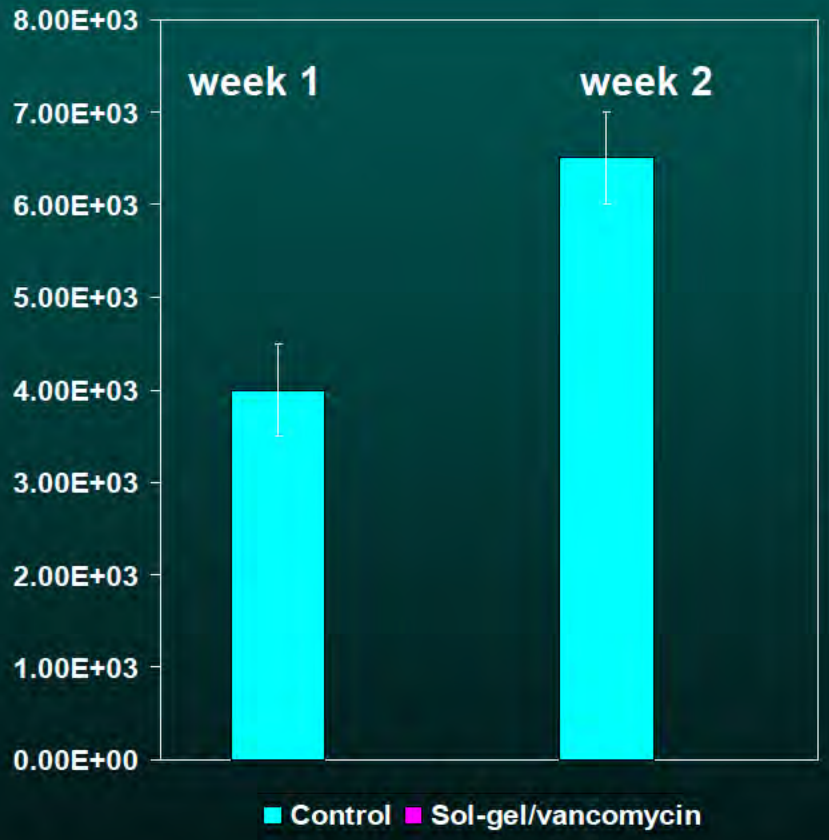
In vivo bactericidal activity

- Wistar rats
- Implants: sol gel coated with and without vancomycin
- Surgery
  - » intramedullary femoral canal
  - » insertion via the intercondylar grove of the knee
  - » one side: sol gel / vancomycin coated (12 implants)
  - » other side: sol gel coated controls (12 implants)

In vivo bactericidal activity

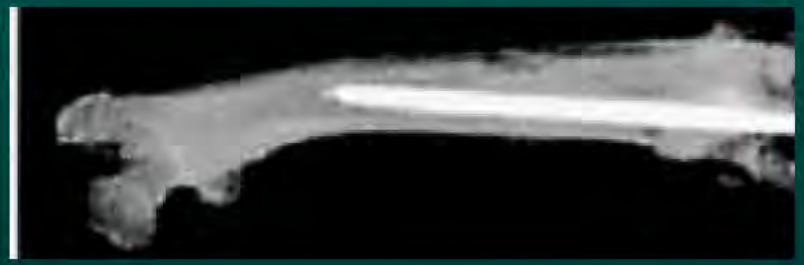
- At time of surgery
  inoculation with a suspension of S. aureus
  (150 µl of 10^4 cfu/ml)
- Sacrifice
  - » 1, 2, 3 and 4 weeks
- Evaluation
  - » cultures on retrieved IM nails
  - » radiographic

In vivo bacterial inhibition –
ex vivo cultures



- Number of S. aureus colonies
  - » cultured from bacteria, if any,
  - » present on IM nails *in vivo*
  - » harvested after 1 week and 2 weeks
- In comparison to control:
  sol gel / vancomycin film is bactericidal
  and inhibits bacterial adhesion

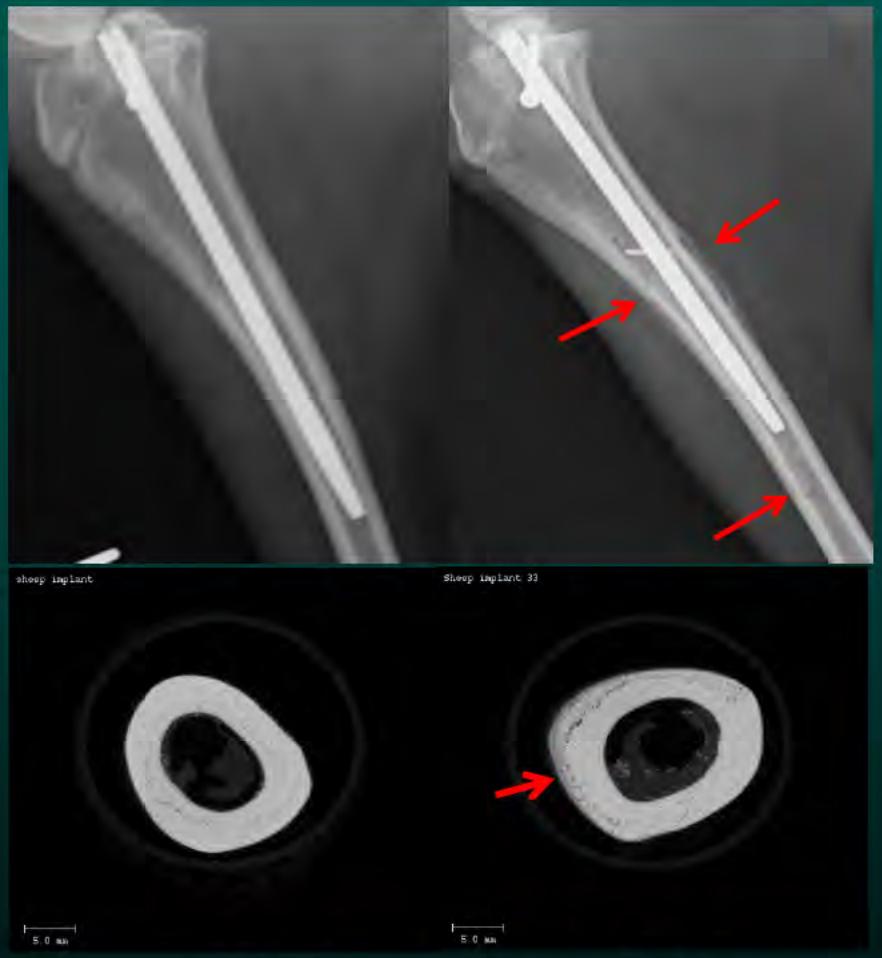
In vivo infection inhibition
4 weeks of implantation



- Sol-gel/vancomycin film (top)
  - » inhibits infection
- Infection on control side (bottom) evidenced by
  - » change in size
  - » periosteal reaction (arrow)
  - » lytic lesions & bone abcesses (*)
  - » extensive bone remodeling

S. Radin et al., Key Engr. Mater. 2006; C. Adams et al., J. Orthop. Res. 2009

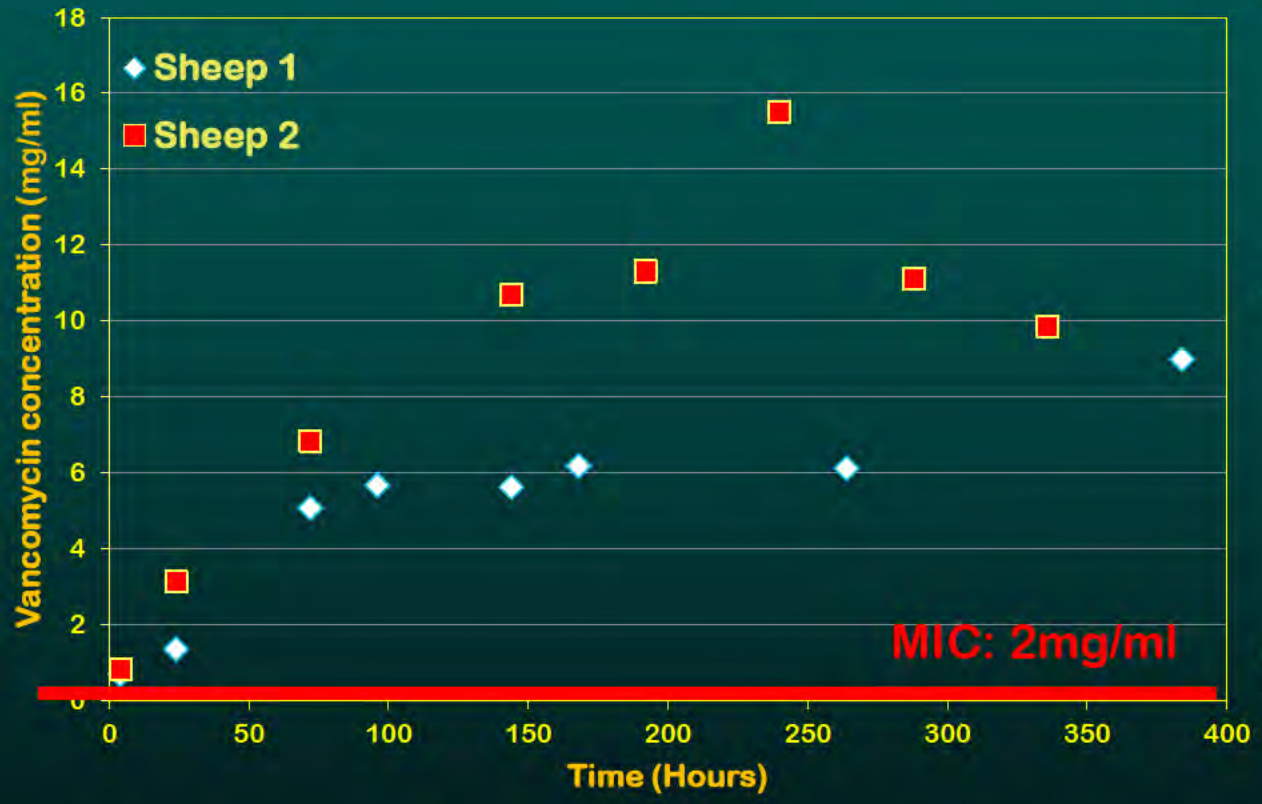
Large animal study - radiographic analysis



SGV SG

For animals (sheep) inoculated with 10^6 or 10^8 CFU *S. aureus*, the X-ray (top) and micro-CT (bottom) results show that SGV coating (left) but not SG coating (right) inhibits osteomyelitis (arrows) **one month post-implantation**.

Local tissue vancomycin concentration



- The local vancomycin concentrations exceed MIC 24 hours after implantation;
- The local vancomycin concentrations exceed MIC for 16 days, the longest time point measured;
- The plasma vancomycin concentrations are below the detection limit (50ng/ml).

T. Schaer et al., 2015

External fracture fixation
A major health care issue

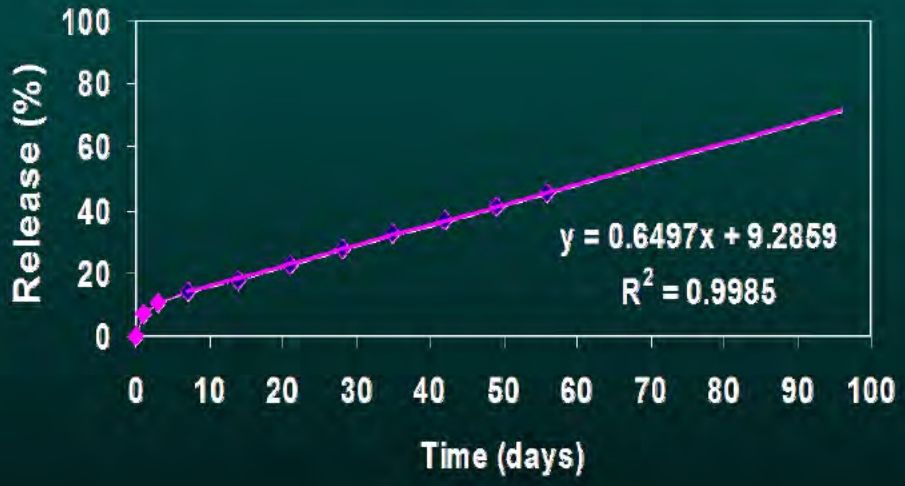
- 2,000,000 fracture fixation devices implanted annually in the USA
  - » Overall postoperative infection rate 5%
- External fixation
  - » Overall incidence of deep infection 16.2%
  - » Overall chronic osteomyelitis rate 4.2%
  - » Infection of femoral fractures, up to 32.2%

External fracture fixation

Constant release (zero order) over 3 months

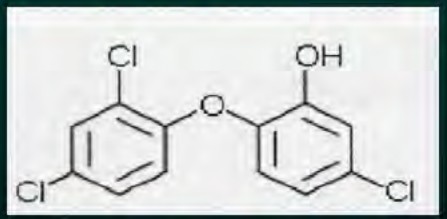
In vitro - triclosan

Cumulative Irgasan release from coatings on grit blasted 4-mm 316L fixator pins (%)



Triclosan (size: 289.55 Da)

- Powerful antibacterial agent extensively used in hospitals
- Disables the activity of the enzyme ENR vital in building cell membranes of many bacteria
- Insoluble in water but soluble in ethanol



$C_{12}H_7Cl_3O_2$

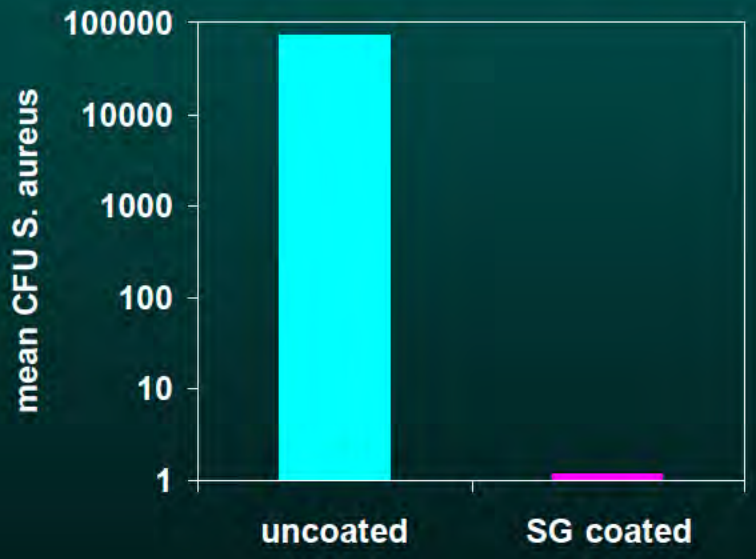
H.Qu, C. Knabe, et al., (2015)

In vitro bactericidal efficacy

- Pins inoculated with Stapyloccocus areus
  - » 1 x10^5 cfu (first), 1 x10^8 cfu (next)
  - » cultured at 37° C, 24h
  - » bacteria count
- Samples:
  - » Controls: uncoated pins
  - » Sol gel/triclosan coated 4-mm fixator pins

In vitro bactericidal efficacy

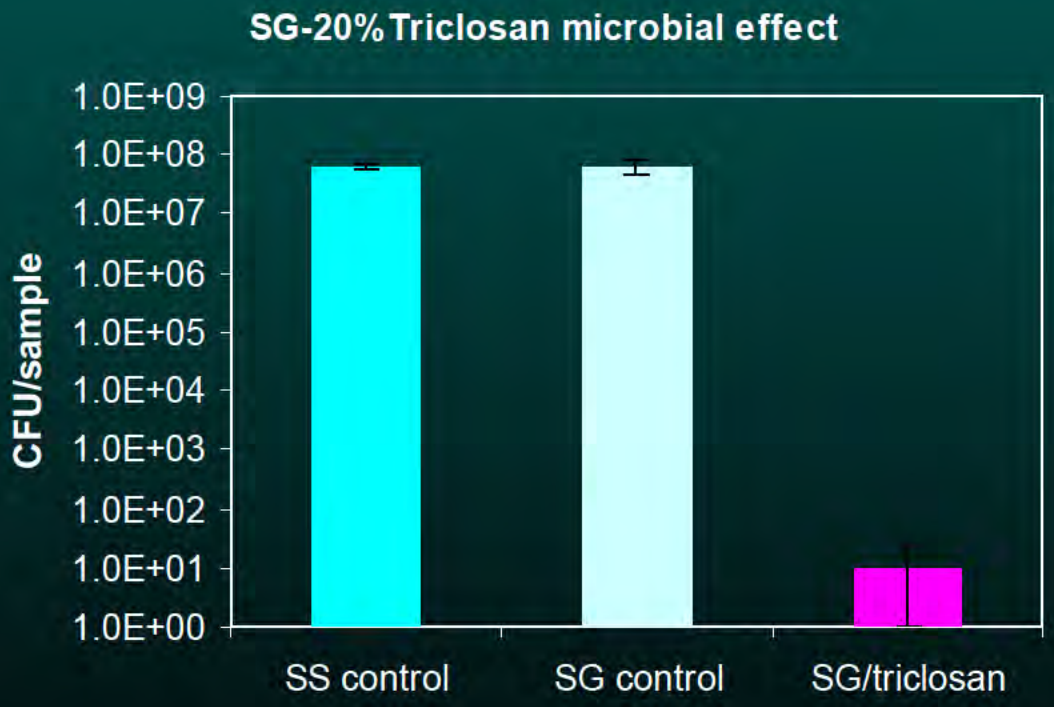
Number of S. aureus colonies compared to uncoated controls (initial time point)



sol-gel/ 10 % triclosan coated pins prevented bacterial colonization - reduction by the maximum - 5 orders of magnitude

In vitro bactericidal efficacy

Number of S. aureus colonies compared to uncoated controls (initial time point)



sol-gel/ 20 % triclosan coated pins reduced bacterial colonization - reduction by 7 orders of magnitude

In vitro bactericidal efficacy

Number of S. aureus colonies compared to uncoated controls (up to 4 weeks of elution)

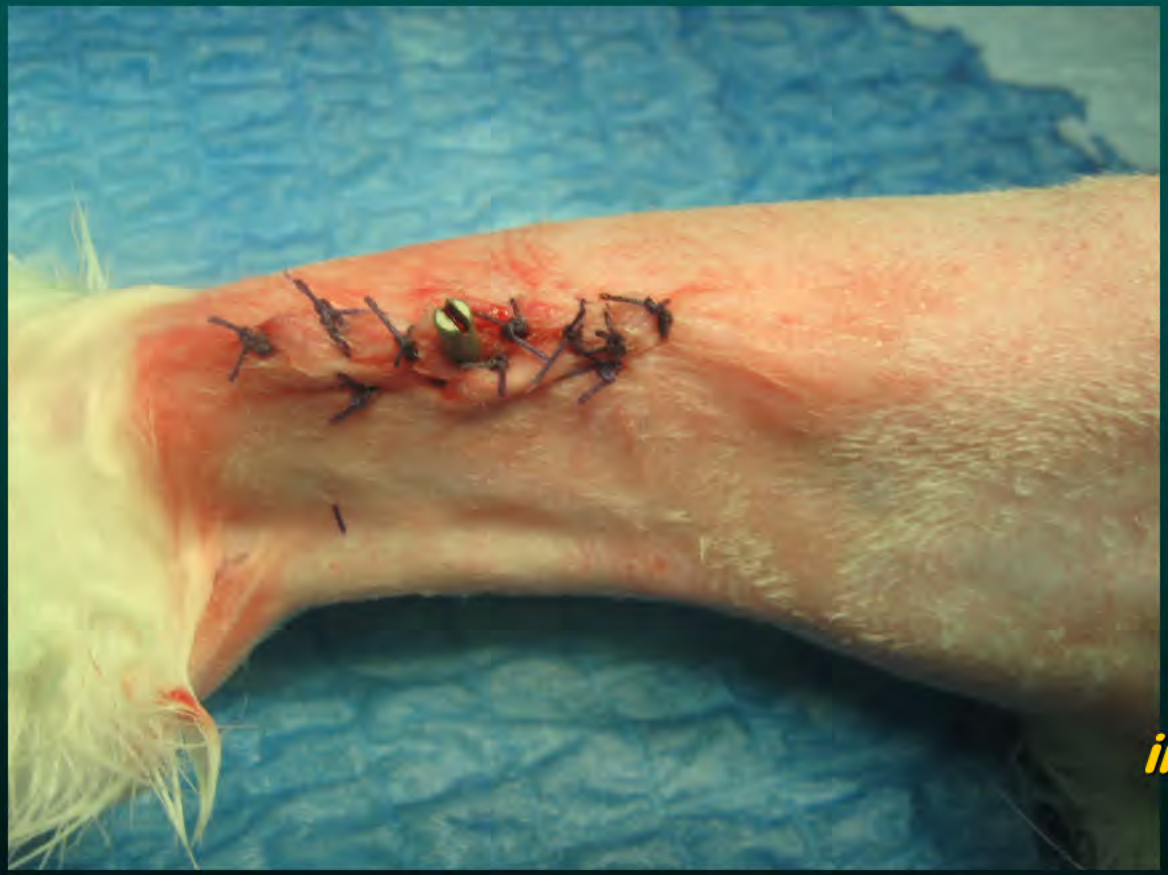
sol-gel/ triclosan coated pins retained bactericidal effect over 4 weeks - reduction by

5 orders of magnitude after 1 week

3 orders of magnitude after 4 weeks

H.Qu, C. Knabe, et al., (2015)

Percutaneous pins – *in vivo*
peroperative photograph



rabbits

distal tibia

inoculation with S. Aureus

H.Qu, C. Knabe, et al., (2015)

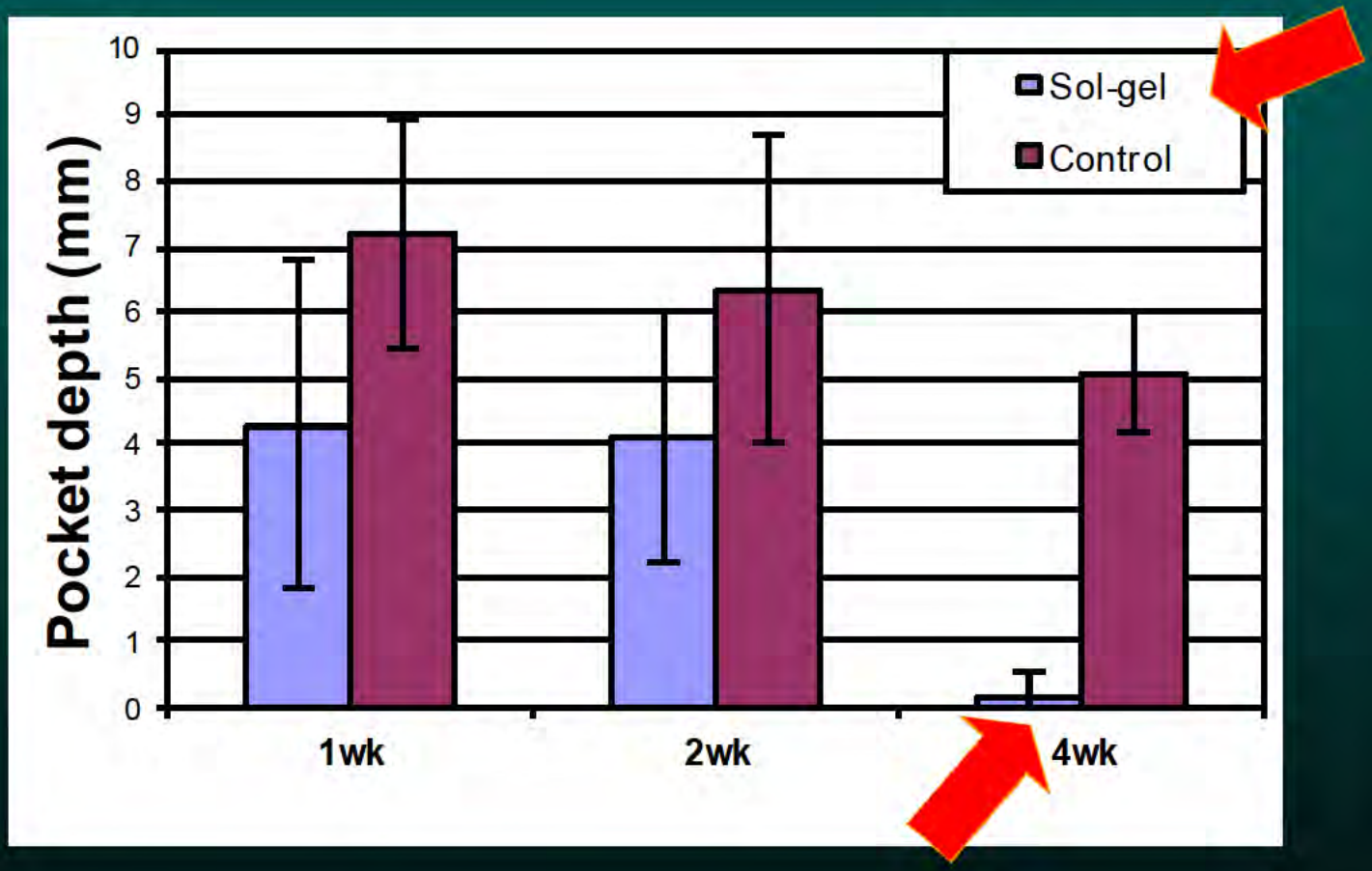
Infection rates

percutaneous pins – *in vivo*

Groups	Animals for evaluation	Animals with clinical signs of infection*	Animals with radiographic signs of infection†
Control (1wk)	4	4	2
Sol-gel (1wk)	3	0	0
Control (2wk)	4	3	2
Sol-gel (2wk)	5	0	0
Control (4wk)	5	4	4
Sol-gel (4wk)	6	0	0

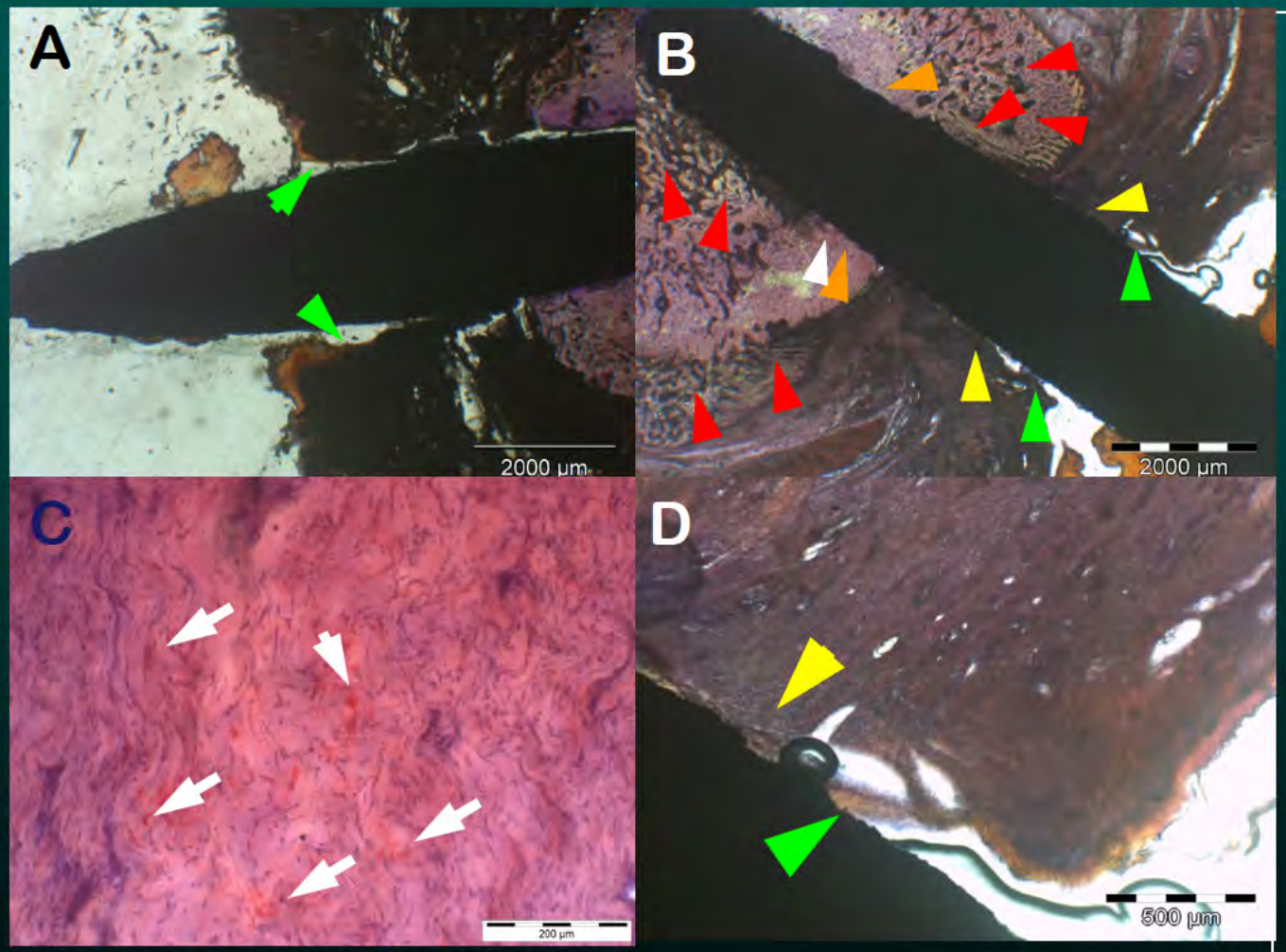
* animal showing either of these signs at the time of sacrifice was checked as infected: serious discharge, superficial cellulitis and deep infection.
† a radiograph revealing osteomyelitis at the time of sacrifice is graded as infected.

Percutaneous pins – *in vivo*
pocket depth



H.Qu, C. Knabe, et al., (2015)

Infection
percutaneous pins – *in vivo*, 4 weeks



Control (A and C) and sol-gel coated (B and D) implants. Control implant (A) shows extensive epithelial downgrowth (green arrows) and bacterial colonization and infiltration of S. aureus in the subcutaneous tissue (C, white arrows). Coated implant (B & D) shows excellent bone integration of the pin (orange arrows) and positive osteocalcin expression (white arrow), extensive new woven bone formation (red arrows), excellent attachment of the subcutaneous tissue to the implant surface (yellow arrows) as well as epithelial attachment (green arrows).

H.Qu, C. Knabe, et al., (2015)

Benefits of silica xerogels (sol-gels), cont..

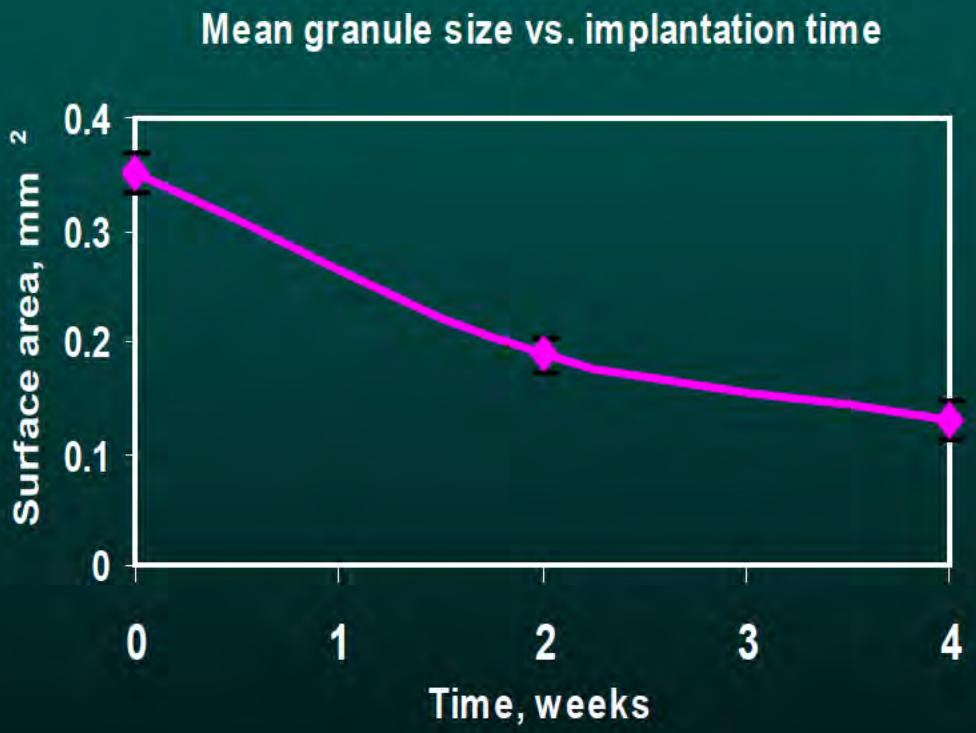
- molecules are protected while in the sol gel (compare to the *in vivo* half life – e.g PDGF: 2 minutes)
- various molecules can be delivered simultaneously
- substantially full release of therapeutic agents
- resorbable
- **biocompatible**
- room temperature processing

Nicoll et al. (1998), Falaize et al. (1998), Santos et al. (1999), Radin et al. (2002)

In vivo biocompatibility study

- New Zealand white rabbits
- Experimental groups:
  - » sol gel discs (8 mm in diameter, 2 mm thick) subcutaneously in the back
  - » sol gel granules (710 - 1000 μm) defects in the illiac crest (5 mm in diameter, 2 mm deep)
  - » controls: sham surgery (defects without material)
- Implantation time: 2 & 4 weeks

Resorption –
Mean granule size v implantation time



Gradual reduction in granule size reflects time-dependent granule resorption

Minimal inflammatory response

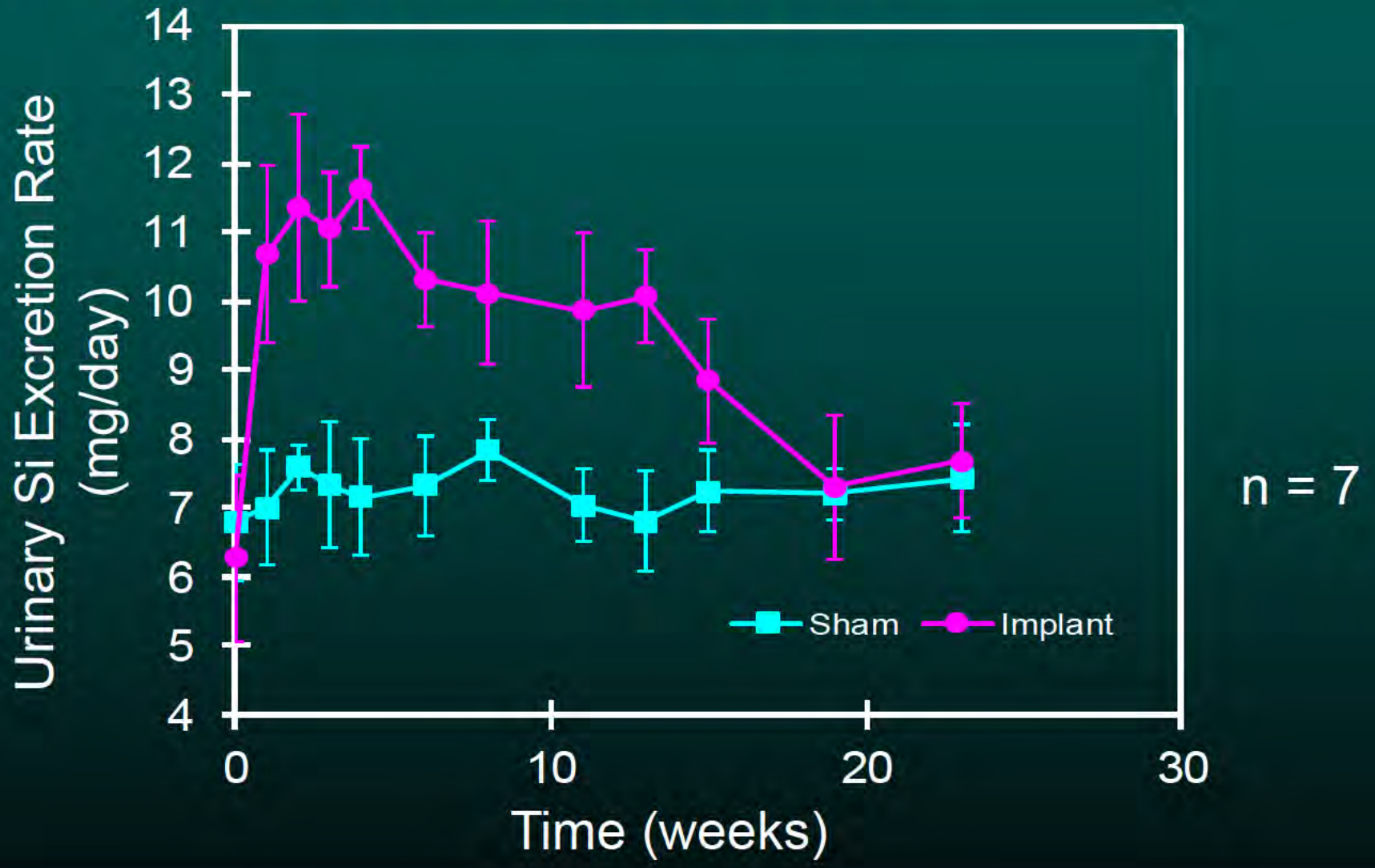
Radin et al. (2002)

Methods – animal model (*)

- 1500 mg of resorbable glass granules (300-355 µm) were implanted into the paraspinal muscle of 4 kg NZW rabbits for 24 weeks
- Clinically relevant dose of 30 cc for a 70 kg human (e.g. large compression fracture in the proximal tibia)
- Muscle implantation site heals faster than bone and possibly leads to an enhanced resorption rate in comparison to bone

(*) One of two models
Other model: bone implantation site
Lai et al., Biomaterials (2002), J. Biomed. Mater. Res. (2005)

Silicon Excretion in Urine



Results - creatinine

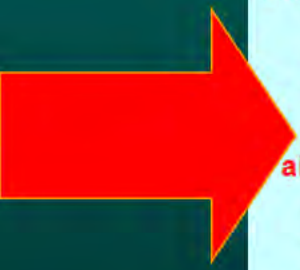
- Creatinine: natural metabolite found in urine. Its production is proportional to total muscle mass. Excretion rate reflects kidney function.
- Excretion rates remained normal and stable for both implanted and sham groups. Kidney function was normal throughout experiment.

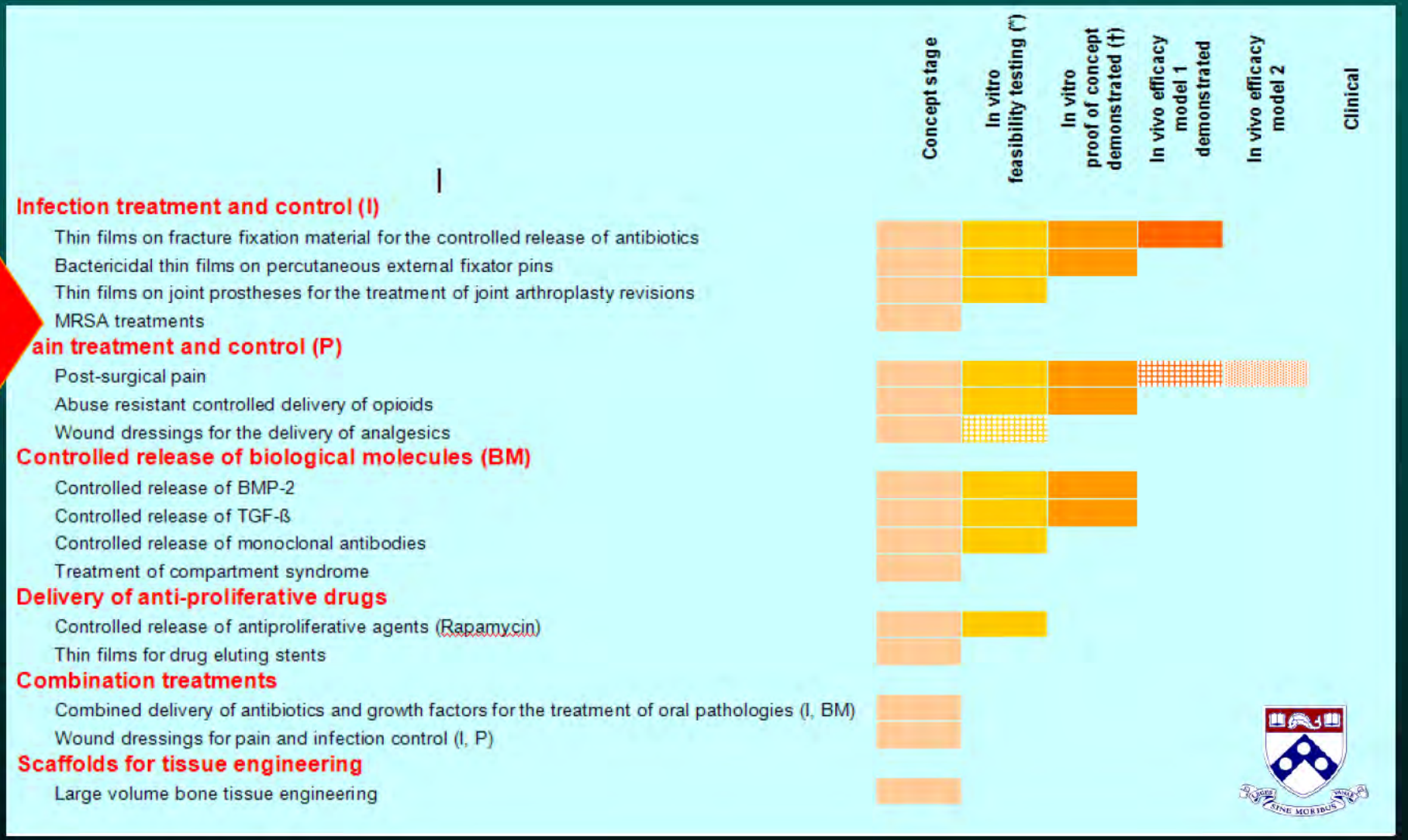
sham	38.3±5.1 mg/day/kg
implant	36.8±6.5 mg/day/kg

Discussion

- Increased urinary Si supports the hypothesis that the silica gel from the granules is dissolved into the bloodstream and removed by the kidney.
- The Si release product in the blood must be small enough to pass through kidney filtration (18 Å).
  (Berne and Levy, Physiology, 1988)
- The concentrations of silicon in the urine were well below saturation.
- Elevated Si was not found in any of the major organs. This corroborates findings of previous histological analyses in other glass granule implant studies revealing no pathological changes in kidney, liver or spleen.
- Creatinine excretion rates were similar between implanted and sham rabbits. Therefore, kidney function was not adversely affected by the surgical procedure and the dose of granules.

pipeline



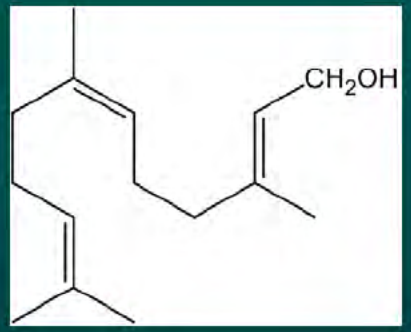

Concept stage
In vitro feasibility testing (*)
In vitro proof of concept demonstrated (†)
In vivo efficacy model 1 demonstrated
In vivo efficacy model 2
Clinical
Infection treatment and control (I)
Thin films on fracture fixation material for the controlled release of antibiotics
Bactericidal thin films on percutaneous external fixator pins
Thin films on joint prostheses for the treatment of joint arthroplasty revisions
MRSA treatments
ain treatment and control (P)
Post-surgical pain
Abuse resistant controlled delivery of opioids
Wound dressings for the delivery of analgesics
Controlled release of biological molecules (BM)
Controlled release of BMP-2
Controlled release of TGF-ß
Controlled release of monoclonal antibodies
Treatment of compartment syndrome
Delivery of anti-proliferative drugs
Controlled release of antiproliferative agents (Rapamycin)
Thin films for drug eluting stents
Combination treatments
Combined delivery of antibiotics and growth factors for the treatment of oral pathologies (I, BM)
Wound dressings for pain and infection control (I, P)
Scaffolds for tissue engineering
Large volume bone tissue engineering

Background

- **Methicillin resistant staphylococcus aureus infection has significantly increased**
  (Matar et al. (2010), Rivera et al. (2011)
  - » From 1999 through 2005, infections outside the lungs or blood tripled
  - » MRSA strains account for >50% of all *S. aureus* strains causing clinical disease

- **Surgical site infection (SSI)**
  - » Treating SSI is complicated by how bacteria colonize implants
  - » Bacteria adhere to implant surface and form a biofilm
  - » High resistance of the biofilm to systemic antibiotic treatment

Farnesol as an adjuvant to vancomycin



- Natural quorum-sensing alcohol molecule
- Antimicrobial activity against *S. aureus* biofilms and synergistic with vancomycin (Gomes et al. (2011))
- It probably damages the cell membrane and impairs ergosterol synthesis
- **Insoluble in water**

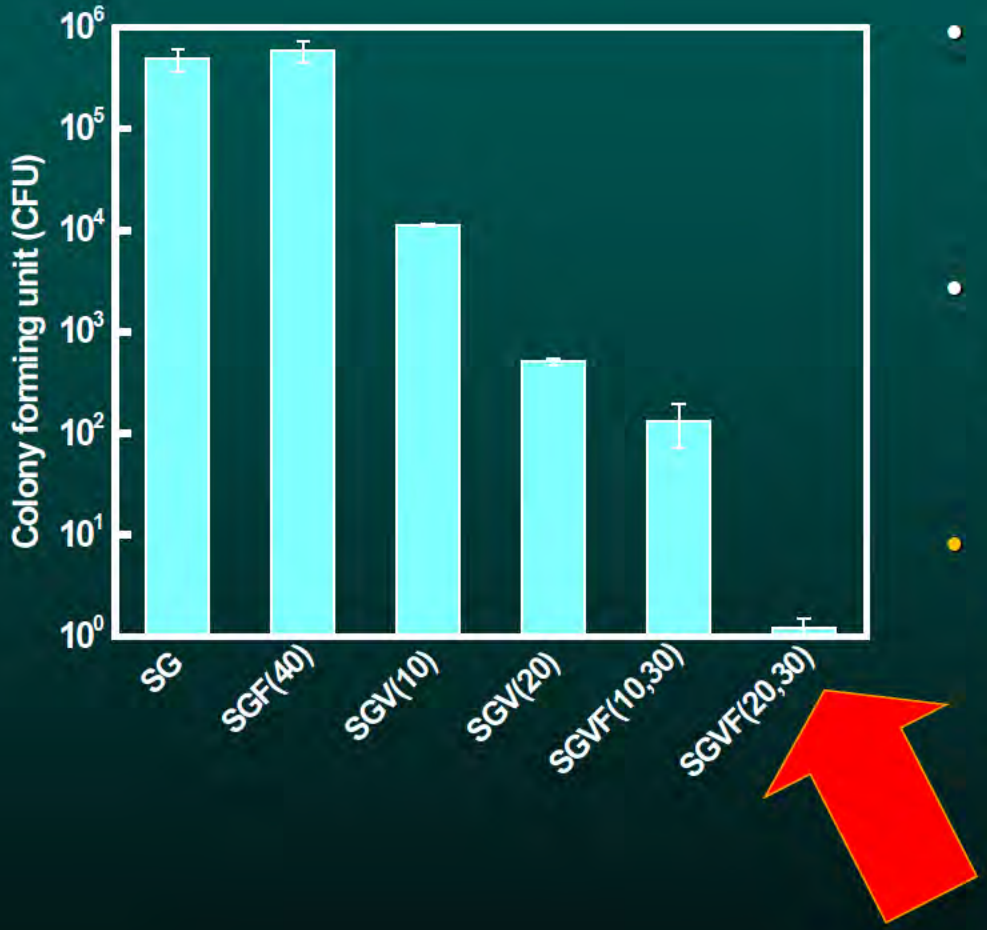
Water insolubility compromises the **bio-availability** of farnesol along with vancomycin at the site of infection *in vivo*

Objective:

To design an efficient therapeutic strategy which can deliver both antibiotic and an adjuvant **simultaneously** at the **infection site** in controlled fashion

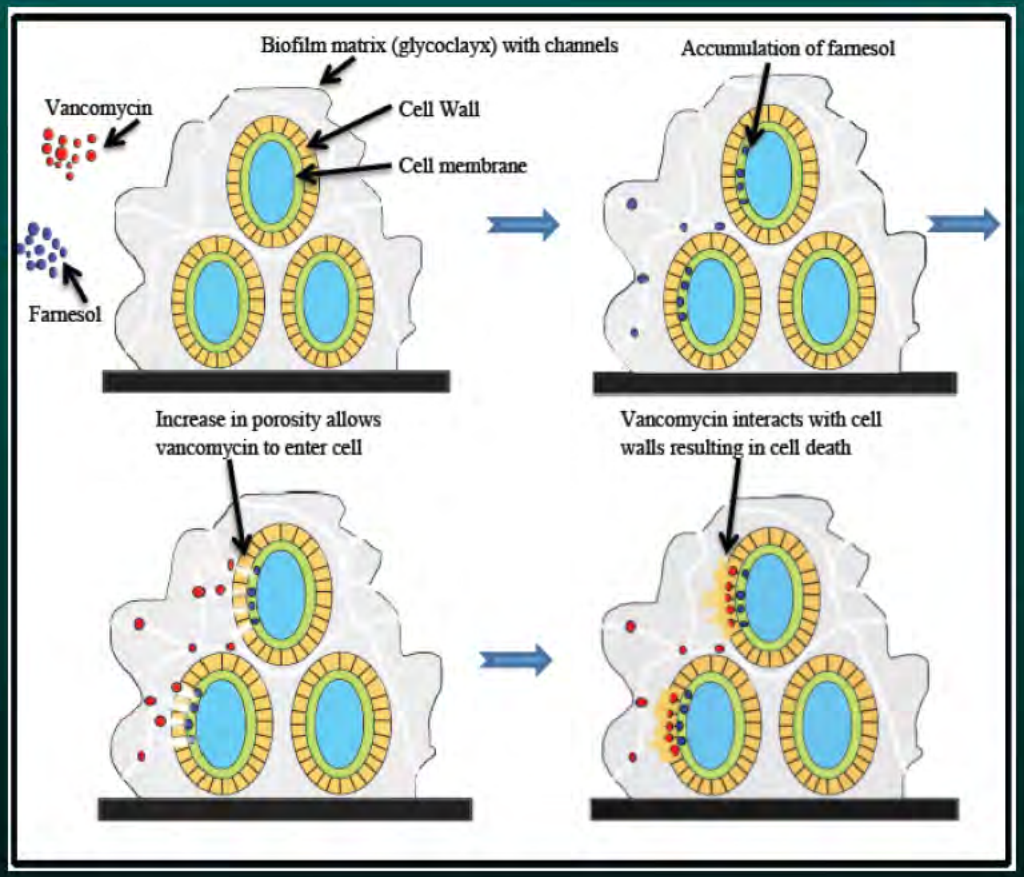
Bhattacharyya et al., (2014)

In vitro bactericidal effect (MRSA)



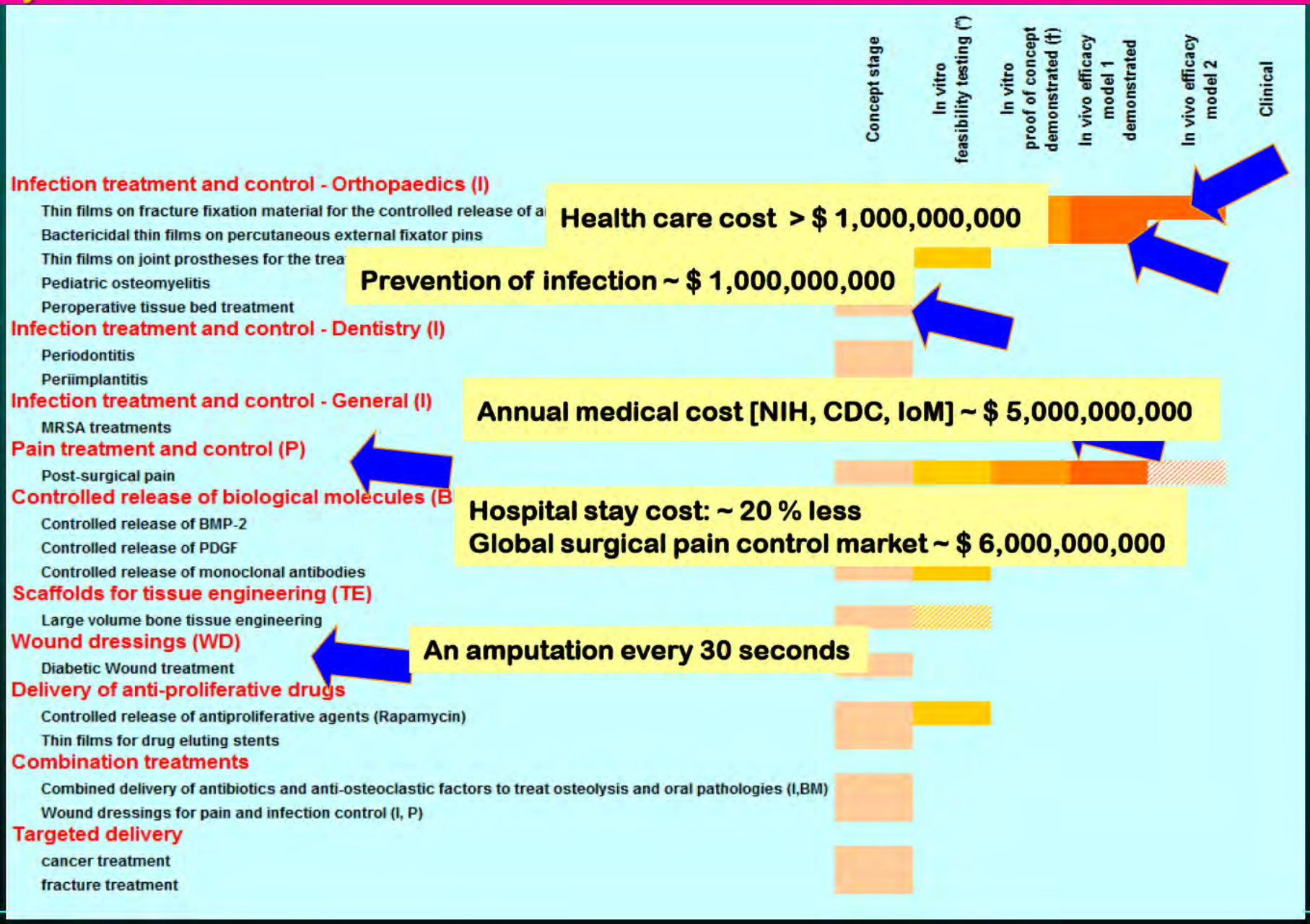
- Film with 10 wt% and 20 wt% vancomycin can reduce the MRSA growth by 10 and 10^2 fold
- When 10 wt% vancomycin combined with 30 wt% farnesol MRSA growth reduced by 10^3 fold
- When 20 wt% vancomycin is combined with 30 wt% farnesol, MRSA growth is completely suppressed (~10^6-fold reduction compared to control)

Working mechanism



- Farnesol penetrates the biofilm and gains access to the bacterial cell
- Farnesol accumulates in the cell membrane, increases the permeability and porosity of the biofilm and of the bacterial cell membrane
- Allows more vancomycin to enter the bacterial cell with greater ease. Vancomycin binds to the cell wall where its normal mode of action results in cell death

pipeline


Concept stage
In vitro feasibility testing (*)
In vitro proof of concept demonstrated (†)
In vivo efficacy model 1 demonstrated
In vivo efficacy model 2
Clinical
Infection treatment and control - Orthopaedics (I)
Thin films on fracture fixation material for the controlled release of a
Bactericidal thin films on percutaneous external fixator pins
Thin films on joint prostheses for the trea
Pediatric osteomyelitis
Peroperative tissue bed treatment
Infection treatment and control - Dentistry (I)
Periodontitis
Periimplantitis
Infection treatment and control - General (I)
MRSA treatments
Pain treatment and control (P)
Post-surgical pain
Controlled release of biological molecules (B
Controlled release of BMP-2
Controlled release of PDGF
Controlled release of monoclonal antibodies
Scaffolds for tissue engineering (TE)
Large volume bone tissue engineering
Wound dressings (WD)
Diabetic Wound treatment
Delivery of anti-proliferative drugs
Controlled release of antiproliferative agents (Rapamycin)
Thin films for drug eluting stents
Combination treatments
Combined delivery of antibiotics and anti-osteoclastic factors to treat osteolysis and oral pathologies (I,BM)
Wound dressings for pain and infection control (I, P)
Targeted delivery
cancer treatment
fracture treatment
Health care cost > $ 1,000,000,000
Prevention of infection ~ $ 1,000,000,000
Annual medical cost [NIH, CDC, IoM] ~ $ 5,000,000,000
Hospital stay cost: ~ 20 % less
Global surgical pain control market ~ $ 6,000,000,000
An amputation every 30 seconds

Mergers - a business term

Business models

- VW

- Mercedes

...

Evert Schepers, KU Leuven, Belgium
David Kohn, U Michigan
Kevin Healy, UC Berkeley
Tim Topoleski, U Maryland
Elsie Effah, U Ghana, Accra, Ghana
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Thank you