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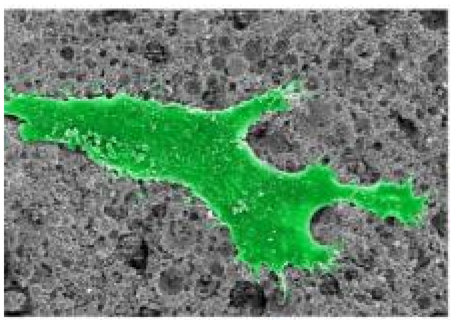
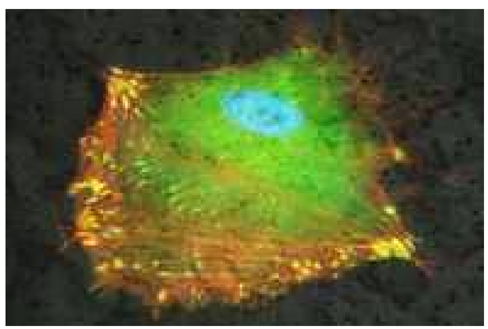
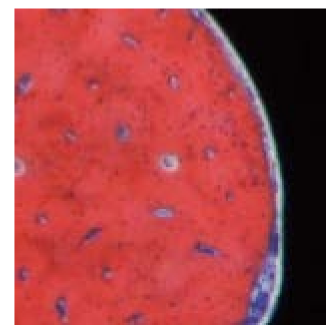
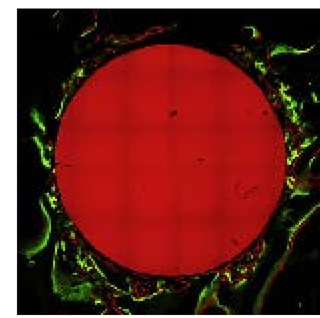
cost

Biological responses of cells and tissues to biomaterials

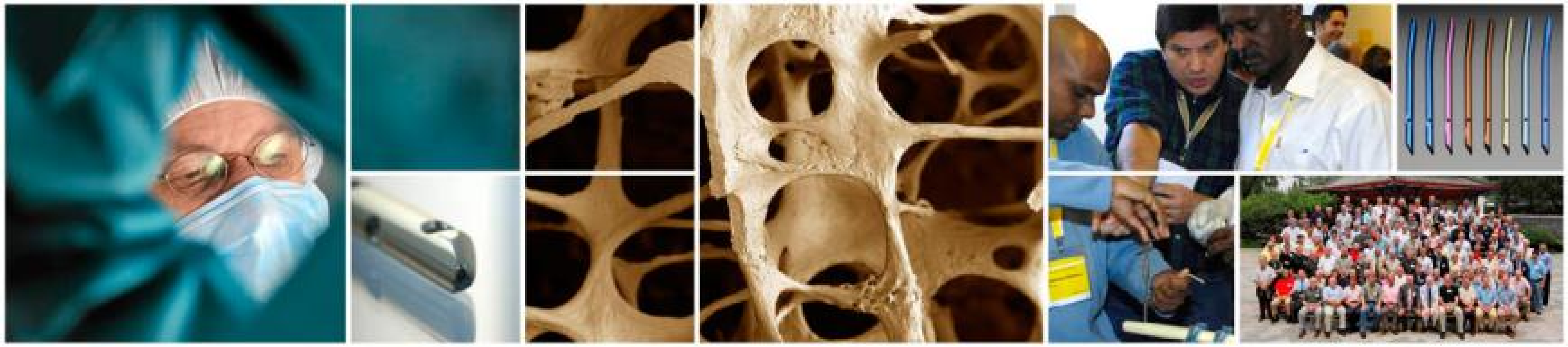



Marianna Peroglio
Research Scientist

Summer School - Ceramic & glass science & technology, application to bioceramics & bioglasses – 17 June 2015 – Madrid, Spain

AO Foundation

- Founded in 1958
- Medically guided, global network of surgeons
- World’s leading educational and research organisation for trauma and musculoskeletal treatment
- With more than 10,000 surgeons, in more than 100 countries, it is one of the most important and extensive networks in medicine
- Global knowledge network—interdisciplinary teamwork
- International faculty of over 3,000 experts



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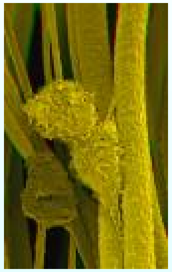
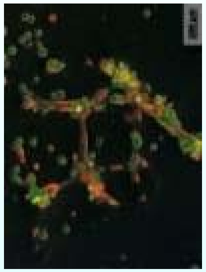
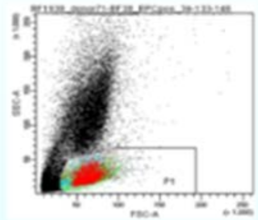
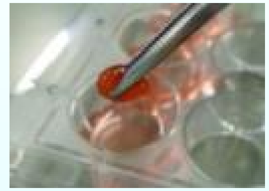
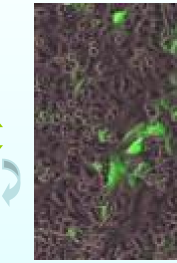
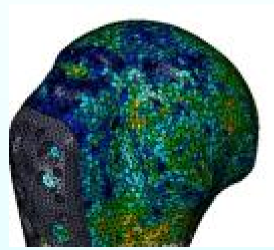
AO Research Institute Davos

Musculoskeletal Regeneration

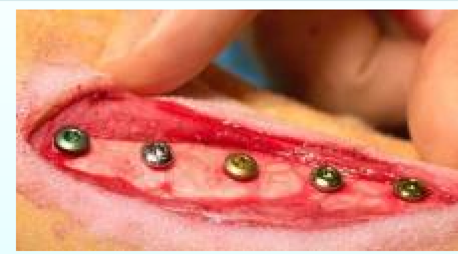




Biomedical Services

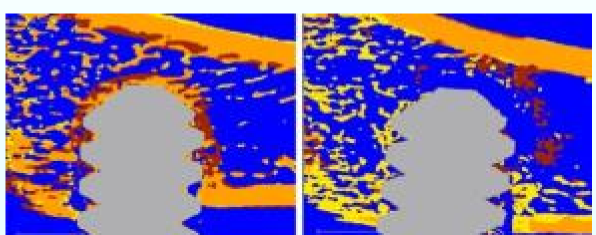
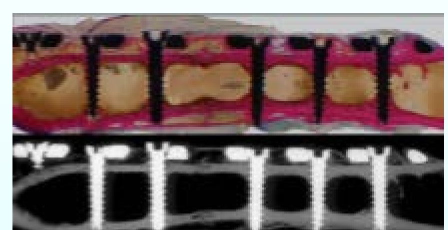
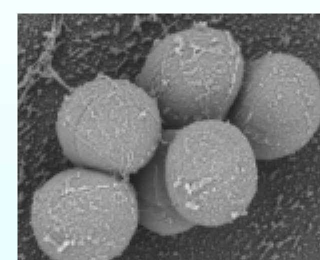






Preclinical Services



Musculoskeletal Infection

Outline

- Lexicon
- Classification of biomaterials
- Cell-material interactions
- Tissue-material interactions
- Examples of cell and tissue interactions with:
    - Ceramics
    - Metals
    - Polymers
- Summary
- Future areas of research

Lexicon

- Biomaterial
- Implant
- Primary and secondary stability
- Osseointegration
- Bone to implant contact
- Fibrous capsule
- Inflammation (acute and chronic)
- Osteoblast
- Stem cell

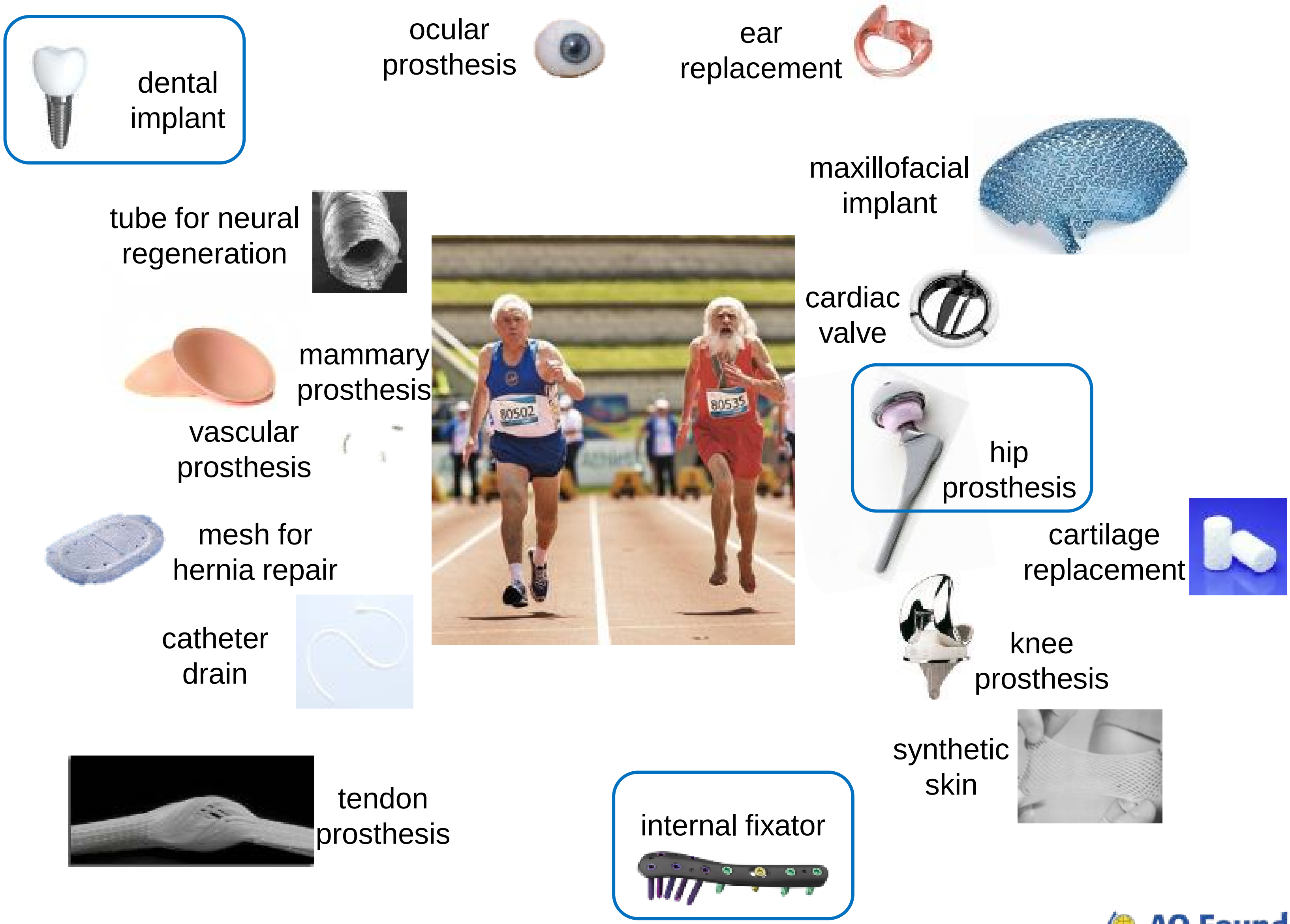
Biomaterial: evolution of the definition

- Williams **1987**: “A biomaterial in a nonviable material used in a medical device, intended to **interact** with biological systems”

- Williams **1999**: “Biocompatibility is the ability of a material to perform with an **appropriate host response** in a specific situation”

- **NIH**: “Biomaterial is any substance or combination of substances, other than drugs, synthetic or natural in origin, which can be used for any period of time, which augments or replaces partially or totally any tissue, organ or function of the body, in order to **maintain or improve the quality of life of the individual**”

Application of biomaterials



Classification of biomaterials

Composition	Metals & alloys → **Ss**, Co-Cr, **Ti**, **Ti-6Al-4V**, Ni-Ti, Mg Polymers → PMMA, PLA, PGA, PE, PEEK Ceramics & glasses → **Al_2O_3**, **ZrO_2**, **CaP**, BAG Composites → bone (unprocessed), BCP-PCL, BAG-PLA, PU-HA
Structure	Bulk → **implants (stems, plates, screws)** Porous → scaffolds Surface → **topography (macro, micro, nano)**, bioactive coating on «bioinert» material
Source	Natural → bone grafts, hyaluronic acid, fibrin, collagen, chitosan, cellulose Synthetic → PCL, PMMA, PEEK
Response	Toxic «Bioinert» → **Al_2O_3, ZrO_2** Bioactive → osteoconductive, osteoinductive → **HA, TCP, BCP**, BAG Bioresorbable → **BCP**, PCL, PU, PLA, PGA, Mg
Function	Temporary ↗ non biodegradable → **temporary implants (polished metals)** Temporary ↘ biodegradable → maxillofacial screws Permanent → hip prostheses, spine cages

Which cells?

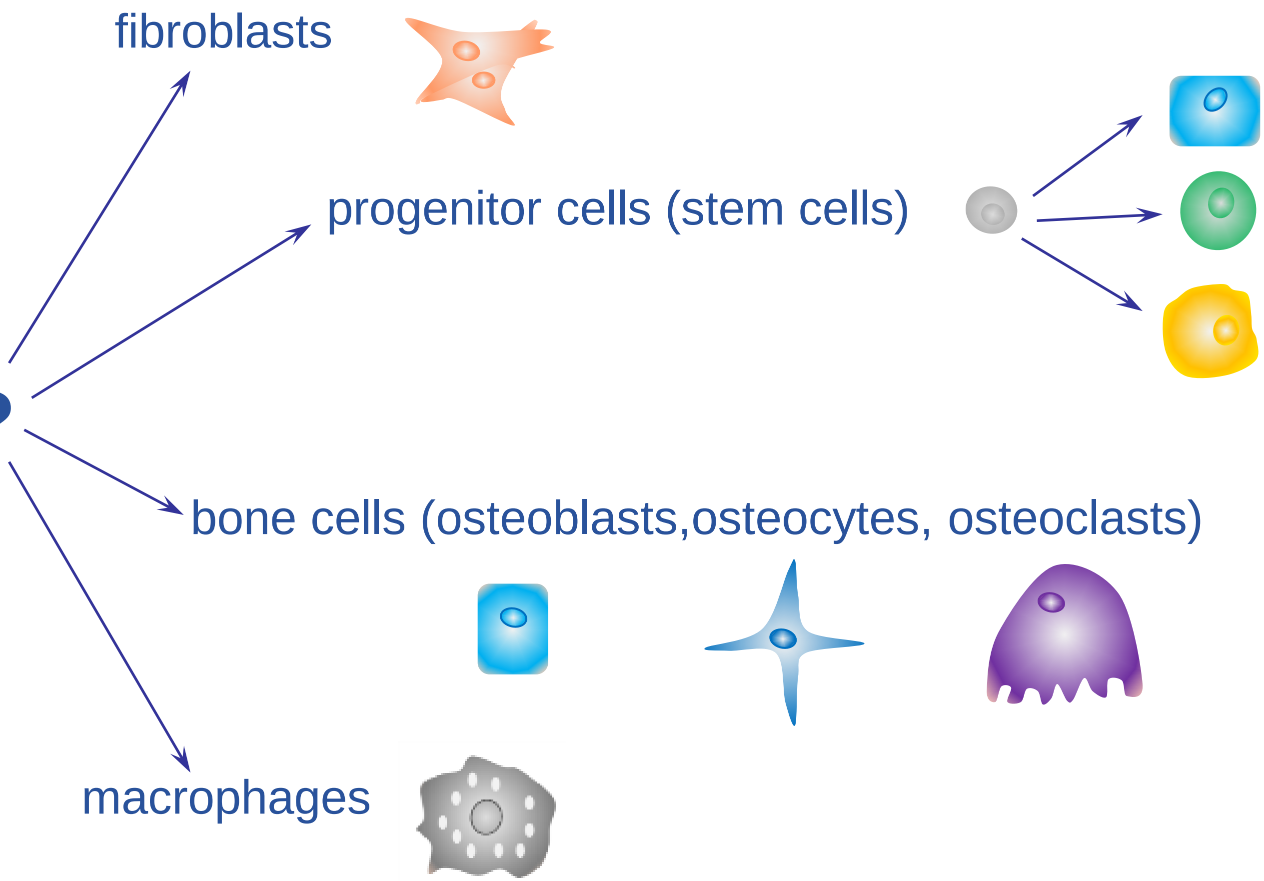
which species?

which location?

healthy or diseased?

primary or cell line?

how many donors?



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Which tissues?

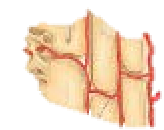
which species?

which location?

healthy or diseased?

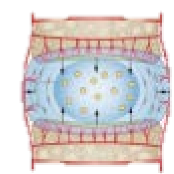
soft tissue
- tendon
- muscle
- skin

hard tissue → bone

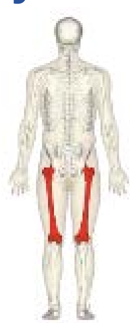


vascularised tissue → bone

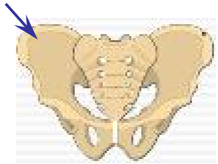
avascular tissue → intervertebral disc



mechanically-loaded tissue



unloaded tissue



Which response?

Focus: bone

cytocompatibility (in vitro)

biocompatibility (in vivo)

cell proliferation
(metabolic assays, DNA)

cell morphology
(microscopy)

gene expression
(runx2, alkaline phosphatase, osteocalcin)

protein expression
(collagen type I, alkaline phosphatase, osteocalcin)

mineral deposition
(staining for Ca and P)

tissue structure
(histology)

tissue mechanics
(micro-indentation)

Biomaterial characteristics?

- **goal**
- **stability**
- **sterilisation**
- **reproducibility**
  minimise material variability
- **cytocompatibility**
- **number of samples**
- **shape & dimensions**
- **surface**
  chemistry
  topography
  wettability
- **porosity**
  macro and micro

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Surfaces … what do you see ?

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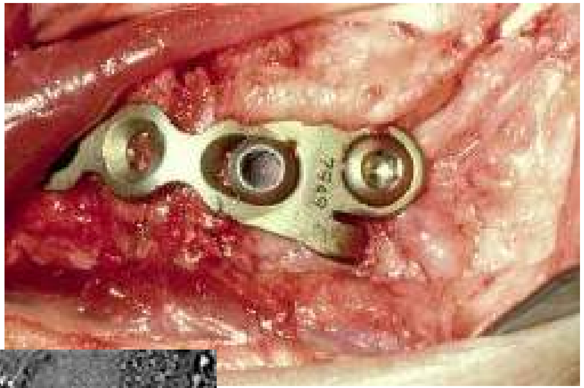
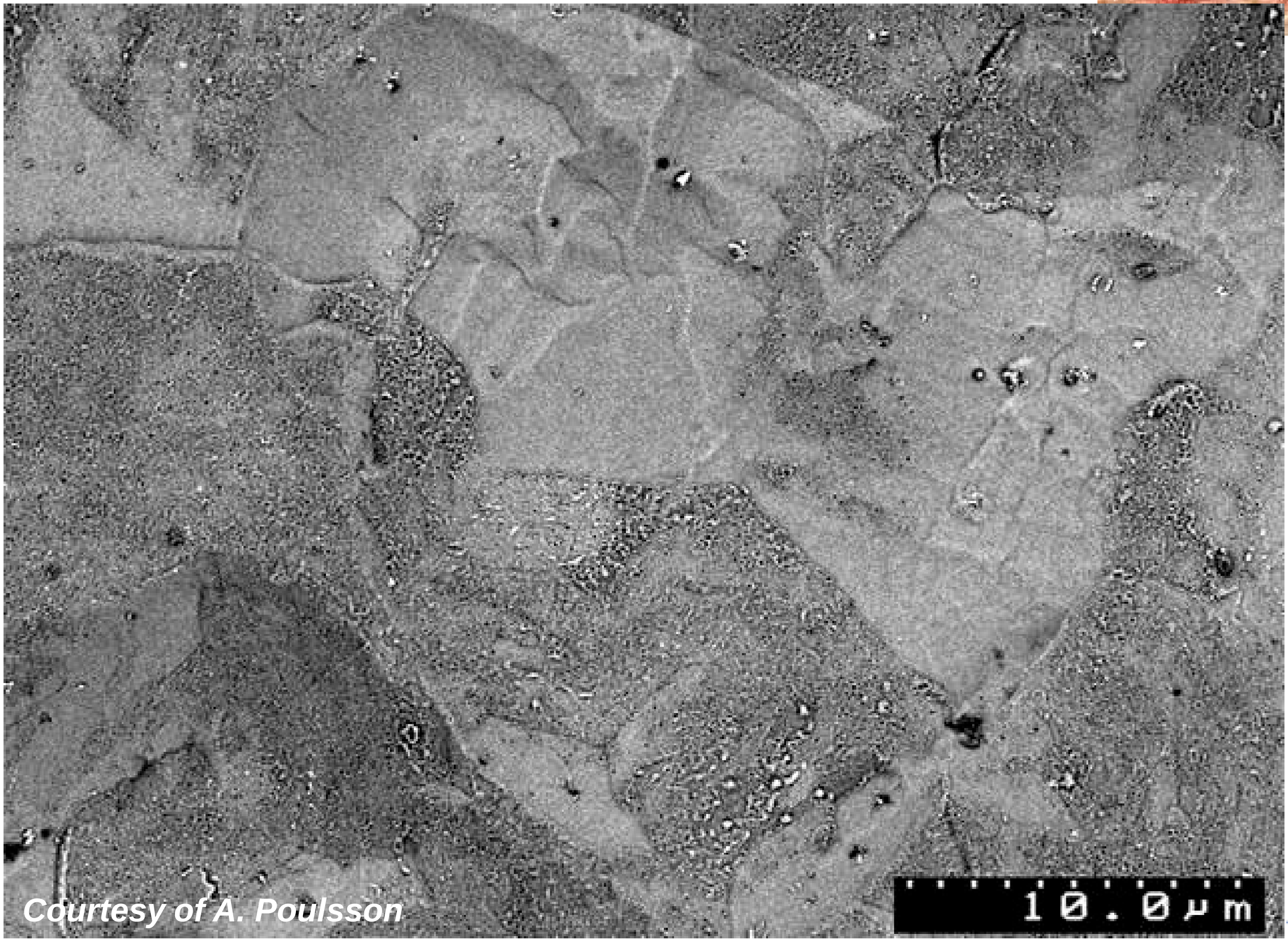
Surfaces… what do cells see ?





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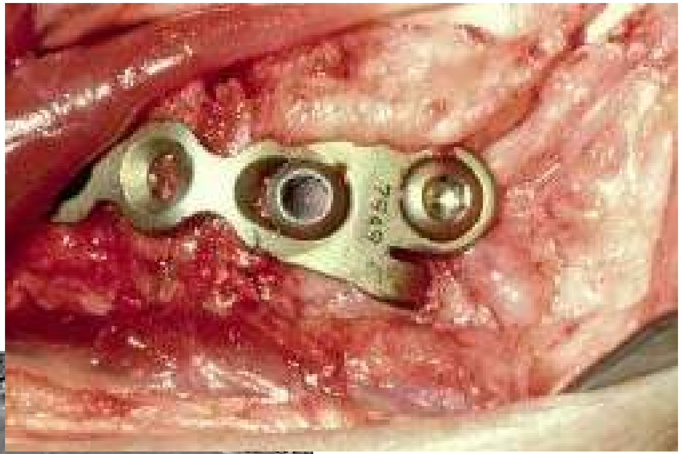
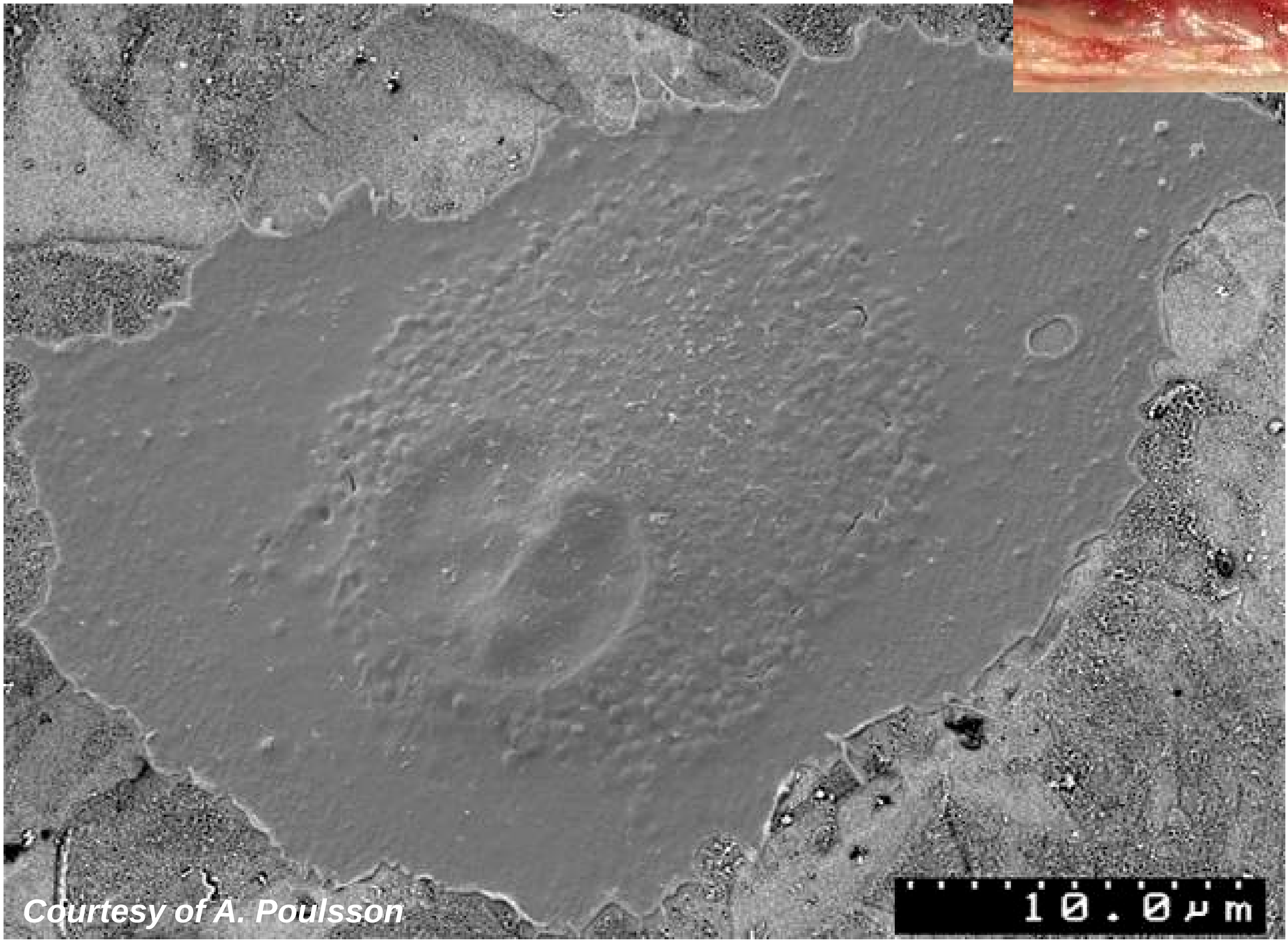
- **Rough & smooth topography (micro/nano range)**





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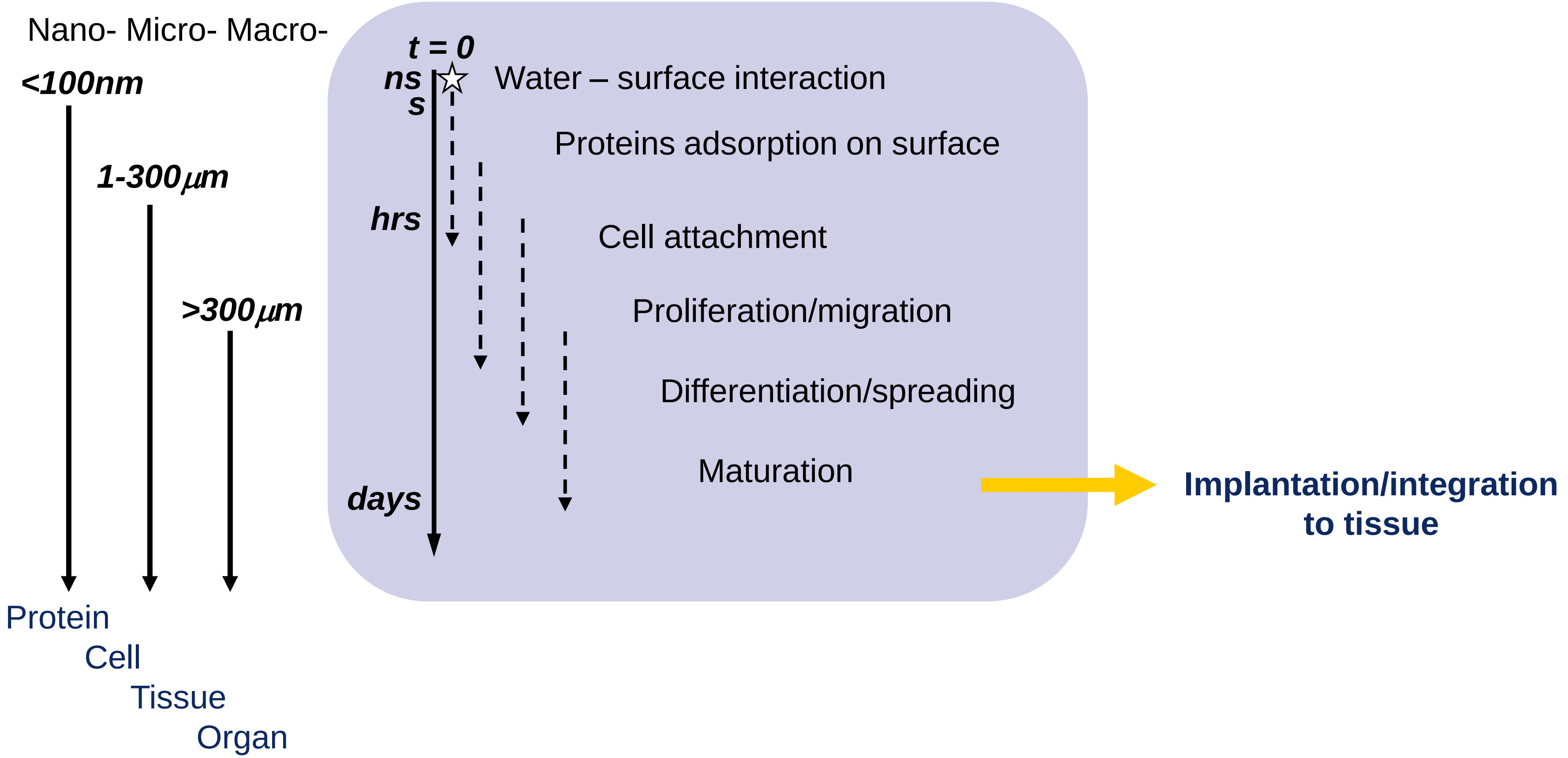
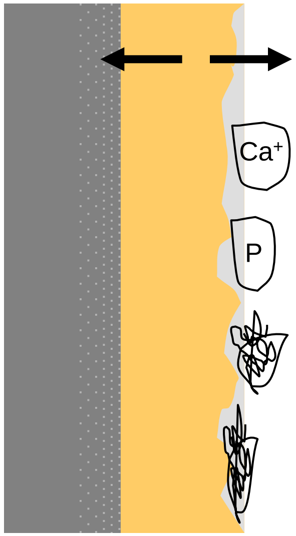
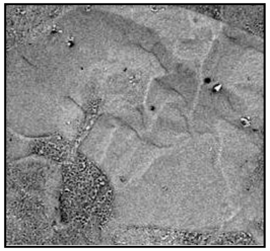
Cell-material interactions
Interactions levels



Molecular level events at implant surface





•***Chemistry*** – determines the types of intermolecular forces, governing interaction with proteins

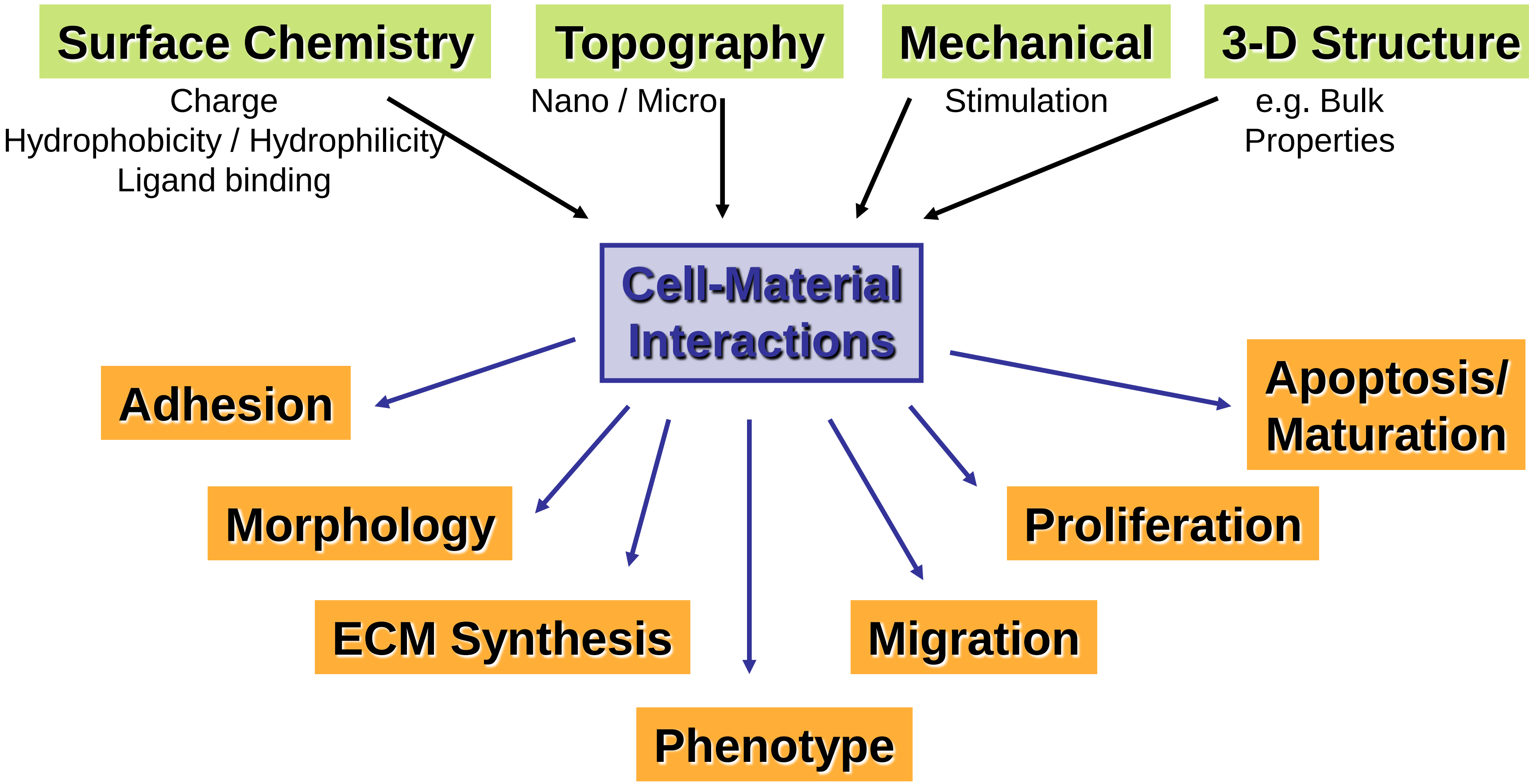
•*Hydrophobicity* – hydrophobic surfaces often bind protein more strongly (can limit cell adhesion)

•*Heterogeneity* – surface non-uniformity, domains interact differently with proteins

•*Potential* – influences ion distribution & interaction with proteins (dependant upon topography / chemistry)

•***Topography*** – greater texture exposes discontinuities for interaction with proteins

Cell-material interactions



Masters K.S., Anseth K.S., *Advances in Chemical Engineering* **2004** 29: 7.

Tissue-material interactions

micromotion

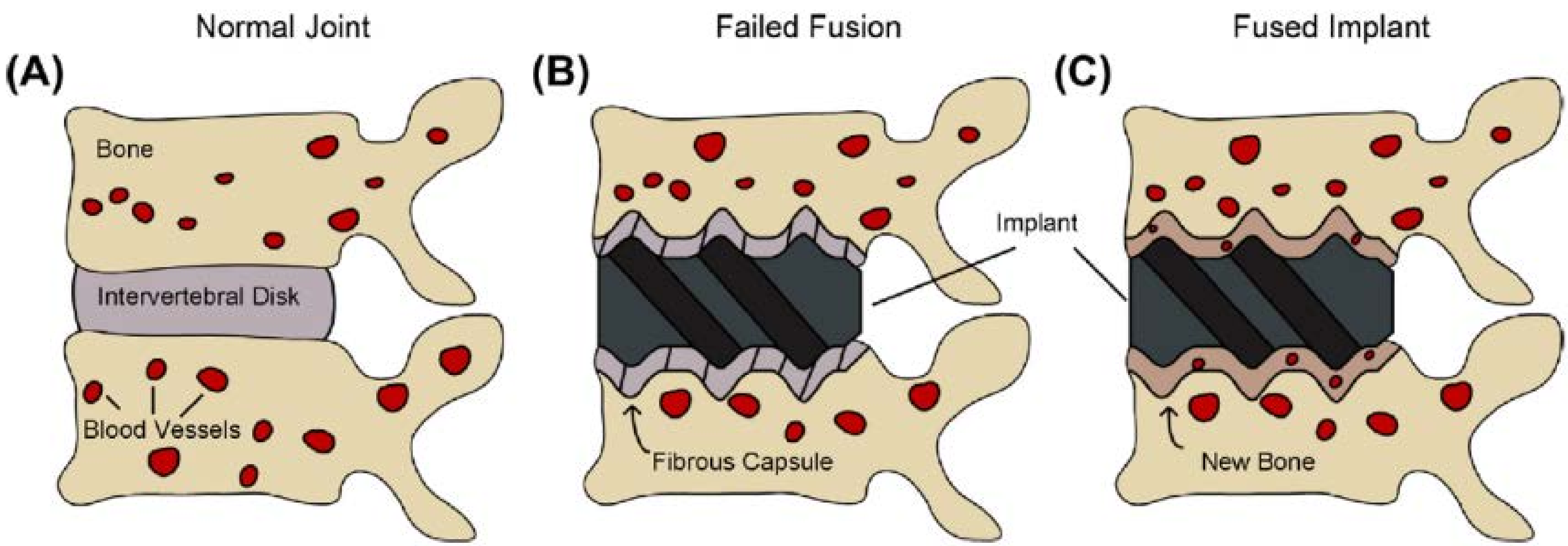
⇕

inflammation

⇓

osteolysis

⇓

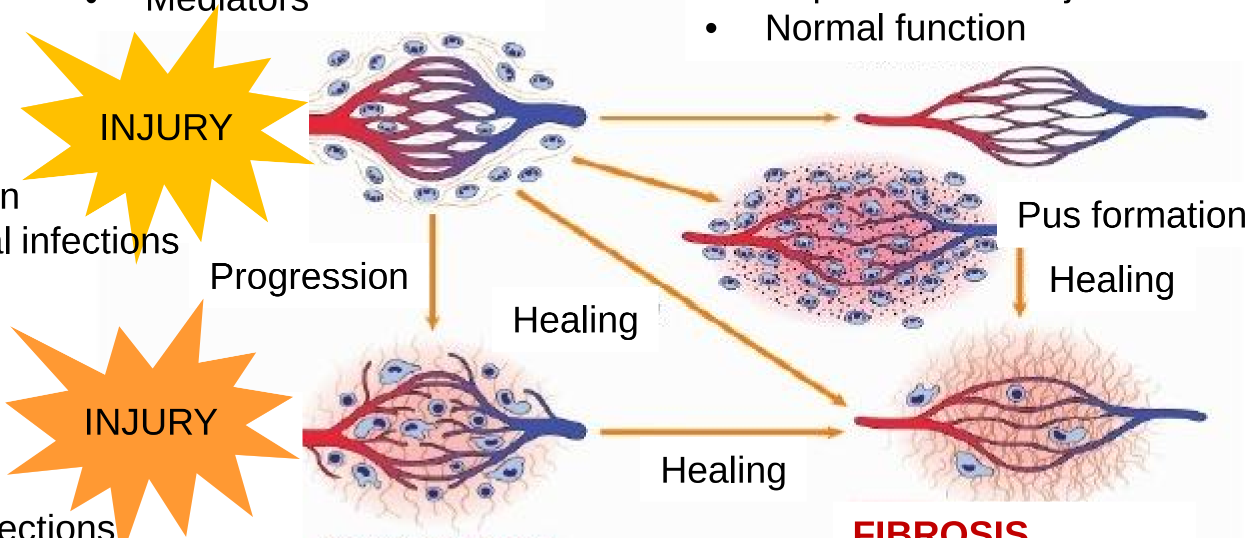


Gittens RA. *Acta Biomaterialia* **2014**
Implant osseointegration and the role of microroughness and nanostructures: Lessons for spine implants

Outcome of acute inflammation

ACUTE INFLAMMATION
- Vascular changes
- Neutrophil recruitment
- Mediators

RESOLUTION
- Clearance of injurious stimuli
- Clearance of mediators and acute inflammatory cells
- Replacement of injured cells
- Normal function



- Infarction
- Bacterial infections
- Toxins
- Trauma

- Viral infections
- Chronic infections
- Persistent injury
- Autoimmune diseases

CHRONIC INFLAMMATION
- Angiogenesis
- Mononuclear cell infiltrate
- Fibrosis (scar)

FIBROSIS
- Loss of function

Adapted from Kumar V, Abbas AK, Aster JC eds. Robbins Basic Pathology 9th Ed. **2013**

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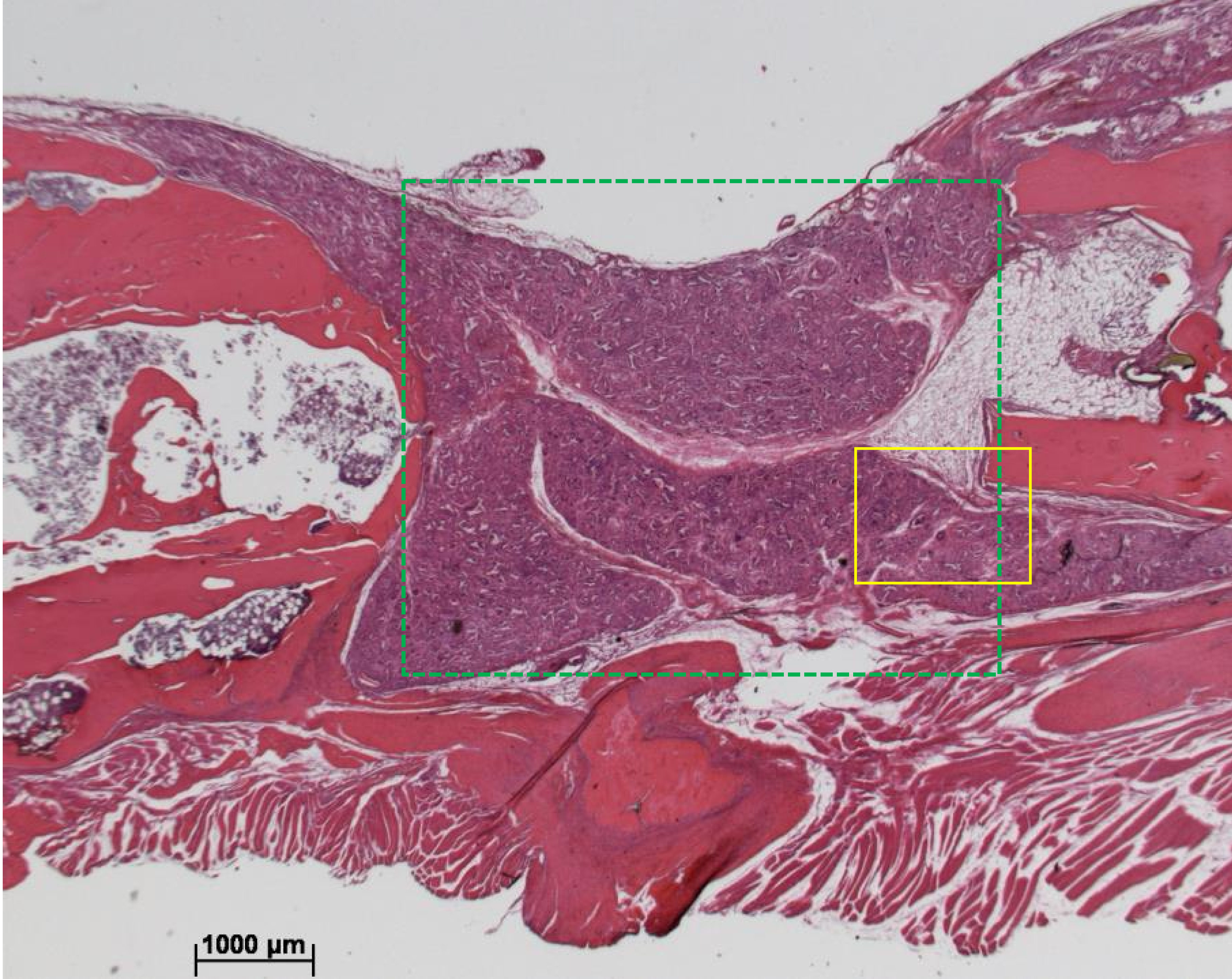
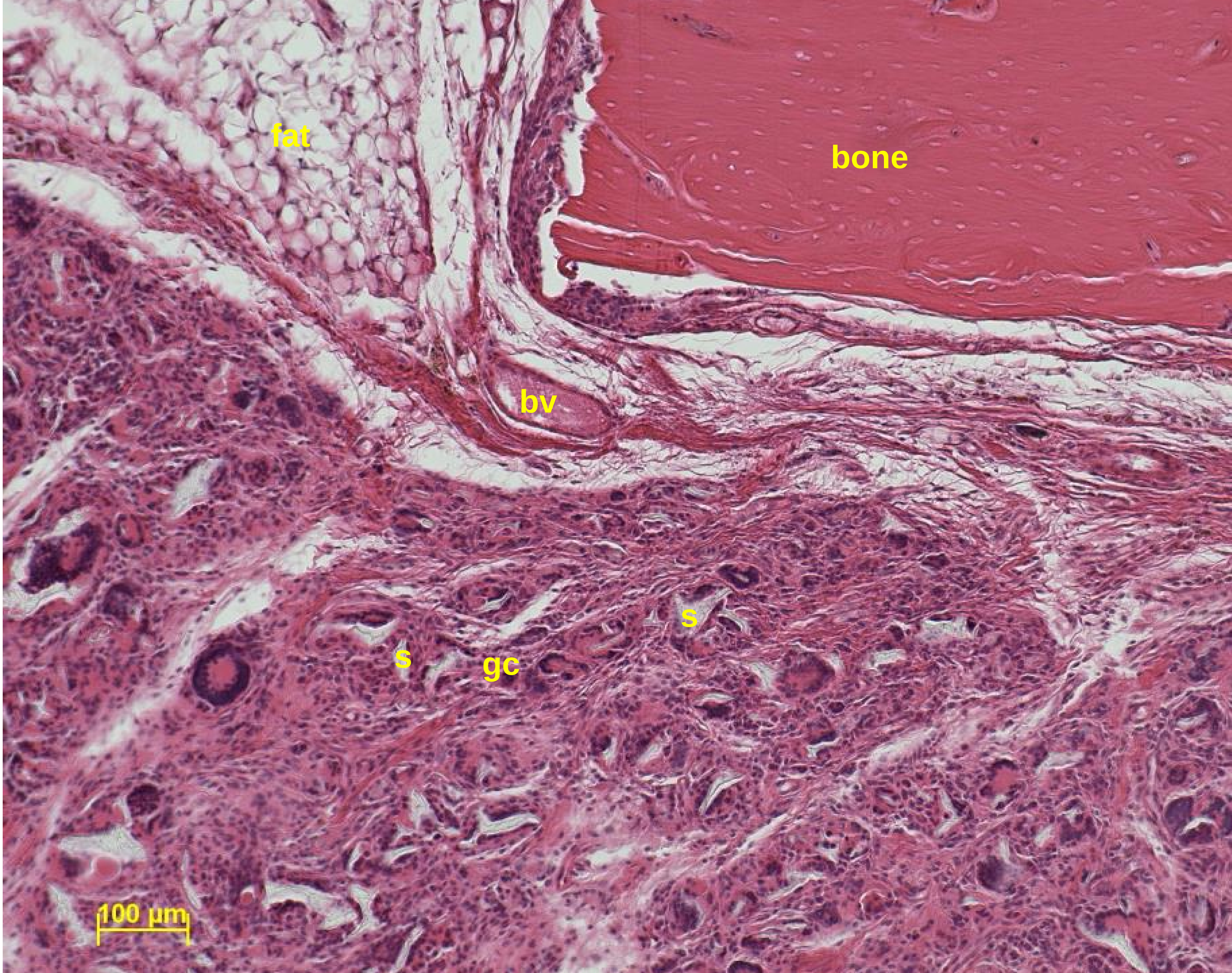
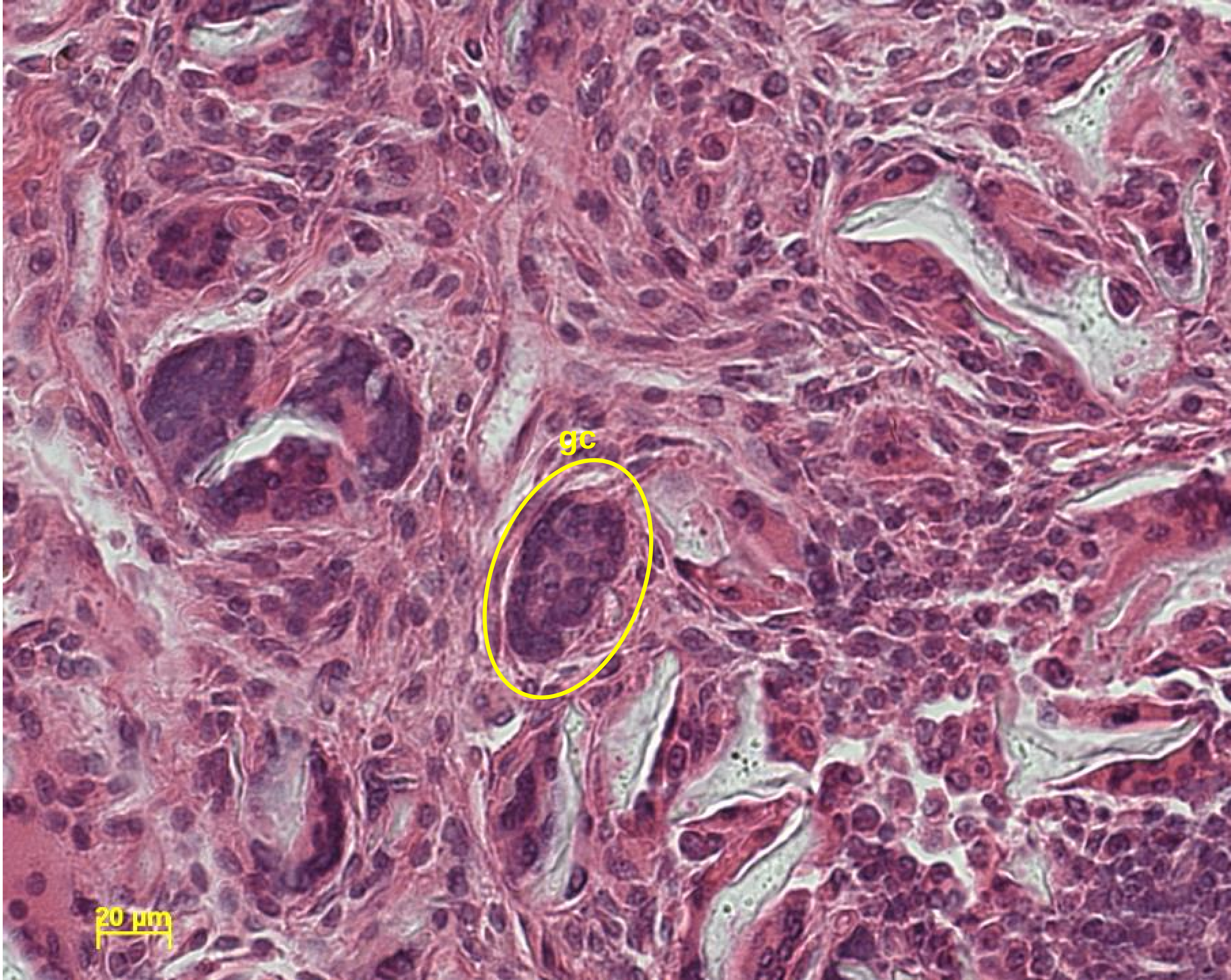
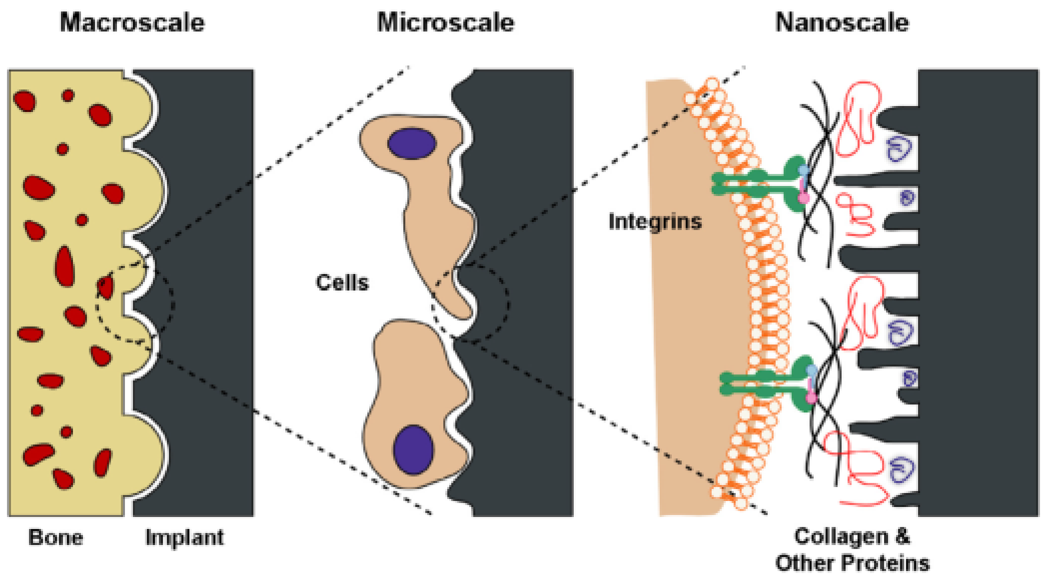

1000 μm


fat
bone
bv
s
s
gc
100 µm


gc
20 µm

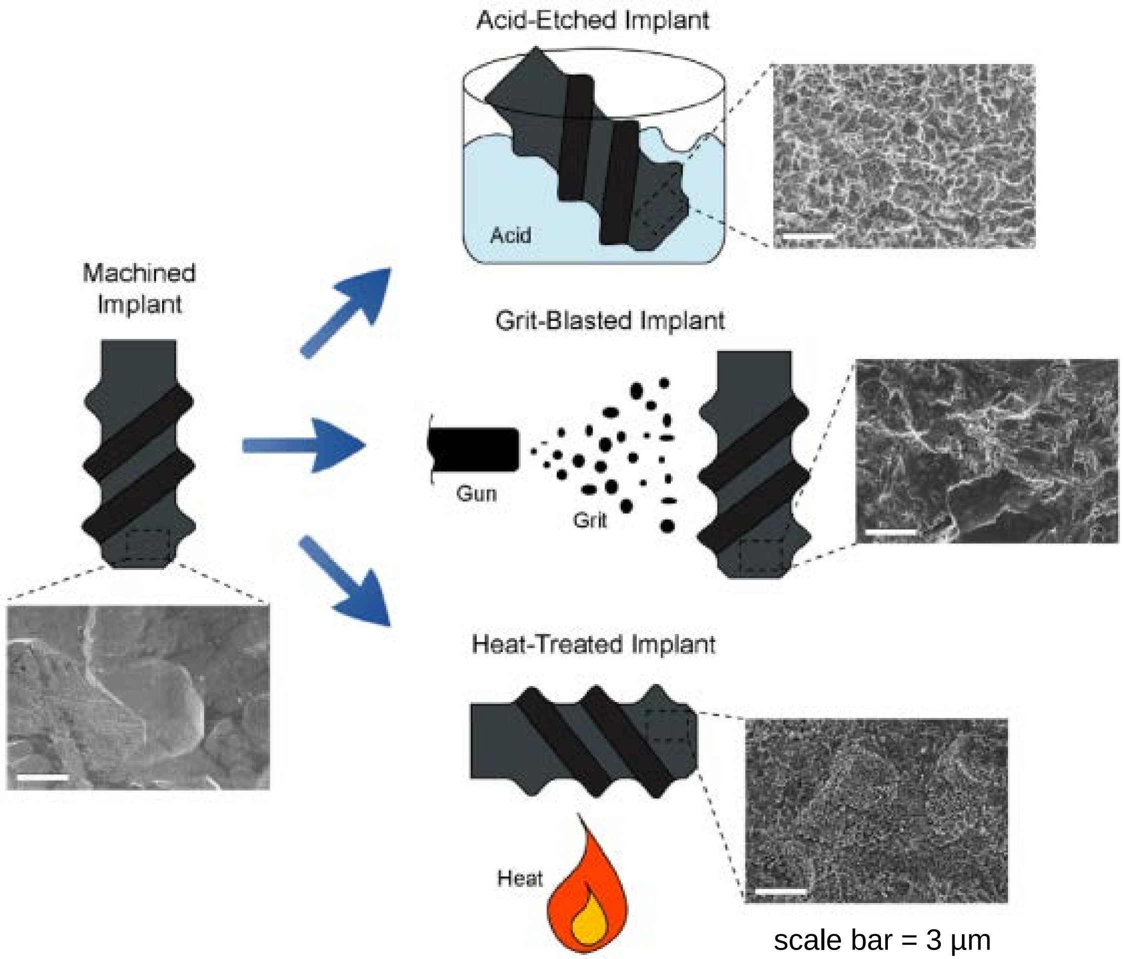
Surface roughness

Surface roughness



Gittens RA. *Acta Biomaterialia* **2014**
Implant osseointegration and the role of microroughness and nanostructures: Lessons for spine implants

Ways to obtain surface roughness



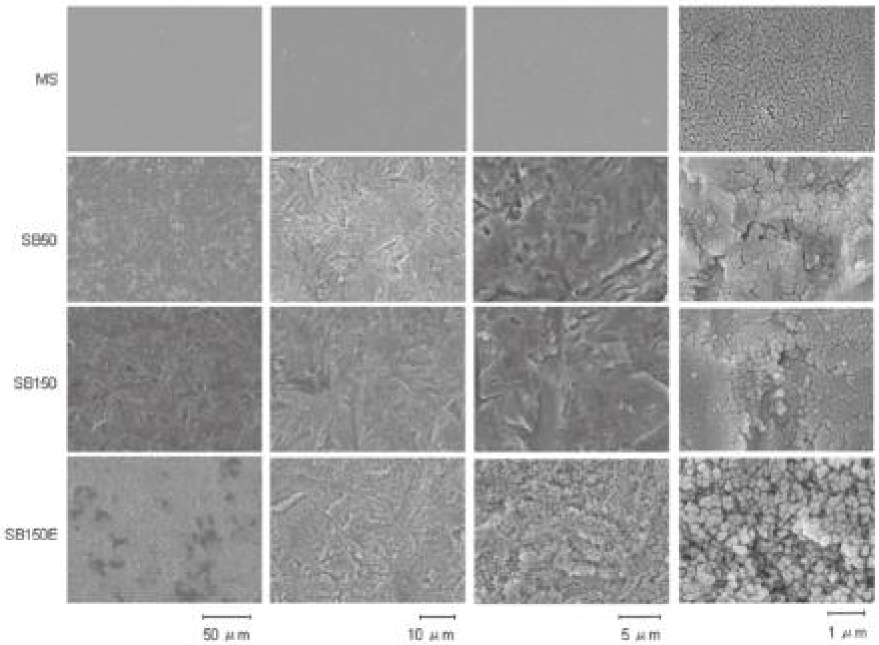
scale bar = 3 µm

Gittens RA. *Acta Biomaterialia* **2014**
Implant osseointegration and the role of microroughness and nanostructures: Lessons for spine implants

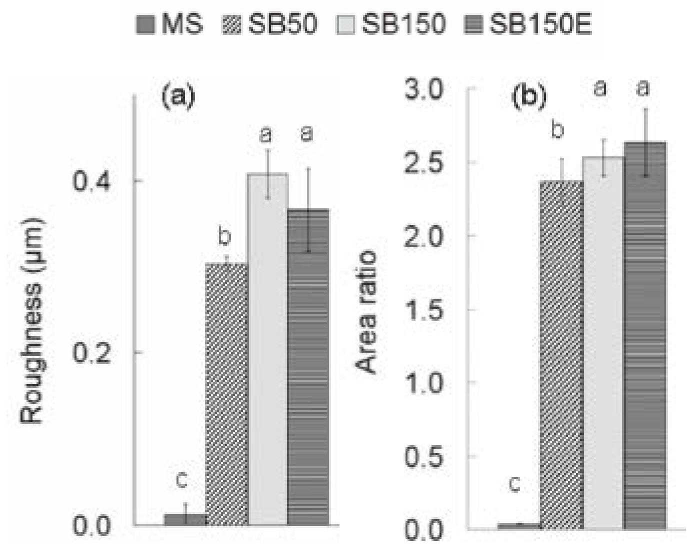
Examples: “bioinert” ceramics

Synergic effect of micro & nanoroughness

SEM



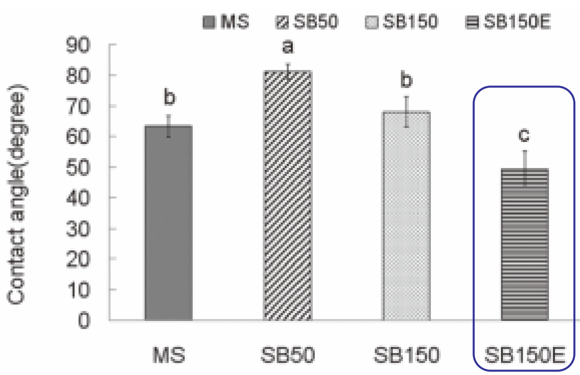
Profilometry



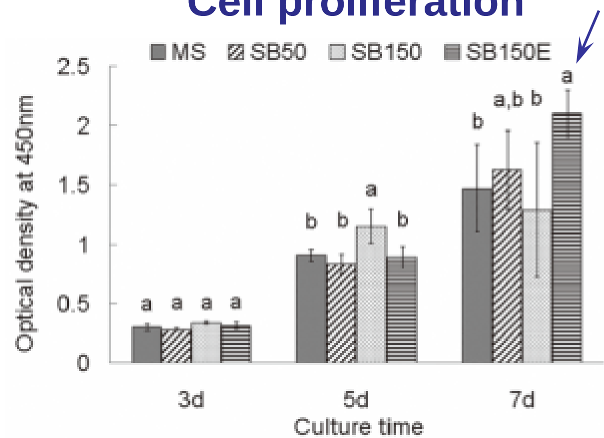
MS: mirror-polished, SB50: sand-blasted 50 µm
SB150: sand-blasted 150 µm, E: etched

MC3T3-E1 (murine cell line)

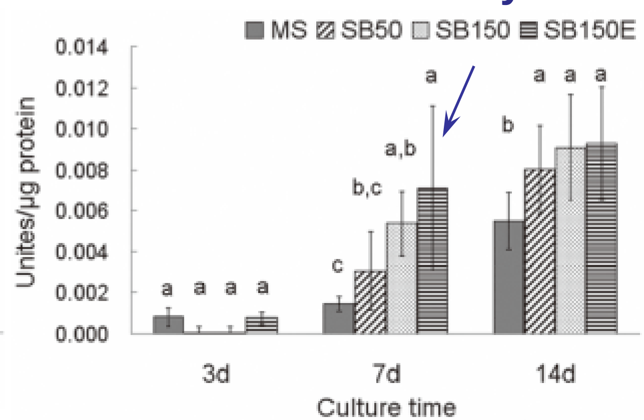
Wettability



Cell proliferation

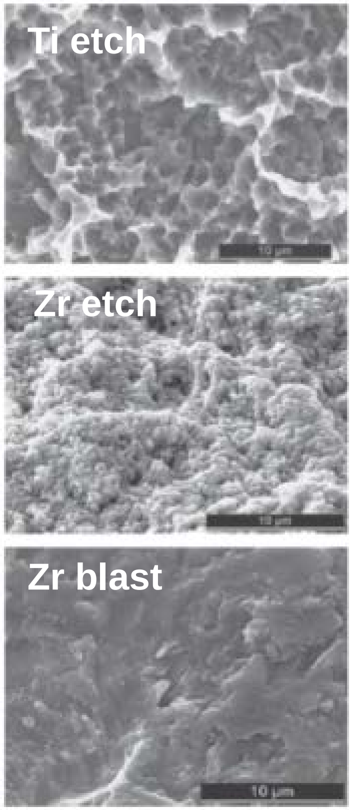


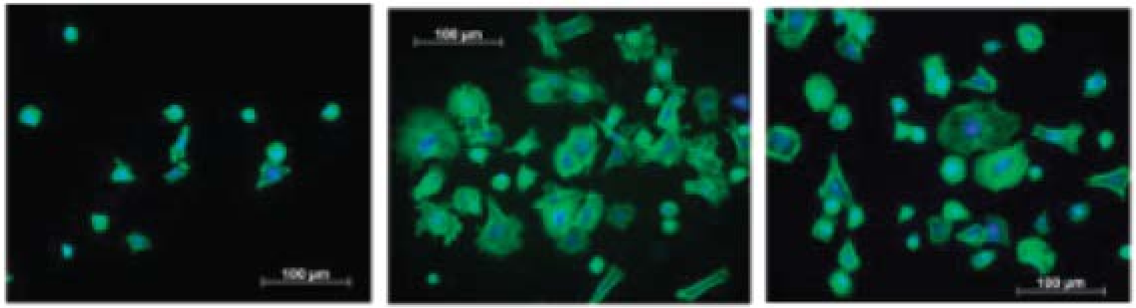
ALP activity



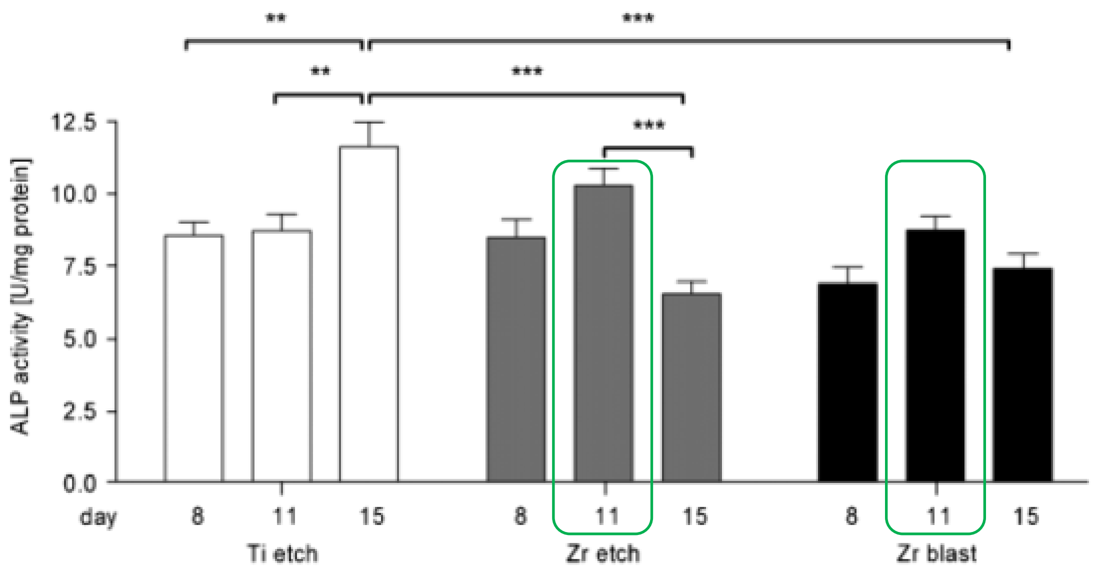
Ito H. *Dent Mater J* **2013**
Response of osteblast-like cells to zirconia with different surface topography

Synergic effect of micro & nanoroughness





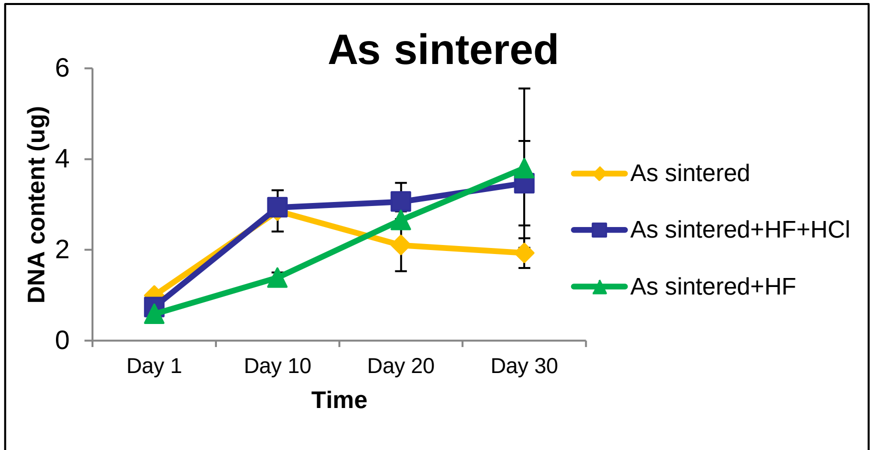
green: actin
blue: nuclei

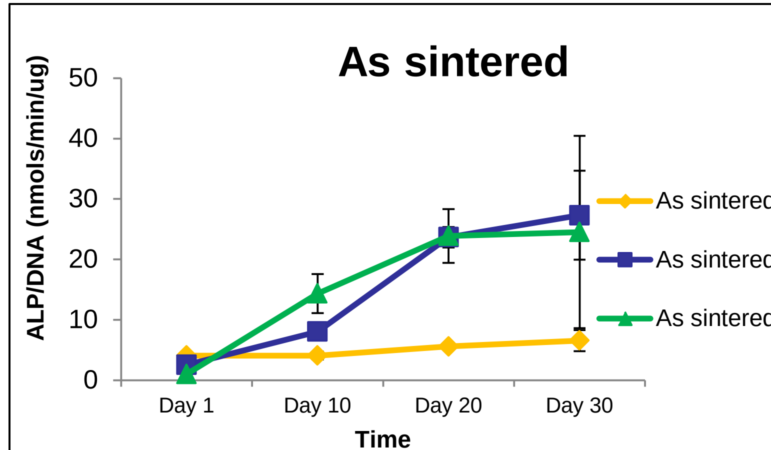


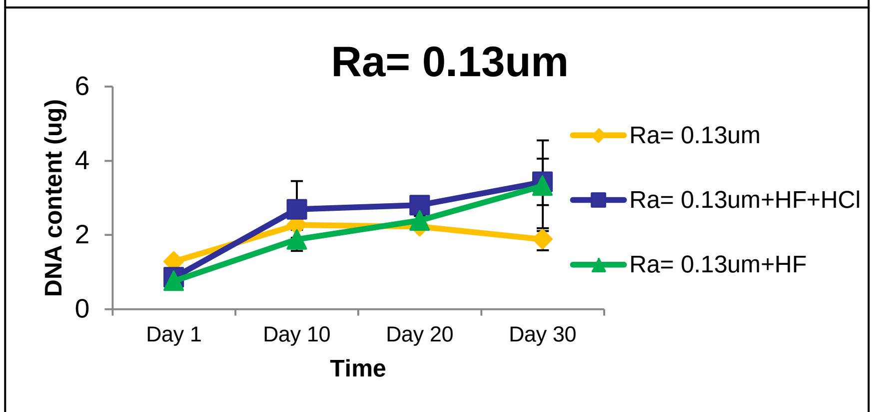
Ti etch: sand-blasted (100-150 µm) + hot acid etched
Zr etch: sand-blasted (100-150 µm) + hot alkaline etched
Zr blast: sand-blasted (100-150 µm)

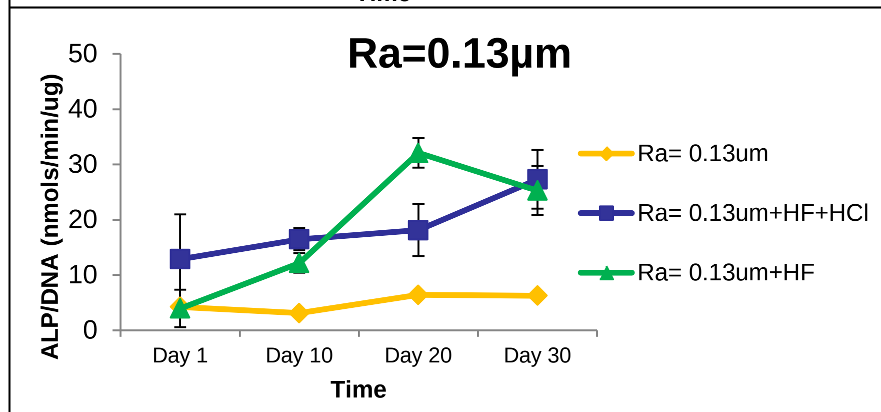
Hempel U. *Clin Oral Implant Res* **2009**
Response of osteblast-like SAOS-2 cells to zirconia ceramics with different surface topographies

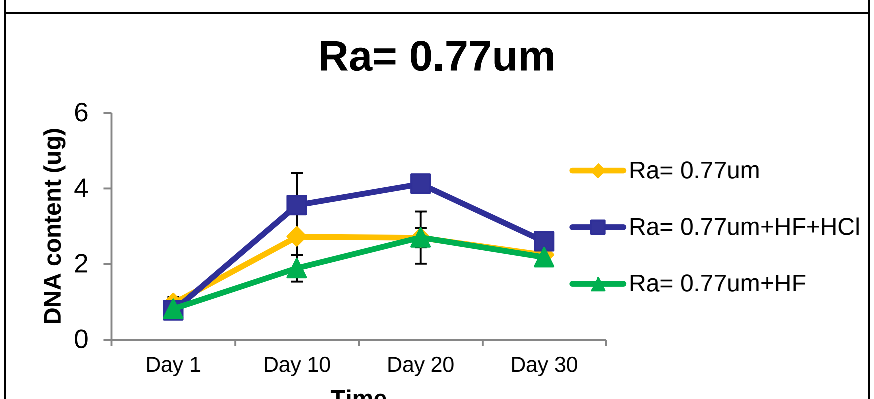
Synergic effect of micro & nanoroughness

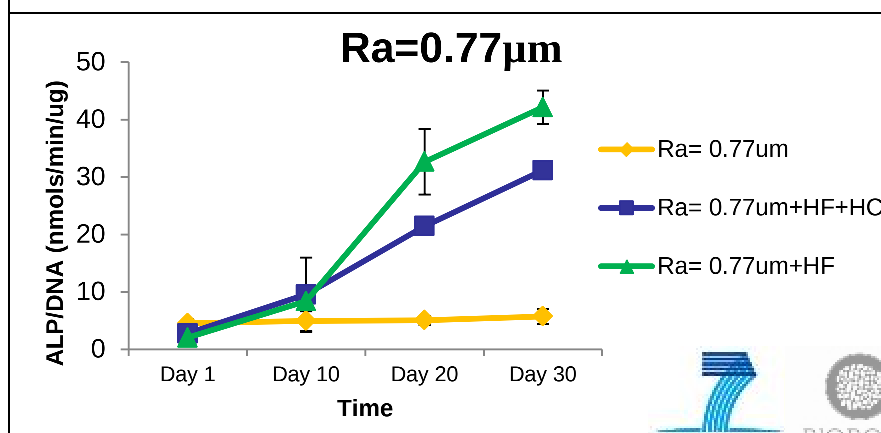






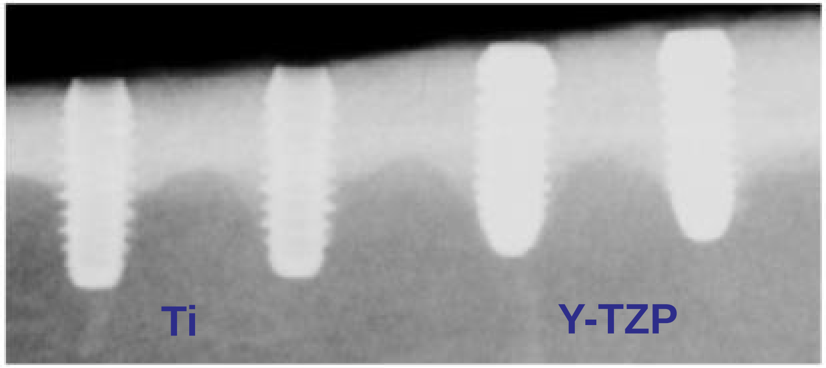




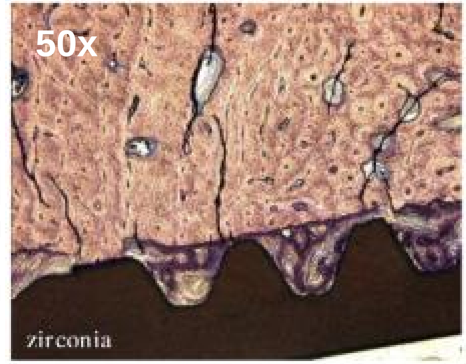


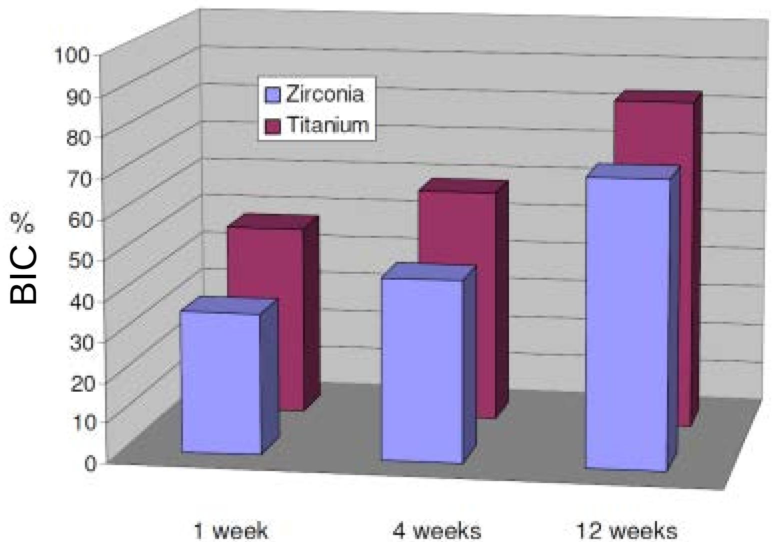
SEVENTH FRAMEWORK PROGRAMME BIOBONE

Zirconia vs. Ti *in vivo*

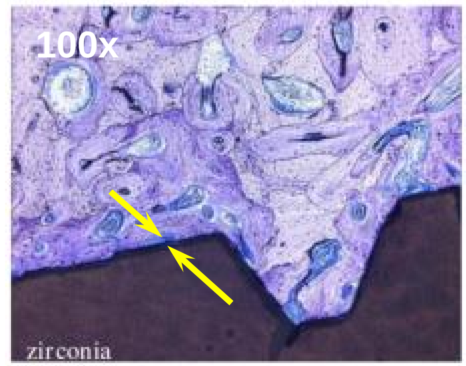


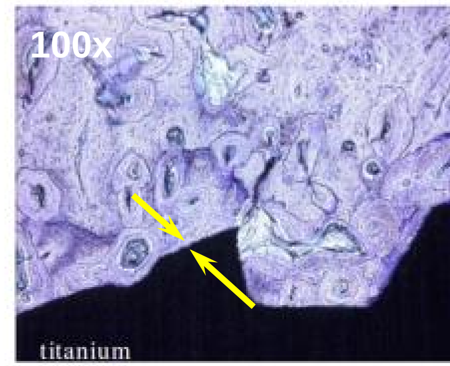
4 weeks



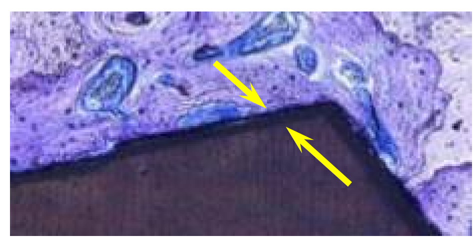


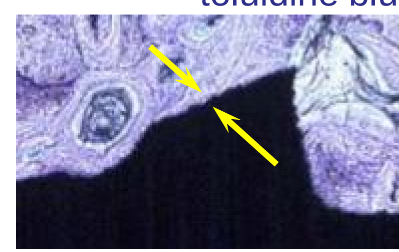
12 weeks





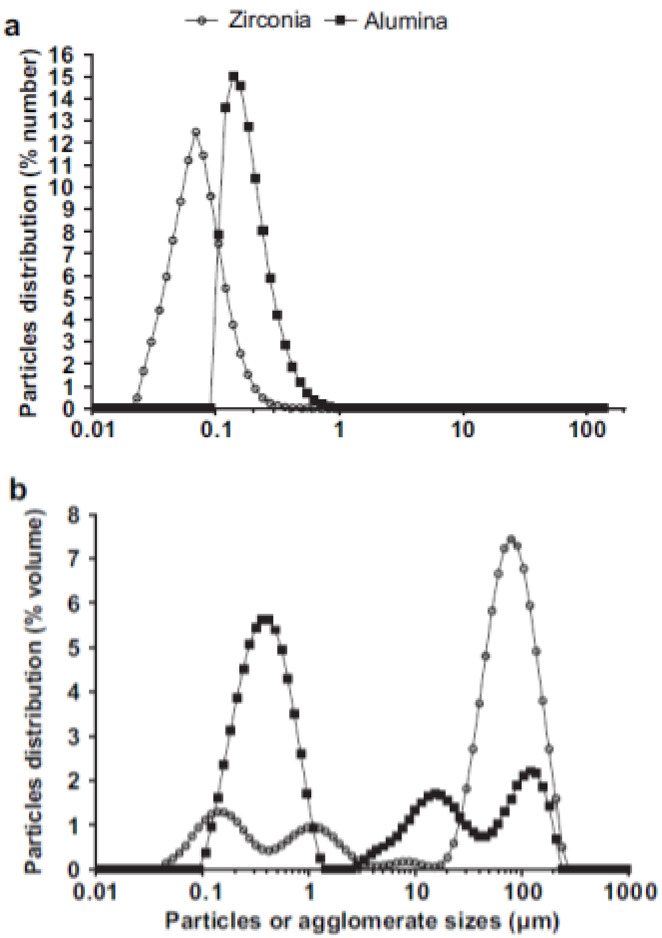
toluidine blue

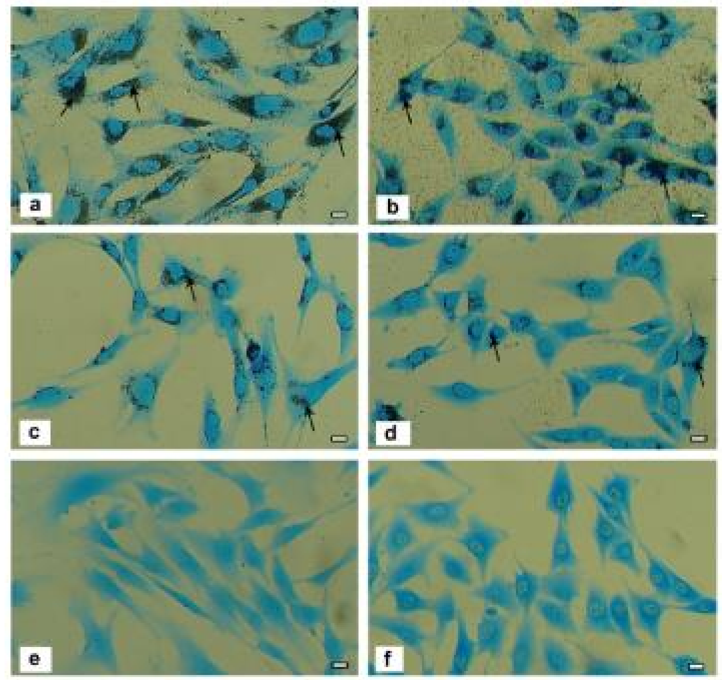


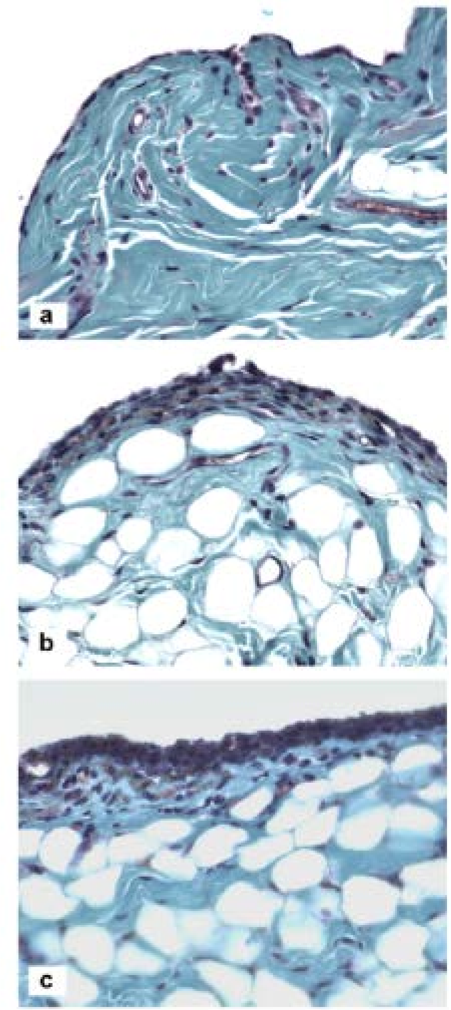


Depprich R. *Head & Face Medicine* **2008**
Osseointegration of zirconia implants compared with titanium: an in vivo study.

Zirconia and alumina particles







Roualdes O. *Biomaterials* **2010**

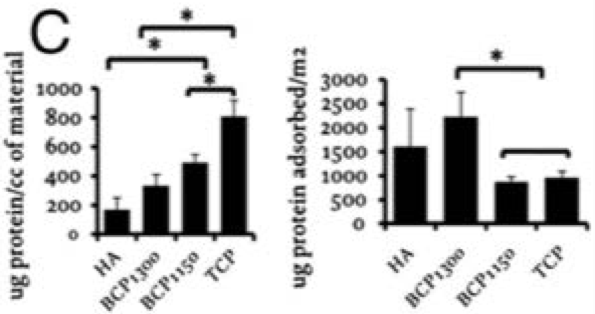
In vitro and *in vivo* evaluation of an alumina-zirconia composite for arthroplasty applications.

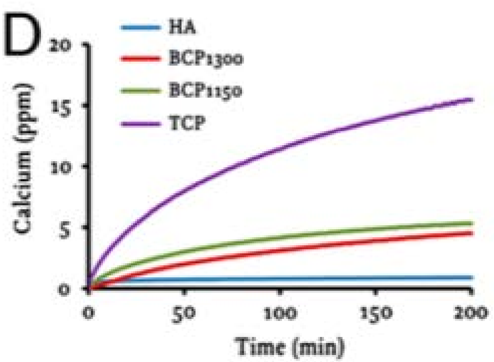
AO Foundation

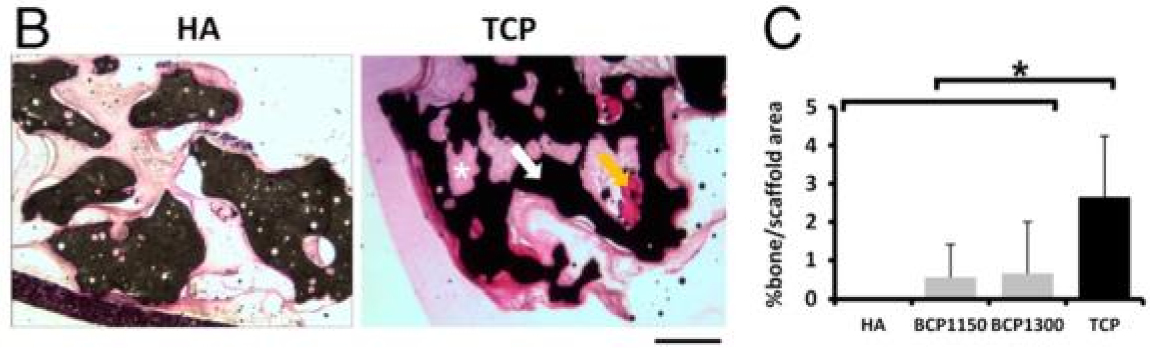
Examples: “bioactive” ceramics

Biphasic calcium phosphates

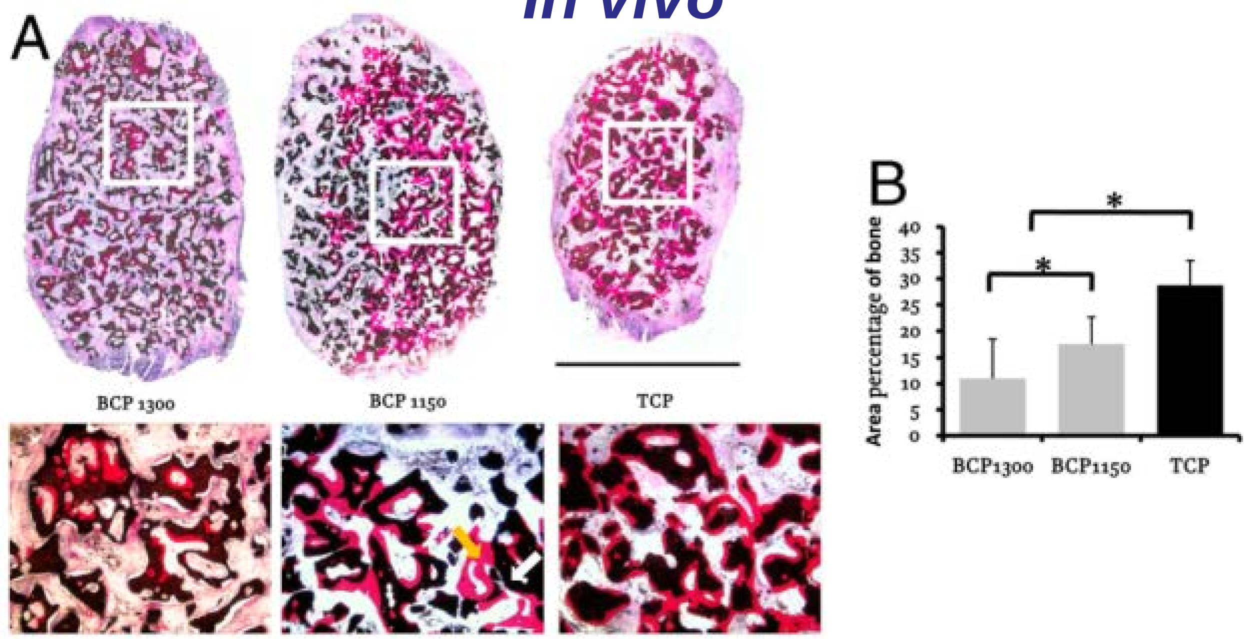
In vitro







In vivo

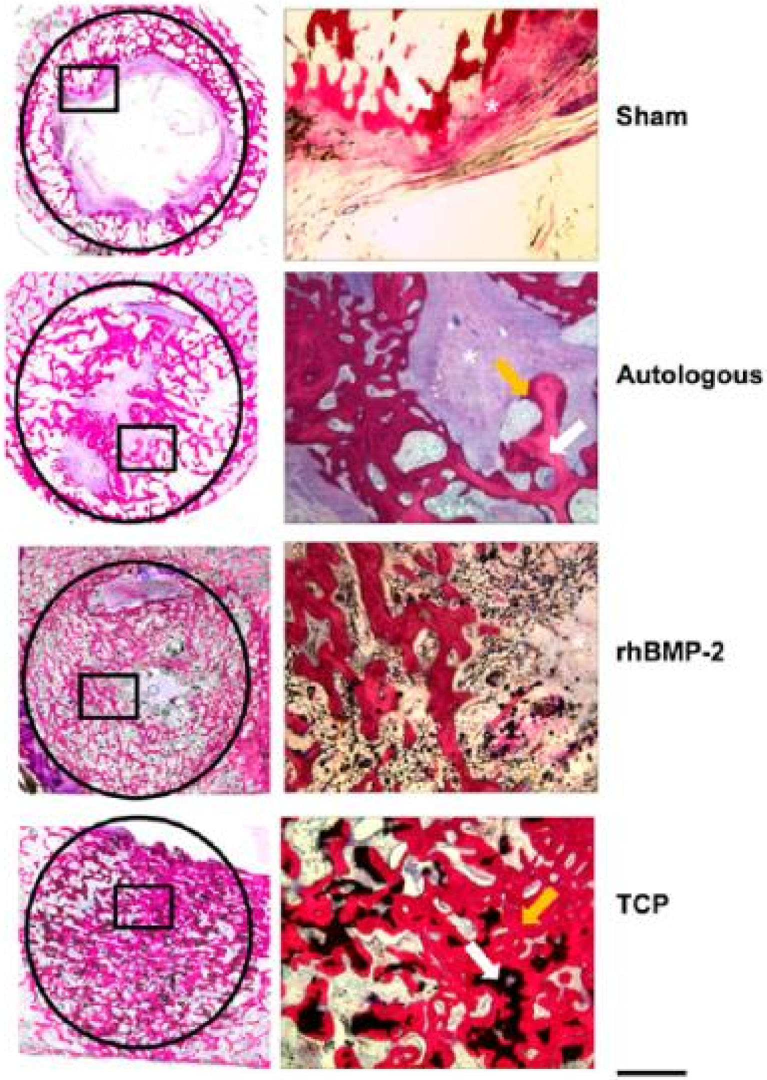


Yuan H. *PNAS* **2010**

Osteoinductive ceramics as a synthetic alternative to autologous bone grafting.

AO Foundation

Biphasic calcium phosphates



Yuan H. *PNAS* **2010**
Osteoinductive ceramics as a synthetic alternative to autologous bone grafting.

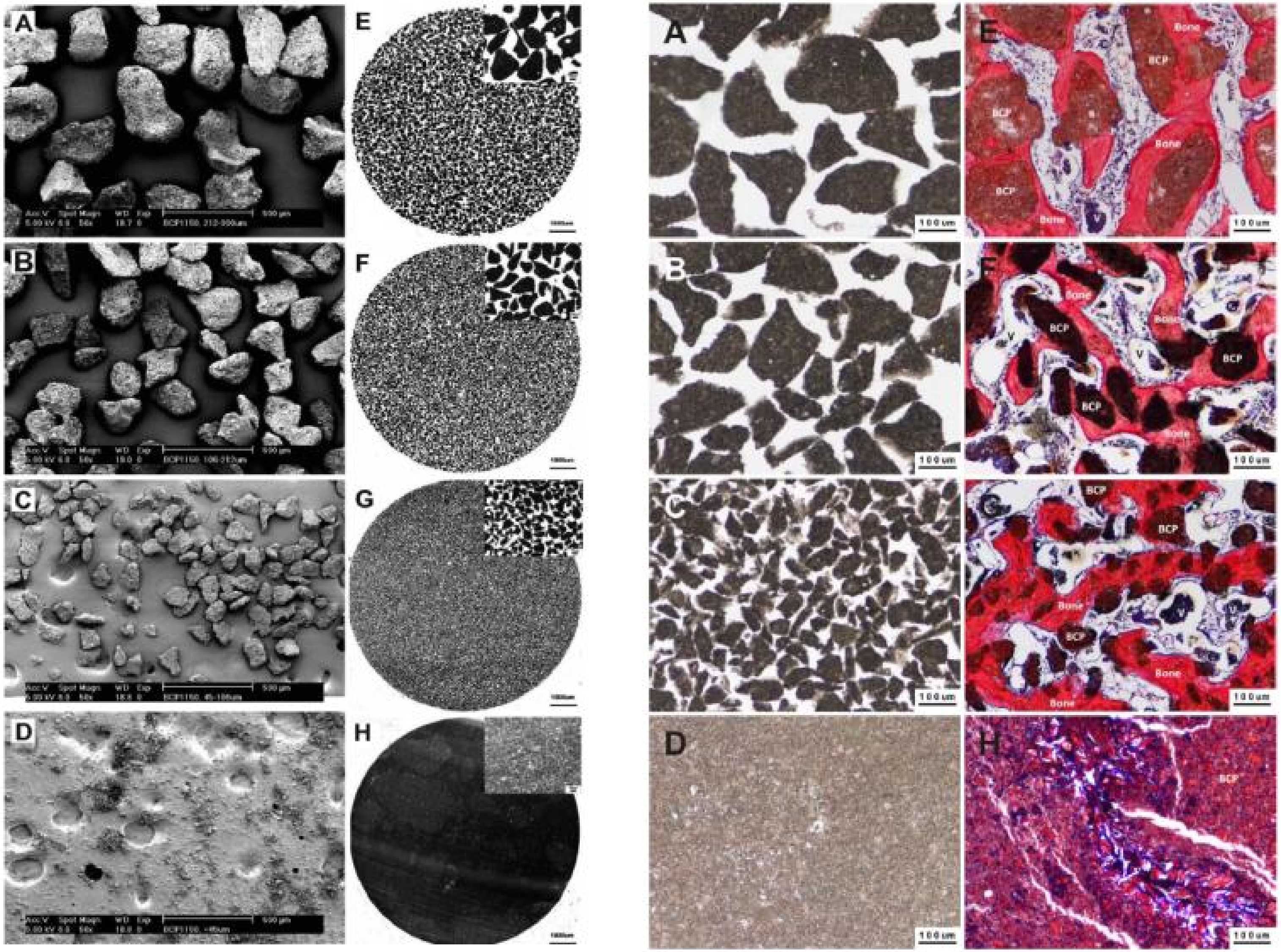
Biphasic calcium phosphates

212-300 µm

106-212 µm

45-106 µm

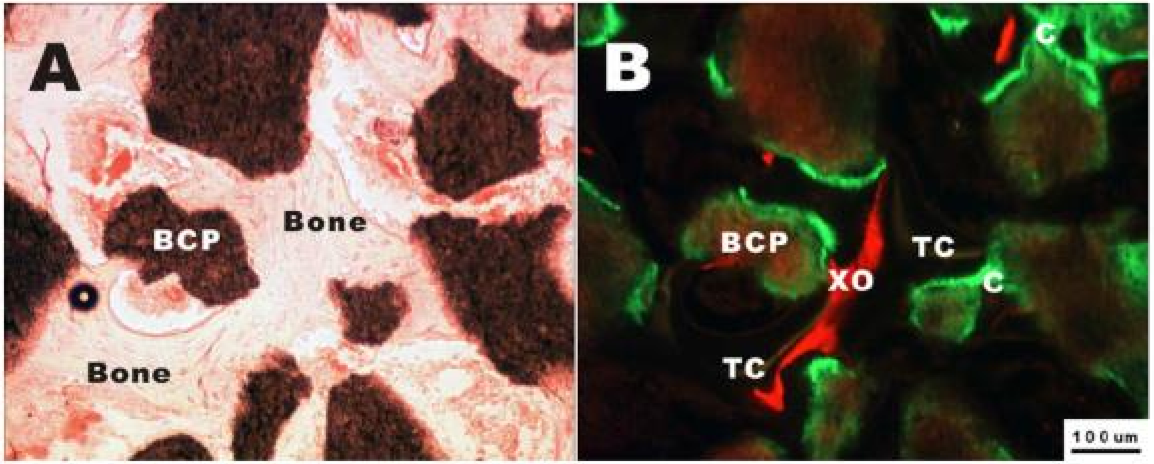
<45 µm

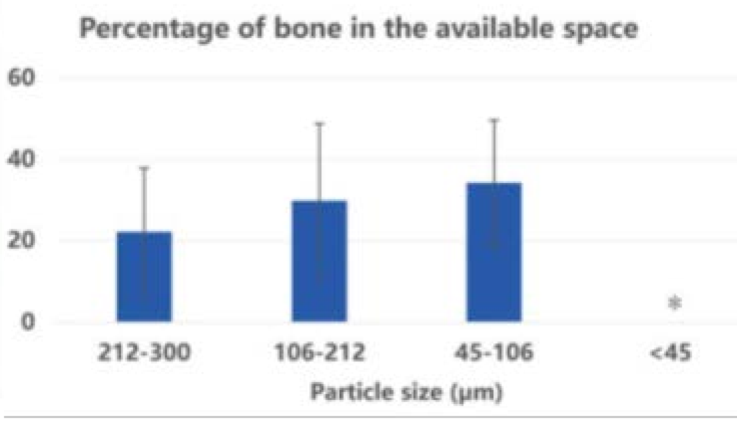


Wang L. *J Biomed Mater Res A* **2015**

Effect of particle size on osteoinductive potential of microstructured biphasic calcium phosphate ceramic.

Biphasic calcium phosphates





- “Cut-off” ~ 50 µm particle size/porosity
- Vascularisation → nutrients and mesenchymal stem cell infiltration
- Micropores are a pre-requisite for inductive bone formation → accumulation of growth factors
- Particle-size mediated inflammation (initial stimulation and further protease/anti-protease balance)
- Compared to previous studies (blocks instead of particles): earlier mineralisation (~half time)
- Resorption: TCP prepared from calcium-deficient apatite did not resorb after 2.5 years of implantation

Wang L. *J Biomed Mater Res A* **2015**
Effect of particle size on osteoinductive potential of microstructured biphasic calcium phosphate ceramic.

Examples: metals

Soft tissue reaction to metal surfaces: polished versus rough

From Hand Problem to Research Based Solution …

- 1 in 6 fractures are distal radius fractures
- Tendons in contact with the implant may incur a cellular reaction, tendon adhesions, limited palmar flexion & rupture.
- Tendon damage & rupture more common with Ti & Ti alloy implants, compared to steel of similar design.
(Sinicropi, M.S et al., 2001)
- Why?

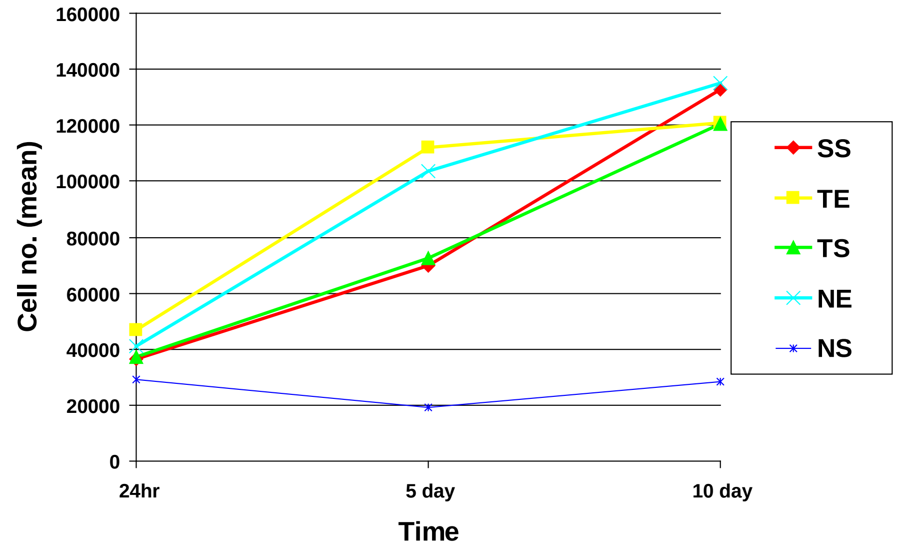
Courtesy D.L. Fernandez

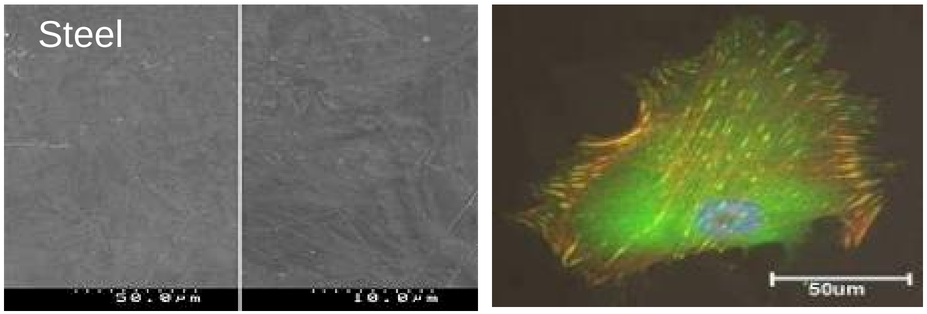
Courtesy D.L. Fernandez

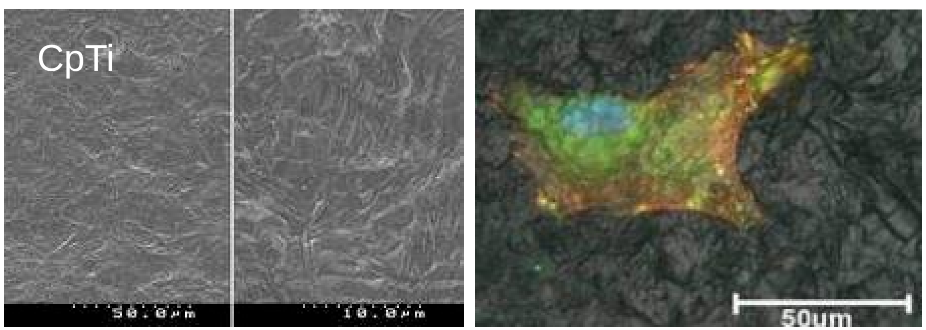
AO Foundation

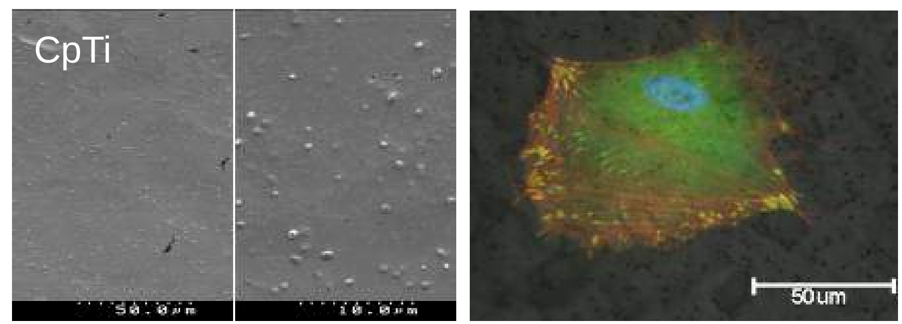
In vitro fibroblast cell behaviour

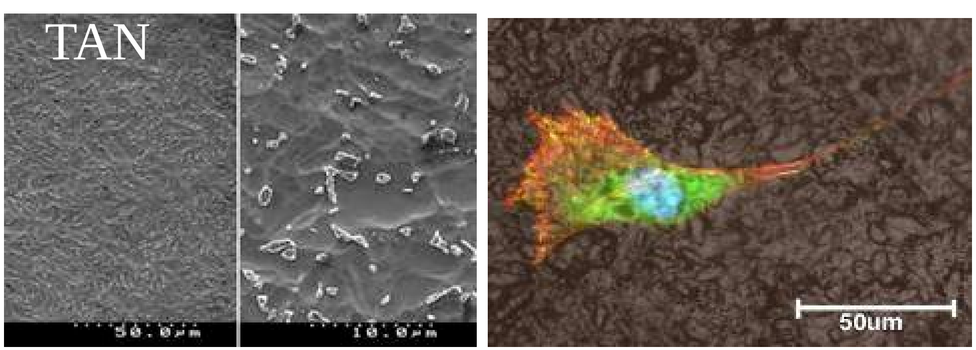
Surface microtopography can control cell growth, spreading & behaviour.

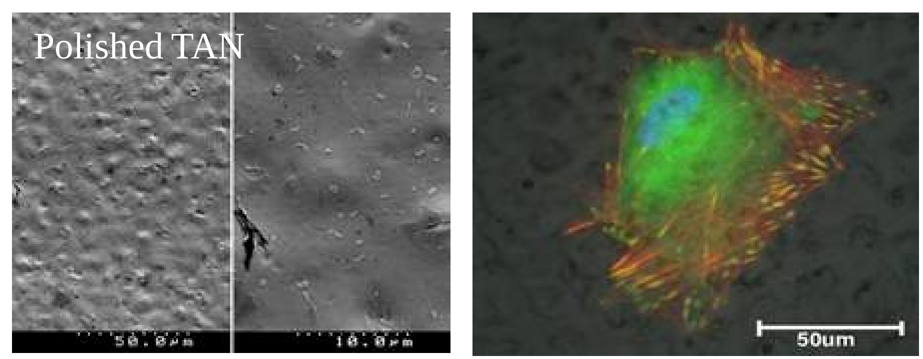




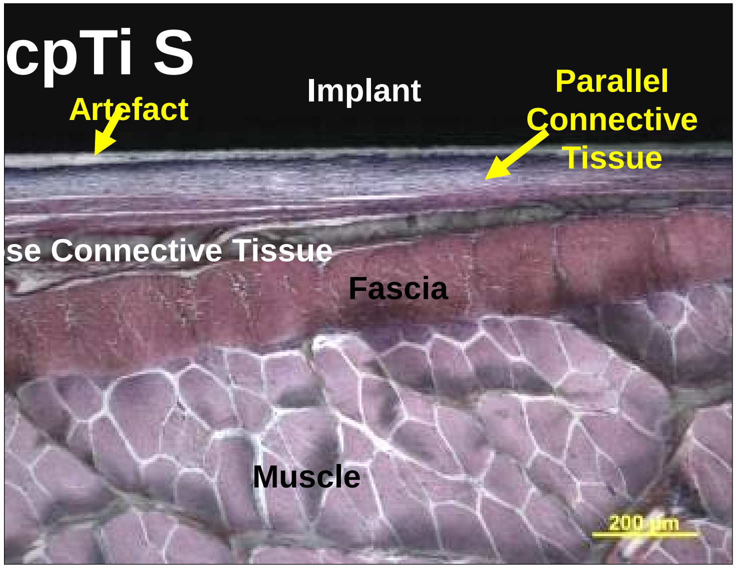


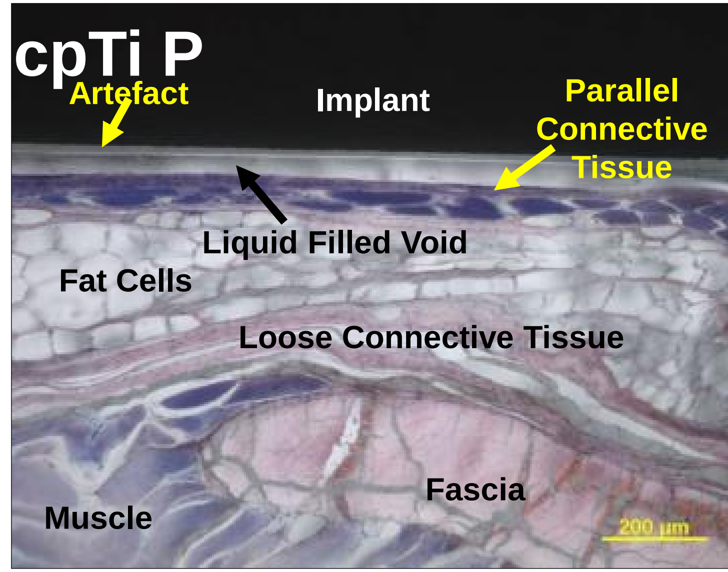




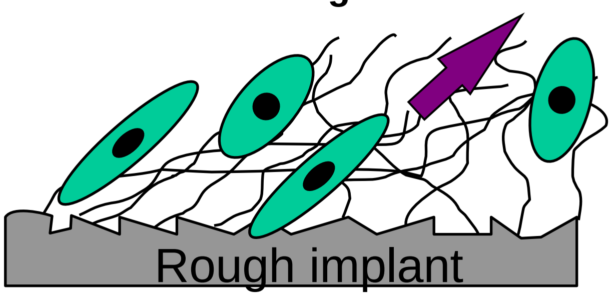


Soft tissue reaction - cpTi surfaces

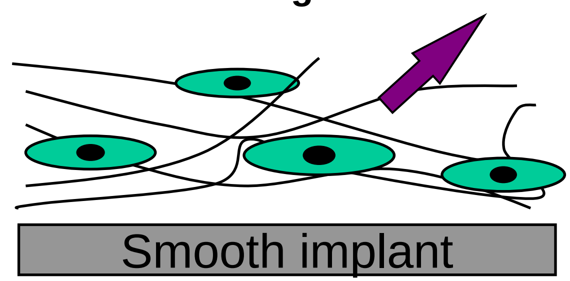




Wound healing contraction force



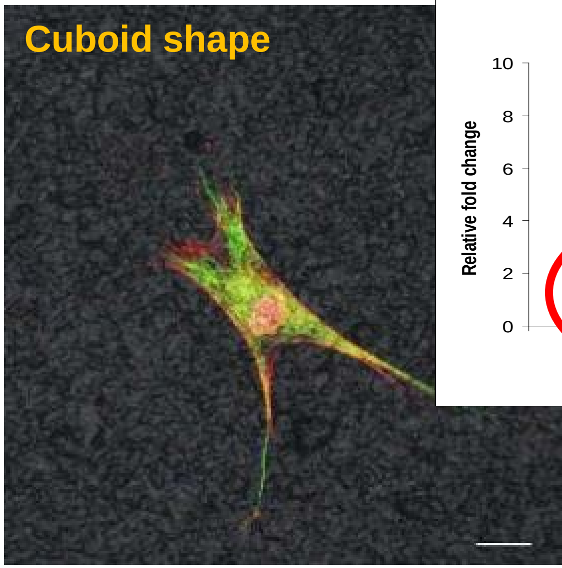
Wound healing contraction force

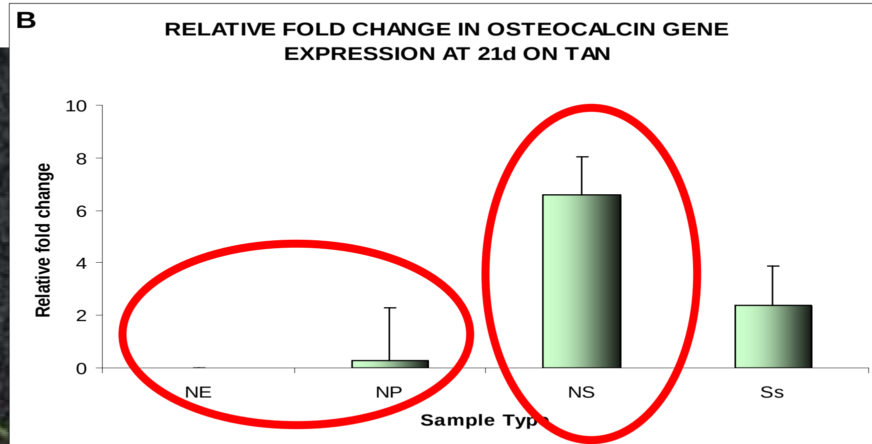


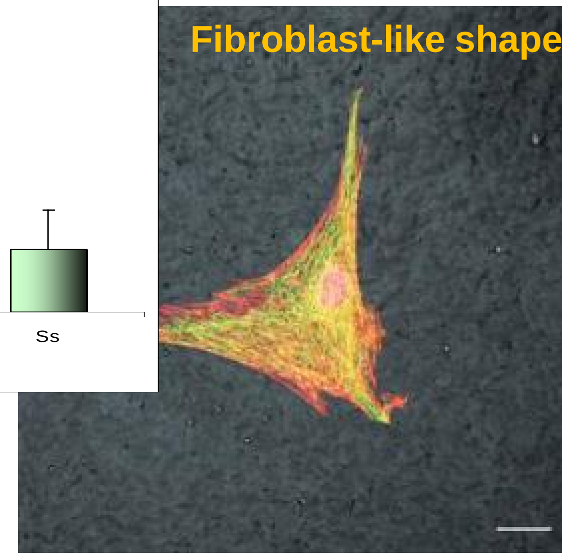
Hayes JS. *J Biomed Mater Res Part B* **2012**
In vivo evaluation of defined polished titanium surfaces to prevent soft tissue adhesion.

Bone tissue reaction to metal surfaces: polished versus rough

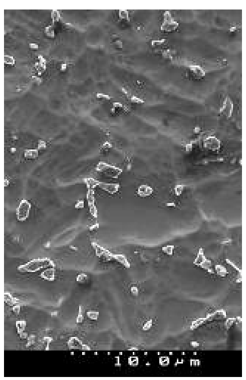
Surface microtopography & osteoblast shape TAN



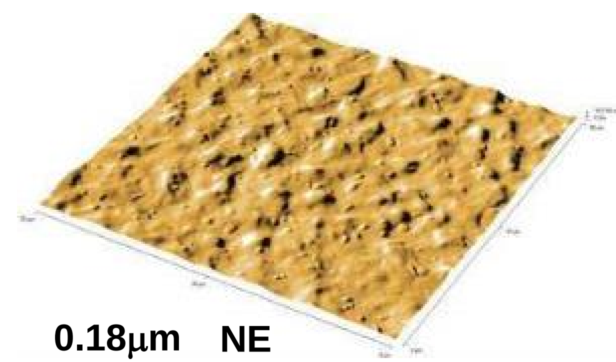




NE-TAN electropolished
NP-TAN polished
NS-TAN standard
Ss-Stainless steel



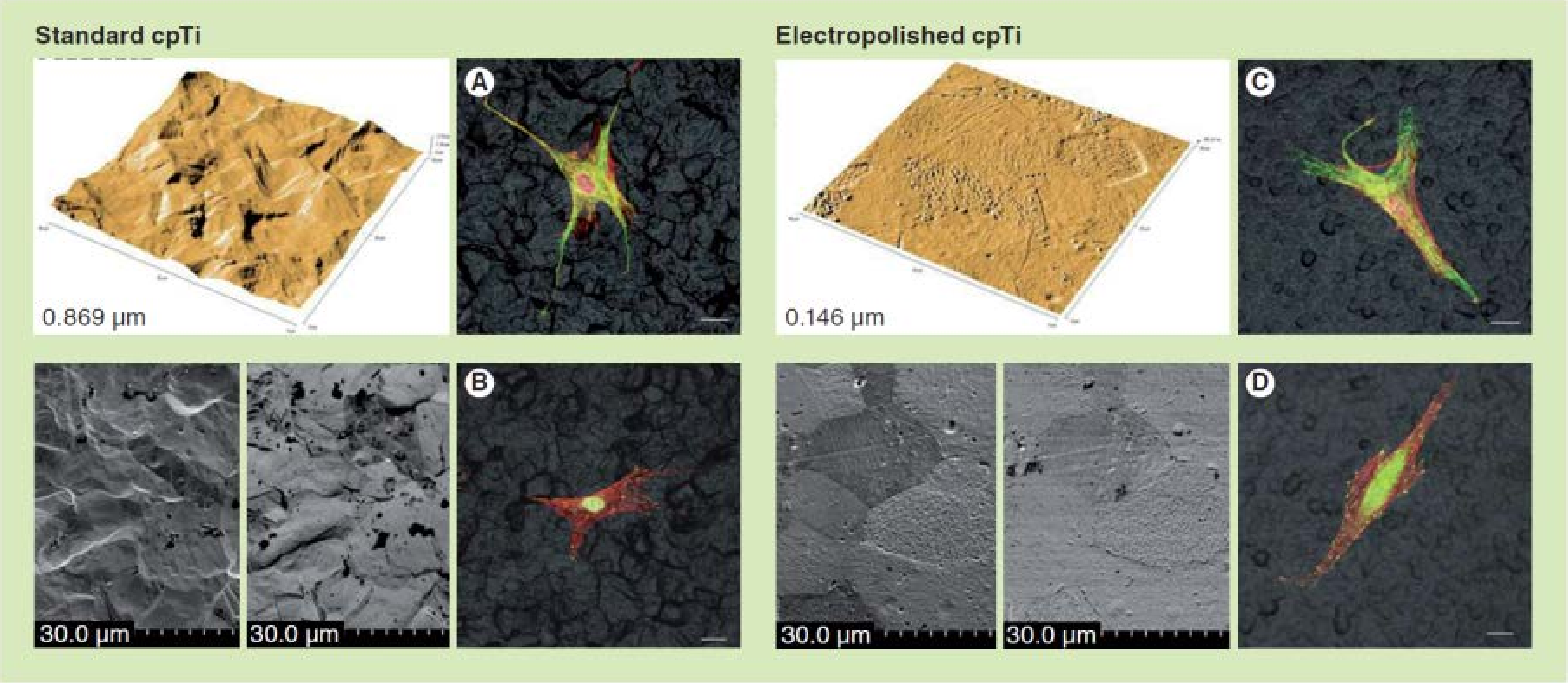
0.758µm NS



0.18µm NE

Hayes JS *Eur Cell Mater* **2010**.
The role of surface microtopography in the modulation of osteoblast differentiation.

Another example: cpTi



Labelling for cytoskeletal components. Red: actin, green: tubulin

Hayes JS *Exp Reviews* **2010**
Surfaces to control tissue adhesion for osteosynthesis with metal implants.

Effect of surface on screw removal

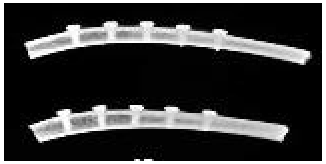
3 biomaterials:

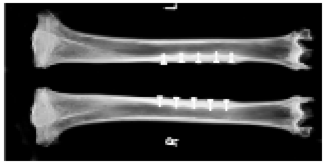
- **Stainless steel (ISO 5832-1),**
- **Commercially pure titanium (cpTi; ISO 5832-2)**
- **Titanium alloy: Titanium-6%Aluminium-7%Niobium (TAN; ISO 5832-11)**

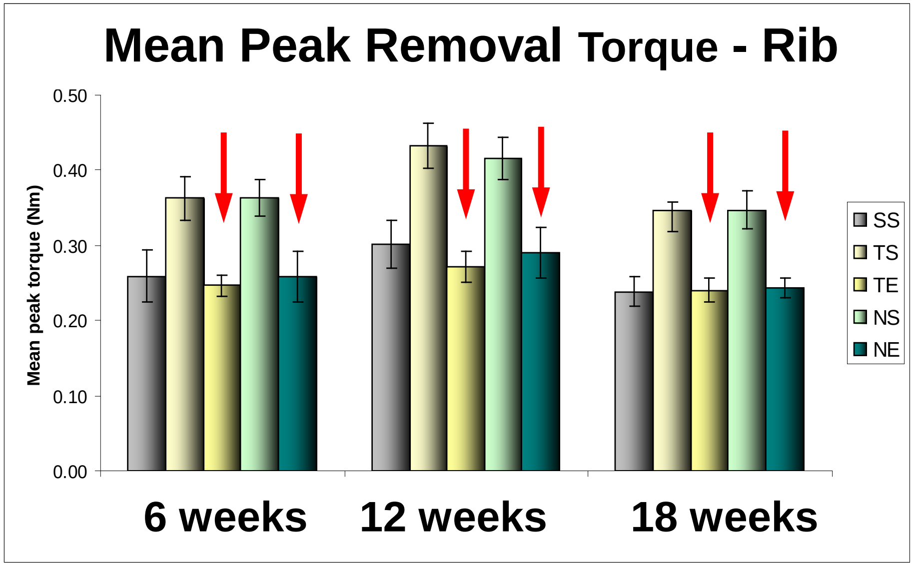
5 surface treatments:

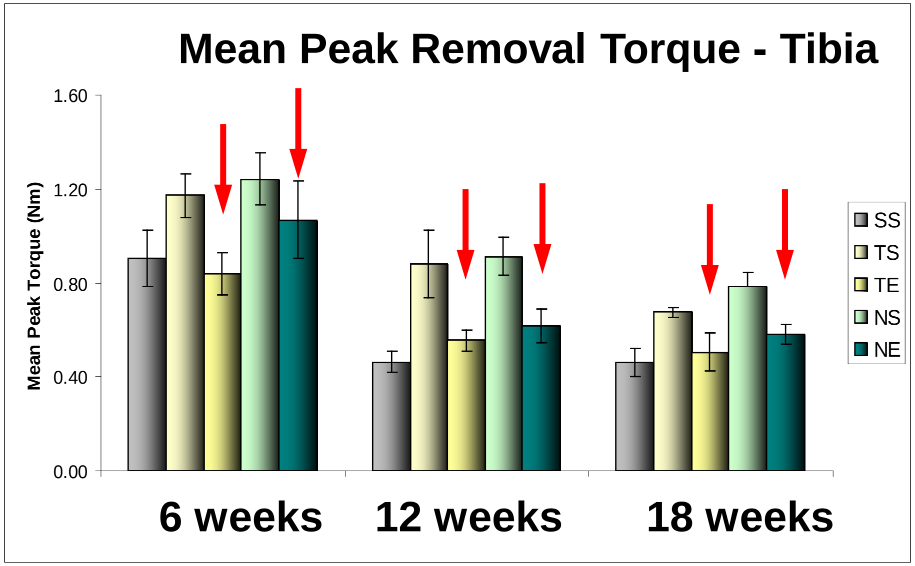
- SS - polished stainless steel
- TS - microrough Ti
- NS - microrough TAN,
- TE - electropolished Ti
- NE - electropolished TAN

Effect of surface on screw removal







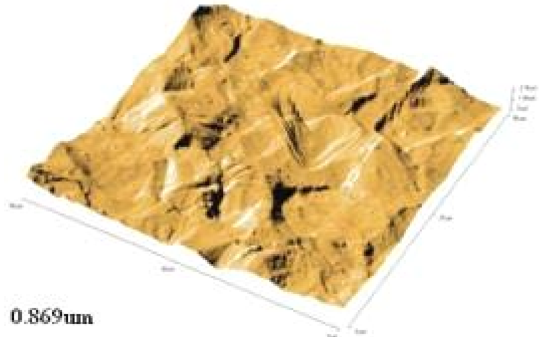


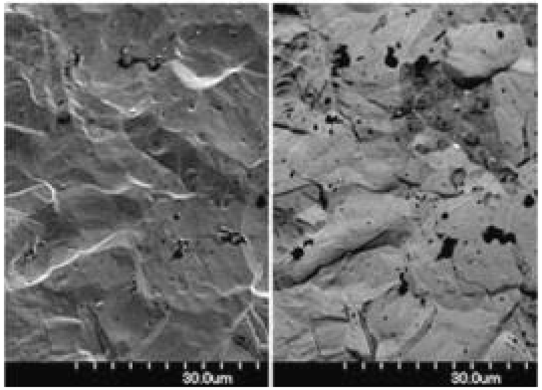
SS-polished stainless steel, TS-microrough Ti, NS-microrough TAN, TE-electropolished Ti, NE-electropolished TAN

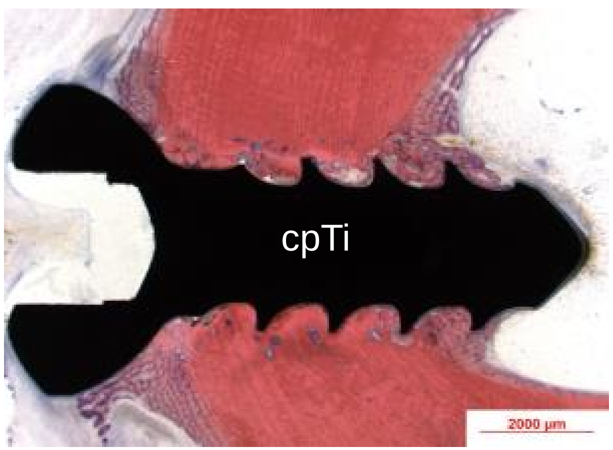
Polishing significantly reduces the torque required for screw removal in both cancellous & cortical bone

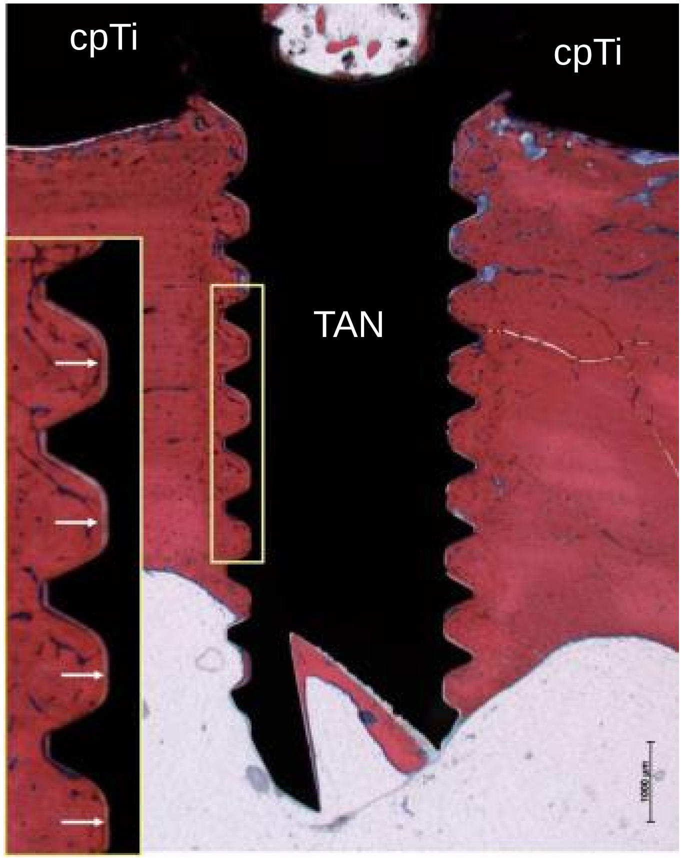
Pearce AI. *J Orthop Res* **2008** AO Foundation

Biological reaction to bone – cpTi / TAN

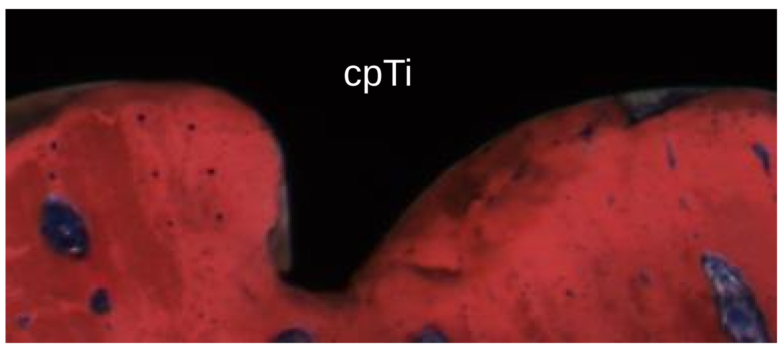








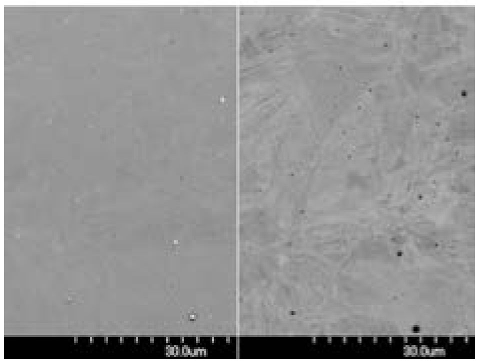
Direct osseointegration

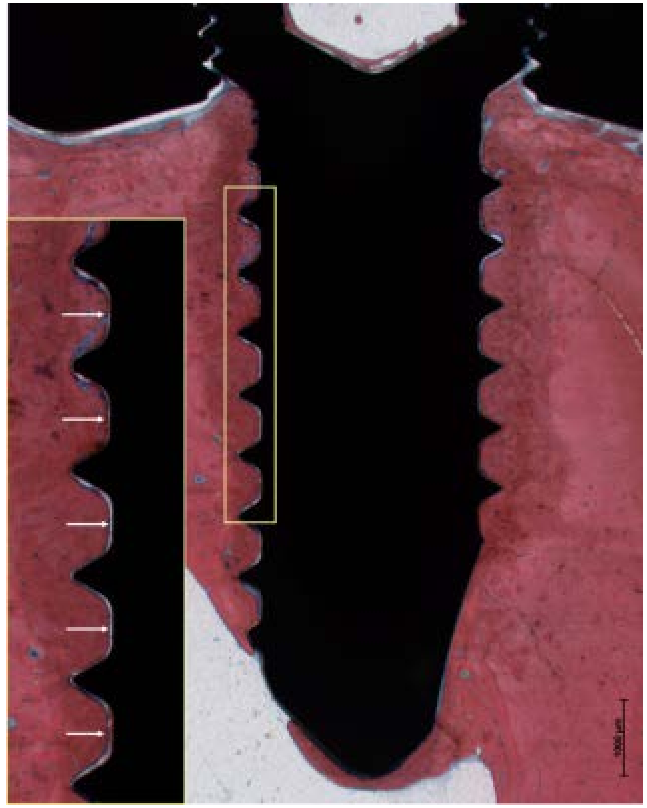


Courtesy of Geoff Richards

AO Foundation

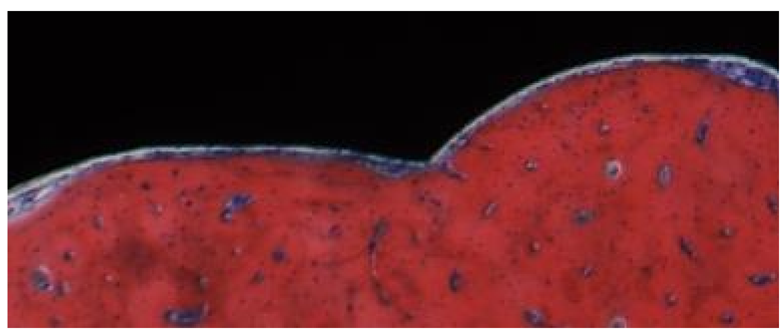
Biological reaction to bone - EPSS





Fibro-osseointegration

No issues with stability!



Courtesy of Geoff Richards

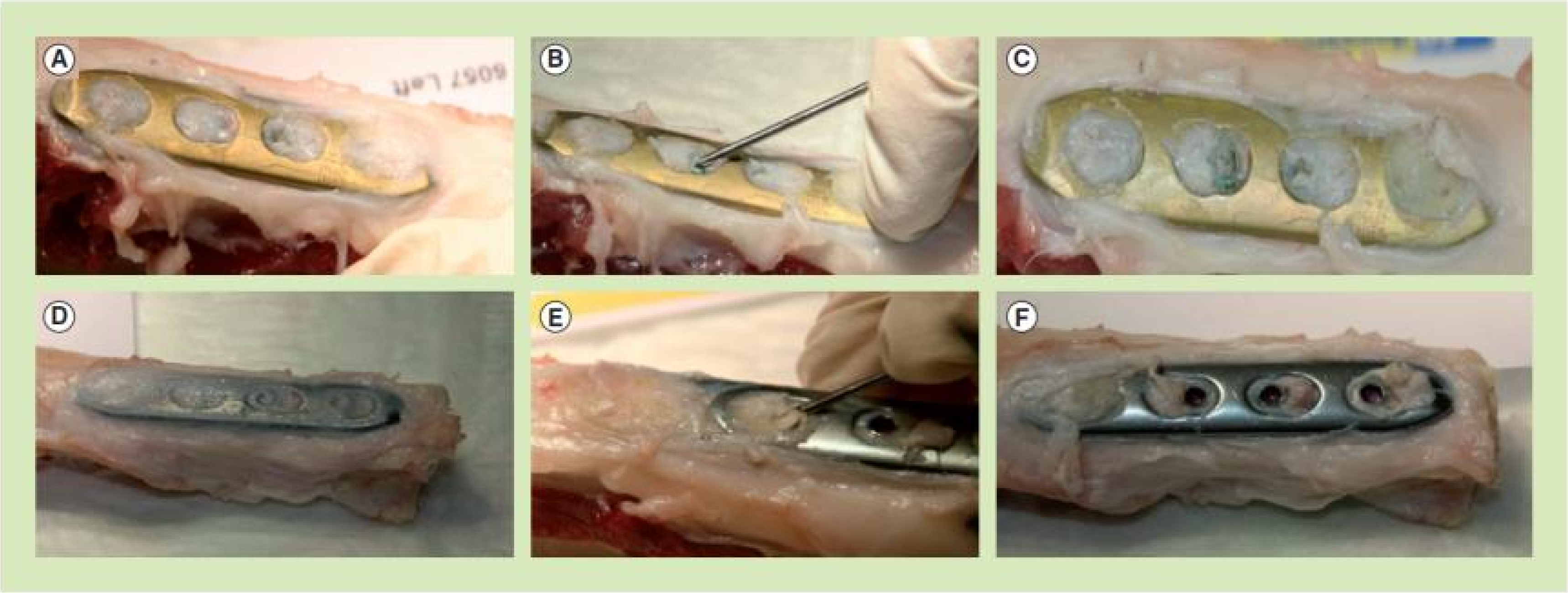
AO Foundation

Smooth versus rough surface

18 months in sheep tibia

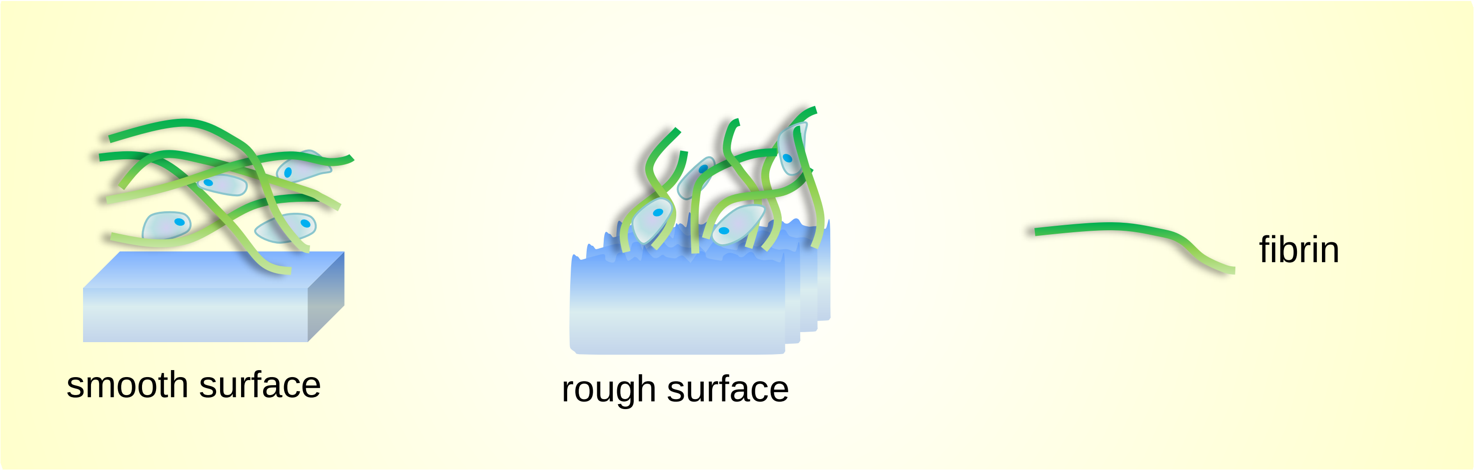
standard

polished



Hayes JS *Exp Reviews* **2010**
Surfaces to control tissue adhesion for osteosynthesis with metal implants.

Smooth versus rough surface

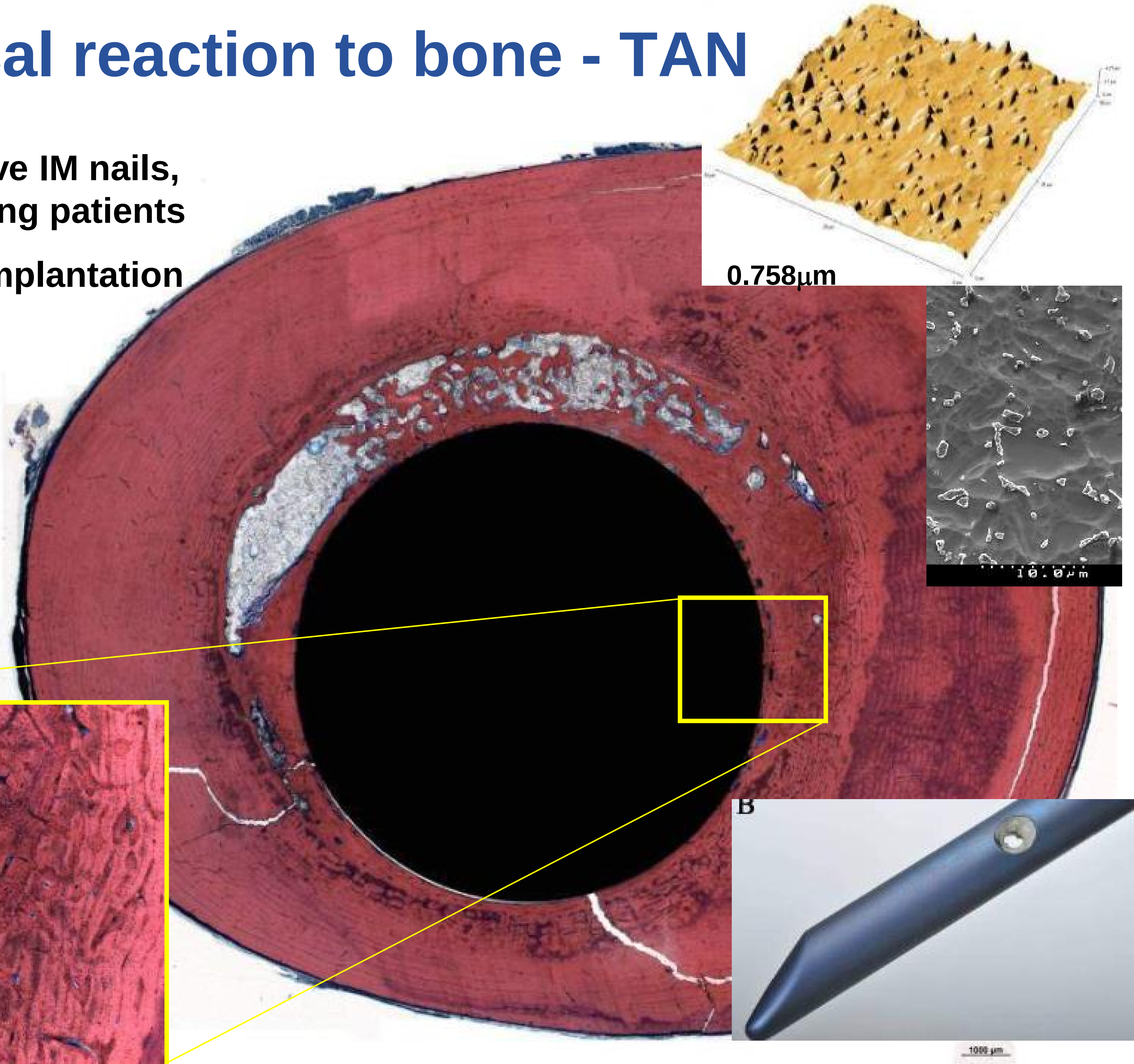


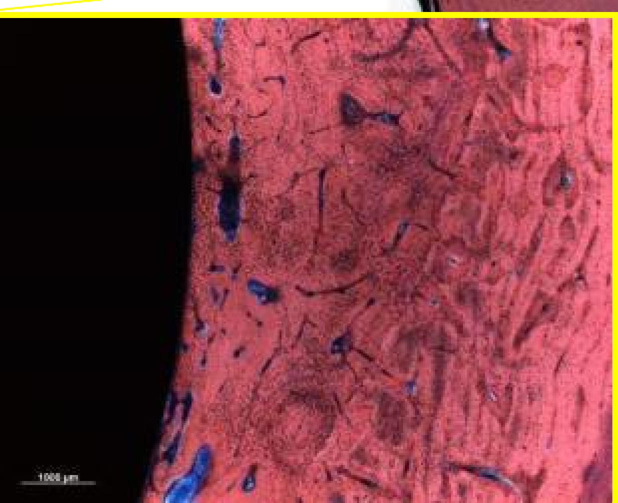
Adapted from Hayes JS *Exp Reviews* **2010**
Surfaces to control tissue adhesion for osteosynthesis with metal implants.

Biological reaction to bone - TAN

Difficult to remove IM nails, especially in young patients

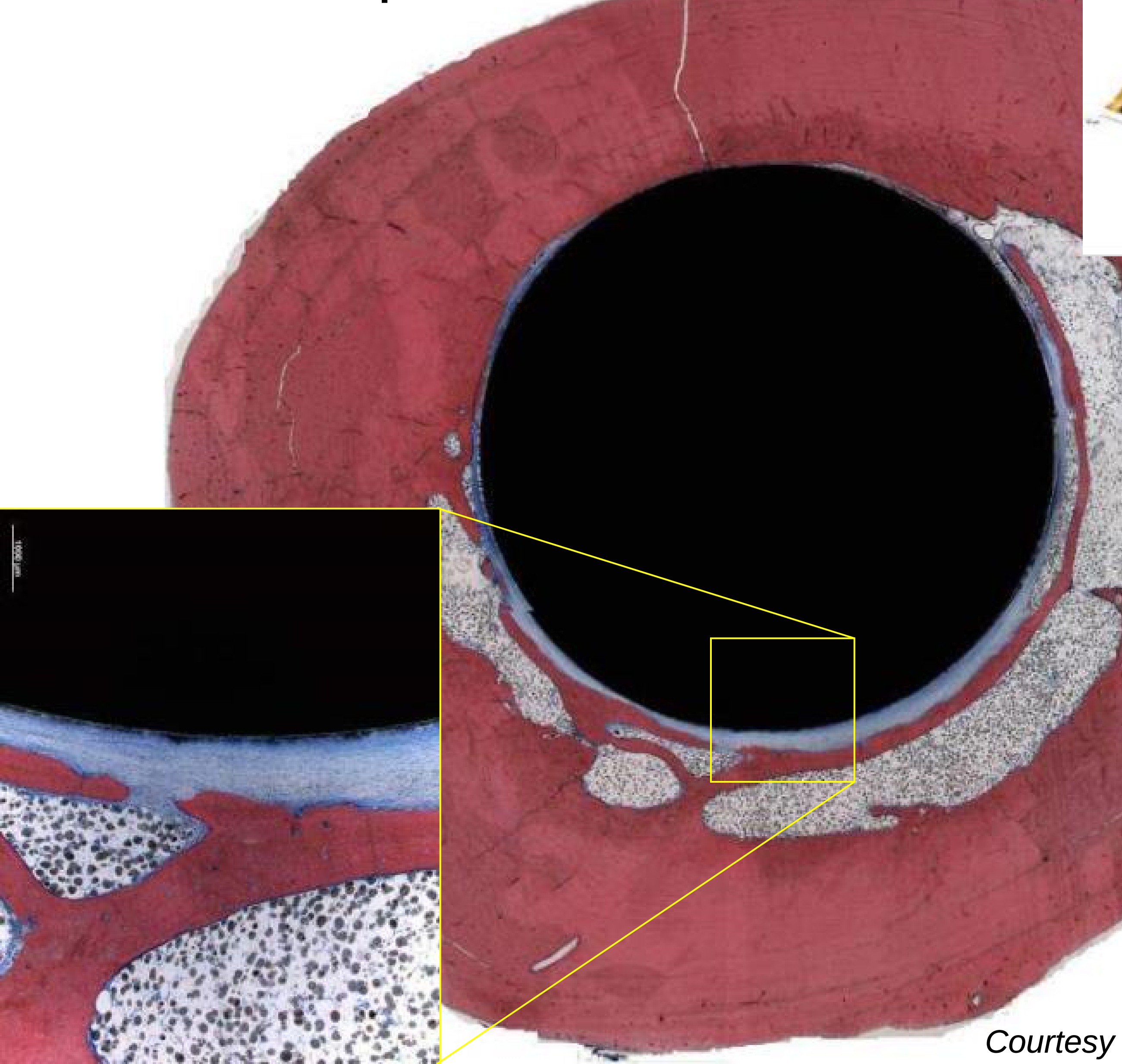
IM Nail - 12 mo implantation

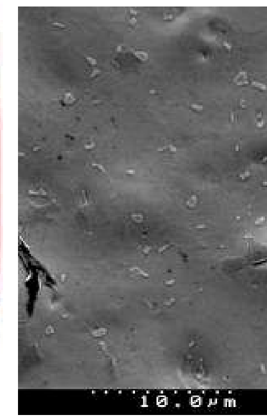


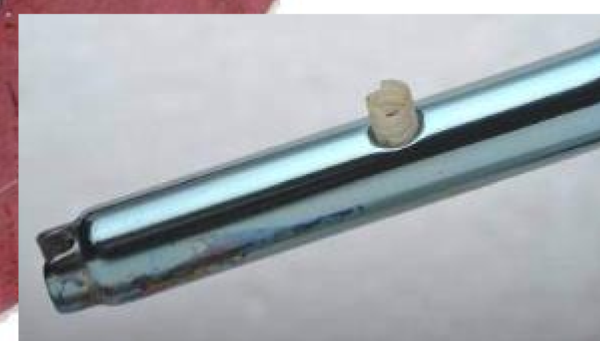


Biological reaction to bone – TAN (polished)

IM Nail - 12 mo implantation







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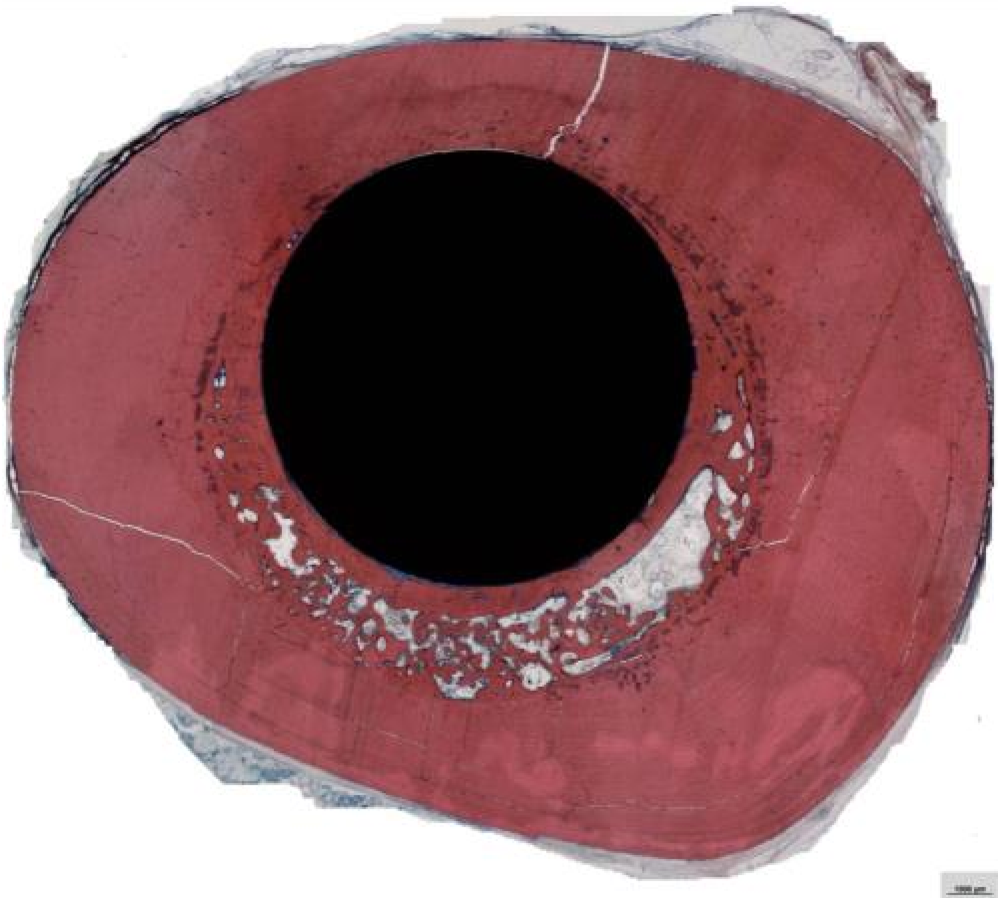
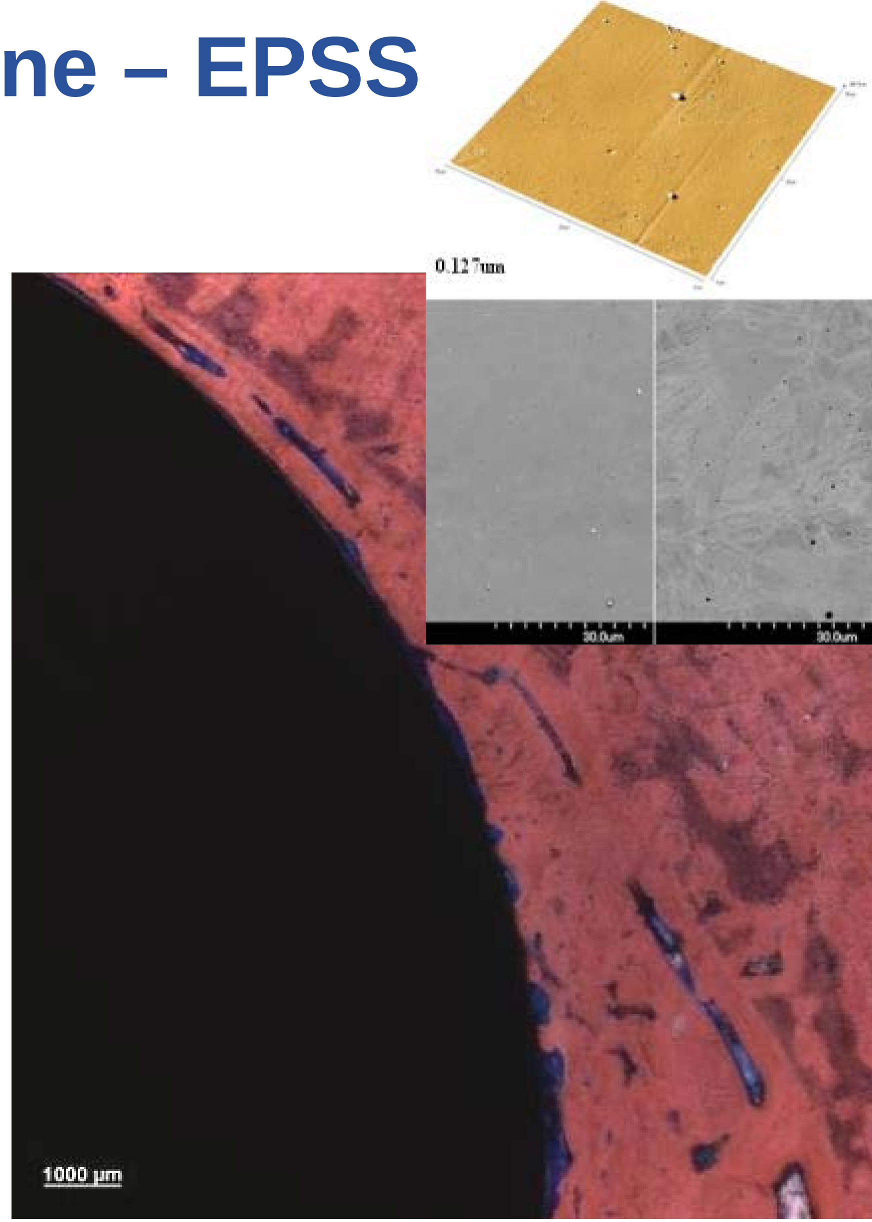
Courtesy of Geoff Richards

Biological reaction to bone – EPSS

IM Nail - 12 mo implantation

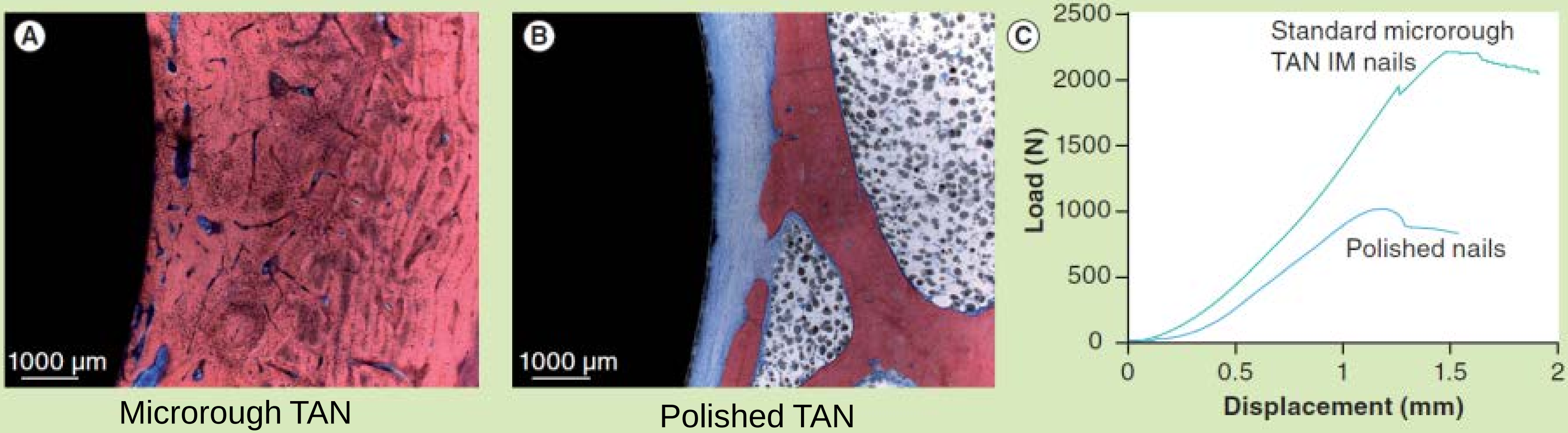




Hayes JS *Eur Cell Mater* **2009**
An in vivo evaluation of surface polishing of TAN IM nails for ease of removal.

Effect of polishing

12 months, sheep tibia



Microrough TAN

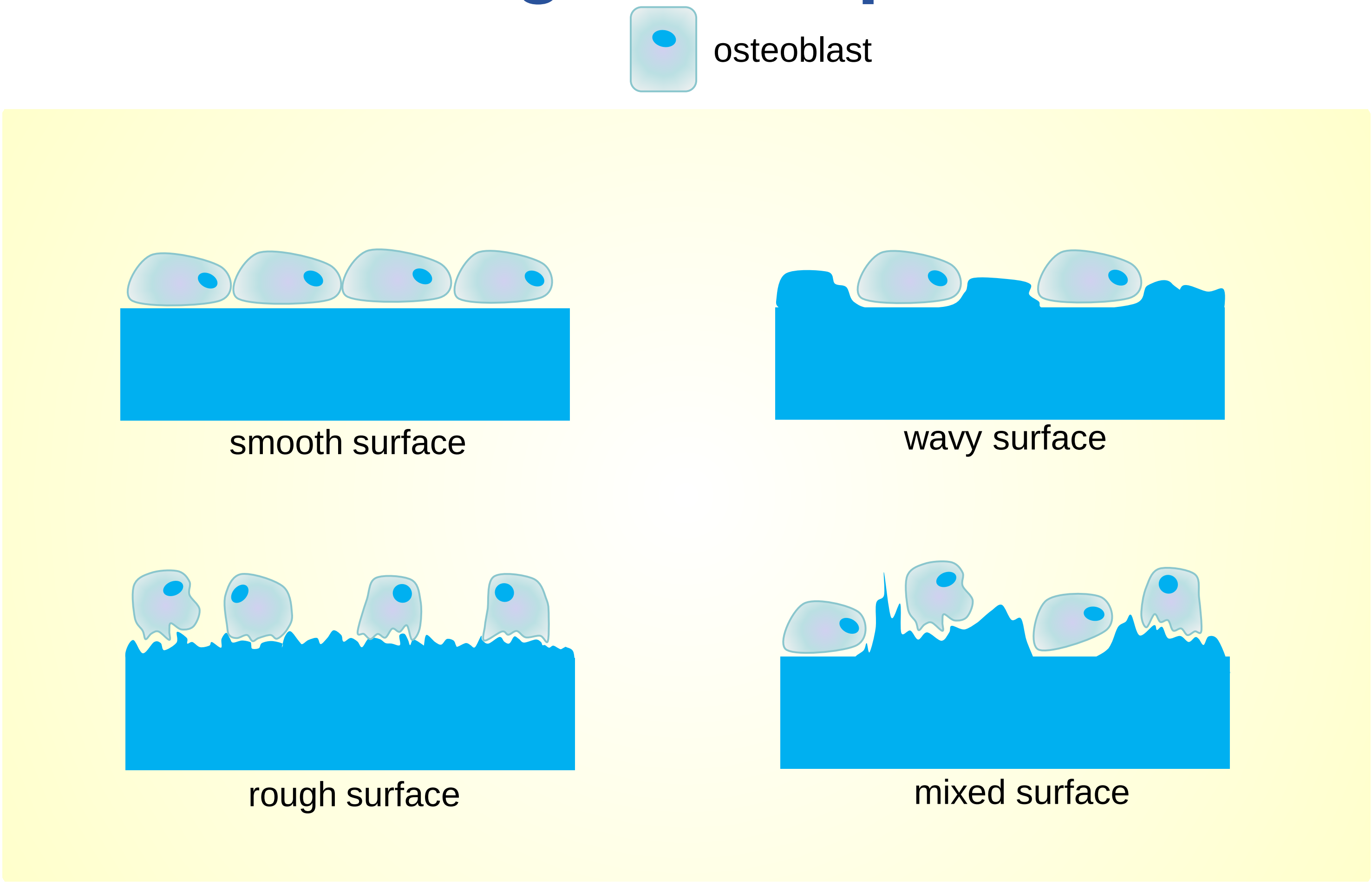
Polished TAN

IM: intramedullary; TAN: titanium-6% aluminium-7% niobium (wt%)

Hayes JS *Exp Reviews* **2010**

Surfaces to control tissue adhesion for osteosynthesis with metal implants.

The effective roughness spectrum



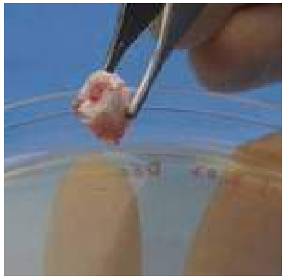
Adapted from Hayes JS *Exp Reviews* **2010**
Surfaces to control tissue adhesion for osteosynthesis with metal implants.

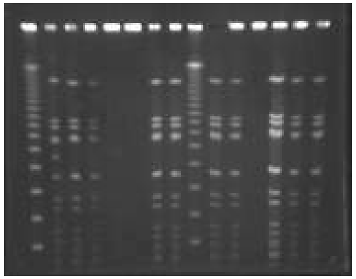
0.2 - 2 µm

Infection rates - surfaces

LCP Type	*n*	Rate of Infection (%)	ID $_{50}$ (CFU)
Polished TAN	22	45	7.1×10^6
Standard TAN	21	38	6.3×10^6
Standard Ti	19	42	3.9×10^6
EPSS	22	54	3.2×10^6
Polished Ti	20	50	2.7×10^6

In a stable locking IF plate system **no large differences found bet materials** (cpTi, TAN, EPSS) **or surface roughness** for infection susceptibility ***in vivo*** *(without fracture or major tissue trauma)*





Moriarty TF. *Int J Artif Organs* **2009**
Influence of material and microtopography on the development of local infection *in vivo*

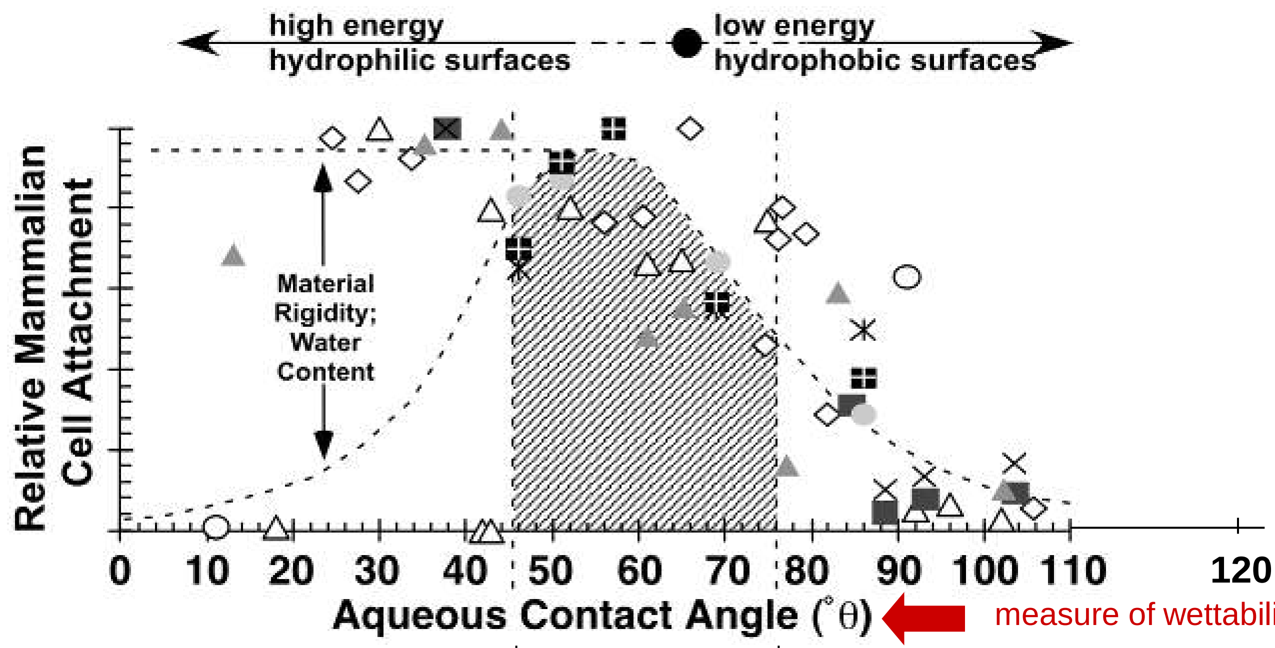
Examples: polymers

Plasma-modified PEEK: *in vitro*

Survey of cell adhesion to materials (hydrophobicity on very smooth surface)

cells attach best to surfaces that are neither too hydrophobic or too hydrophilic

Manufacturing & contamination moves these boundaries



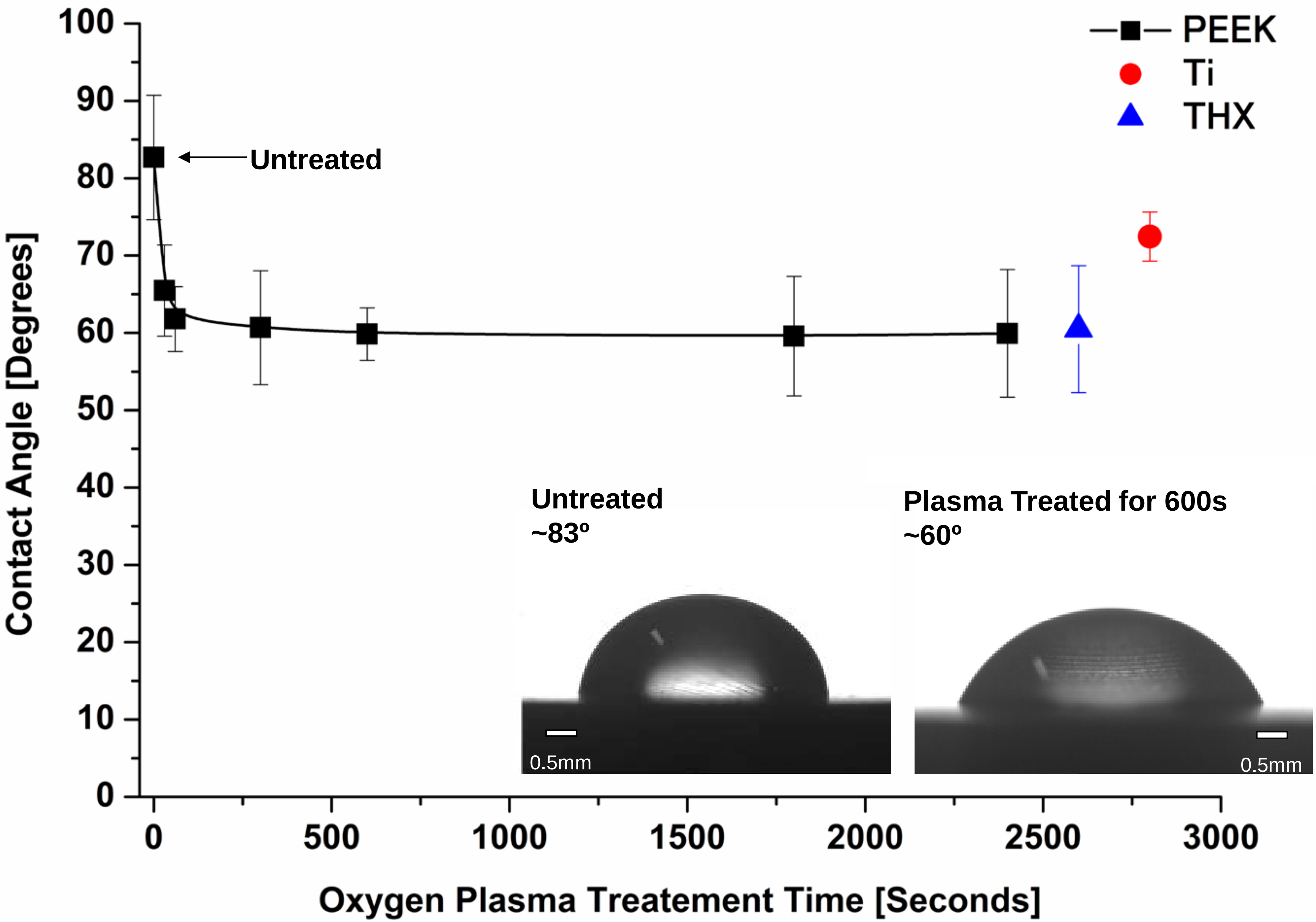
measure of wettability

conditionally (non) adhesive	adhesive	non-adhesive
PEG, PEO, dextran, others	*TCPS, PMMA, PU, collagen, etc.*	*PS, Teflon®s, PTFE, FEP, PCL, PEEK, PP, others*

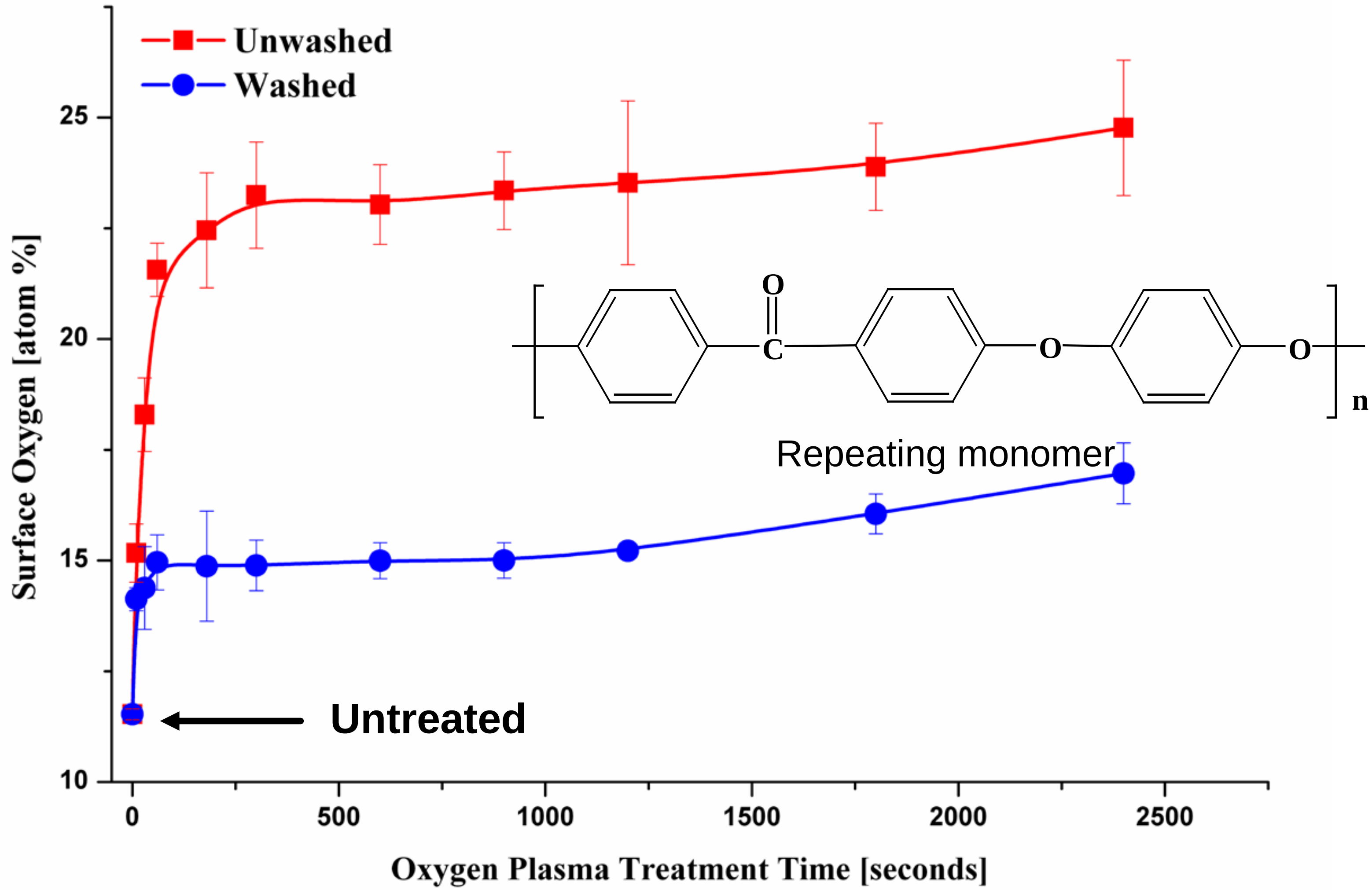
Adapted graph courtesy (Harbers, G. M., & Grainger, D. W.)

AO Foundation

Surface wettability of plasma treated PEEK



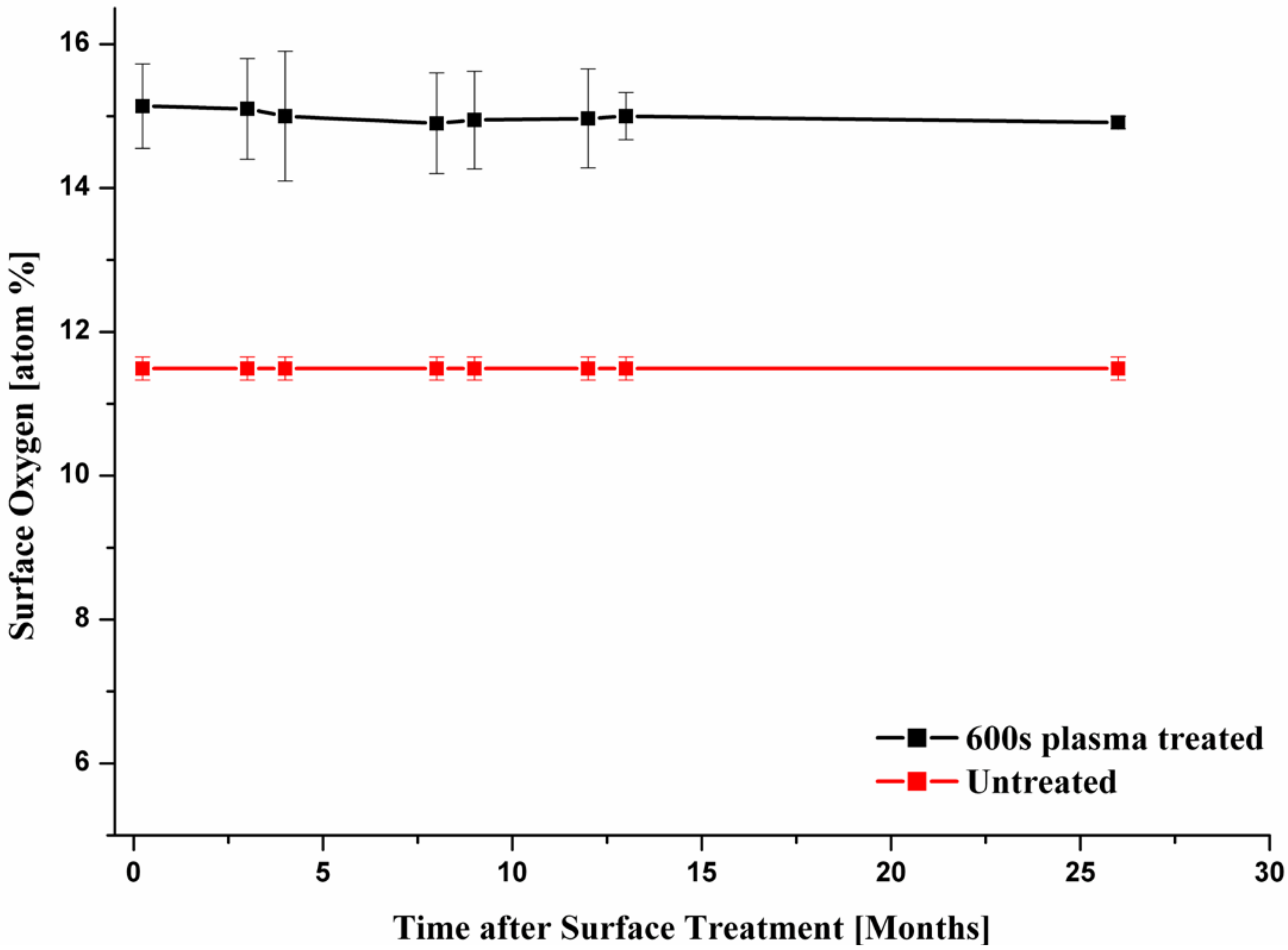
XPS surface analysis of oxygen incorporation as a function of plasma treatment time



Poulsson AHC, Richards RG WO2009/149827A1.

AO Foundation

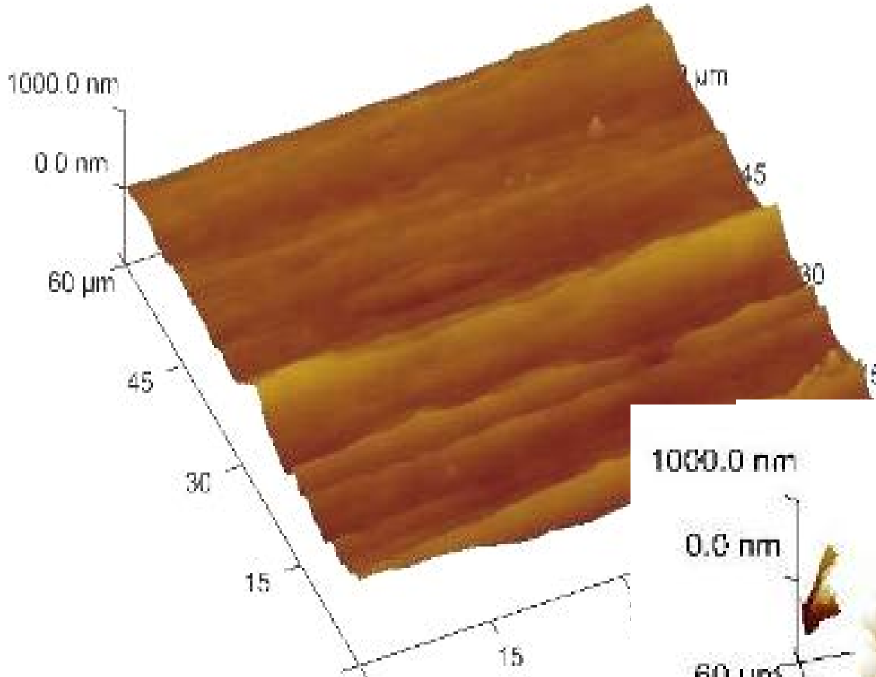
Long-term stability of surface treatment



AO Foundation

Poulsson AHC, Richards RG WO2009/149827A1.

AFM of evaluation of surface topography

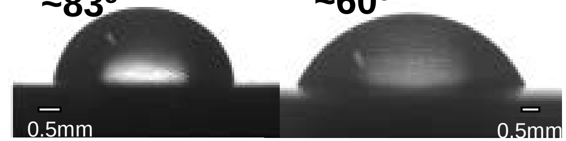


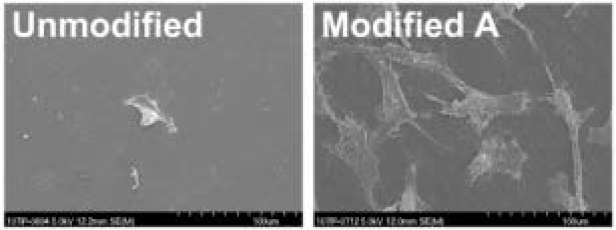
Inj. Moulded PEEK

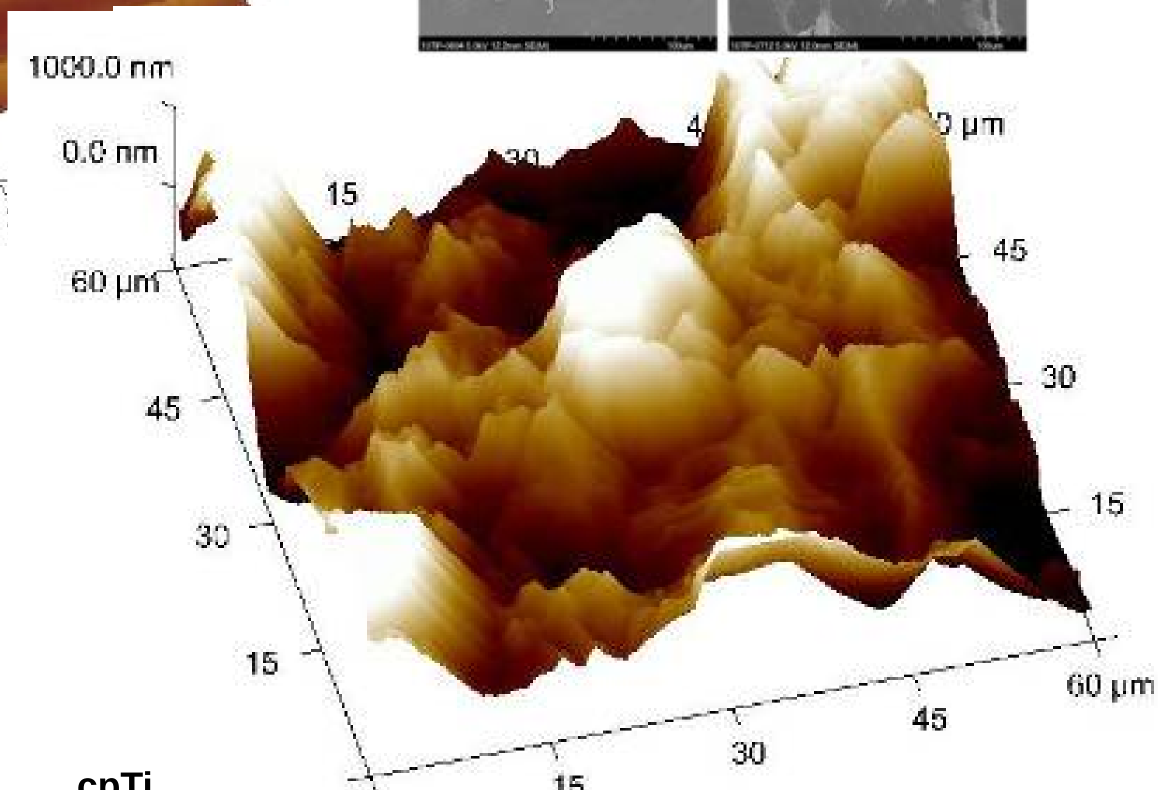
Plasma surface modification

Unmodified **Modified**

~83º **~60º**

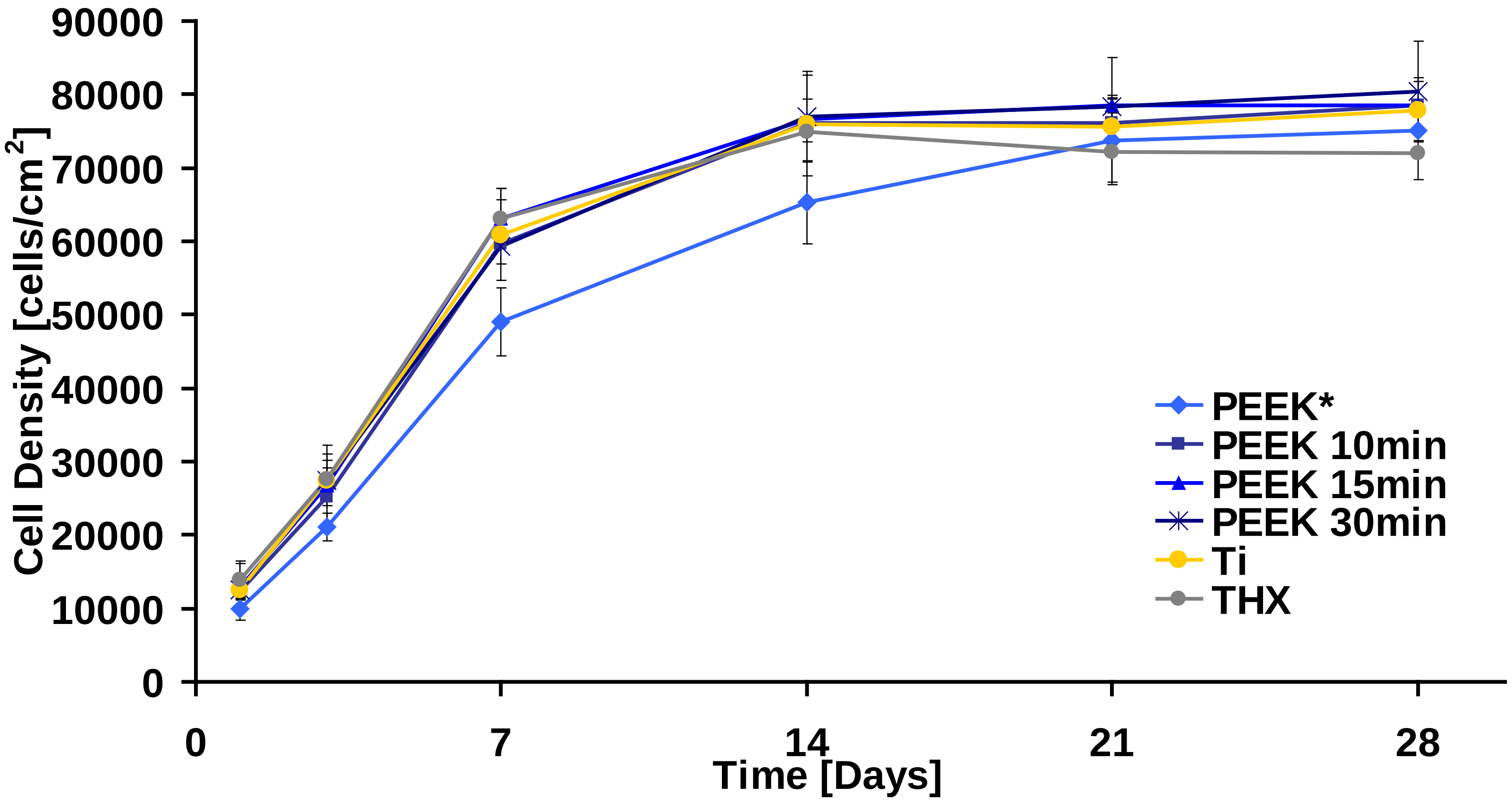






cpTi

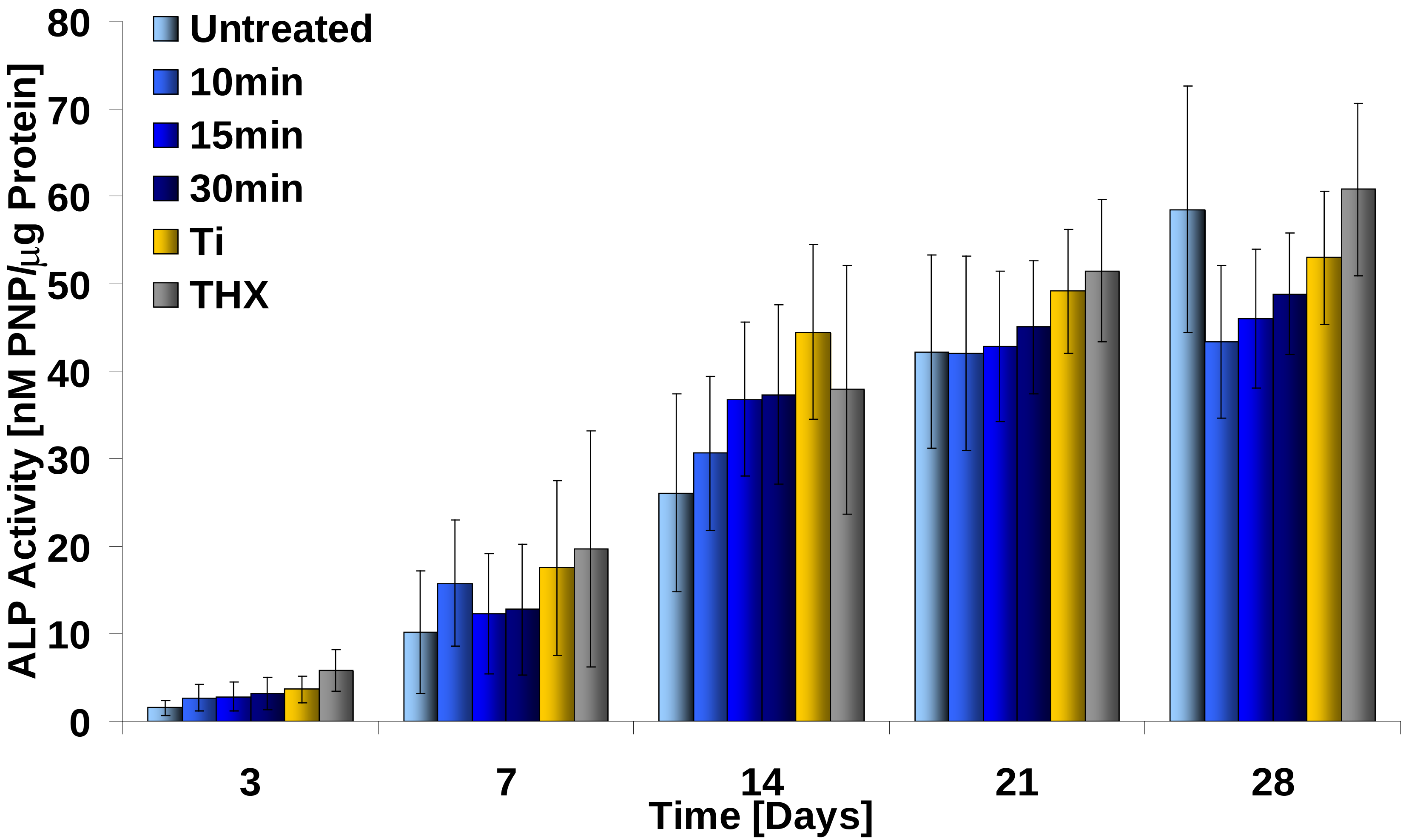
Cell proliferation on PEEK



Poulsson AHC in PEEK Biomaterials Handbook (Kurtz SM, Elsevier ed). **2012**
Surfaces to control tissue adhesion for osteosynthesis with metal implants.

 Data from 5 independent femoral heads, ± st. dev. GLM ANOVA with Tukey *post-hoc,* significance $P<0.05$

Alkaline phosphatase activity on PEEK



Poulsson AHC in PEEK Biomaterials Handbook (Kurtz SM, Elsevier ed). **2012**
Surfaces to control tissue adhesion for osteosynthesis with metal implants.

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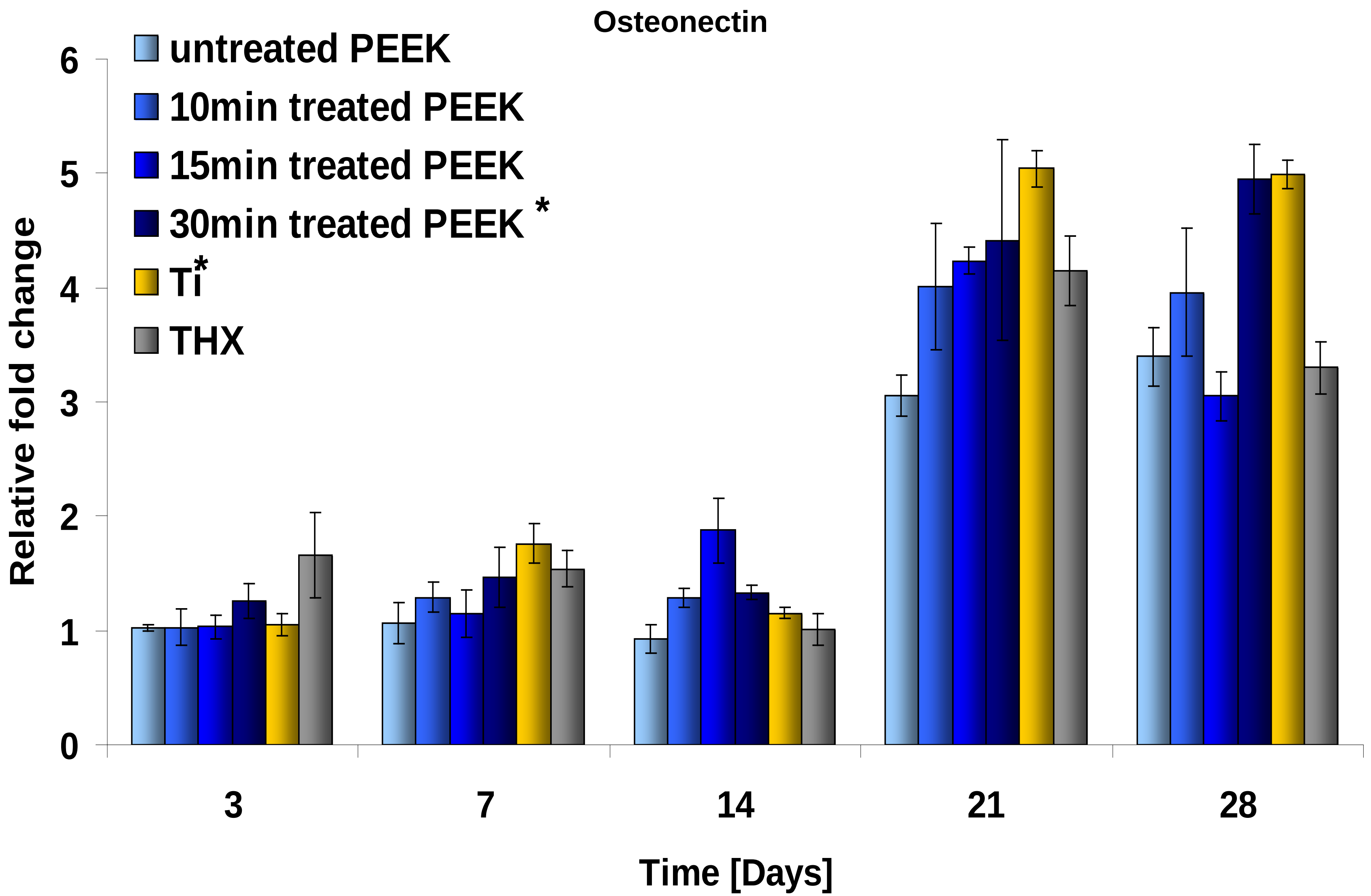
Gene expression profile of HOB on PEEK



Poulsson AHC in PEEK Biomaterials Handbook (Kurtz SM, Elsevier ed). **2012**
Surfaces to control tissue adhesion for osteosynthesis with metal implants.

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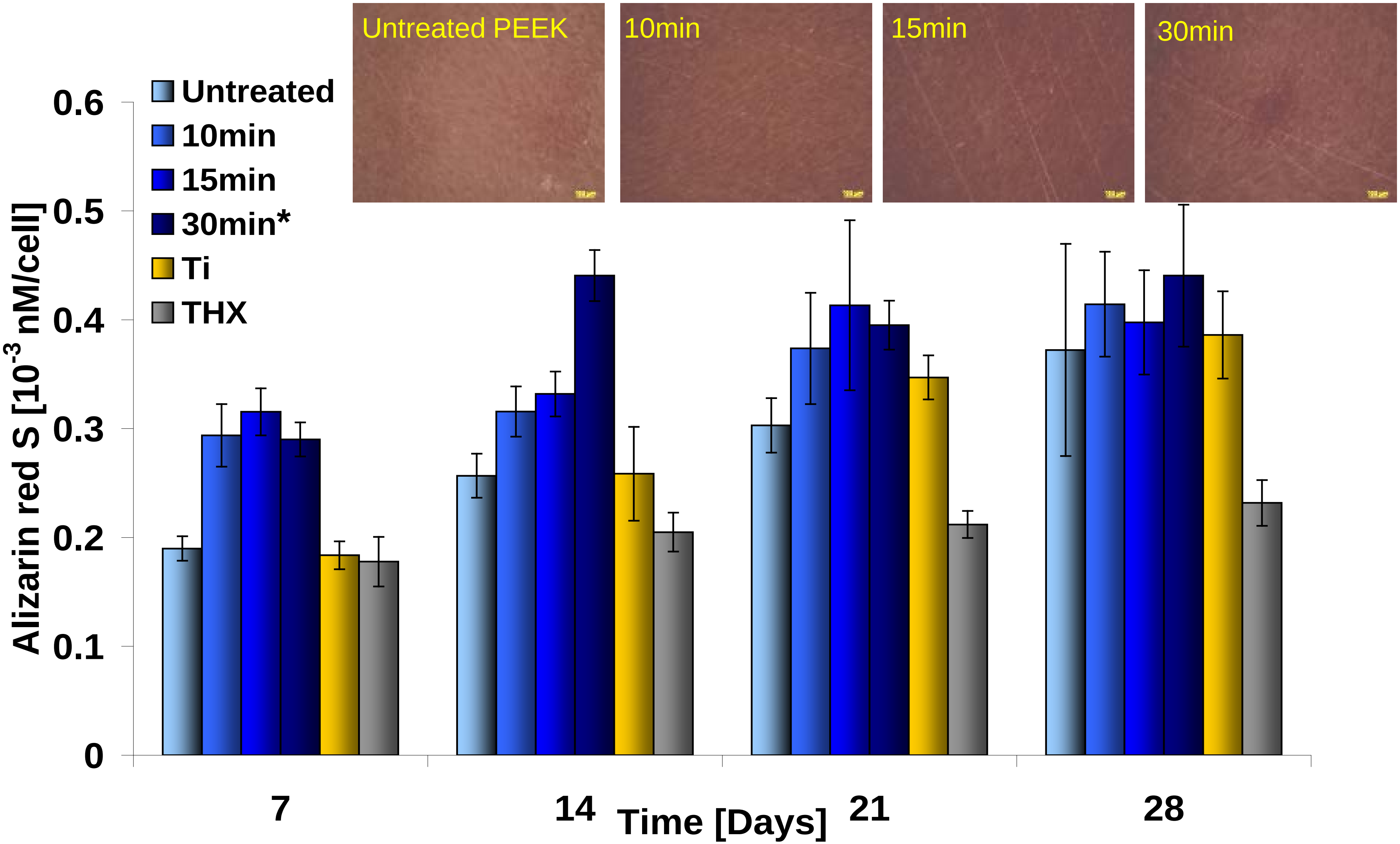
Nodule formation on PEEK



Poulsson AHC in PEEK Biomaterials Handbook (Kurtz SM, Elsevier ed). **2012**

Surfaces to control tissue adhesion for osteosynthesis with metal implants.

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Conclusions: *in vitro* study

- Oxygen plasma treatment has increased the **surface energy** of PEEK substrates
- Surface treatment is **stable** for 26 months in air (also > 18 months in PBS at 37ºC)
- **Optimal levels** of surface treatment have been identified for HOB cells
- **ALP expression** is more characteristic for hOB cells on the treated surfaces
- **Nodule formation** was higher from day 7 on all treated surfaces compared to untreated PEEK
- The influence of these surfaces on hOB cell **gene expression** indicates that the differentiation is up-regulated at earlier time points

These *in vitro* findings indicate that this surface modification is likely to improve bone integration to PEEK implants

Plasma-modified PEEK:
in vivo

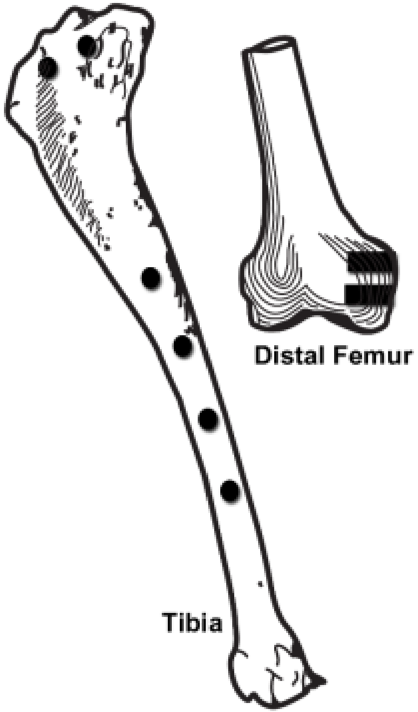
Materials & methods – in vivo

Groups

Machined PEEK Implant	**PA**
Injection Moulded PEEK Implant	**PO**
Plasma modified Machined PEEK Implant	**PAm**
Plasma modified Injection Moulded PEEK Implant	**POm**

Ovine Model

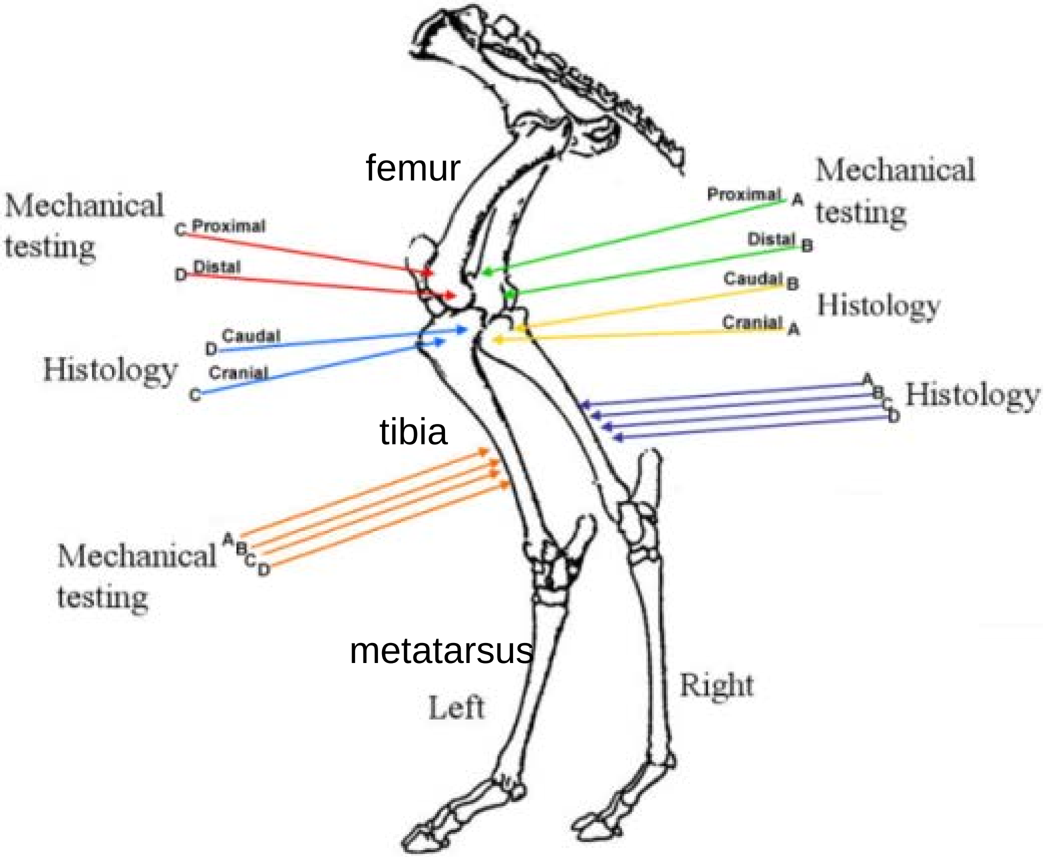
24 Swiss Alpine Sheep
Female, 60-65kg, 3-4yrs
Cancellous bone of the proximal tibia and distal femur
Cortical bone of the tibiae
Time-points: 4, 12 and 26 weeks, 8 per time-point



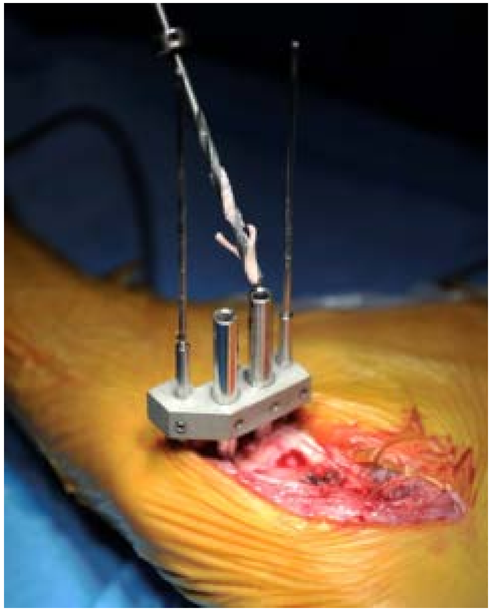
Characterisations

Surface analyses: XPS, WLP, AFM and WCA.
In vivo analysis: Radiographs, Fluorochrome labelling
Explant analyses: Radiographs, Mechanical push-out testing, histology and histomorphometry

Preclinical study



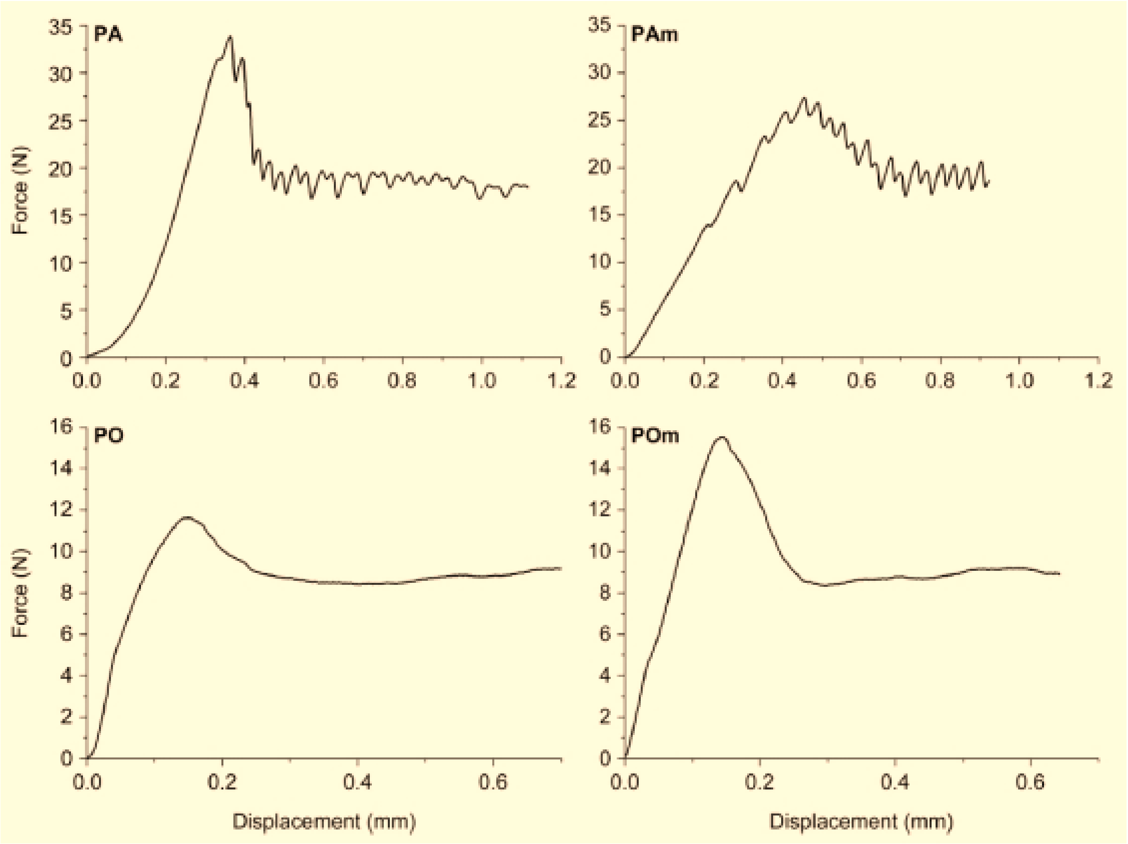
Schematic of the bilateral model implantation areas in the tibiae and femurs, where the implant sites are annotated and division between histology and mechanical testing is shown.

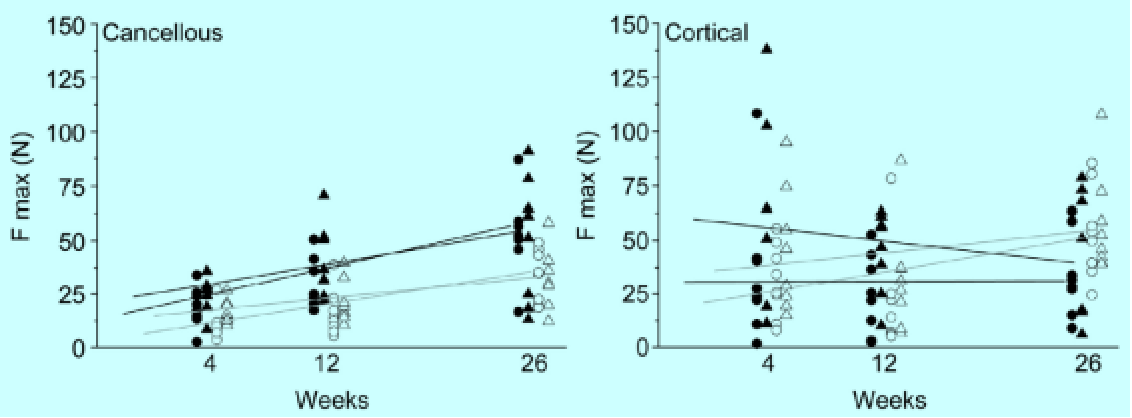


Custom made jig with k-wires

All 4 implants in place in the tibial diaphysis with 2 marker screws on either side

Push-out force





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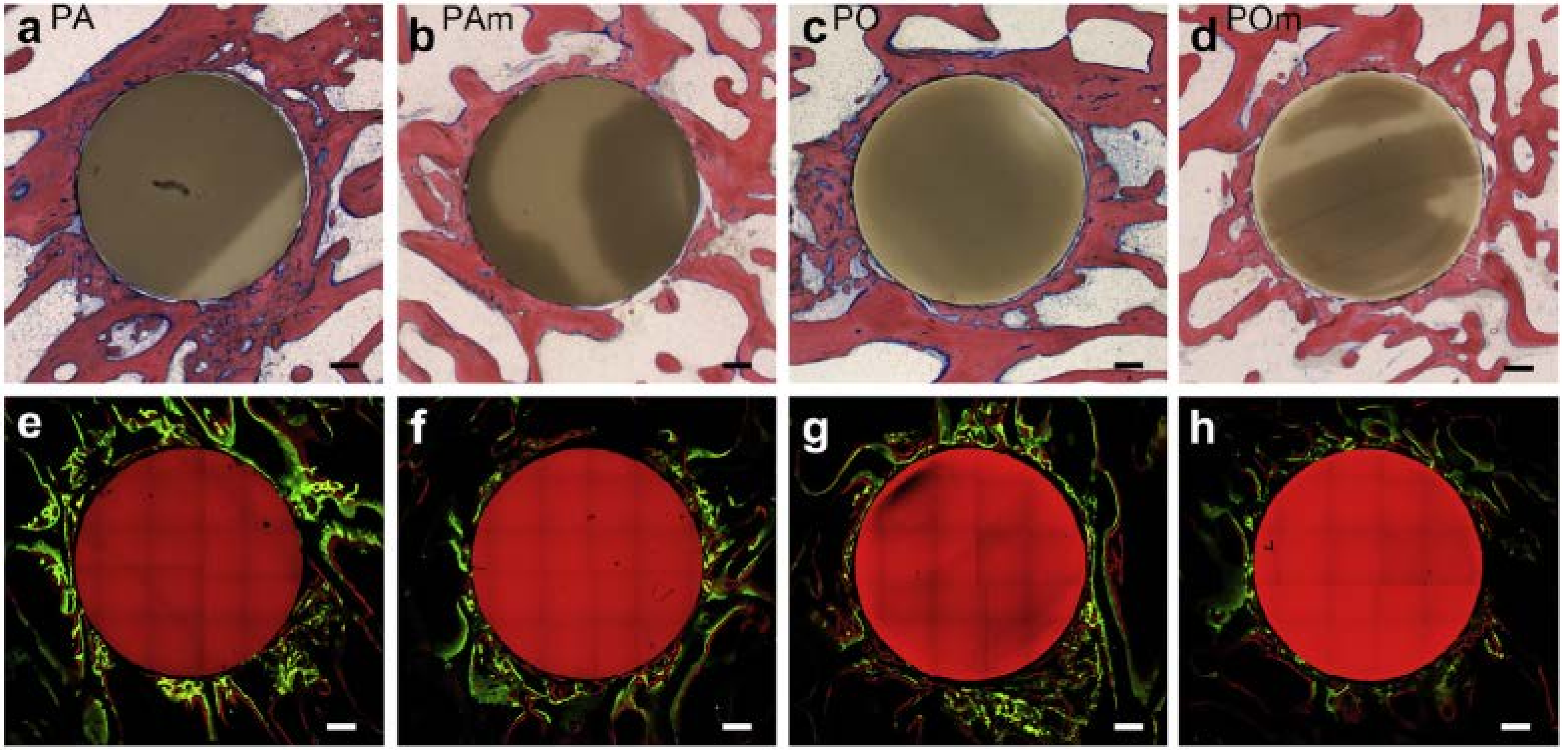
PEEK in vivo: new bone formation

Proximal tibia (cancellous bone). 4 weeks after implantation

Giemsa-eosin

Intravital calcein green and xylenol orange



PA -machined PEEK, PAm- modified machined PEEK, PO- moulded PEEK, POm- modified moulded PEEK

Pink: bone, blue: soft tissue, white: bone marrow.

Poulsson AHC *Biomaterials* **2014**
Osseointegration of machined, injection moulded and oxygen plasma modified PEEK implants in a sheep model.

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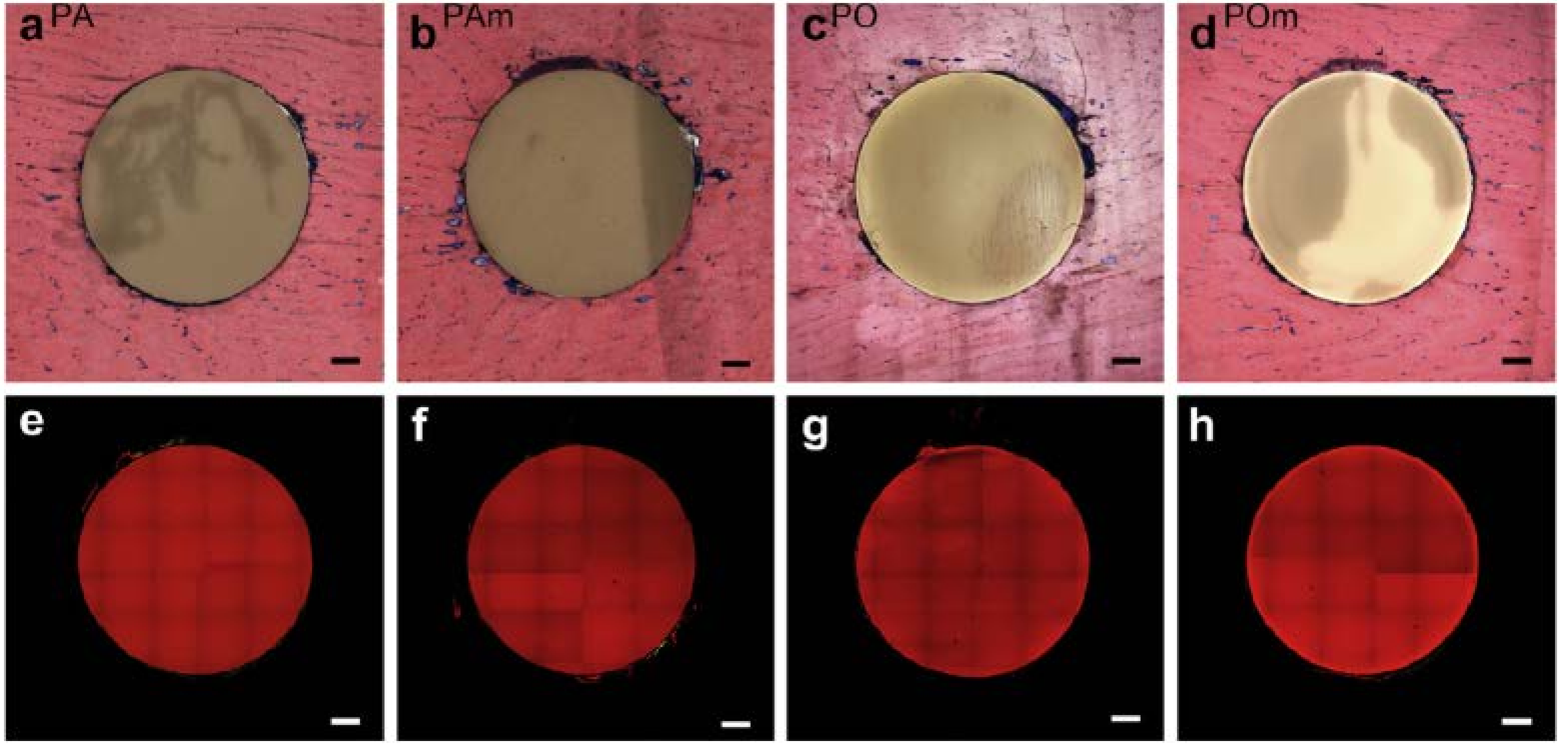
PEEK in vivo: new bone formation

Tibial diaphysis (cortical bone). 4 weeks after implantation

Giemsa-eosin

Intravital calcein green and xylenol orange



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Poulsson AHC *Biomaterials* **2014**
Osseointegration of machined, injection moulded and oxygen plasma modified PEEK implants in a sheep model.

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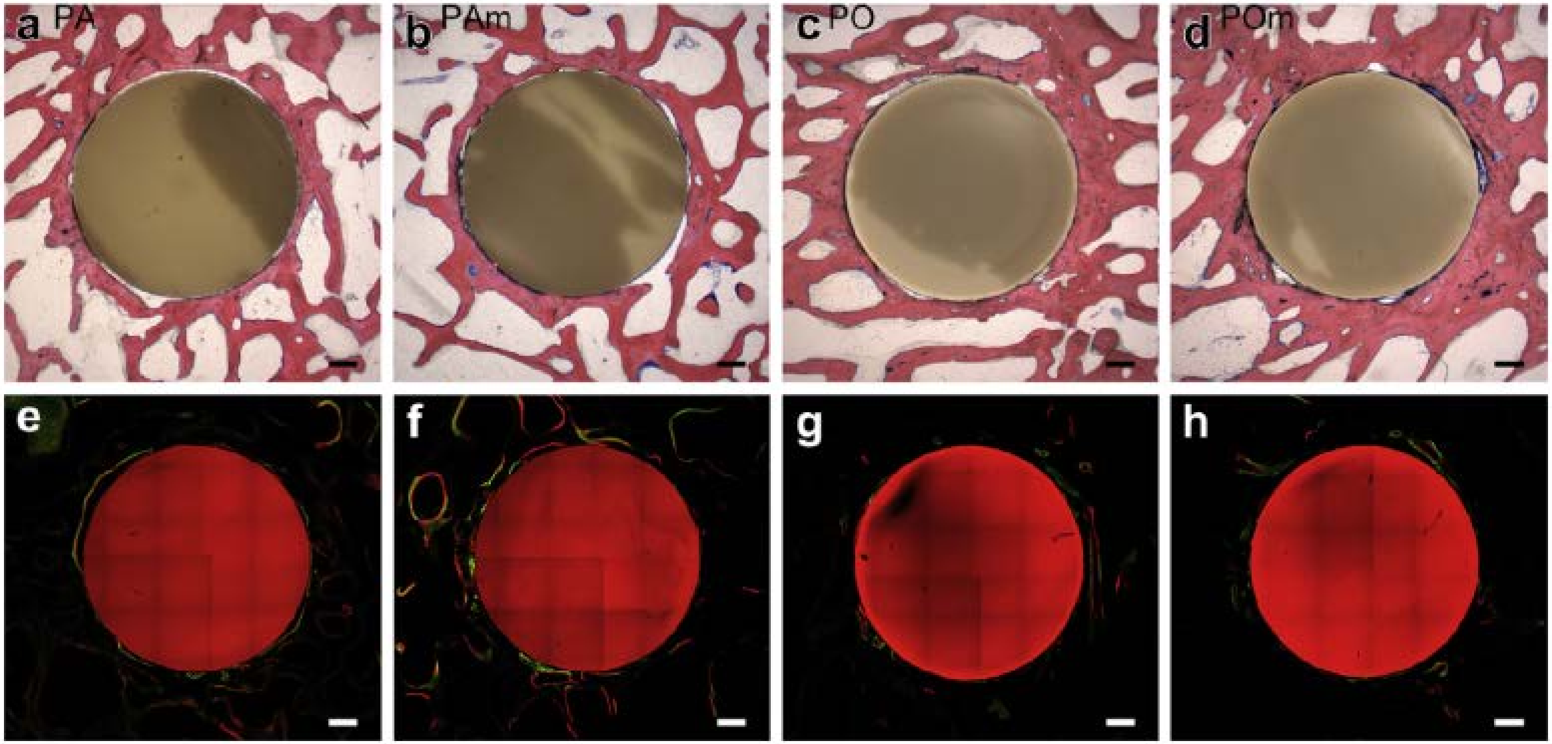
PEEK in vivo: new bone formation

Proximal tibia (cancellous bone). 12 weeks implantation.

Giemsa-eosin

Intravital calcein green and xylenol orange



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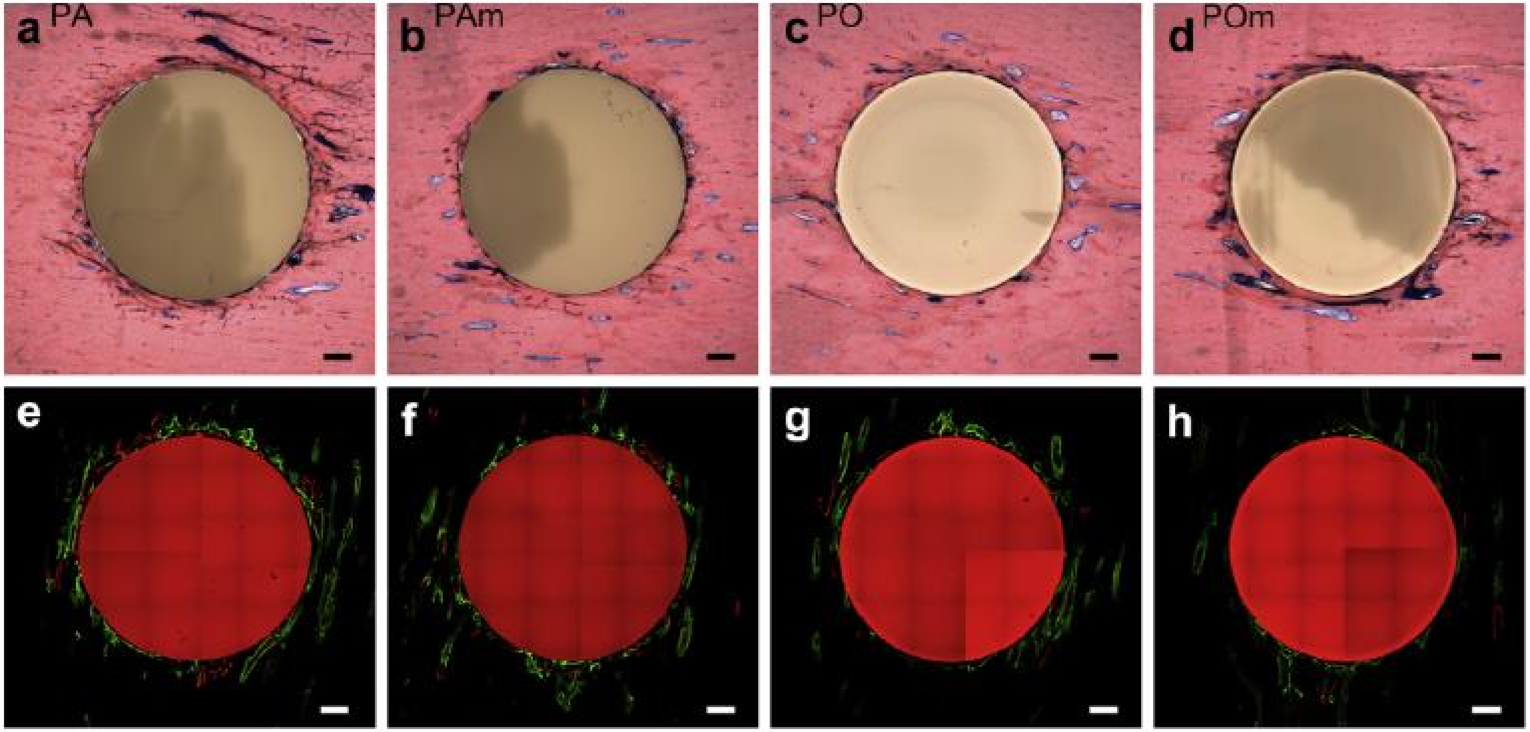
Poulsson AHC *Biomaterials* **2014**
Osseointegration of machined, injection moulded and oxygen plasma modified PEEK implants in a sheep model.

PEEK in vivo: new bone formation

Tibial diaphysis (cortical bone). 12 weeks after implantation

Giemsa-eosin

Intravital calcein green and xylenol orange



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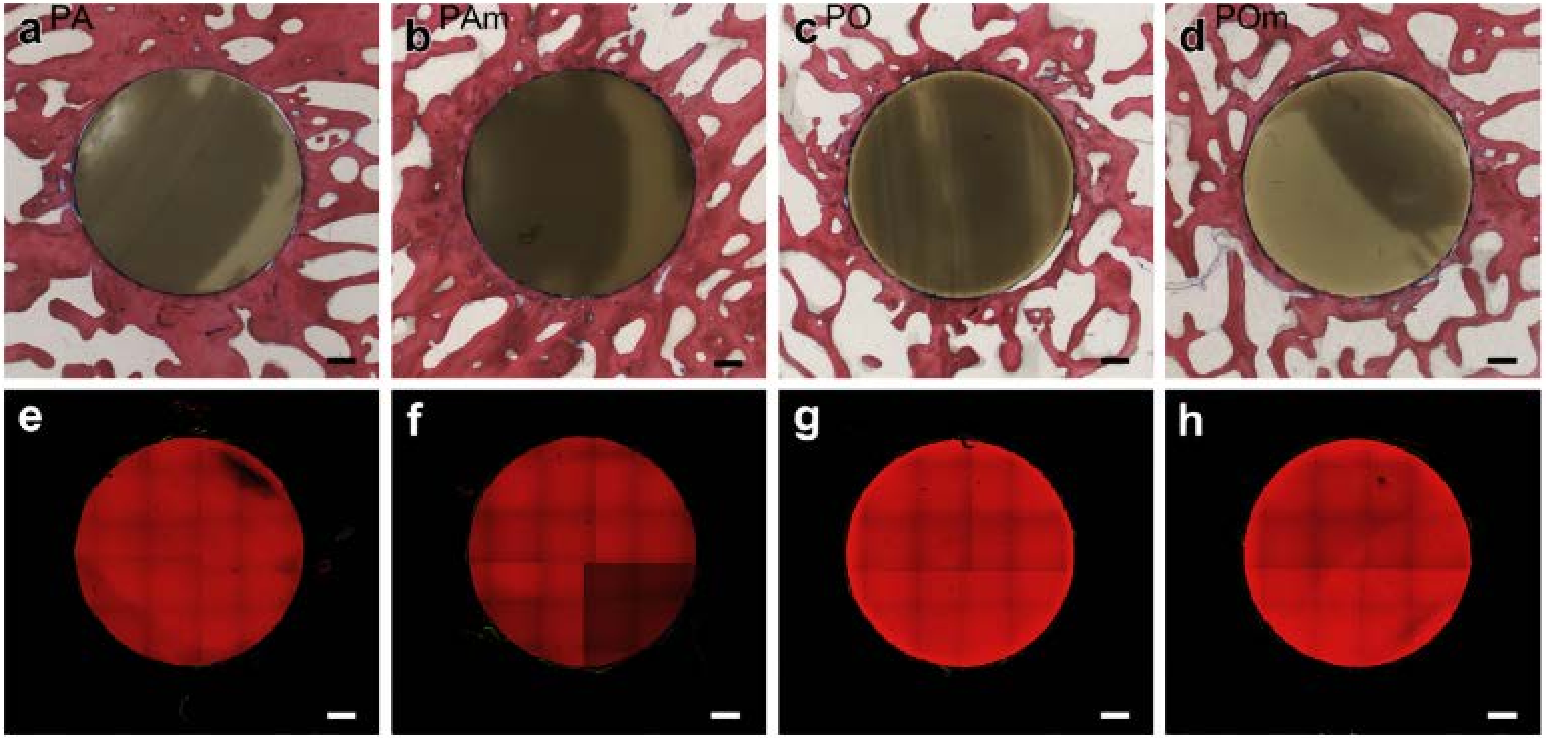
Poulsson AHC *Biomaterials* **2014**
Osseointegration of machined, injection moulded and oxygen plasma modified PEEK implants in a sheep model.

PEEK in vivo: new bone formation

Proximal tibia (cancellous bone). 26 weeks implantation.

Giemsa-eosin

Intravital calcein green and xylenol orange



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PEEK in vivo: new bone formation

Tibial diaphysis (cortical bone). 26 weeks after implantation

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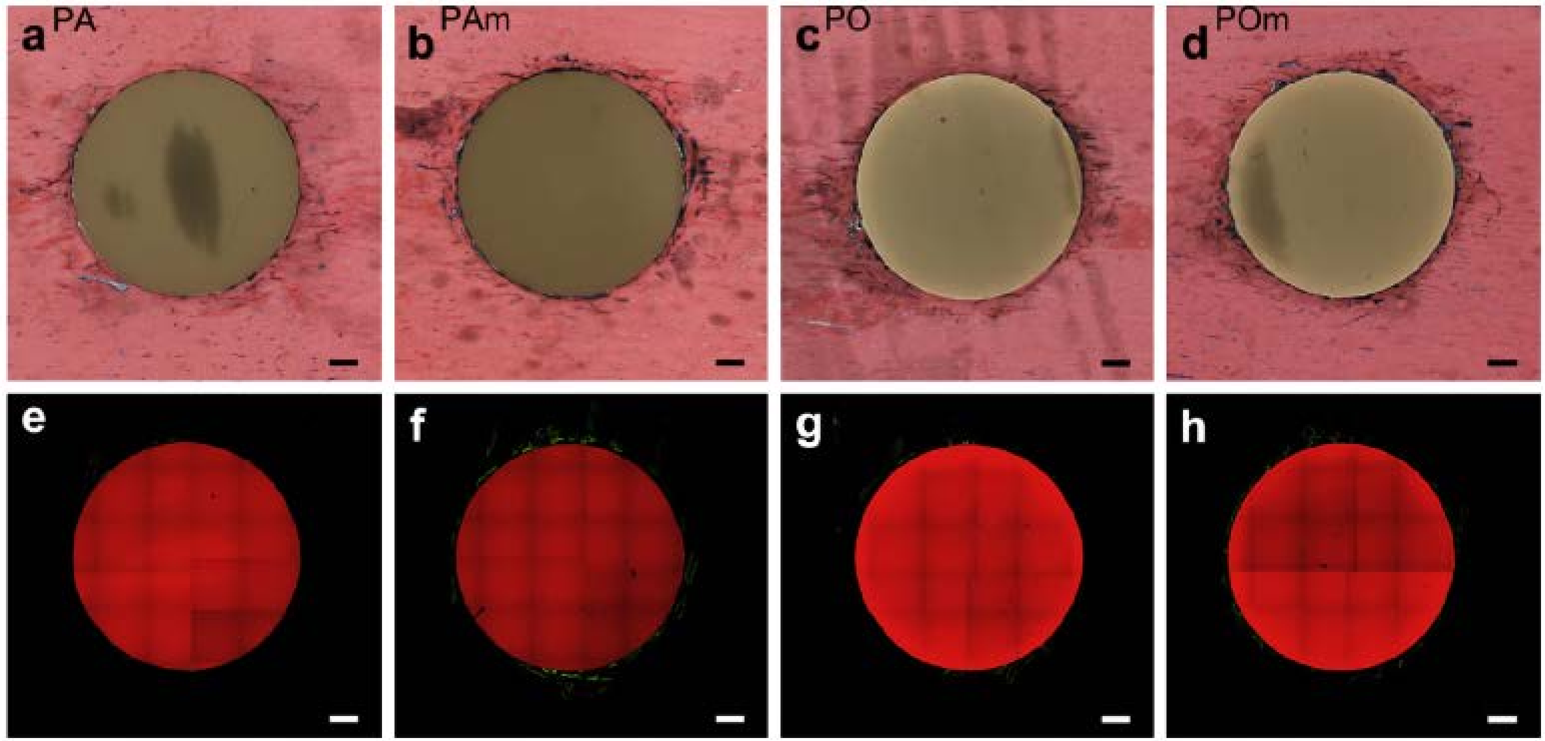

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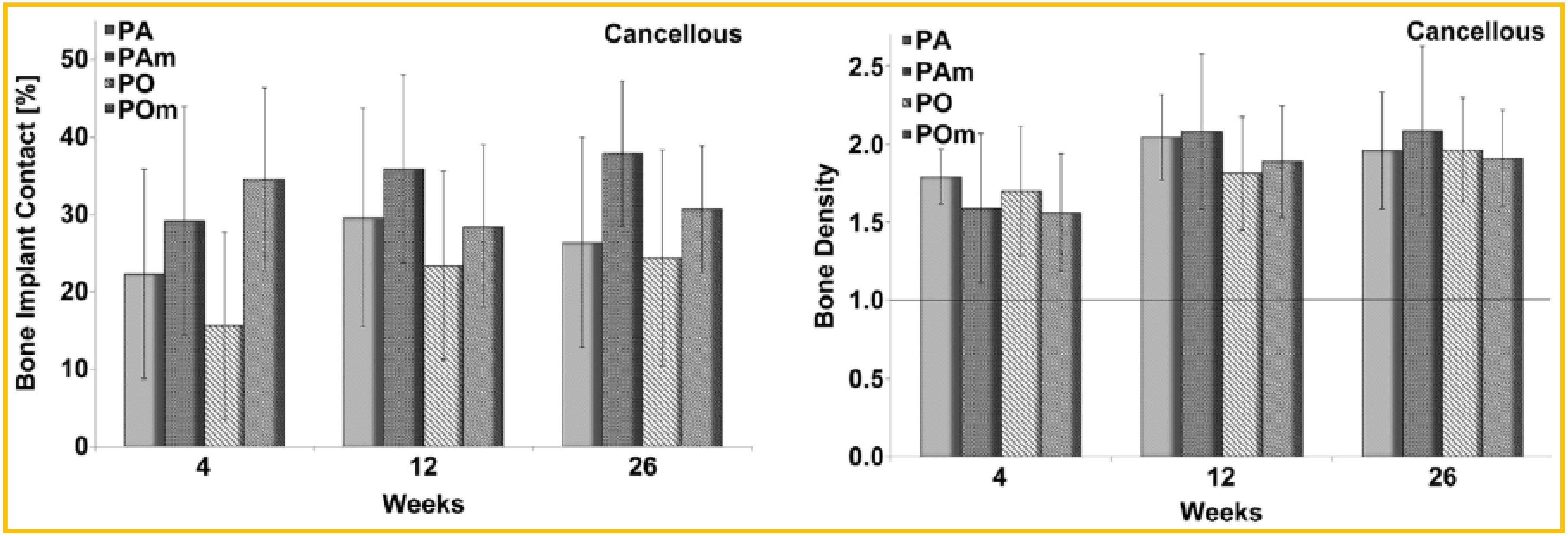
Poulsson AHC *Biomaterials* **2014**
Osseointegration of machined, injection moulded and oxygen plasma modified PEEK implants in a sheep model.

PEEK in vivo: cancellous bone: BIC and BD



PA -machined PEEK, PAm- modified machined PEEK, PO- moulded PEEK, POm- modified moulded PEEK

Poulsson AHC *Biomaterials* **2014**
Osseointegration of machined, injection moulded and oxygen plasma modified PEEK implants in a sheep model.

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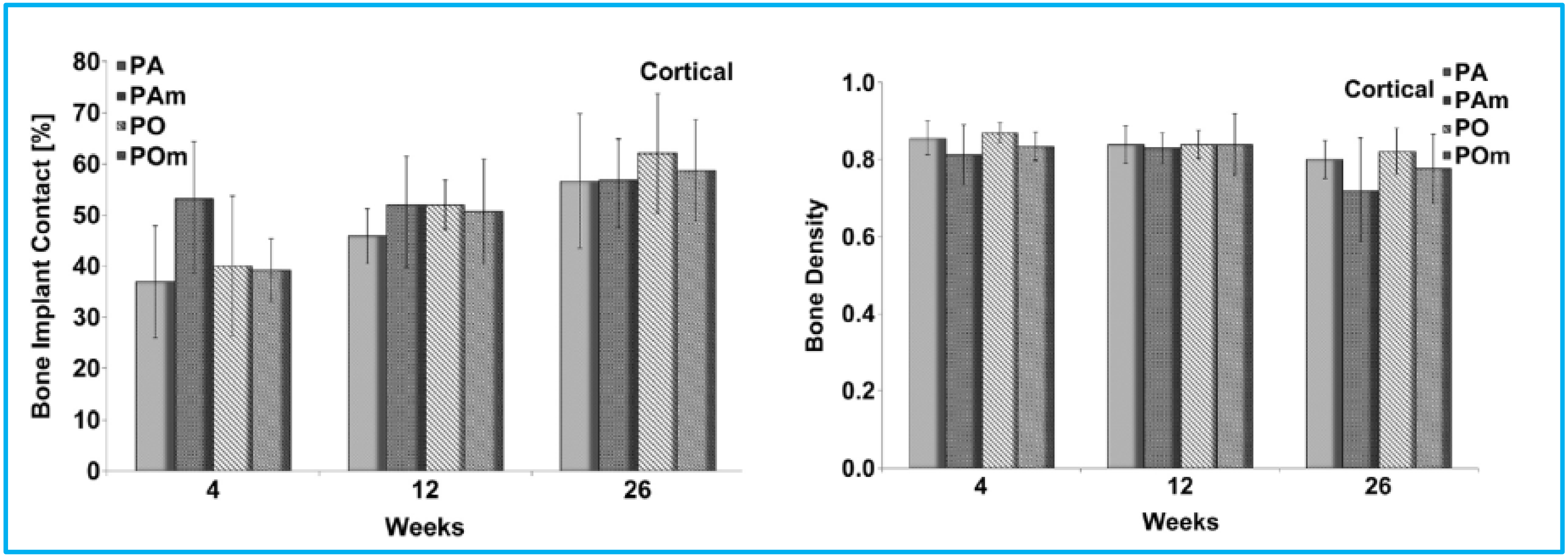
PEEK in vivo: cortical bone: BIC and BD



PA -machined PEEK, PAm- modified machined PEEK, PO- moulded PEEK, POm- modified moulded PEEK

Poulsson AHC *Biomaterials* **2014**
Osseointegration of machined, injection moulded and oxygen plasma modified PEEK implants in a sheep model.

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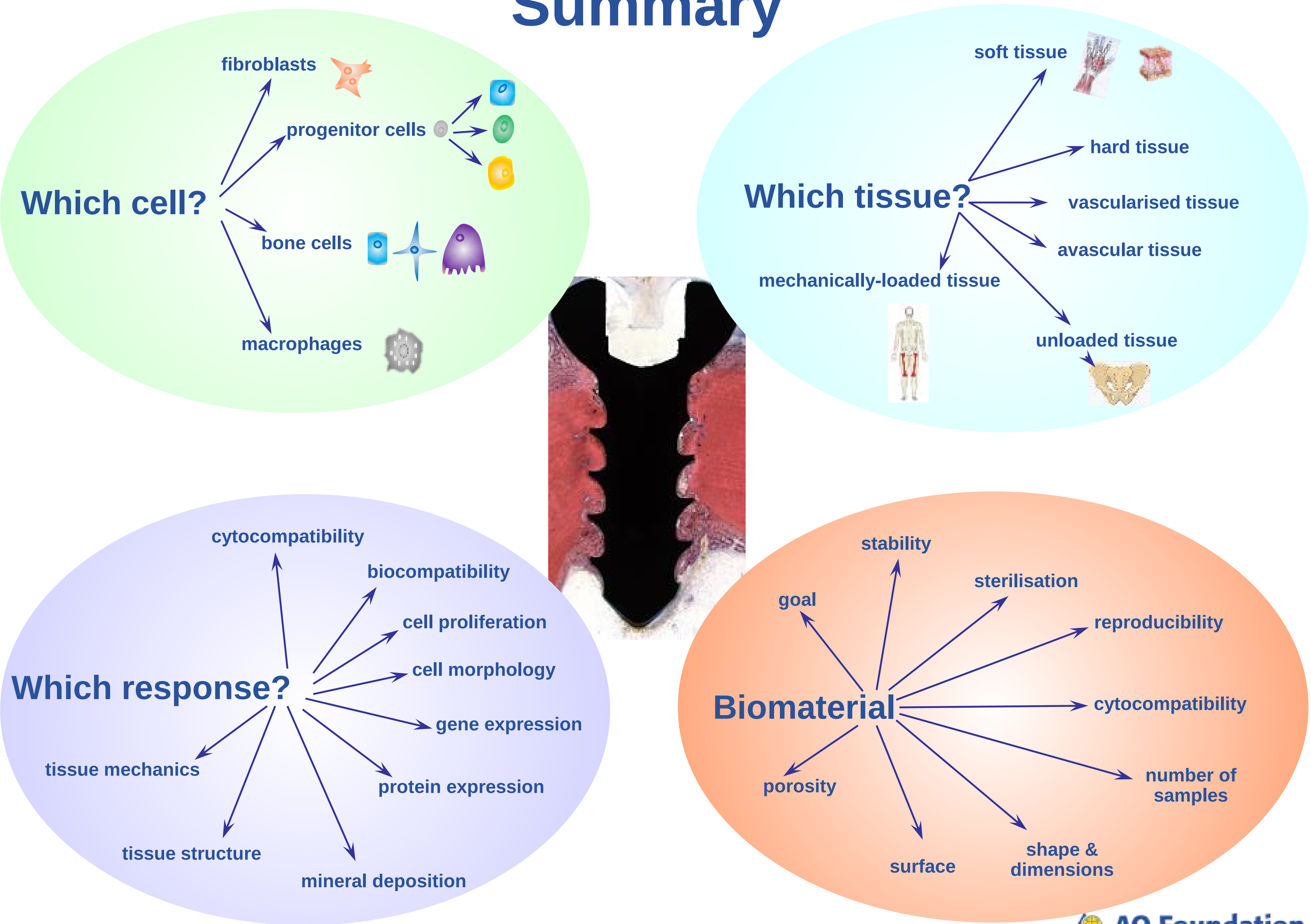
Conclusions: *in vivo* study

- Limited inflammatory response for all materials
- Good osseointegration of all materials
- Micro-roughness (machining) has a significant influence on bone-to-implant contact and push-out force
- Oxygen plasma induced an improved osseointegration and implant stability at early time point in cancellous bone

From in vitro → to in vivo → to the patient? → which patient?

Summary

Summary



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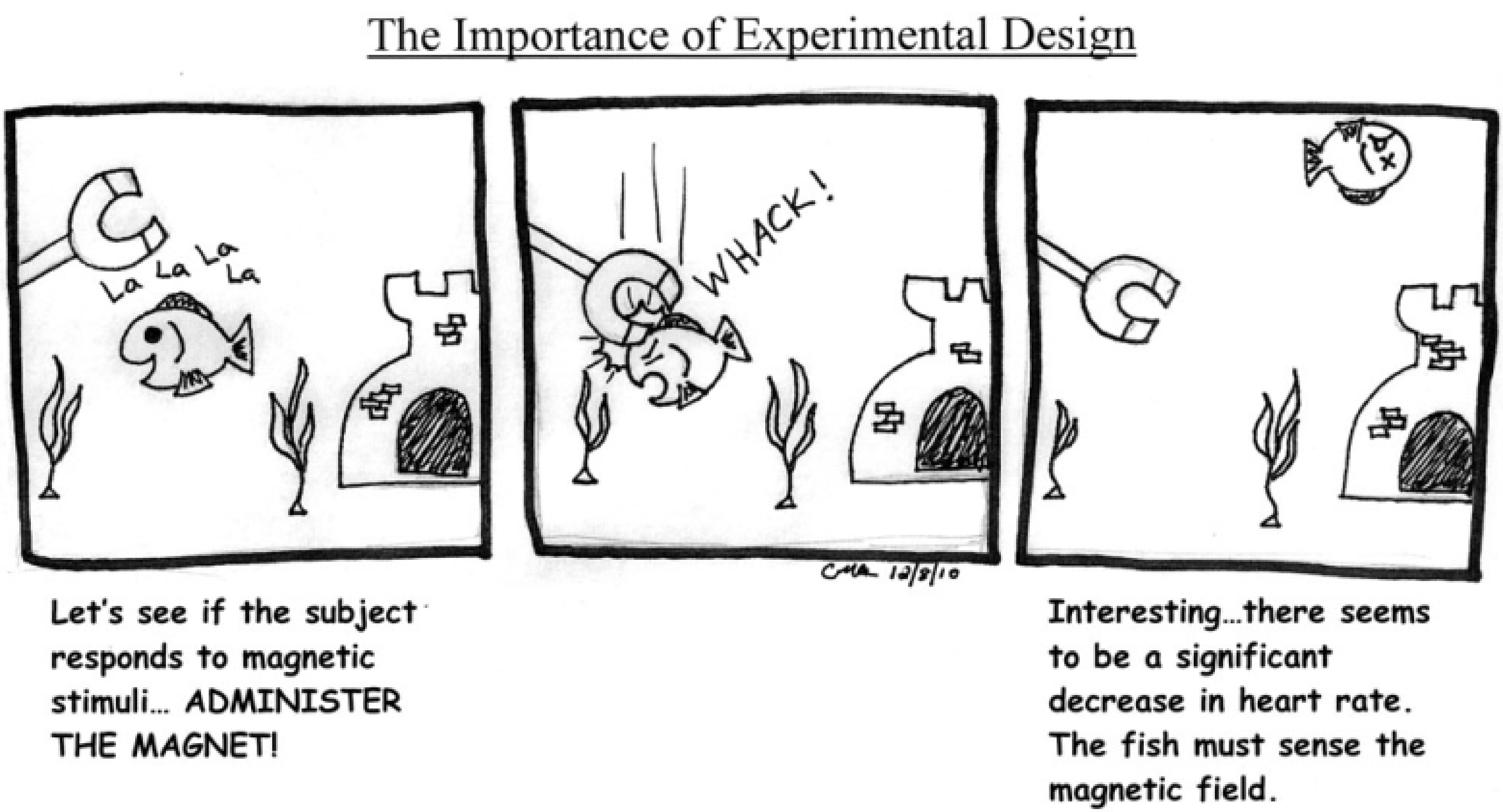
Summary

- Definition of goal/research question is fundamental
- Experimental design is the next key step



http://www.hawaii.edu/fishlab/NearsideFrame.htm

What else?

- Gene level and protein level
- Short term vs. long term cultures
- In vivo veritas?
- How comparable are different studies?
- How important are the controls, the blanks (e.g. materials cultured in the same conditions but without cells) and the artifacts!
- Be critical:

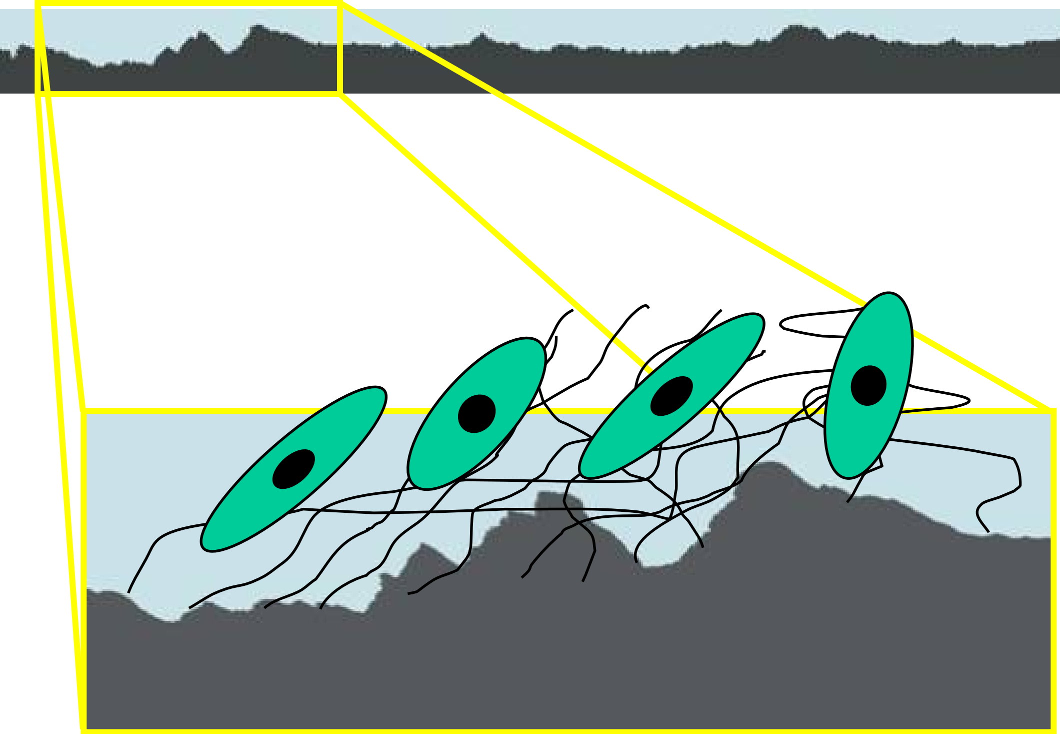
statistically significant difference
may be ≠
biologically significant difference

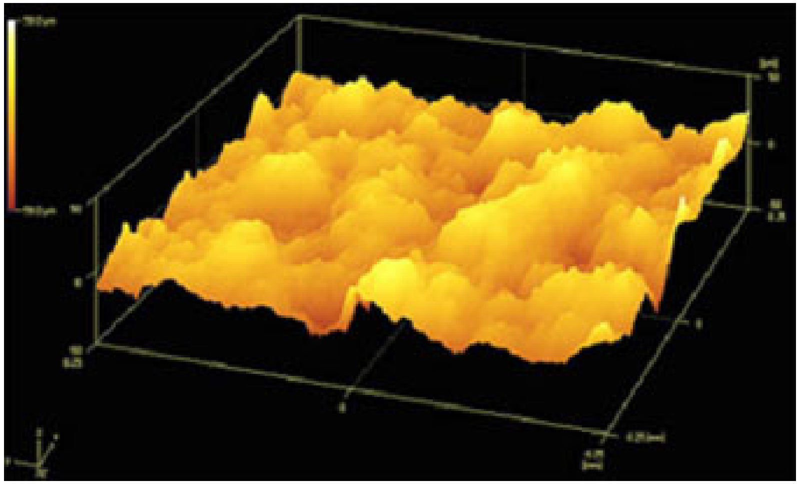
- Controversies:
  - do not look only at one paper
  - high impact journal in the field is important

Future areas of research

Surfaces: What to mimic ?

Swiss Mountain Mimetics





Courtesy of Geoff Richards

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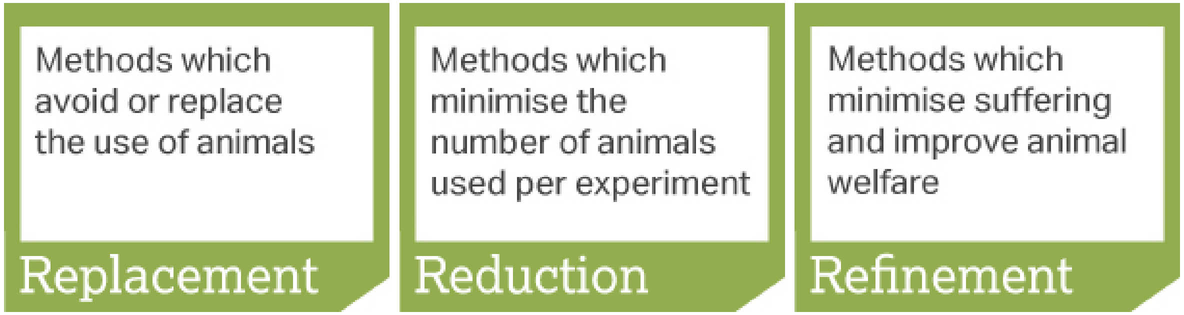
Future lines of research

- Advanced materials:
  - surface patterning
  - gradient materials
  - 3D printing

- More predictable in vitro tests

- Application of 3R principle to *in vivo* tests: https://www.nc3rs.org.uk/the-3rs



- As complete documentation as possible, especially for in vivo

- Bridge the gap between *in vitro* and *in vivo* with *ex-vivo* models

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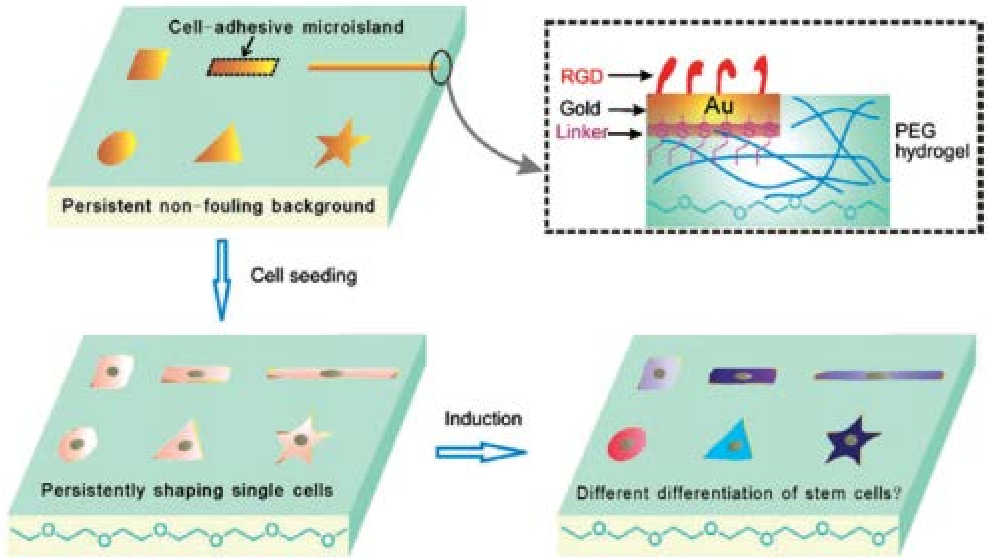
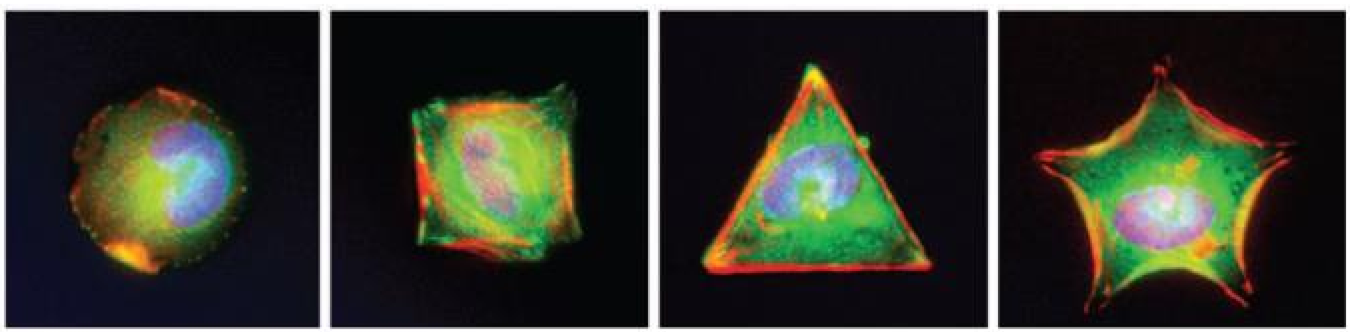
Surface patterning





Peng R. *Biomaterials* **2012**

Yao X. *Advanced Materials* **2013**
Cell-material interactions revealed via techniques of surface patterning.

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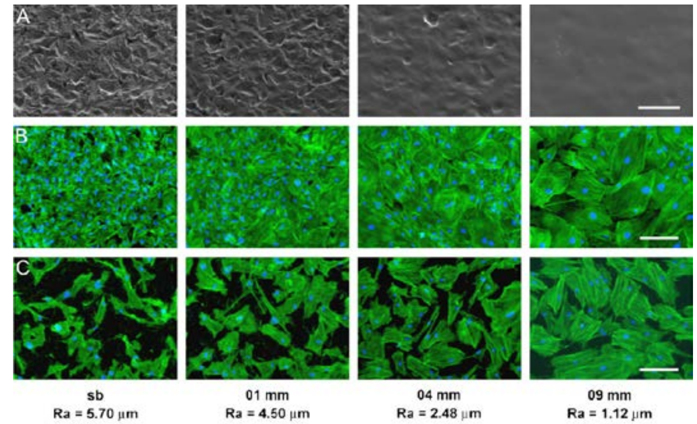
Gradient materials

Kunzler TP. *Biomaterials* **2007**

Cell response of osteoblasts and fibroblasts to surface roughness was studied by means of gradient substrata with a continuously varying roughness value and similar topographical features.

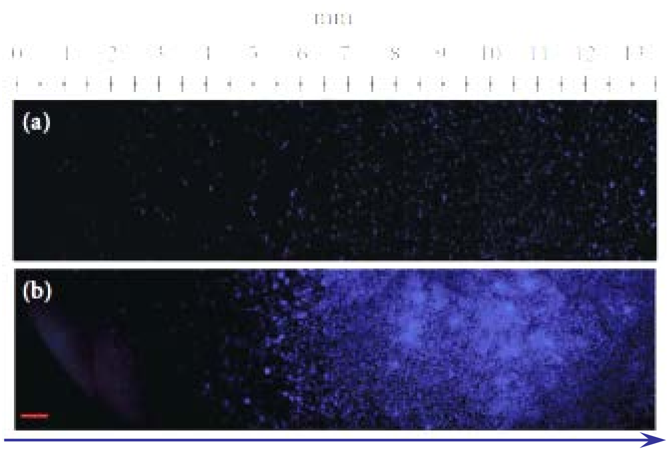
Osteoblasts prefer the rougher part whereas fibroblasts favored the smoother part of the roughness gradient.



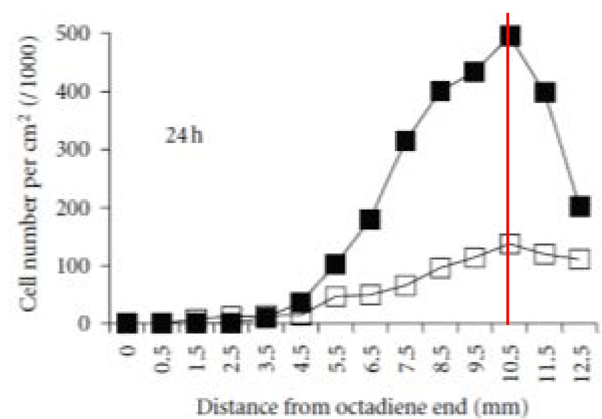
titanium surface with micro-roughness gradient

Cell-material interactions are cell-type specific

Michelmore A. *J Nanomater* **2012**



carboxylic groups



Cells sense chemical gradients

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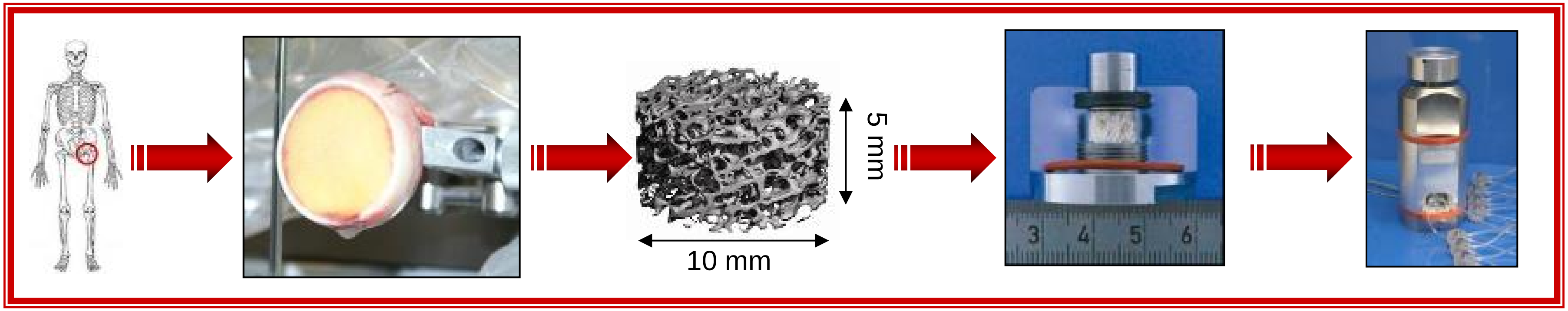
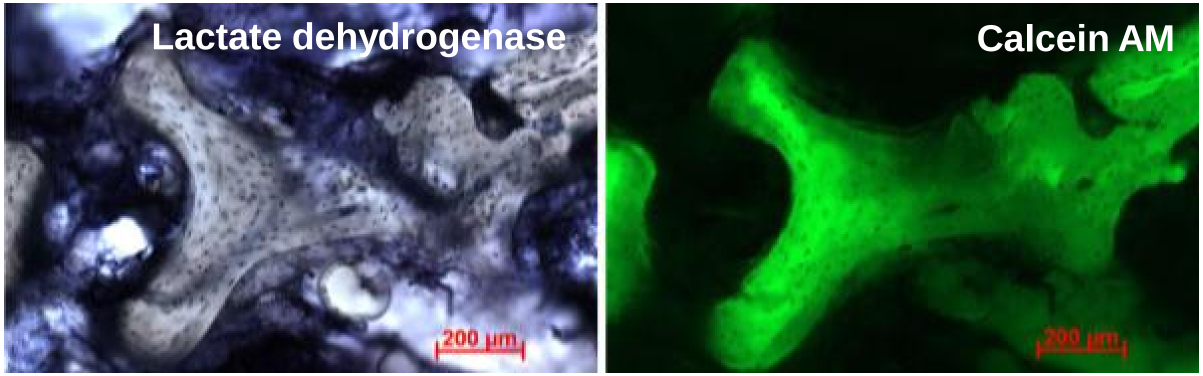
Ex-vivo bone culture in a bioreactor

- Osteoarthritic human femoral heads (total hip replacement)



[C.M. Davies *et al.* (2006)]

Viability of bone cores after 2 week culture



[M.J. Stoddart *et al.* (2006)]

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24th - 26th June 2015, Congress Center, Davos, Switzerland

2016 eCM XVII: Stem cells, Bone Fixation, Repair & Regeneration
20th – 23rd June 2016, Congress Center, Davos, Switzerland

2017 TERMIS-EU Conference (no eCM in 2017) **TERMIS-EU**
26th-30th June 2017 Congress Center, Davos, Switzerland.
Conference Chair: Prof. R. Geoff Richards, PhD Conference
Program Chair: Prof. Mauro Alini, PhD

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2018 eCM XVIII: Cartilage & Disc: Repair and Regeneration
25th - 28th June 2018, Congress Center, Davos, Switzerland

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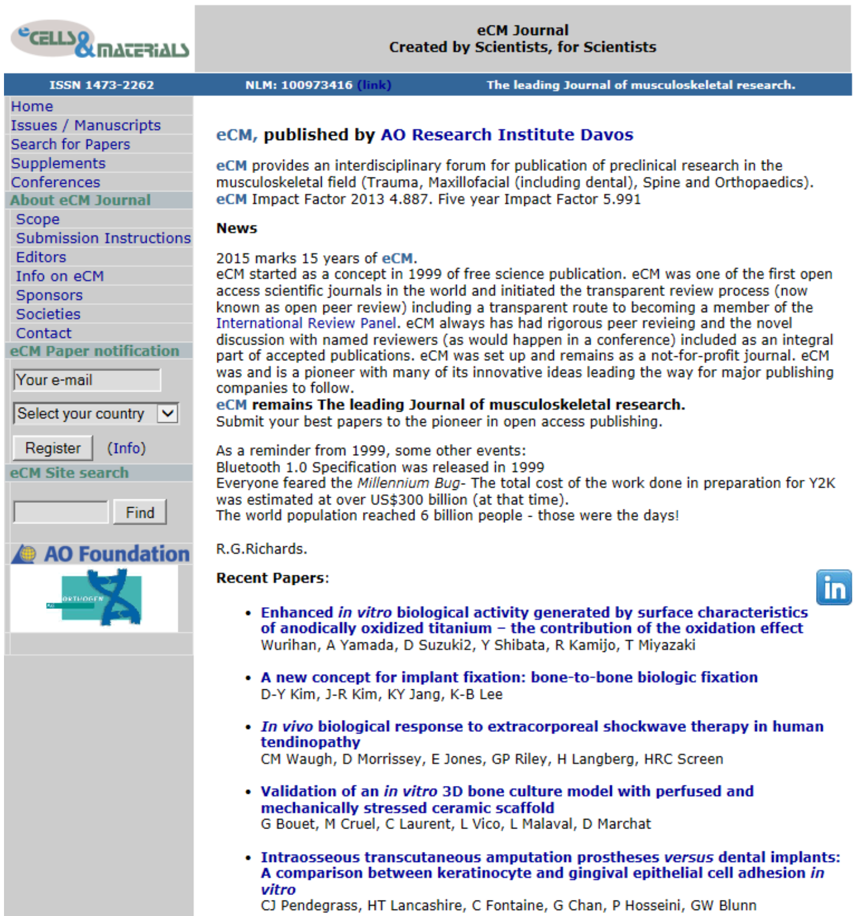
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News

2015 marks 15 years of eCM.
eCM started as a concept in 1999 of free science publication. eCM was one of the first open access scientific journals in the world and initiated the transparent review process (now known as open peer review) including a transparent route to becoming a member of the International Review Panel. eCM always has had rigorous peer revieing and the novel discussion with named reviewers (as would happen in a conference) included as an integral part of accepted publications. eCM was set up and remains as a not-for-profit journal. eCM was and is a pioneer with many of its innovative ideas leading the way for major publishing companies to follow.
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As a reminder from 1999, some other events:
Bluetooth 1.0 Specification was released in 1999
Everyone feared the *Millennium Bug*- The total cost of the work done in preparation for Y2K was estimated at over US$300 billion (at that time).
The world population reached 6 billion people - those were the days!

R.G.Richards.

Recent Papers:

- **Enhanced *in vitro* biological activity generated by surface characteristics of anodically oxidized titanium – the contribution of the oxidation effect**
  Wurihan, A Yamada, D Suzuki2, Y Shibata, R Kamijo, T Miyazaki
- **A new concept for implant fixation: bone-to-bone biologic fixation**
  D-Y Kim, J-R Kim, KY Jang, K-B Lee
- ***In vivo* biological response to extracorporeal shockwave therapy in human tendinopathy**
  CM Waugh, D Morrissey, E Jones, GP Riley, H Langberg, HRC Screen
- **Validation of an *in vitro* 3D bone culture model with perfused and mechanically stressed ceramic scaffold**
  G Bouet, M Cruel, C Laurent, L Vico, L Malaval, D Marchat
- **Intraosseous transcutaneous amputation prostheses *versus* dental implants: A comparison between keratinocyte and gingival epithelial cell adhesion *in vitro***
  CJ Pendegrass, HT Lancashire, C Fontaine, G Chan, P Hosseini, GW Blunn

Official Research Journal of :
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5-year Impact Factor 2013- 5.991

Yearly Impact Factor: 2013 - 4.887

ORS Orthopaedic Research Society
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ORS Orthopaedic Research Society
ORS endorses the educational goals and objectives of the 2014 eCM XV Cartilage and Disc Repair and Regeneration

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Thank you for your attention!

marianna.peroglio@aofoundation.org

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