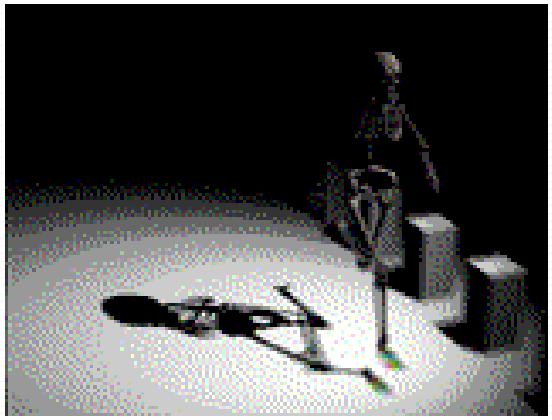
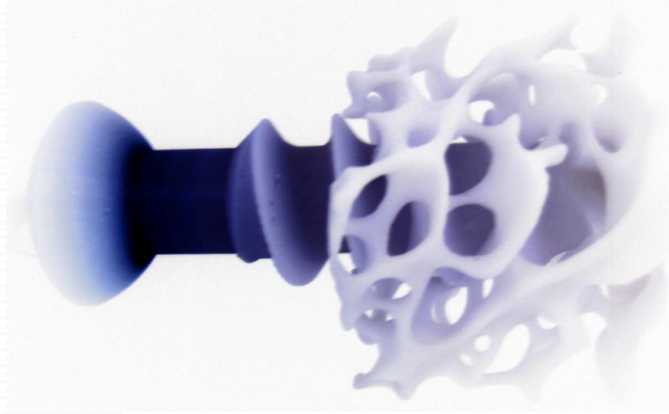
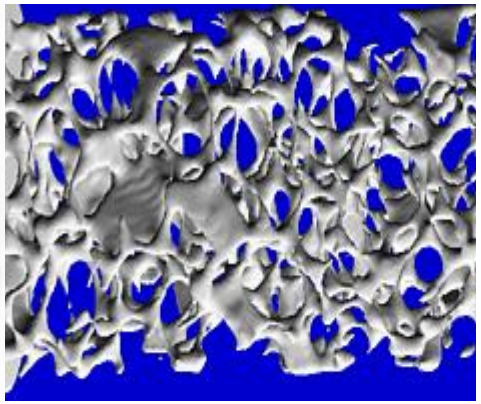

A look into biomaterials - present and future

Eur Ing Prof Philip Procter PhD CEng, CSci,
Medical Device Industry Consultant, Divonne les Bains, FRANCE

- What made me look at biomaterials
- Case study 1 CaP cements
  - Hydroset
  - iN3
- Case study 2 Adhesives that bond bone

- What made me look at biomaterials
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The clinical issues

Whilst biology tolerates hardware well, when it fails there are 3 main issues

Hardware failure <1 %

Infection ~ 2%

Bony failure >3-10+%

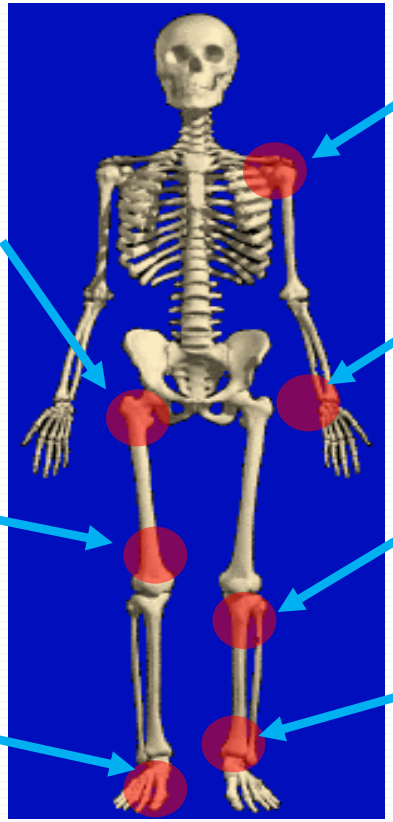
(Usually a screw)

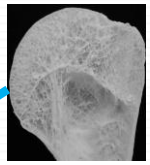
Associated medical devices for fracture repair…..

Note: most connect to bone with screws

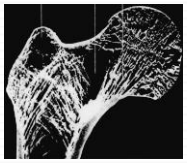
Wherever metallic screws are used in poor bone there are failures.....

Typical screw migration/cut –out /loosening rates





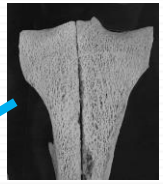
15-40%



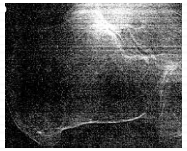
2-8%

1-2%

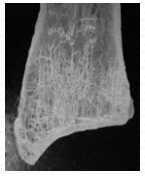
3-6%



3-7%



~4%



2-6%

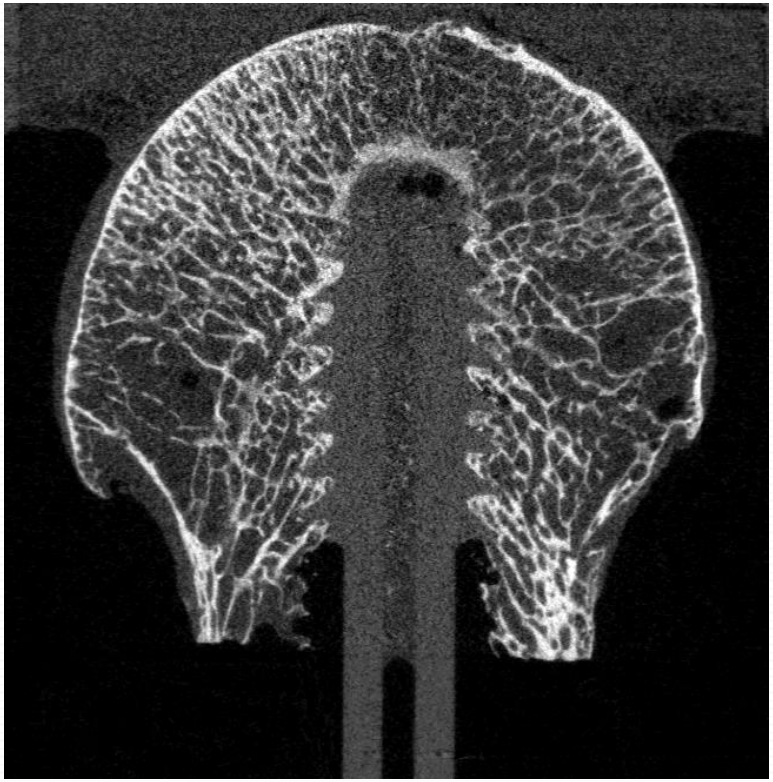
Of 100 000 000 Screws implanted per year US/EU

> 1%

=

1 000 000 failed screws

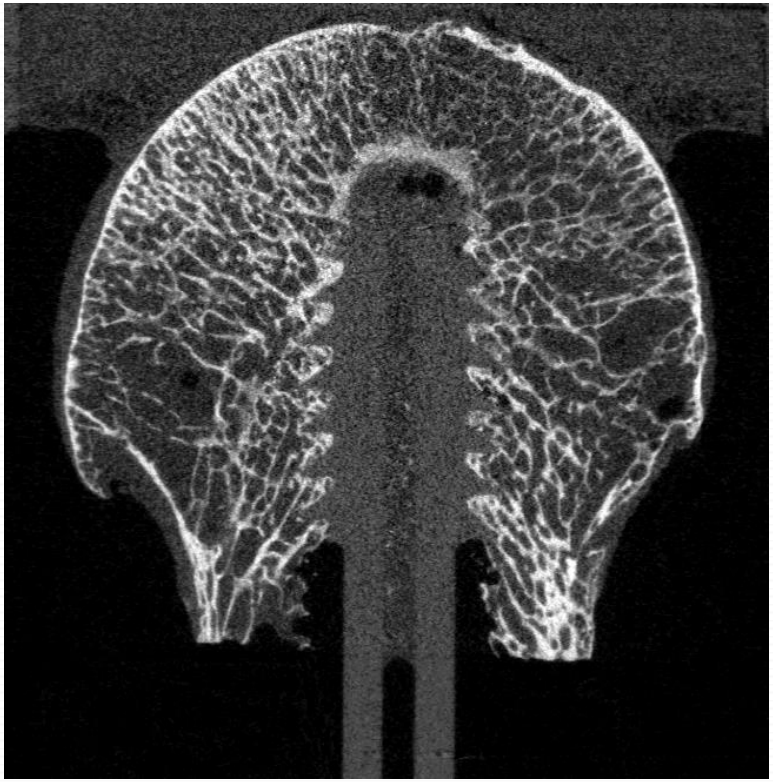
Bone mass close to the fixation device an unresolved mechanobiological challenge



high bone mass:
support of peri-implant bone

Mueller et al. (2013). *MedEngPhys*
With courtesy of Prof Van Lenthe, Leuven University, Belgium

Bone mass close to the fixation device an unresolved mechanobiological challenge



high bone mass:
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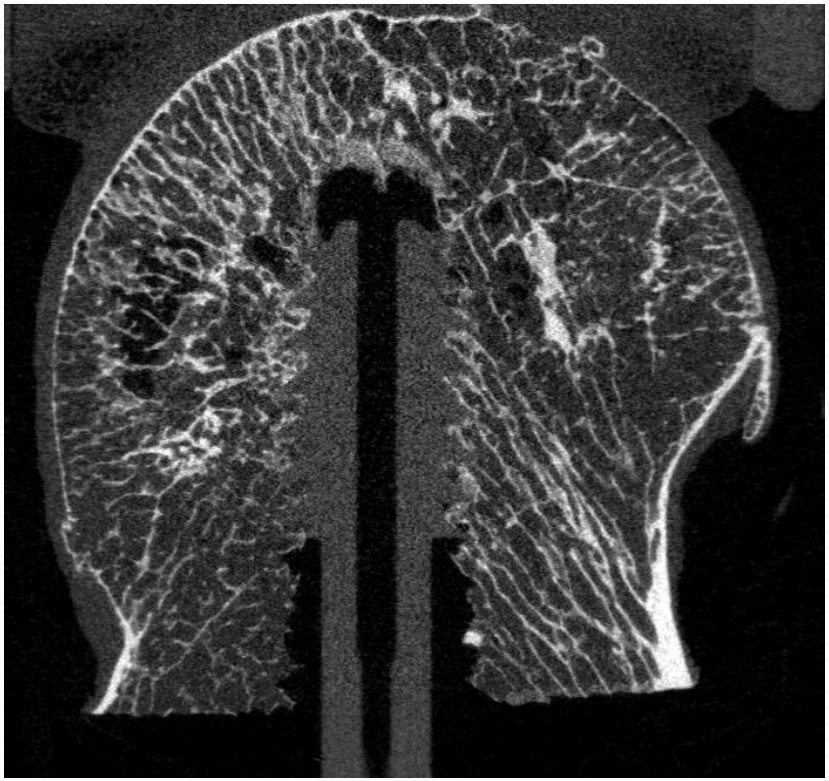
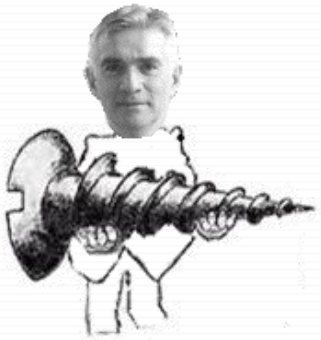


low bone mass:
direct failure at the interface

Mueller et al. (2013). *MedEngPhys*
With courtesy of Prof Van Lenthe, Leuven University, Belgium

This lead me to look at augmenting fixation of screws using biomaterial technologies



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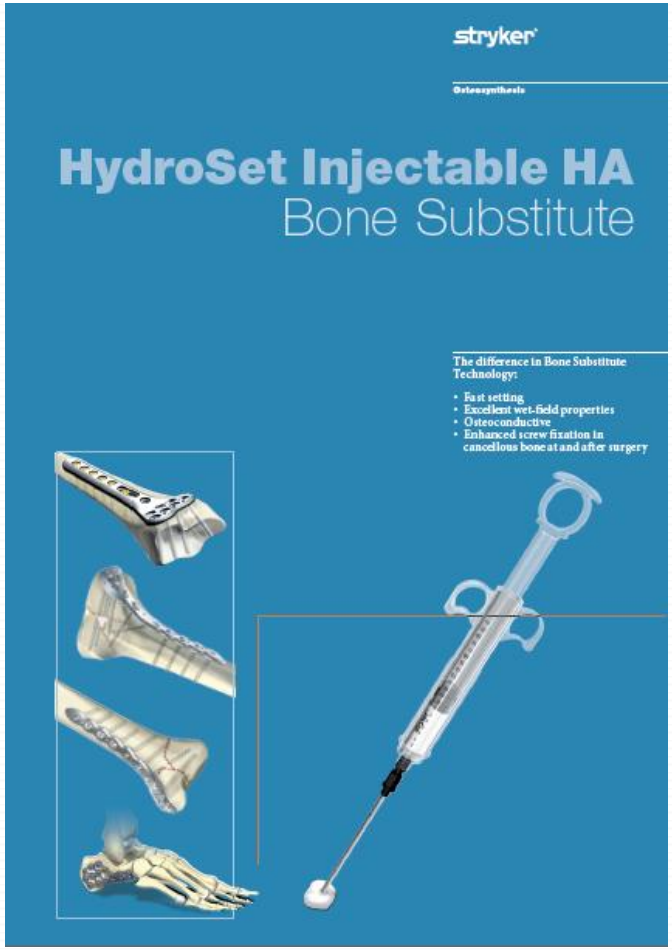
Injectable cements: Meeting a clinical need

Many years ago surgeons recognised that

- Many fractures result in bone voids....
- Holding power of screws in poor cancellous bone was a concern…
- A synthetic bone substitute with potential for remodelling/osteoconduction! was a potential solution

We developed a CaP for void filling and screw augmentation



HydroSet: What is it?

Powder

Liquid

Di + Tetra Calcium Phosphate

+

TriSodium Citrate

Mix,

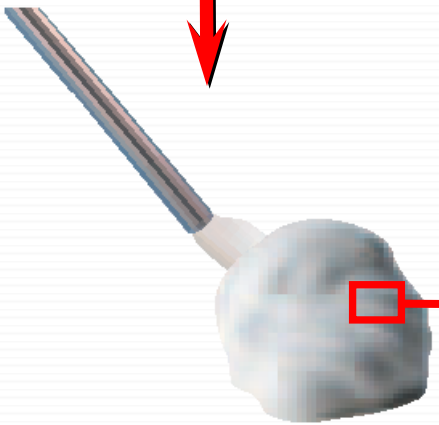
Inject,

Set

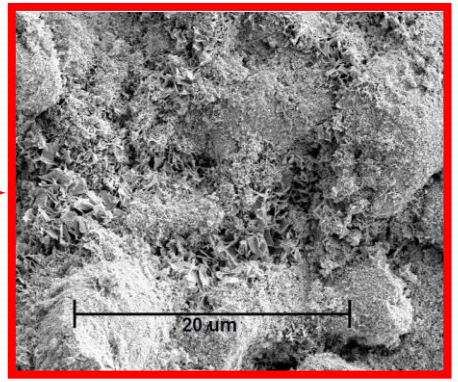
Sodium Phosphate

+

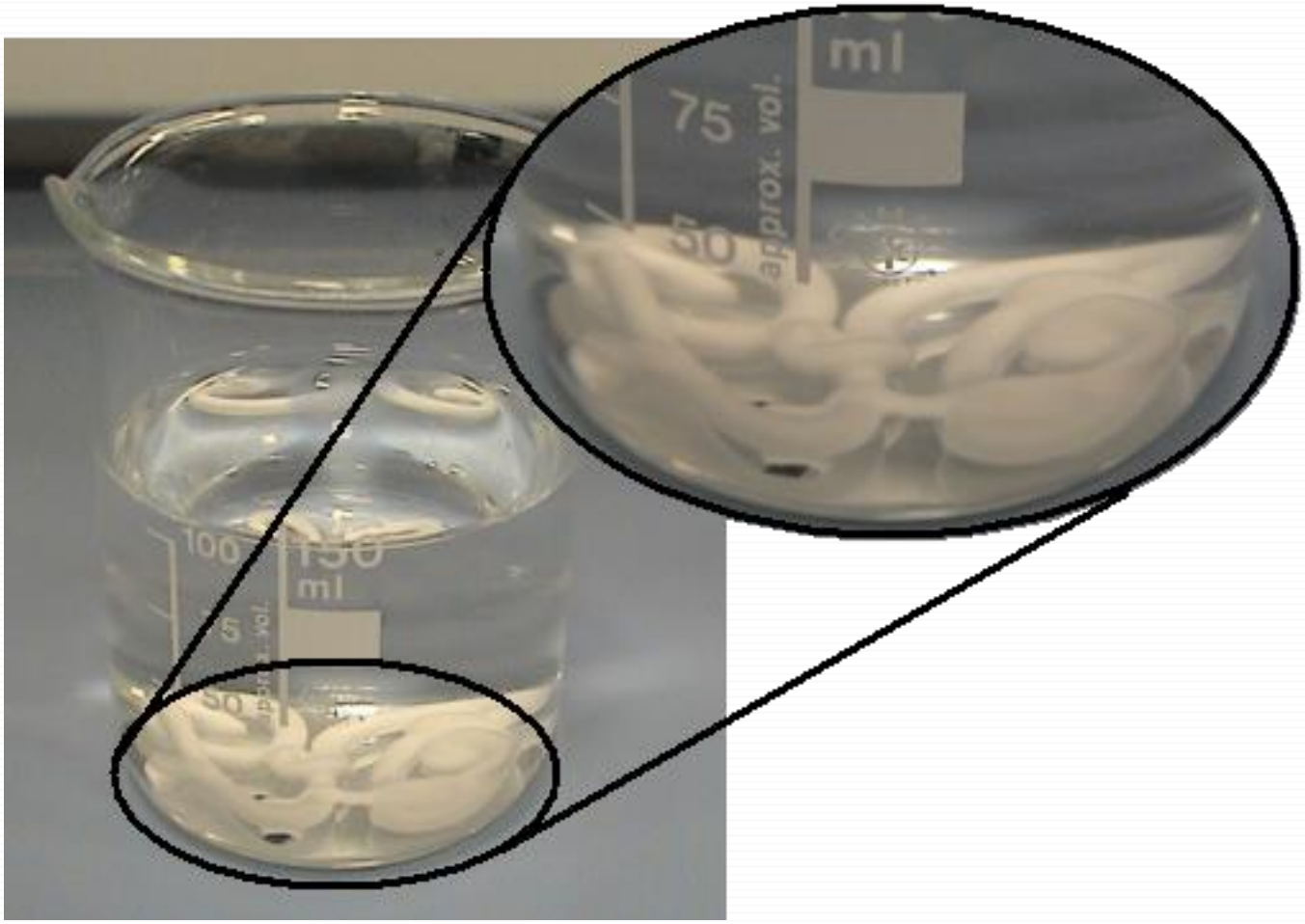
PolyVinylPyrrolidone



Hydroxyapatite (HA)



We were good (lucky ☺) as it had excellent wet field & setting properties



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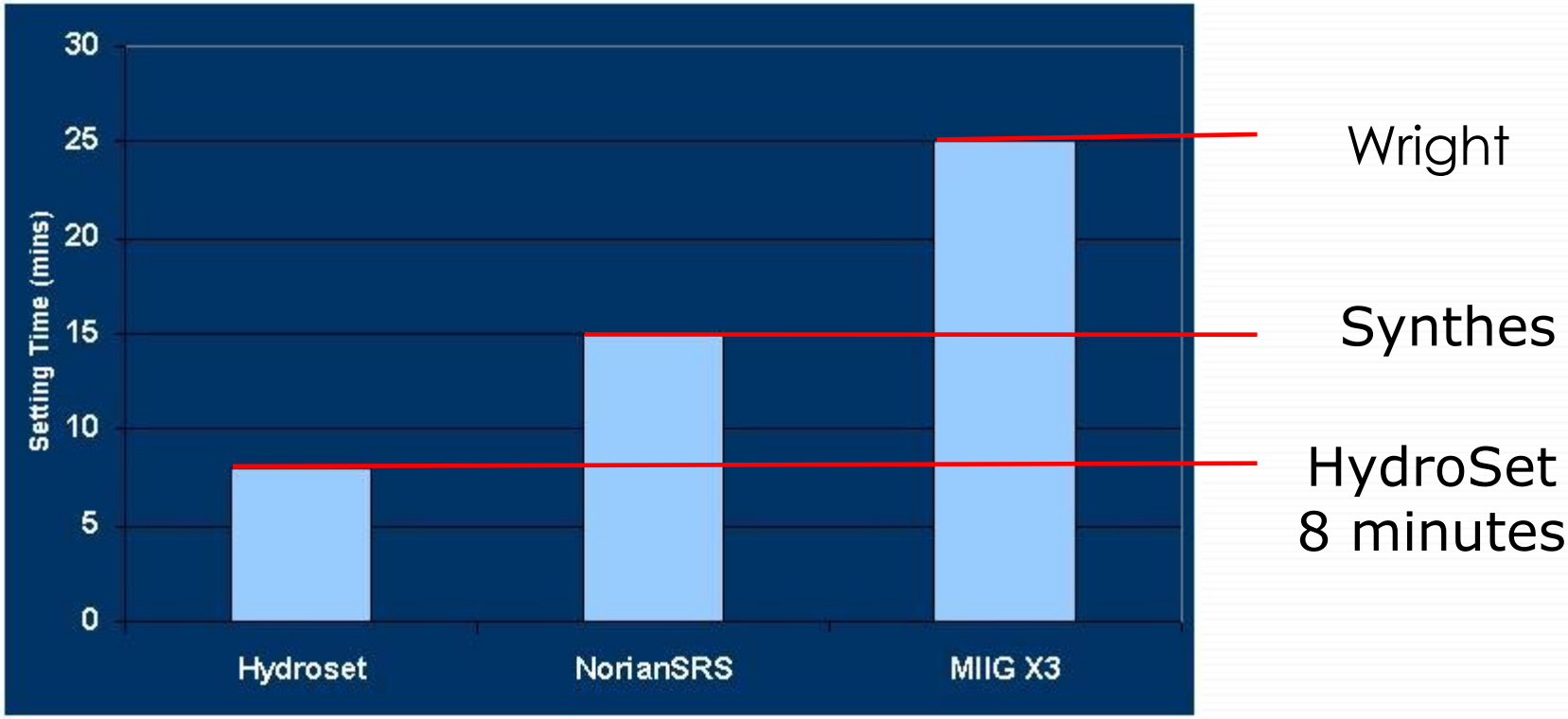


Typical Trauma Void Filling Application.....

Augmentation of Tibial Plateau Fractures with Calcium Phosphate Cement: A Randomized Study Using Radiostereometry

Sune Larsson, MD (n); Per Berg, MD (n); Marcus Sagerfors, MD (n);
Department of Orthopedics, Uppsala University Hospital,
Uppsala, Sweden

Average depression at 12 months
1.4 mm with CaP Cement
3.9 mm with Bone Graft

- Depressed tibial plateau

HydroSet

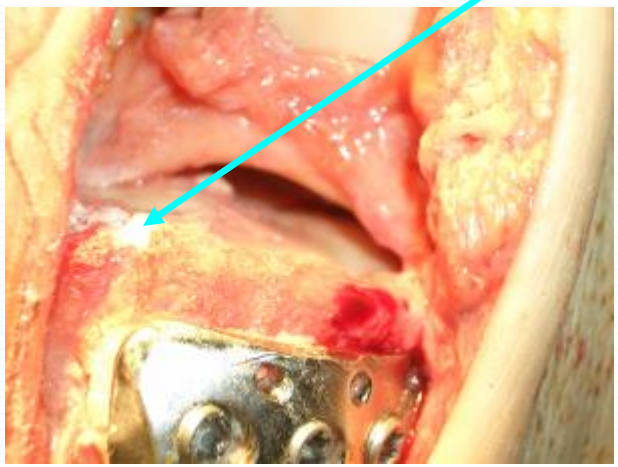
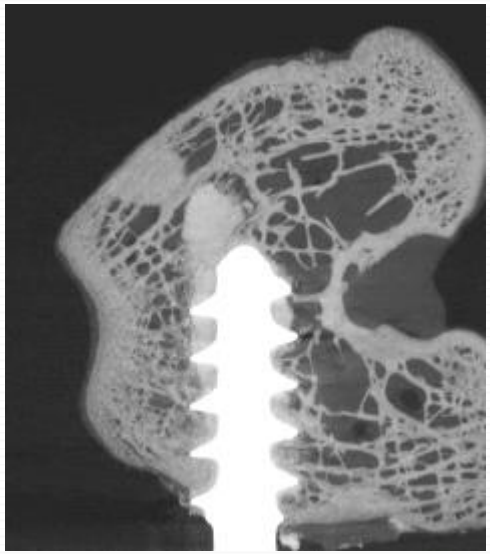


Plate and screws

Screws alone

HydroSet^{tm} Bone Augmentation Rabbit Study



4mm cancellous screws

Overdrilled to weaken bone

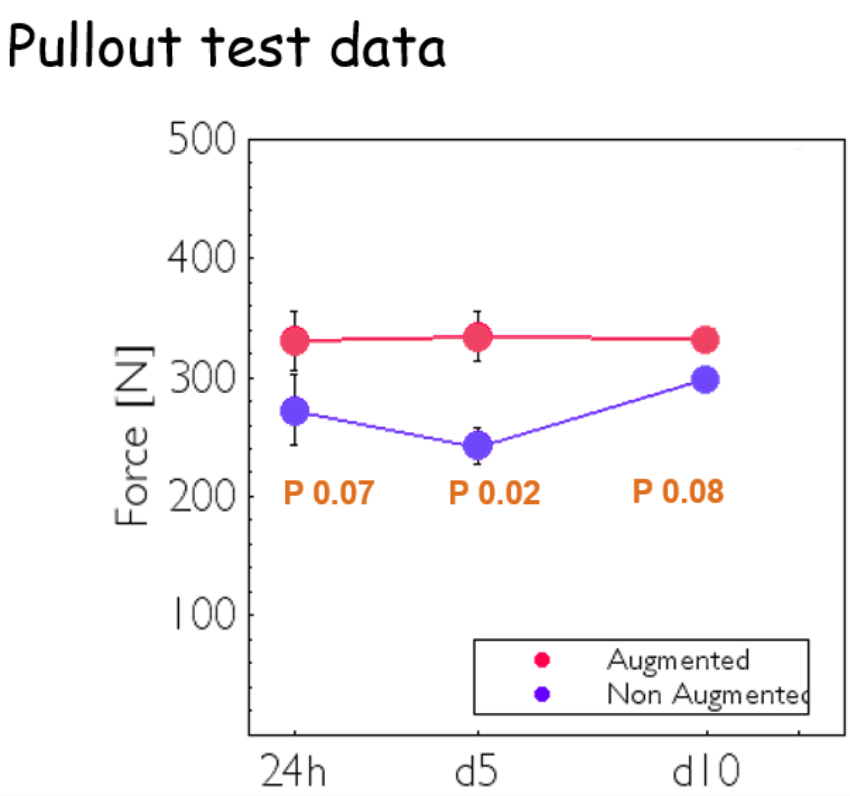
Hoshikawa A, Fukui N, Fukuda A, Sawamura T, Hattori M, Nakamura K, Oda H, 2003: Quantitative analysis of the resorption and osteoconduction process of a calcium phosphate cement and its mechanical effect for screw fixation.
Biomaterials Vol. 24, 4967-4975
Gardner MJ, Griffith MH, Demetrakopoulos D, Brophy RH, Grose A, Helfet DL, Lorich DG , 2006. Hybrid locked plating of osteoporotic fractures of the humerus.
J B J S Vol 88 A, No 9, 1962-7

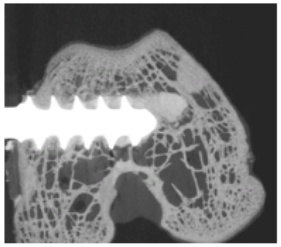
Goals to demonstrate:

Safety: Addition of HydroSet^{tm} did not diminish holding power

Efficacy: Hydroset^{tm} enhances screw fixation at and after surgery

HydroSet™ Bone Augmentation Rabbit Study

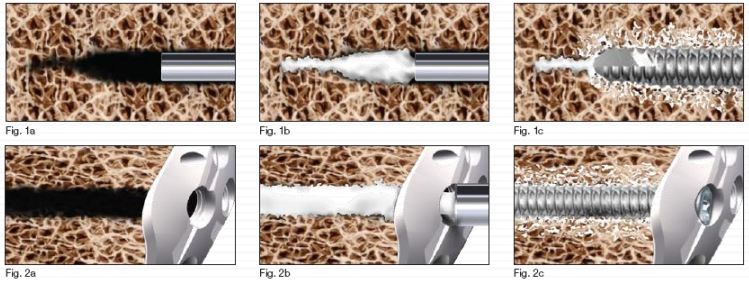


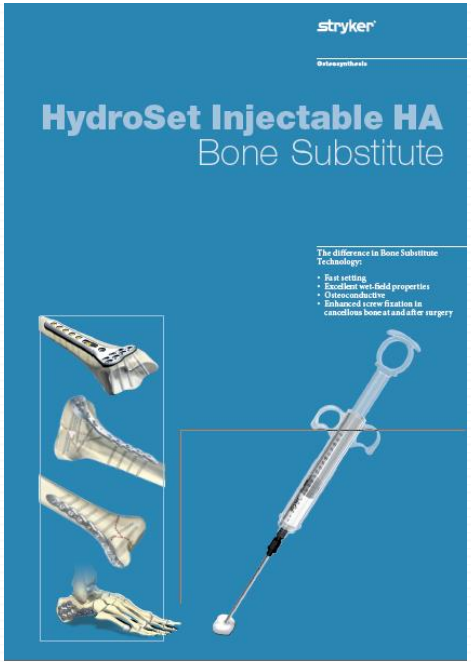


We get regulatory approval September 2008

The difference in Bone Substitute Technology:

- Fast setting
- Excellent wet-field properties
- Osteoconductive
- Enhanced screw fixation in cancellous bone at and after surgery

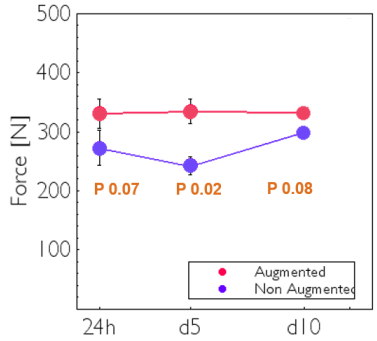


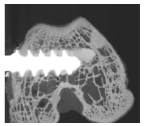


NB No US approval for this claim

Translating from lab data to sales

Pullout test data





Seeing is believing

Does it really work?

Clinical translation is much harder to prove

Arch Orthop Trauma Surg (2013) 133:487–494
DOI 10.1007/s00402-012-1677-2

TRAUMA SURGERY

Absorbable and non-absorbable cement augmentation in fixation of intertrochanteric femur fractures: systematic review of the literature

Surena Namdari · Remy Rabinovich · John Scolaro · Keith Baldwin · Mohit Bhandari · Samir Mehta

Received: 1 July 2012 / Published online: 13 January 2013

5 used PMMA

2 use CaP

«Augmentation of intertrochanteric femur fractures with polymethyl methacrylate or calcium–phosphate **may provide benefits** in terms of radiographic parameters and complication rates; however, **more stringent research methodology is necessary to determine the extent of the benefit"**

- What made me look at biomaterials
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iN3 - A better Calcium Phosphate Cement

- Innovision
  - 1st US approved cement delivery implants
- Innotere
  - Unique cement proposition
- Medmix
  - Biomaterial mixing/delivery technology
- Celgentek
  - Sales and distribution in 3 key EU markets

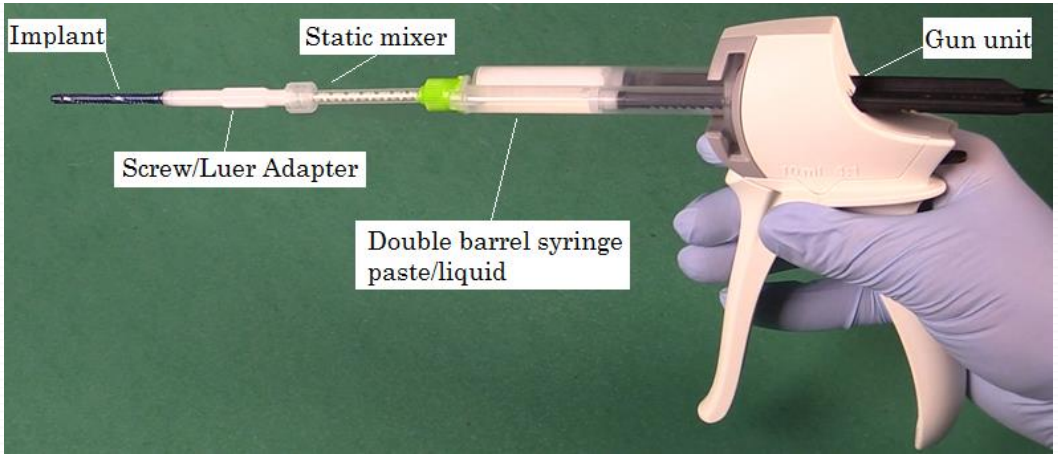
Enabled members to be part of a larger project
«Punch above their individual weight»

One path though the investment/risk paradox: SME's combine forces..

2014 We set up a company syndicate model

2015 Completed CE registration/EU sales proven

2016 Project wholly acquired by ZBT for 20 mil USD



3 of 4 SME's now acquired

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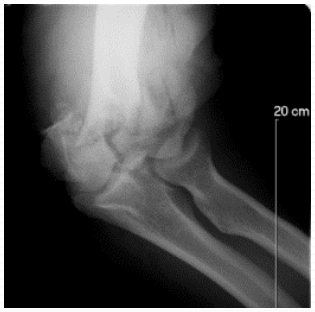
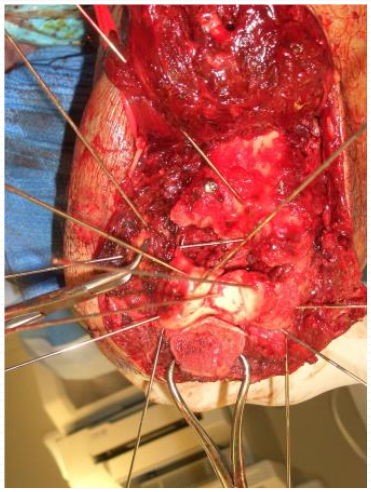
Why an adhesive biomaterial?





Powerful unmet clinical needs

Clinicians dream of bone adhesives

materials

MDPI

Review

Current State of Bone Adhesives—Necessities and Hurdles

Kai O. Böker et al

Department of Trauma Surgery, Orthopaedics and Plastic Surgery, University Medical Center Goettingen, Robert Koch Straße 40, 37075 Göttingen, Germany

Materials 2019, 12, 3975; doi:10.3390/ma12233975 www.mdpi.com/journal/materials

"The vision of gluing two bone fragments with biodegradable and biocompatible adhesives remains highly fascinating and attractive to orthopedic surgeons"

Adhesive biomaterials - many requirements

Must work reliably in bloody, fatty fields

Sufficient strength at & after surgery

Be biologically friendly

Allow healing through itself & then disappears!

Adds clinical value where there are needs, cost effectively.

Product meets the medical device requirements

Few candidates can do all these

We looked into many possible natural sources of an adhesive

Biopolymer
Biopolymer Products of Sweden AB

Pre-commercial MAP Mefp1 extraction process already in place...
Lots of data... appeared feasible

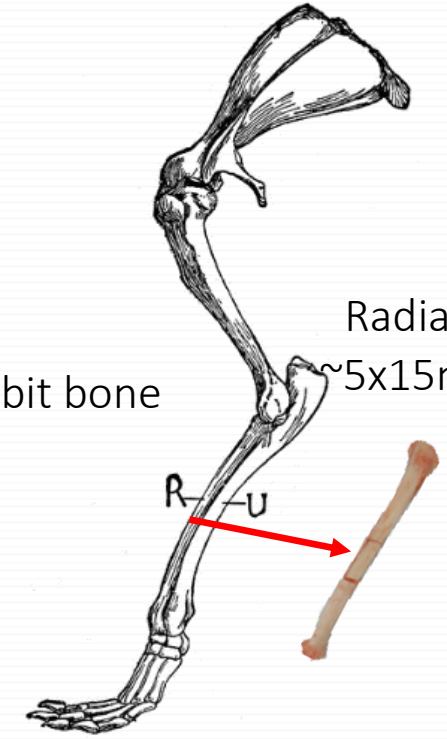
Extraction of Mefp1 from mussel feet ~ 97% purity

The mussel foot

Shucked many 1000's mussel
Removing the foot for processing

Initial lab testing promising

In-vivo there are biocompatibility problems longer term



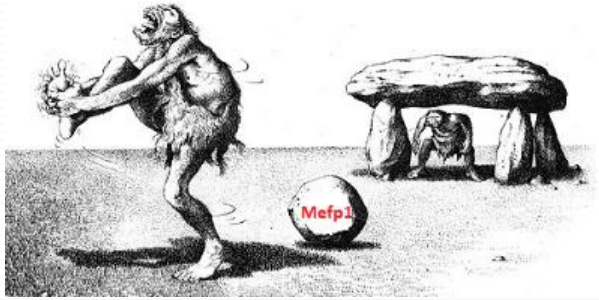
Rabbit bone

Radial bone flap
~5x15mm @ day 1

6/8 detach

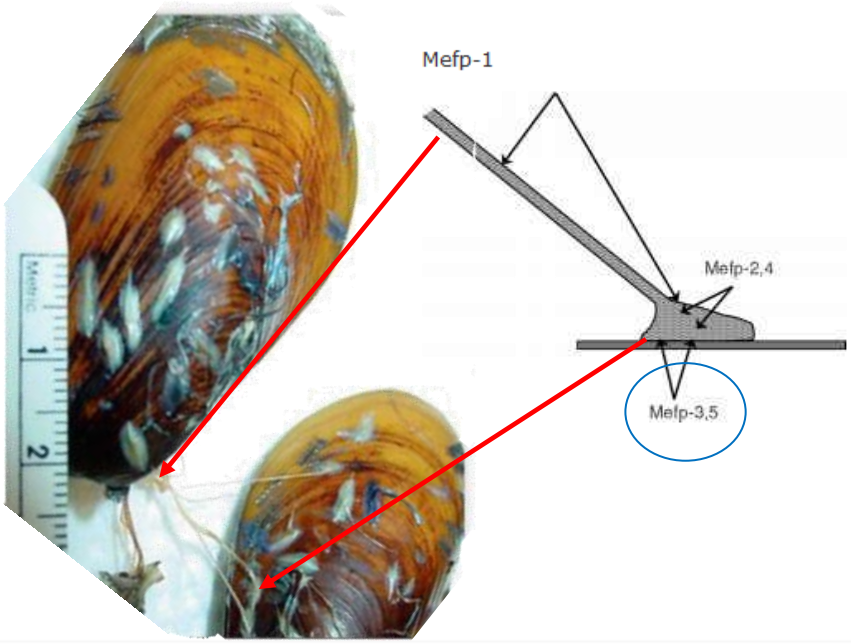
~3 weeks

biocompatibility Issues?



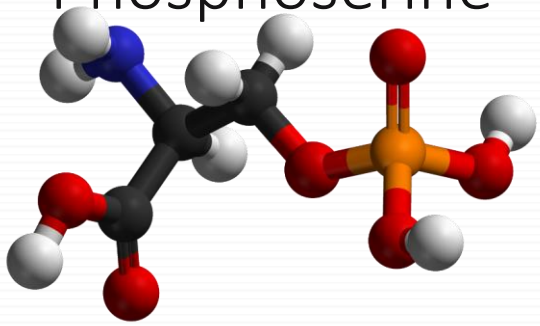
There is a silver lining to the cloud!

Clues to another path!



M. edulis attaches to seaweed, other mussels, stainless steel and even Teflon via mefp 3-5!

Mefp5
rich in an amino acid
Phosphoserine



"Phosphoserine is in proteins that bind calcareous materials e.g., osteopontin"

Understanding Marine Mussel Adhesion Silveman G H, and Roberto F F, Mar Biotechnol (NY). 2007 Dec; 9(6): 661–681.

The story behind OsStic bone adhesive

2012 PP - Consultancy in France.

2013 Demo to Håkan @ Uppsala Uni

2014 PP/GI form GPBio Ltd focus adhesives

36kg@24h

2014 start applied research at UU

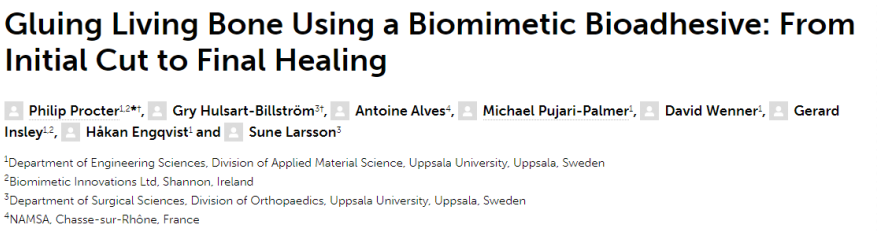
Novel formulations based on PSer, aTCP, CSi & water

3 patents and 10+ publications

OsStic^{R} Adhesive Safety/Efficacy profile

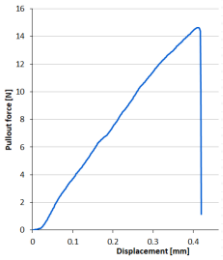
- Safety (soft tissue in-vivo) 6/12 week data excellent biocompatibility

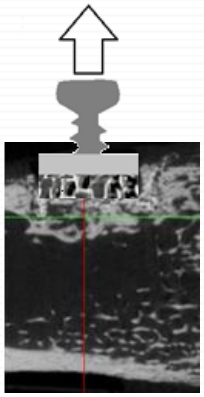
- Efficacy (hard tissue in-vivo) 42 day murine study



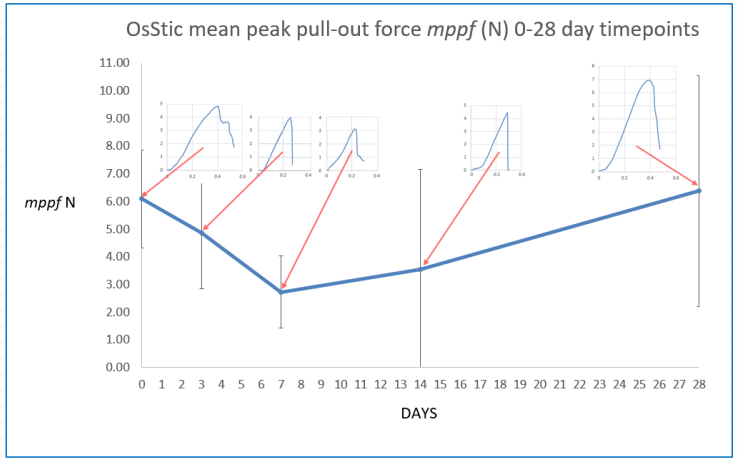
OsStic in-vivo murine bone model

Bone core gluing

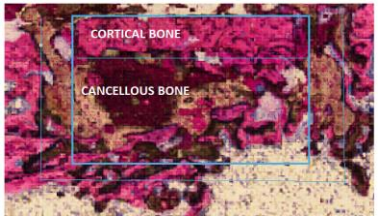




Pull-out testing

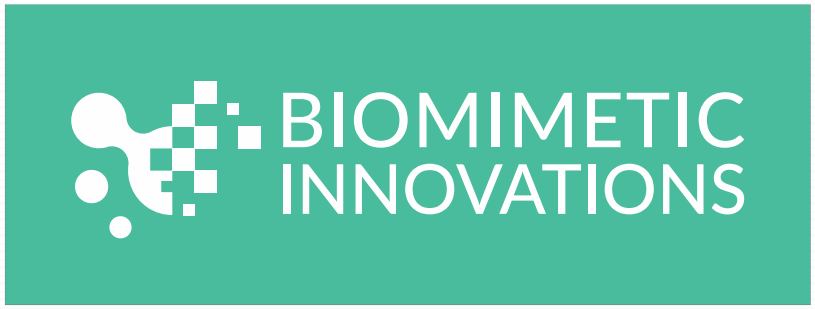


Summary *in vivo* force data



@42 days adhesive remodels >
70% cancellous
50% cortical

In 2020 GPBio and PBC Biomed create



Biomimetic Innovations Ltd

Shareholding of both companies

GP Bio

PBC Biomed

Biomimetic Innovations Ltd

Limited Company registered in Ireland

- Assets include 3 OsStic Patents
- Allows for clear project focus
- Allows for business separation

February 20th 2020

PBC Biomed Ltd

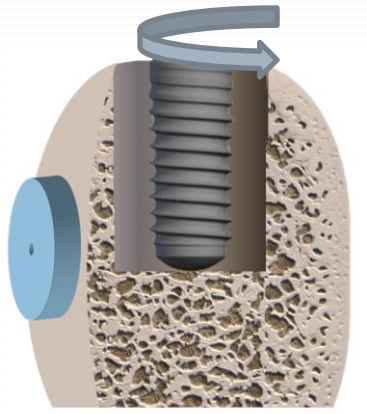
Located in close proximity to Shannon International Airport

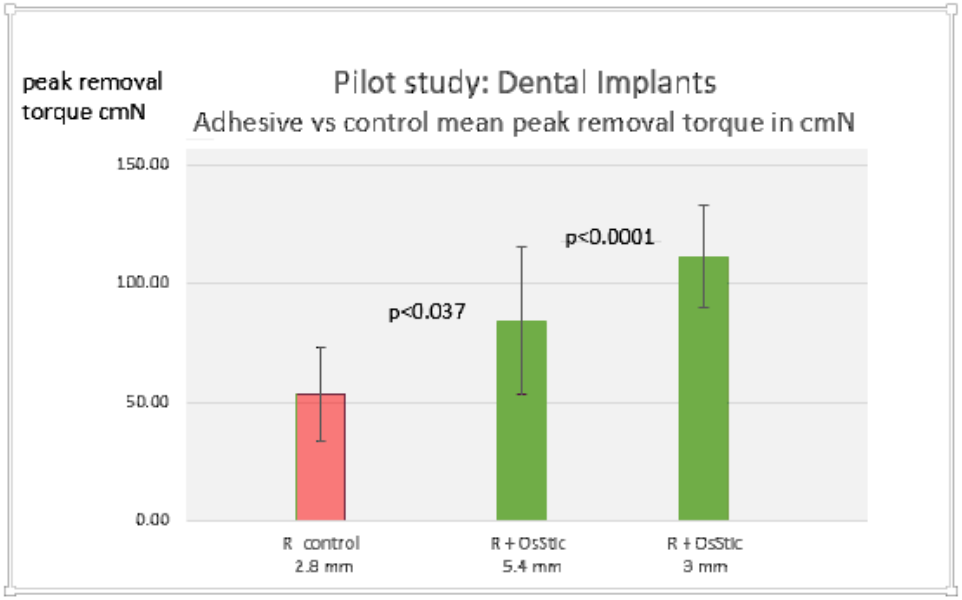
Class 8 Clean room and laboratories.

BSI approved for manufacturing and services

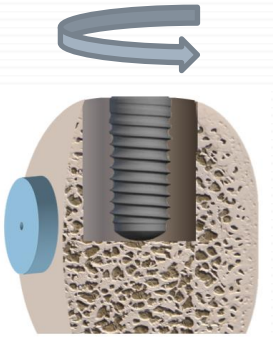
bsi. ISO 13485:2016 Medical devices Quality management ISO 9001:2015 Quality management

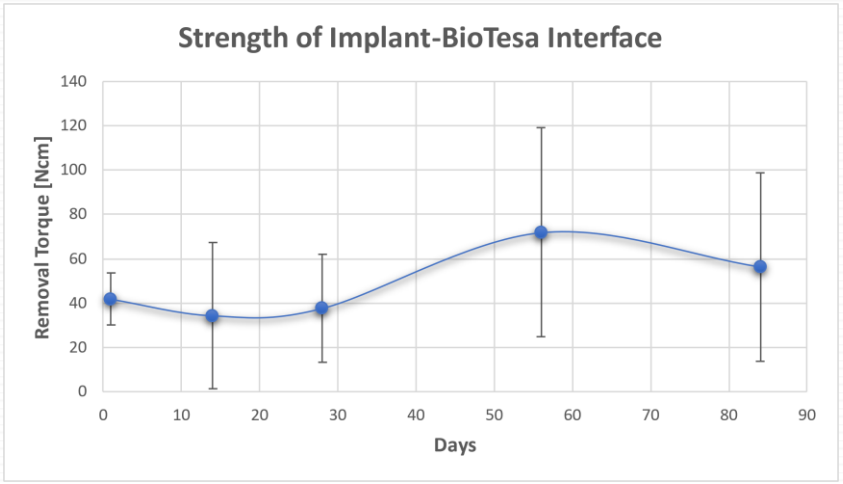
OsStic Dental – POC ex-vivo porcine bone removal torque





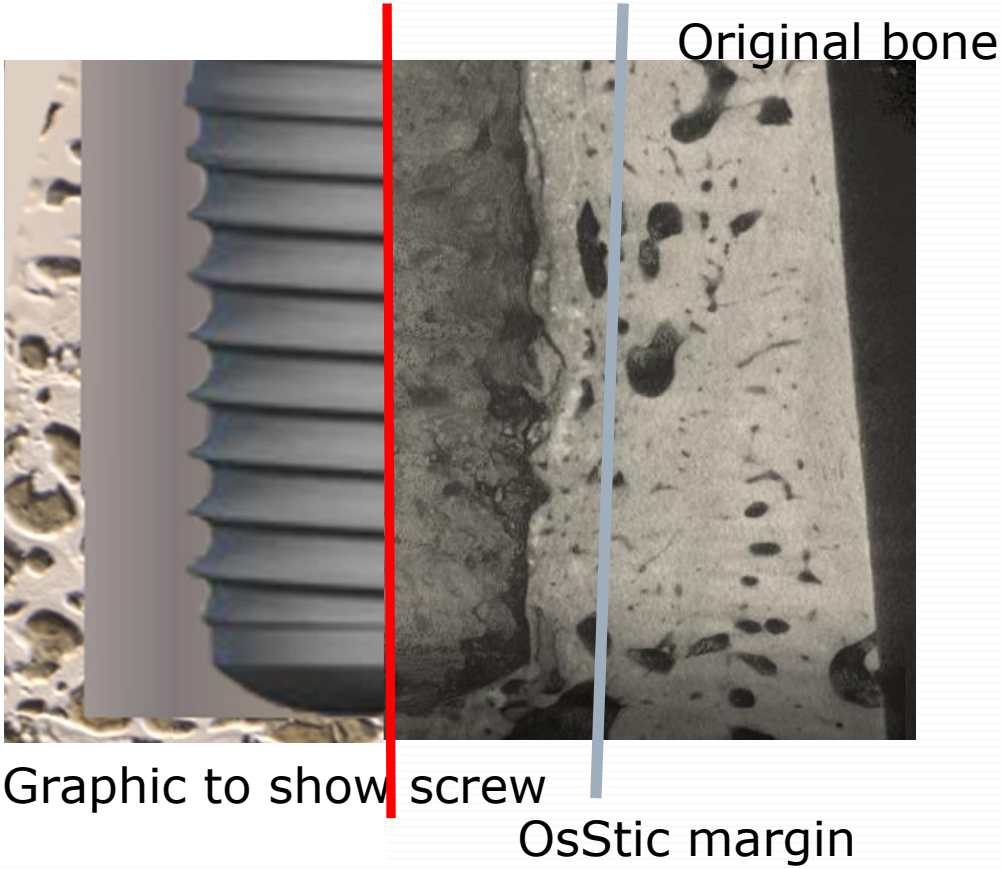
OsStic Dental POC in-vivo porcine removal torque @ 12 weeks

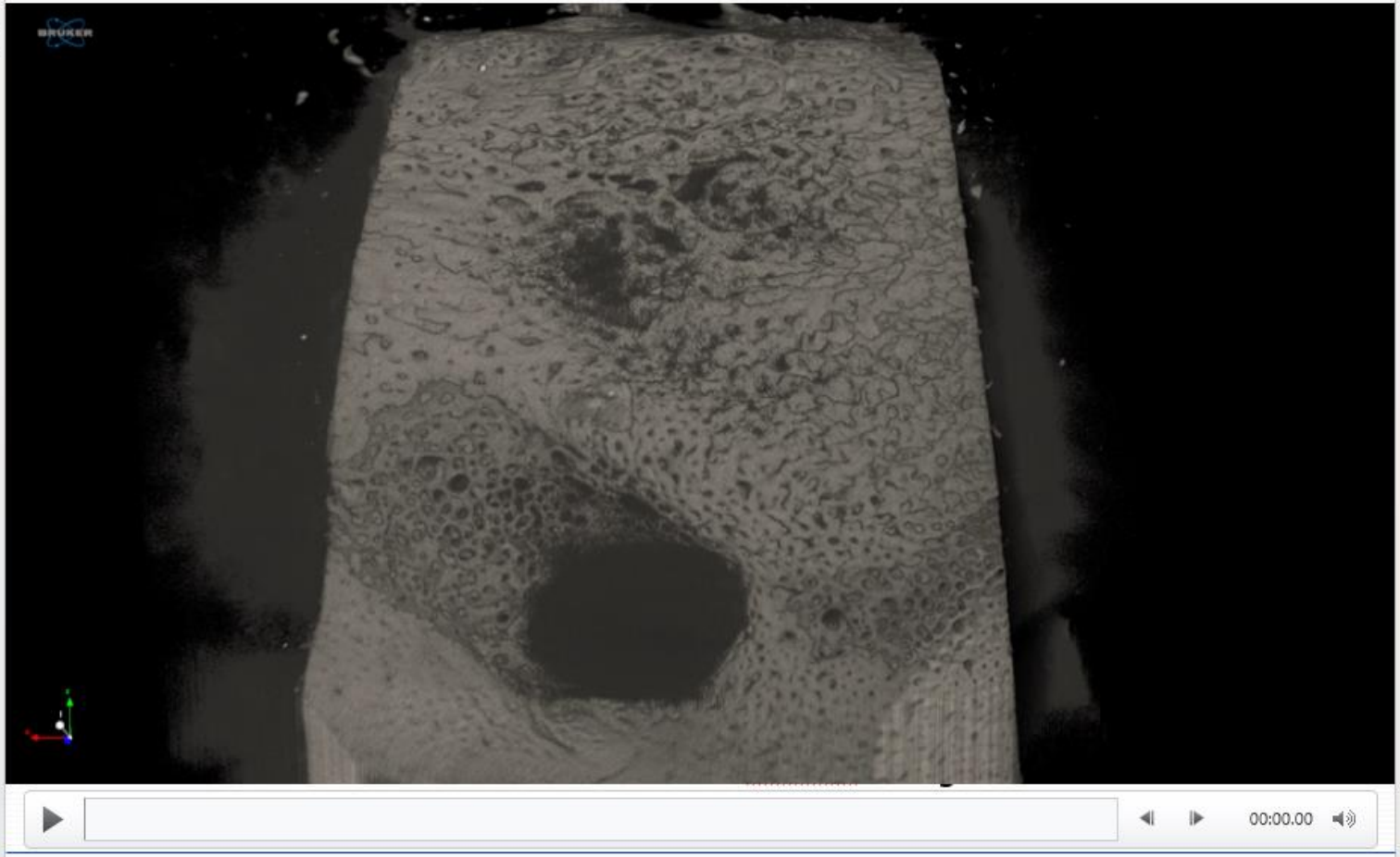




Failure occured at the Implant/BioTesa interface

OsStic Dental in-vivo µCT at 8 weeks

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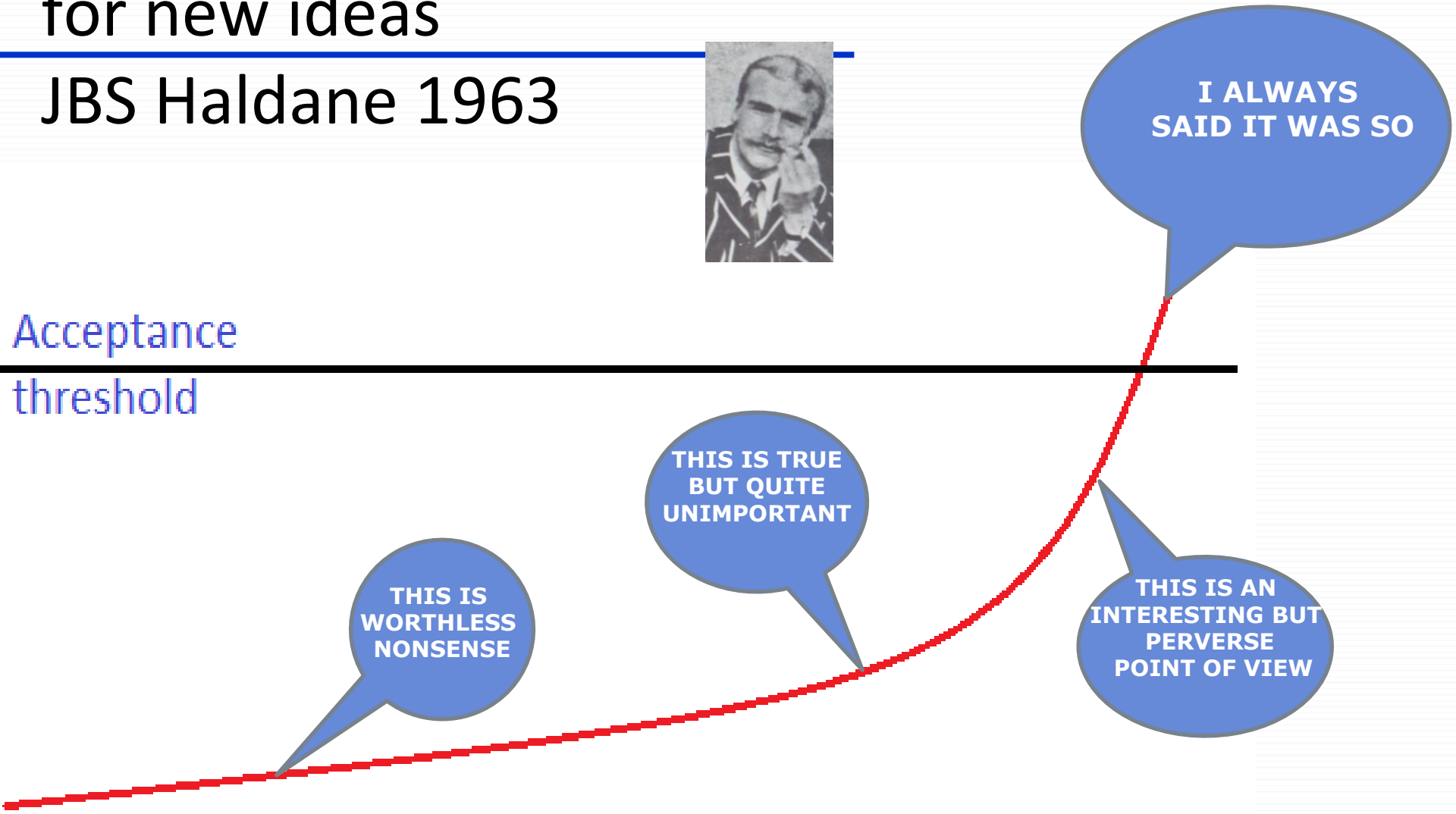
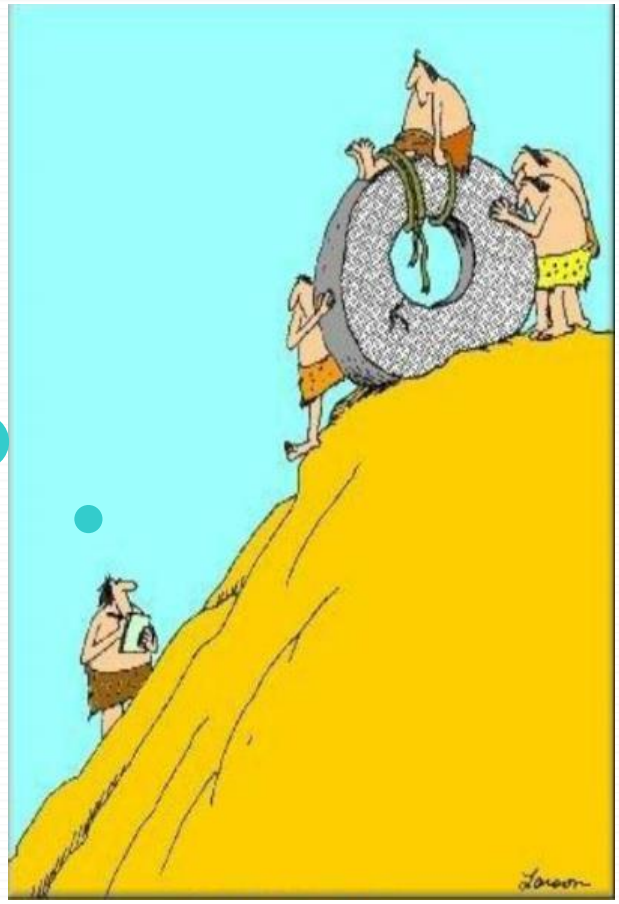
The 4 stages of acceptance for new ideas

JBS Haldane 1963



Just a few more trials
then it will be perfect



A Revolutionary technology takes longer and more trials to perfect than anyone realises

Future technology

Future Technology

Great to aim high

Reasonable balance between evidence of clincal benefit and cost…..

Thank you for your kind attention