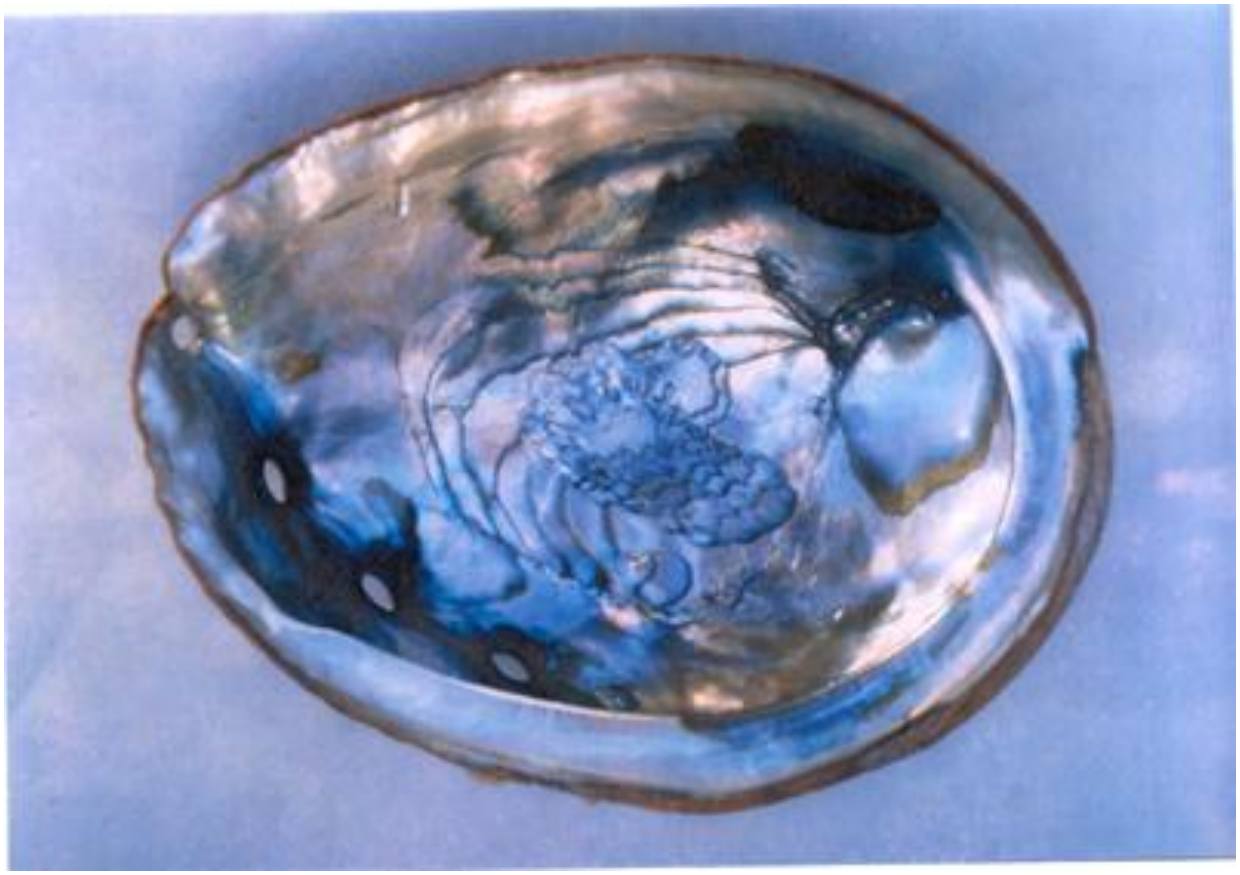
From Broida to Bedside: From Fundamental to Clinical Research on Bone Fracture

Paul Hansma

presenting collaborative work done at

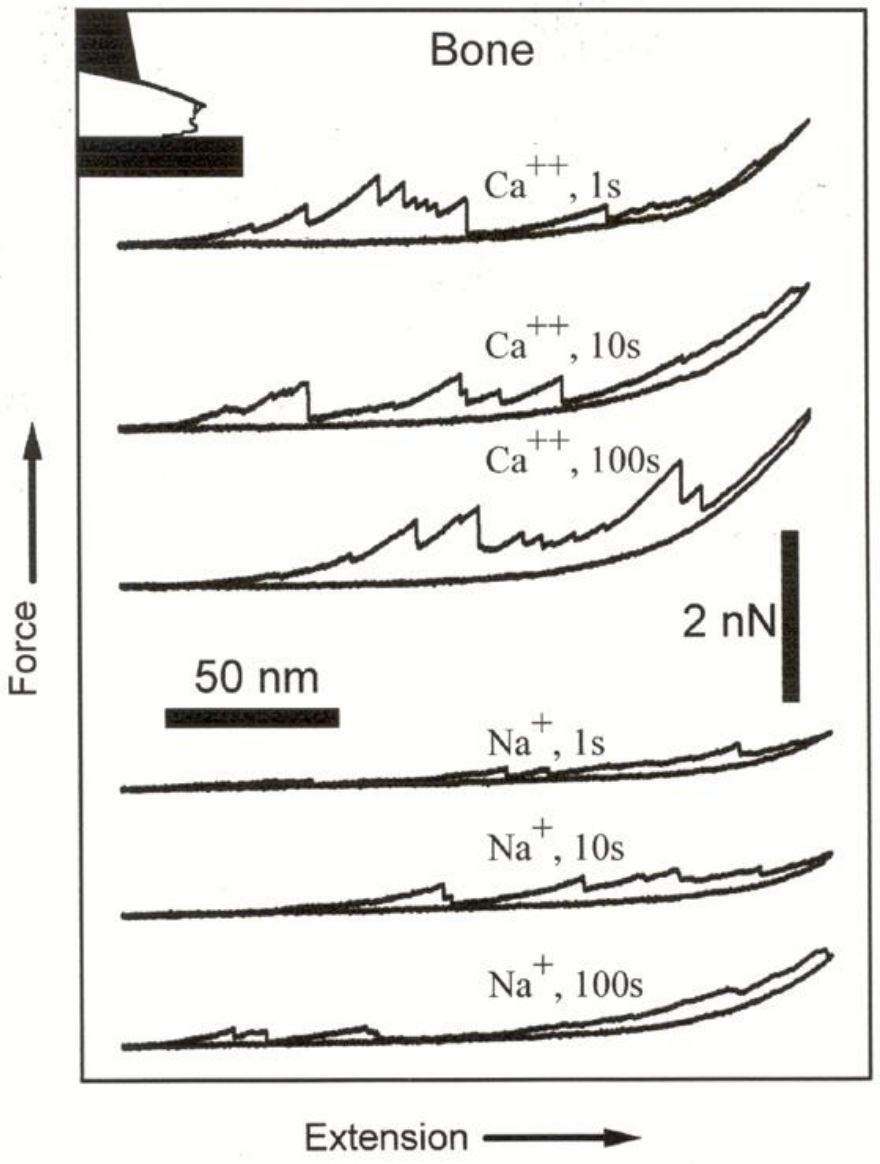
Hospital del Mar-IMIM, Autonomous University of Barcelona
Department of Physics, University of California, Santa Barbara
Active Life Scientific, Inc. Santa Barbara

An Abalone shell is 97% crystalline calcium carbonate



But it is 3000 times more fracture resistant than crystalline calcium carbonate! WHY?

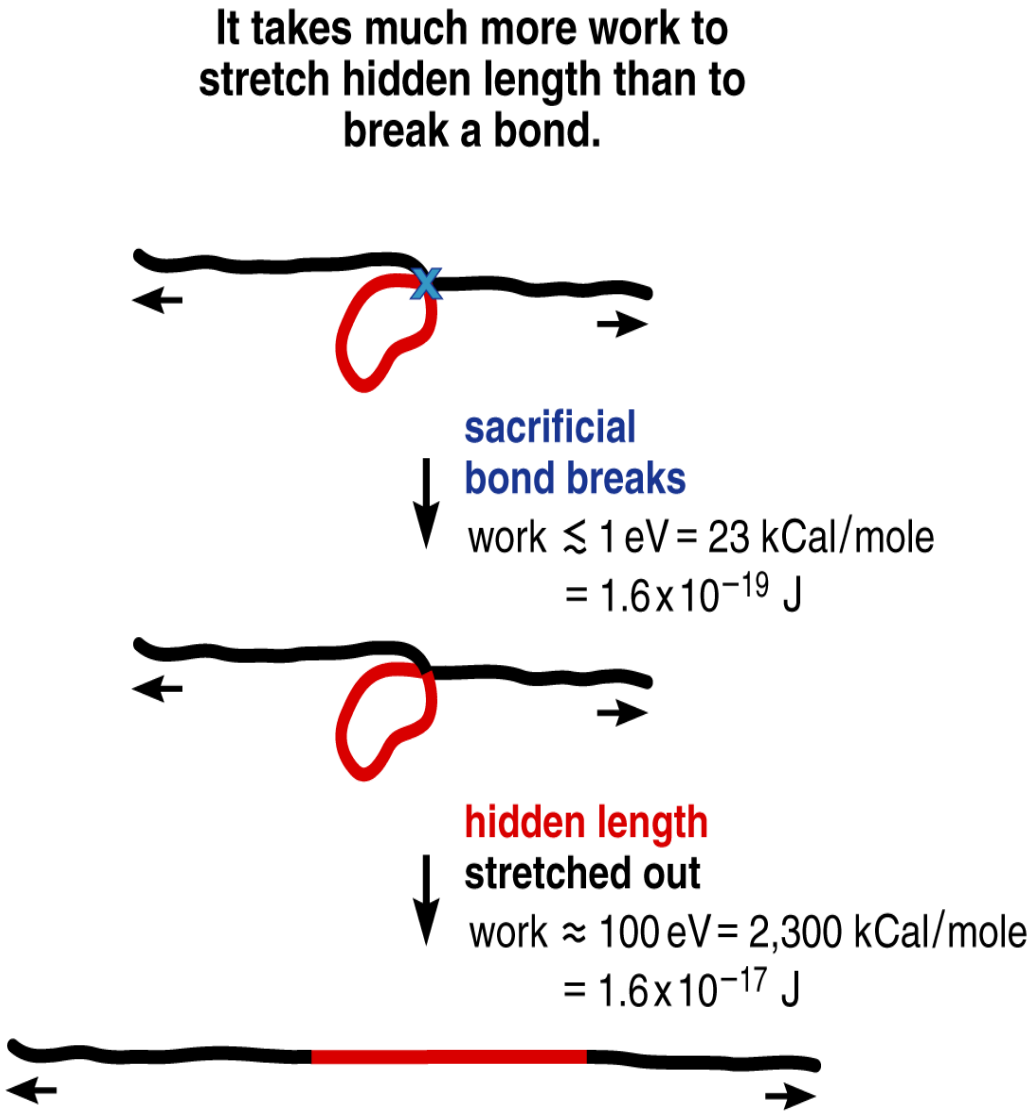
Sacrificial Bonds and Hidden Length in Bone



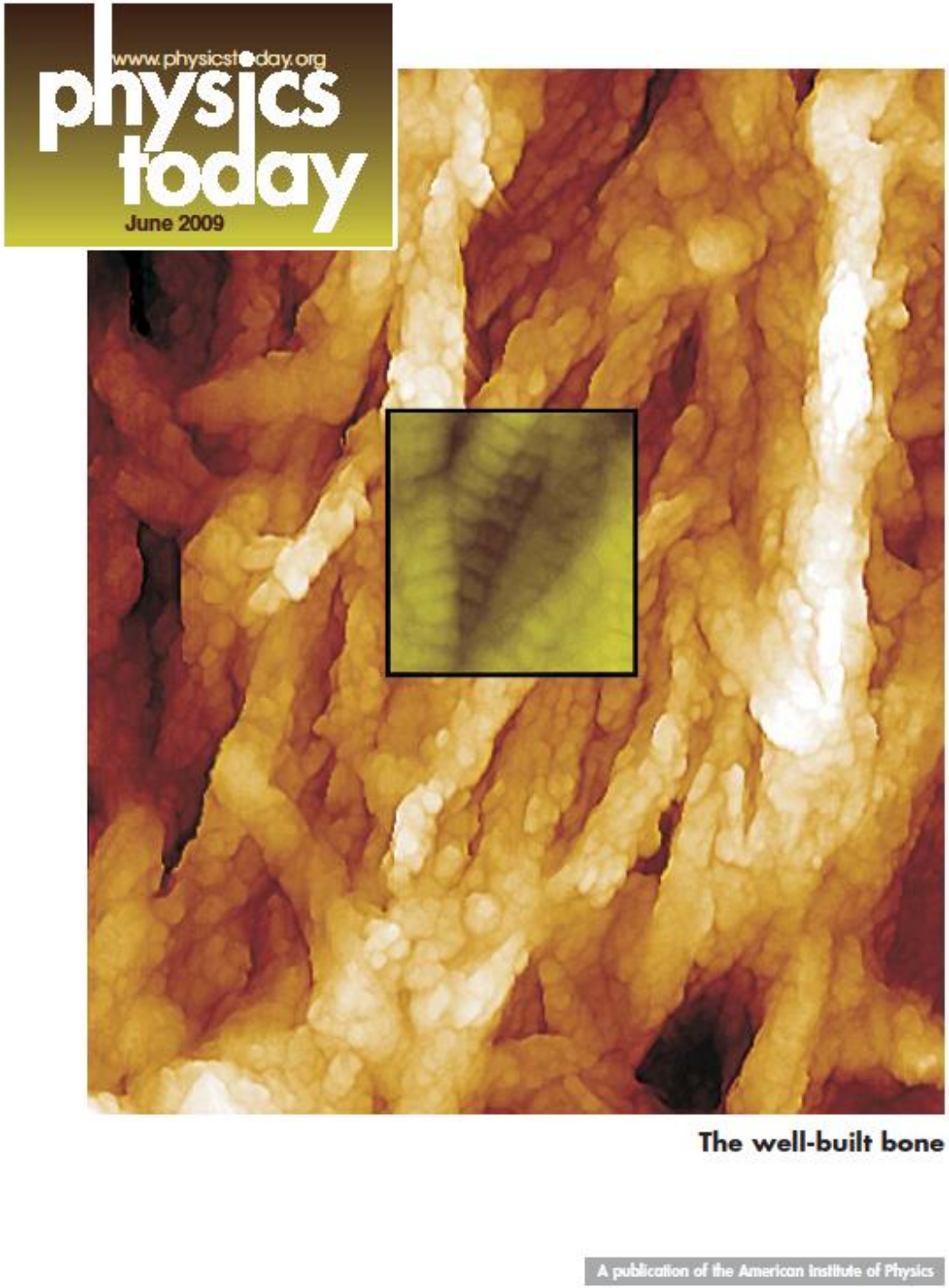
James B. Thompson, Johannes H. Kindt, Barney Drake, Helen G. Hansma, Daniel E. Morse, and Paul K. Hansma

Nature Vol. 414:773-775 (2001)

The sacrificial bond – hidden length mechanism



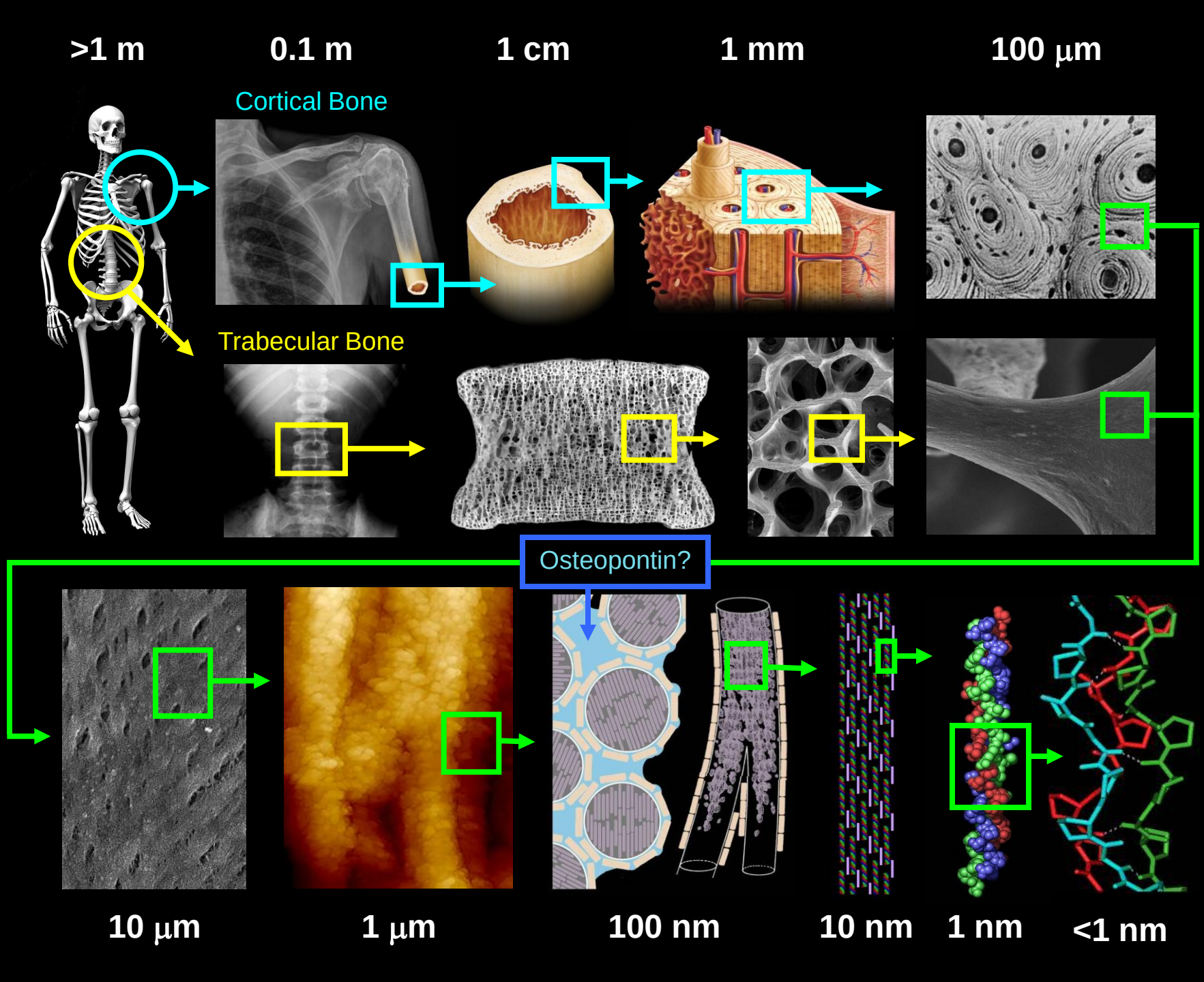
B.L. Smith et al, Molecular Mechanistic Origin of the Toughness of Natural Adhesives, Fibres and Composites Nature, **399**, 761-763, 1999

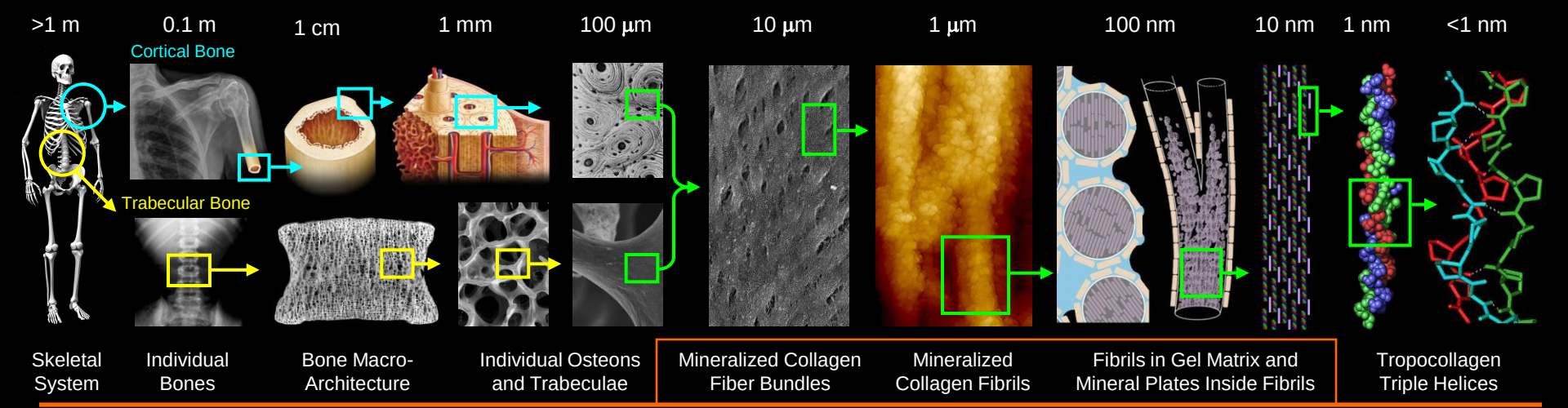


Bone consists of mineralized collagen fibrils that are 100 nm in diameter. The insert shows the effects of demineralization.

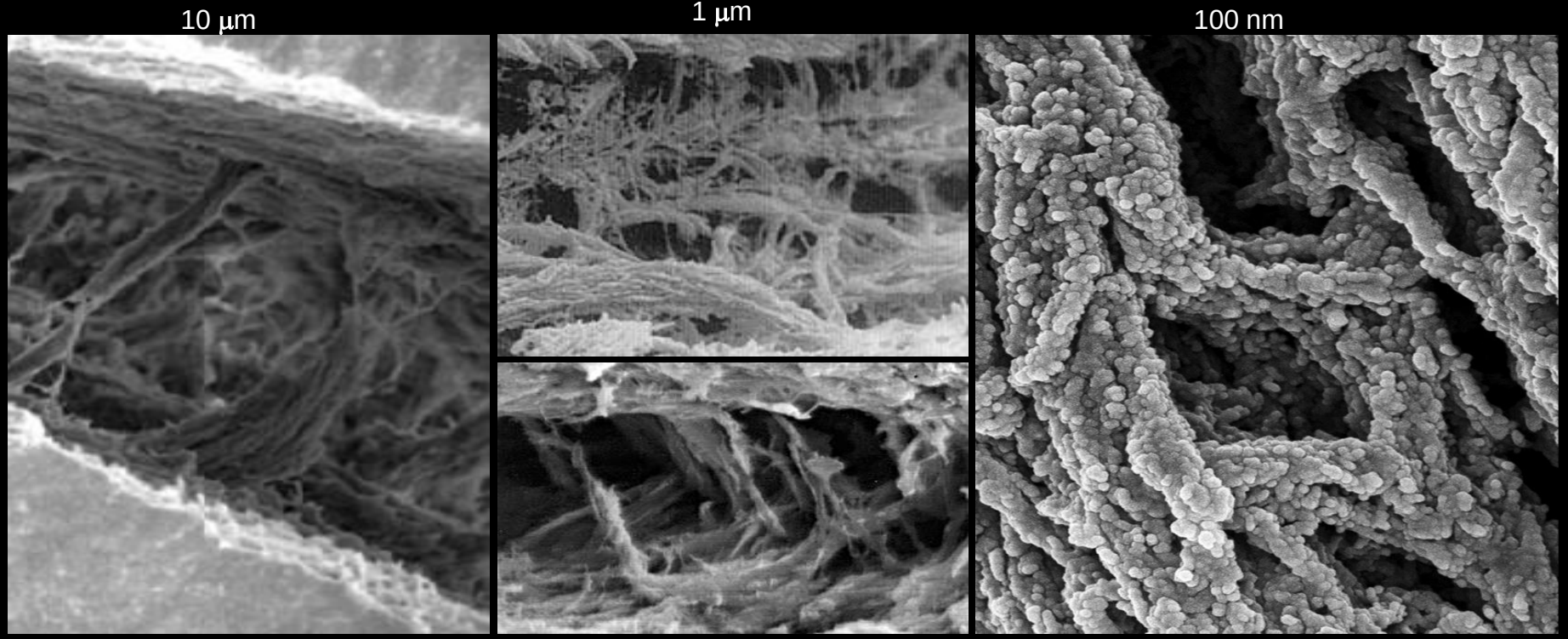
Plasticity and toughness in bone, R. O. Ritchie, M. J. Buehler and P. Hansma, Physics Today 24 (June 2009)

AFM images by Johannes Kindt UCSB


>1 m
0.1 m
1 cm
1 mm
100 μm
Cortical Bone
Trabecular Bone
Osteopontin?
10 μm
1 μm
100 nm
10 nm
1 nm
<1 nm



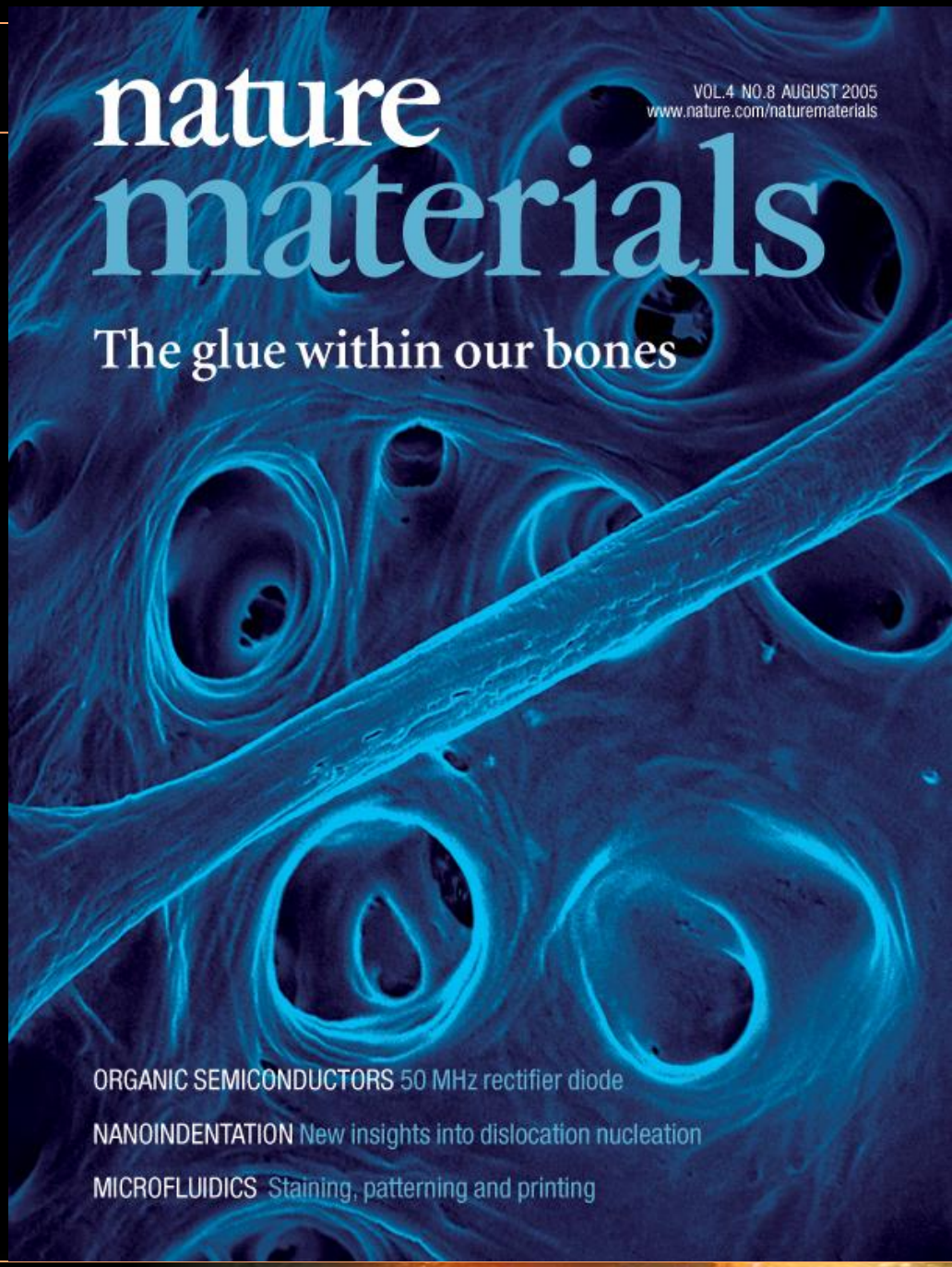
Bone Fracture Mechanisms



This fracture mechanism would be called fiber pullout in a conventional composite material. It would be attributed to bonding failure at the fiber-matrix interface.

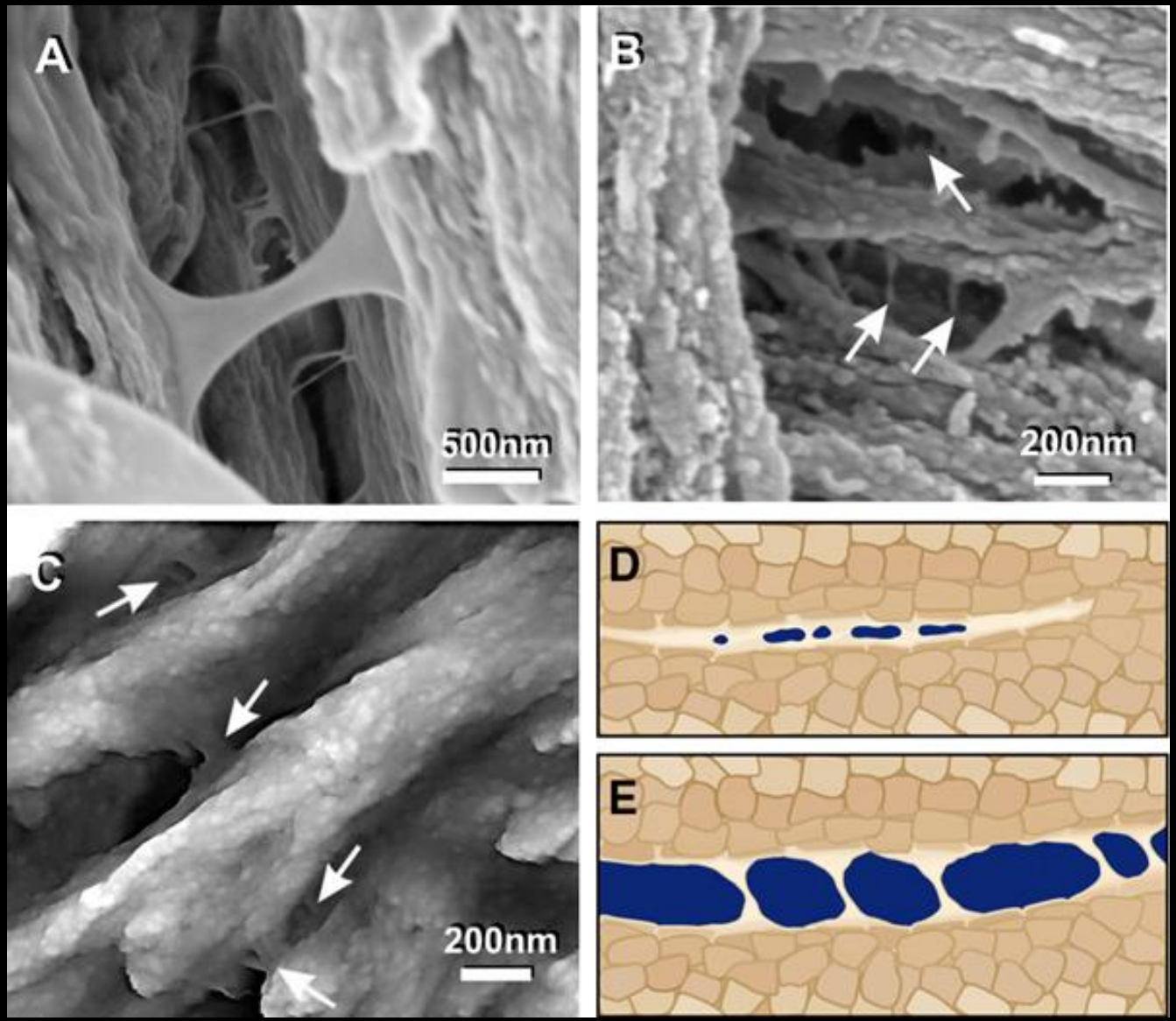
What resists the separation of mineralized collagen fibrils?

We believe that it is the glue within our bones.



Cover photo by: Georg Fantner
"The glue within our bones": Maria Bellantone, Senior Editor, Nature Materials

The glue within our bones appears to resist the separation of mineralized collagen fibrils



Both high resolution SEM (A and B) and AFM (C) show “glue” filaments between mineralized collagen fibrils

Georg Fantner, Tue Hassenkam, Johannes Kindt, James Weaver, Henrik Birkedal, Leonid Pechenik, Jacqueline Cutroni, Geraldo Cidade, Galen Stucky, Daniel Morse, Paul Hansma

Nature Materials 4, p.612 (2005)

bone medicine today

- Bone loss is quantified with X-rays (DXA). Patients with some bone loss are “osteopenic” with more bone loss are “osteoporotic”.
- Bone loss is treated drugs such as Fosamax, Boniva, Estrogen and Forteo.
- Side effects such as jaw necrosis and atypical femoral fracture are rare, but troubling.
- Fracture risk can be reduced by about 50% for the osteoporotic population.

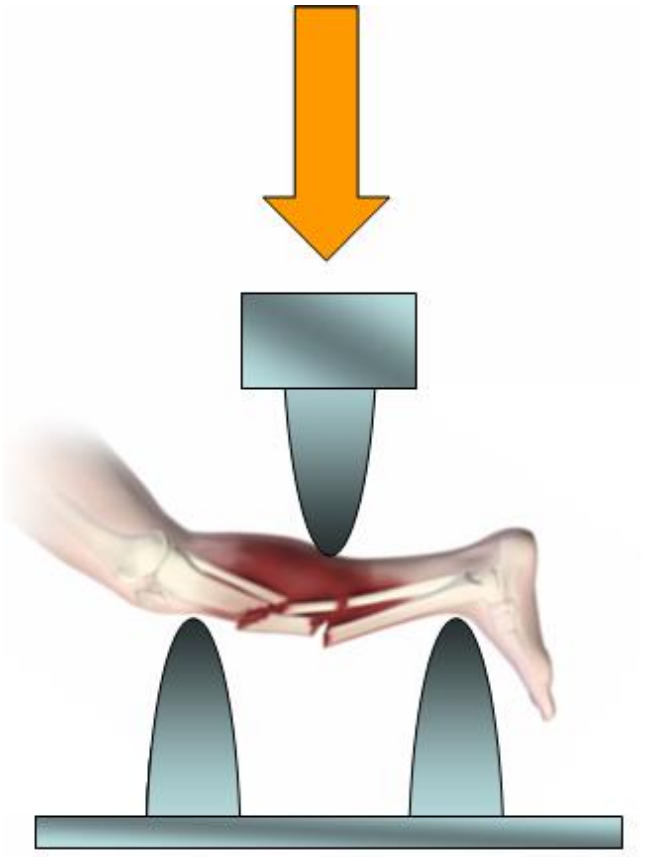
Practical advice

- If you are under 30, get plenty of calcium and exercise to build up your bone.
- For all ages, have your vitamin D level checked. Aim for greater than 50 and less than 125 nmol/l. For most people this takes between 600 and 2000 IU vitamin D3 daily.
- To do online research on health conditions enter the condition plus “NIH” or “Mayo” or “Johns Hopkins” in the search box.

- Perhaps because bone loss is only half the problem!

Demo of good and bad Bone Material Strength

It is not really practical to do three point bending on a patient.



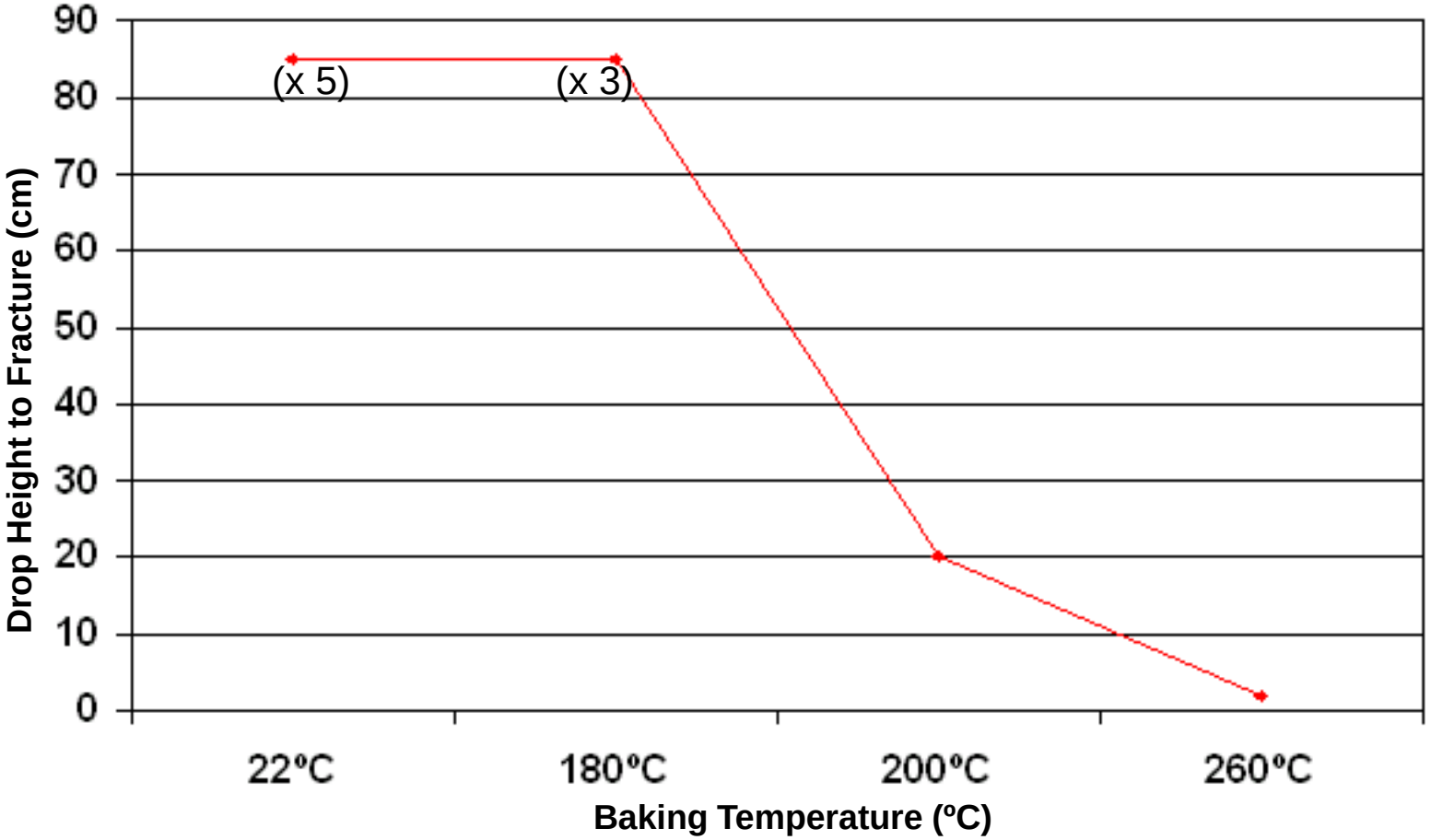
So what can be done?

A short history of the development of

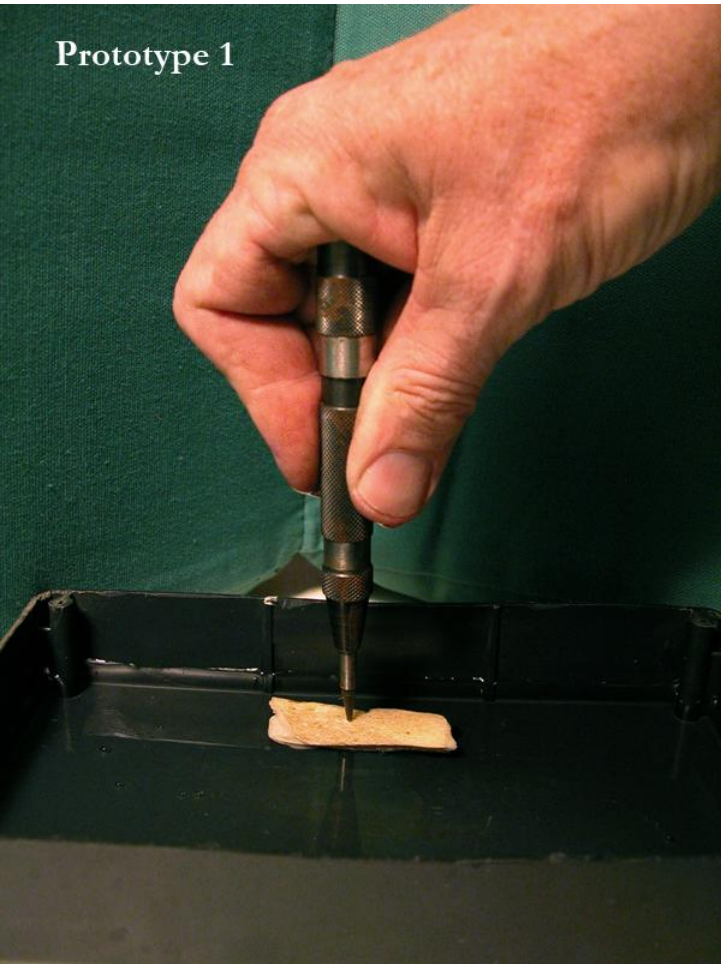
Reference Point Indentation

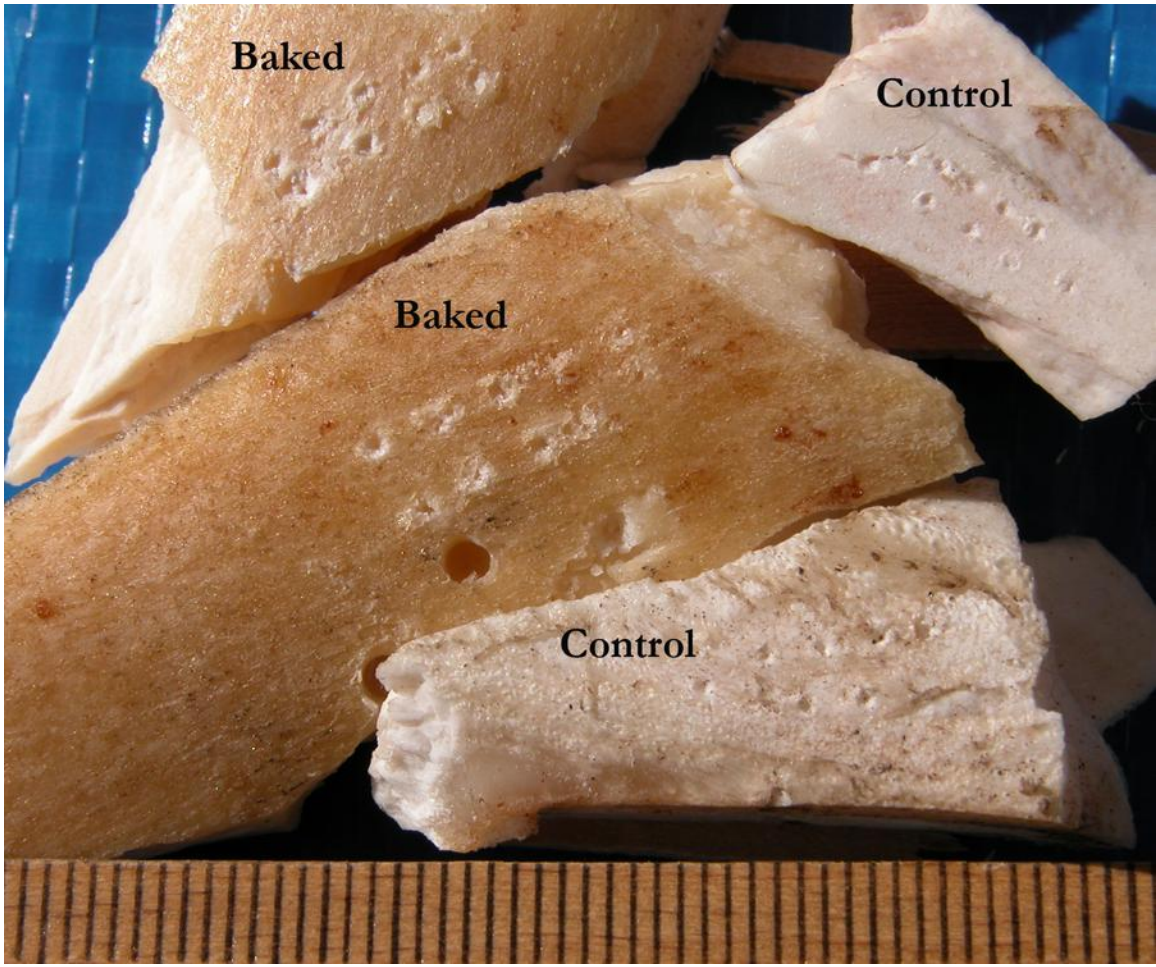
In the beginning.

The resistance to fracture decreases with baking.



The first success.

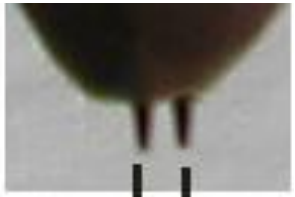




An automatic center punch makes larger indentations in the Baked bone than in the Control bone.

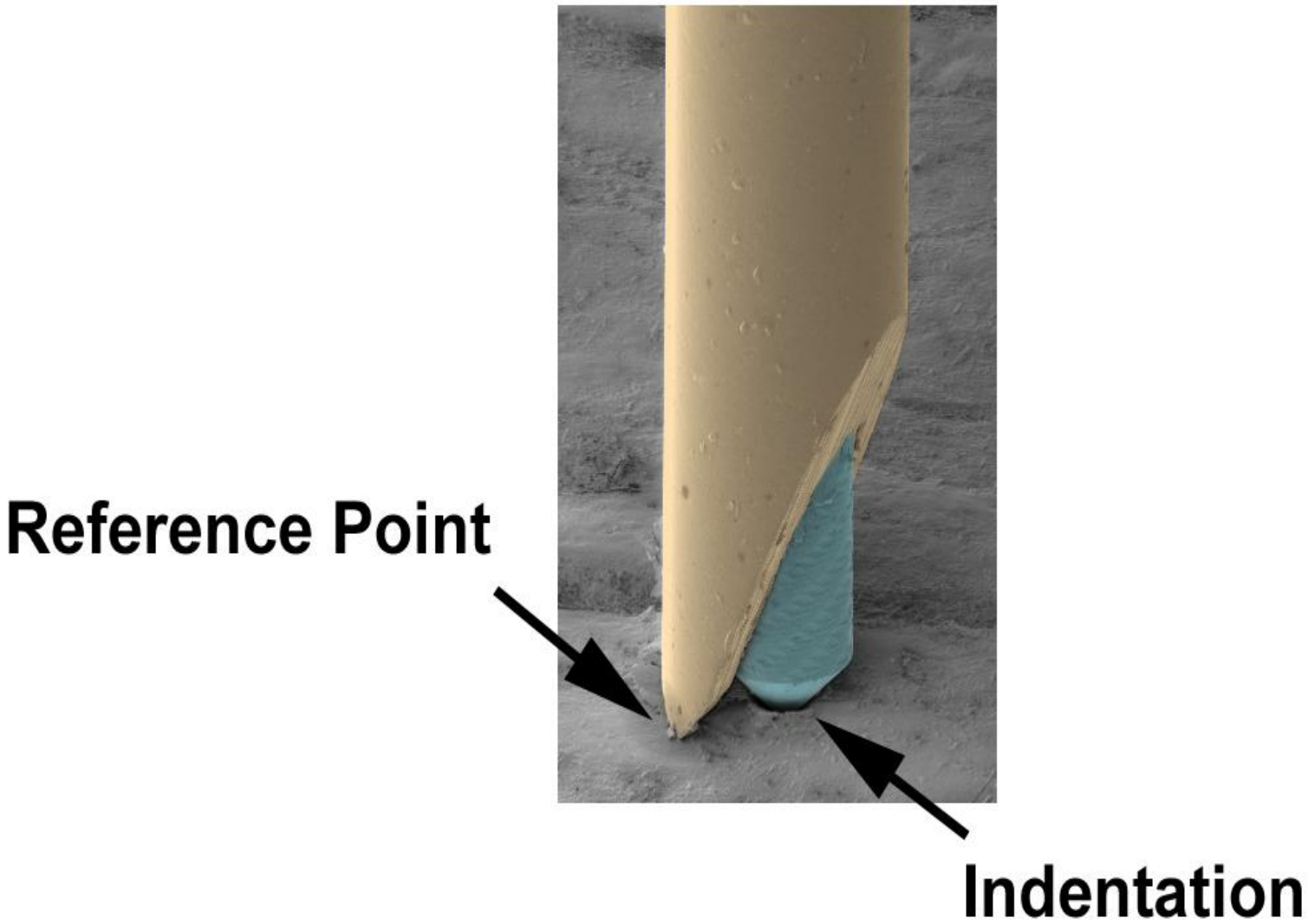
Hansma 2004

Reference Point Indentation RPI

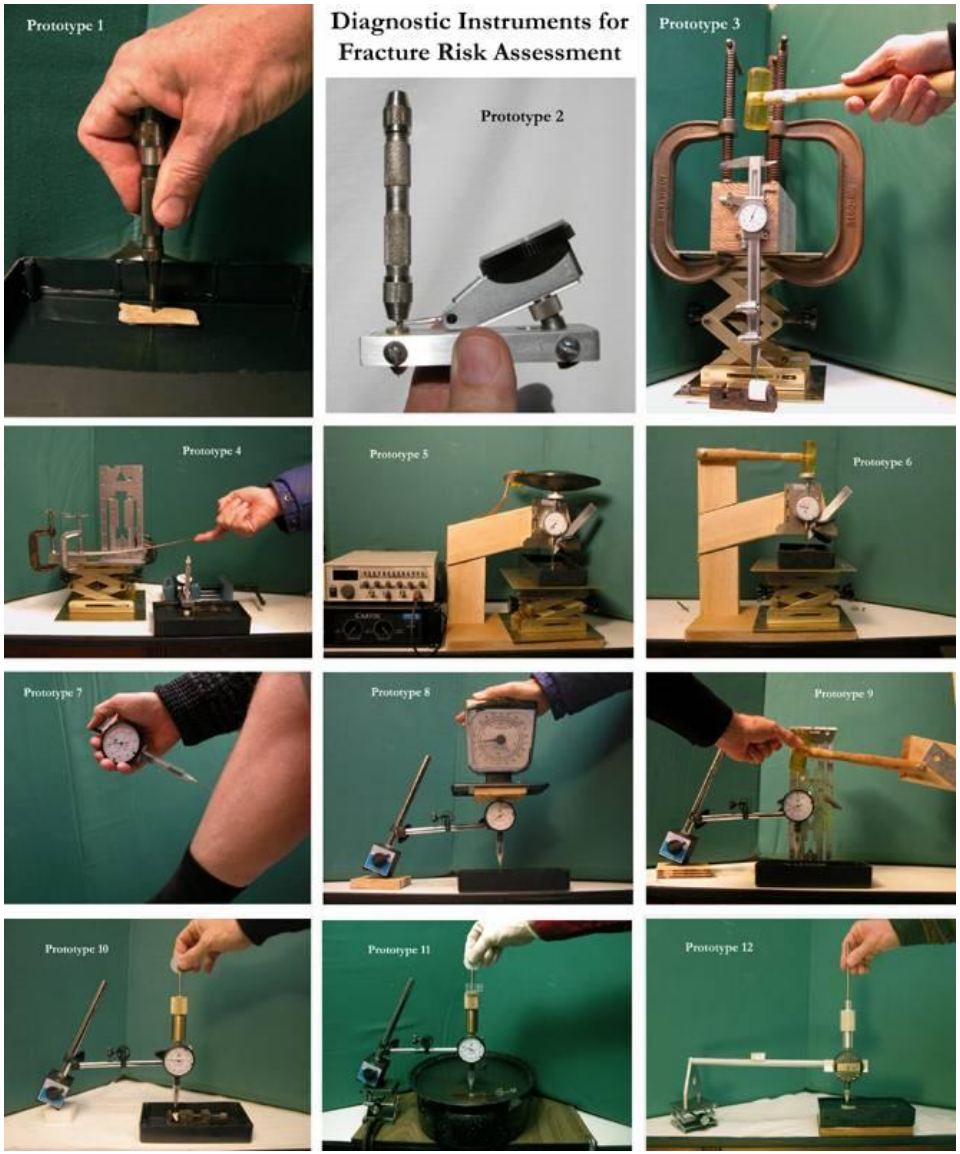


Hansma, January 2005

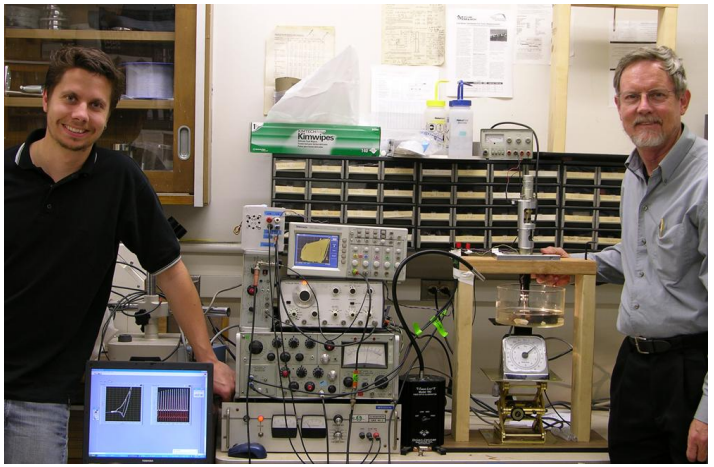
Probe assembly for Reference Point Indentation



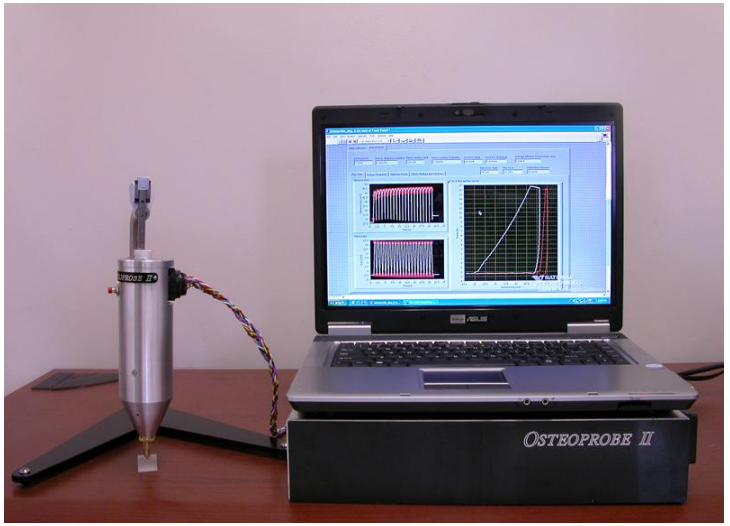
The prototypes.



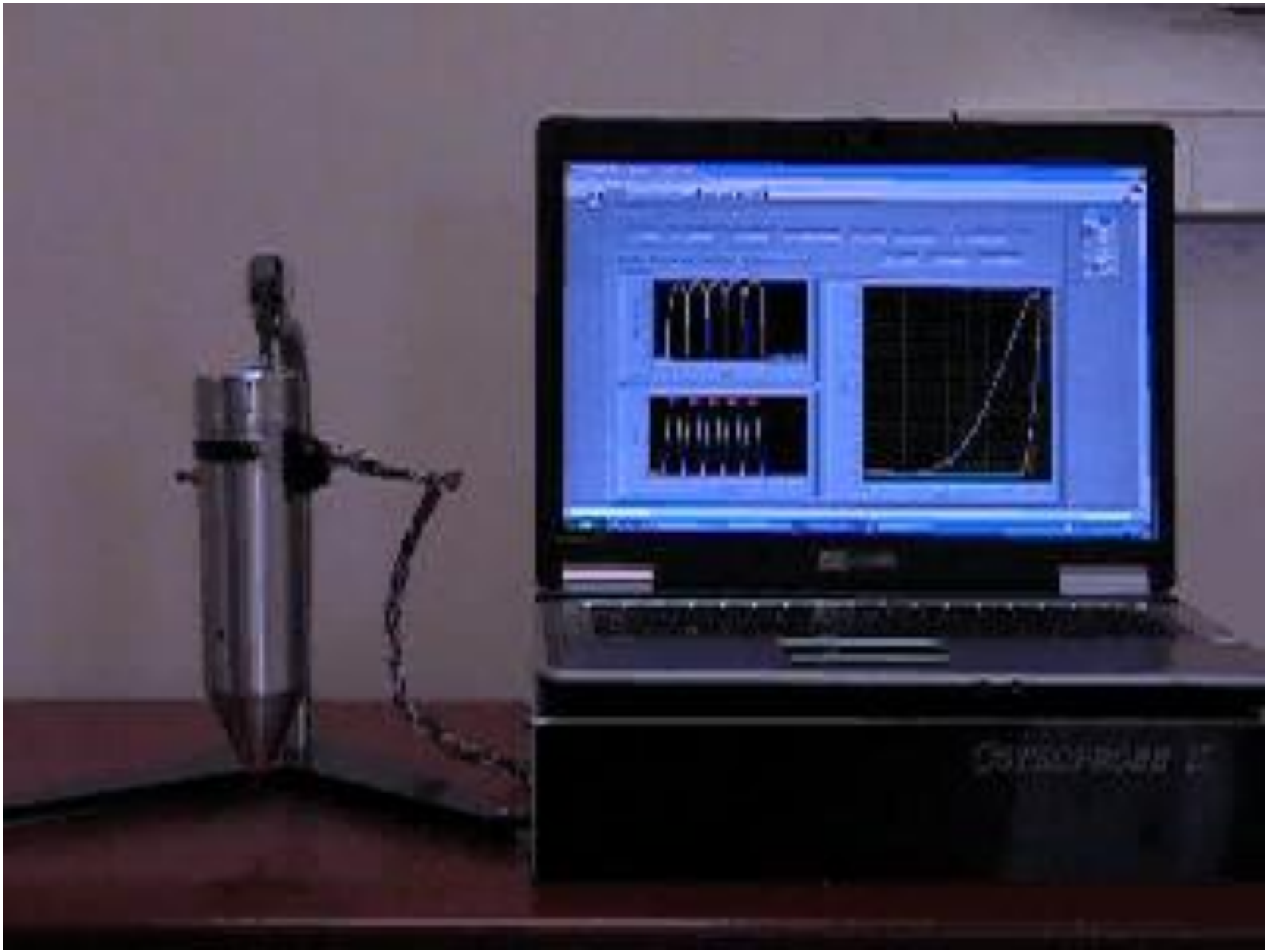
December 2004 to February 2005



Prototype 15 (2006)



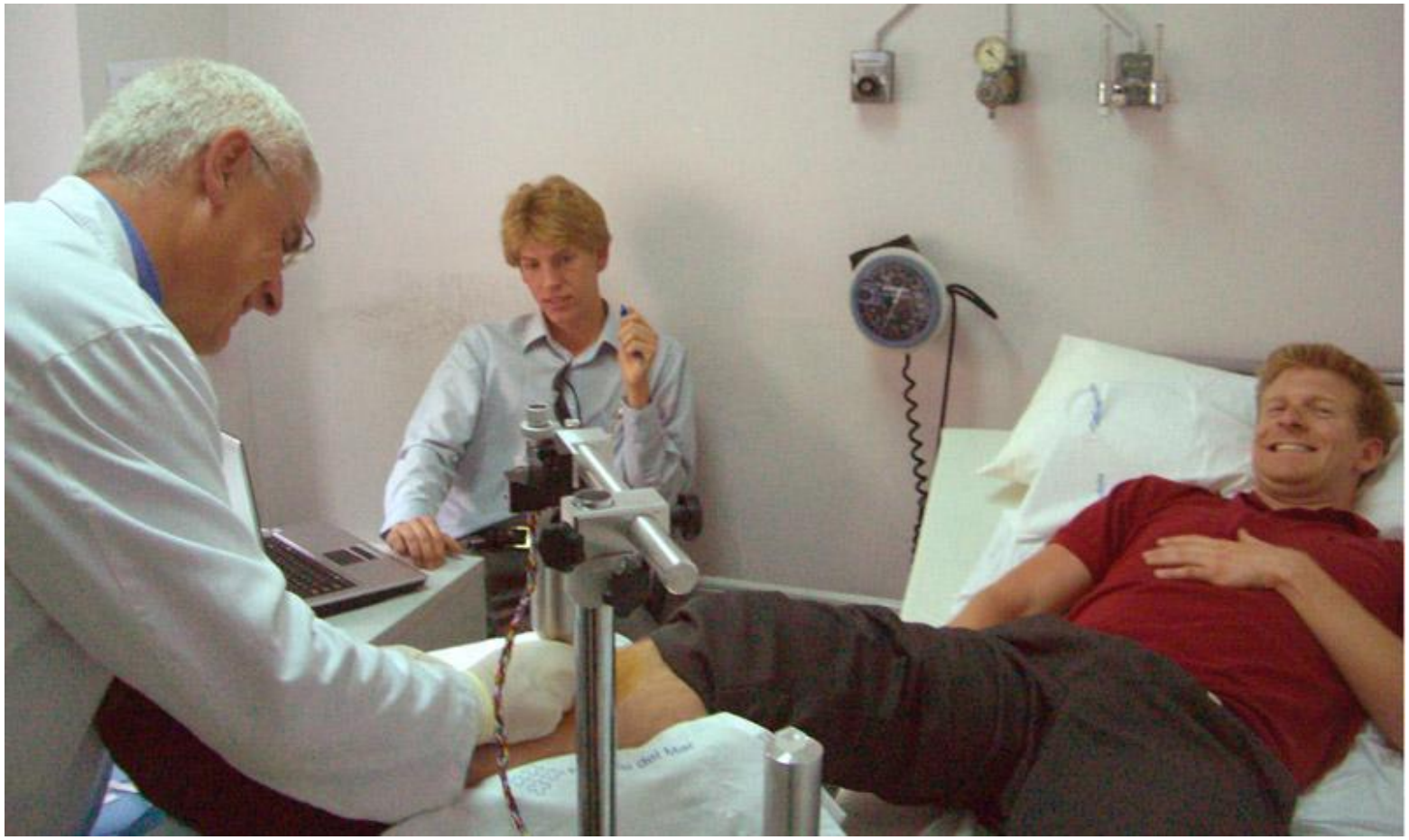
Prototype 19 (2007)

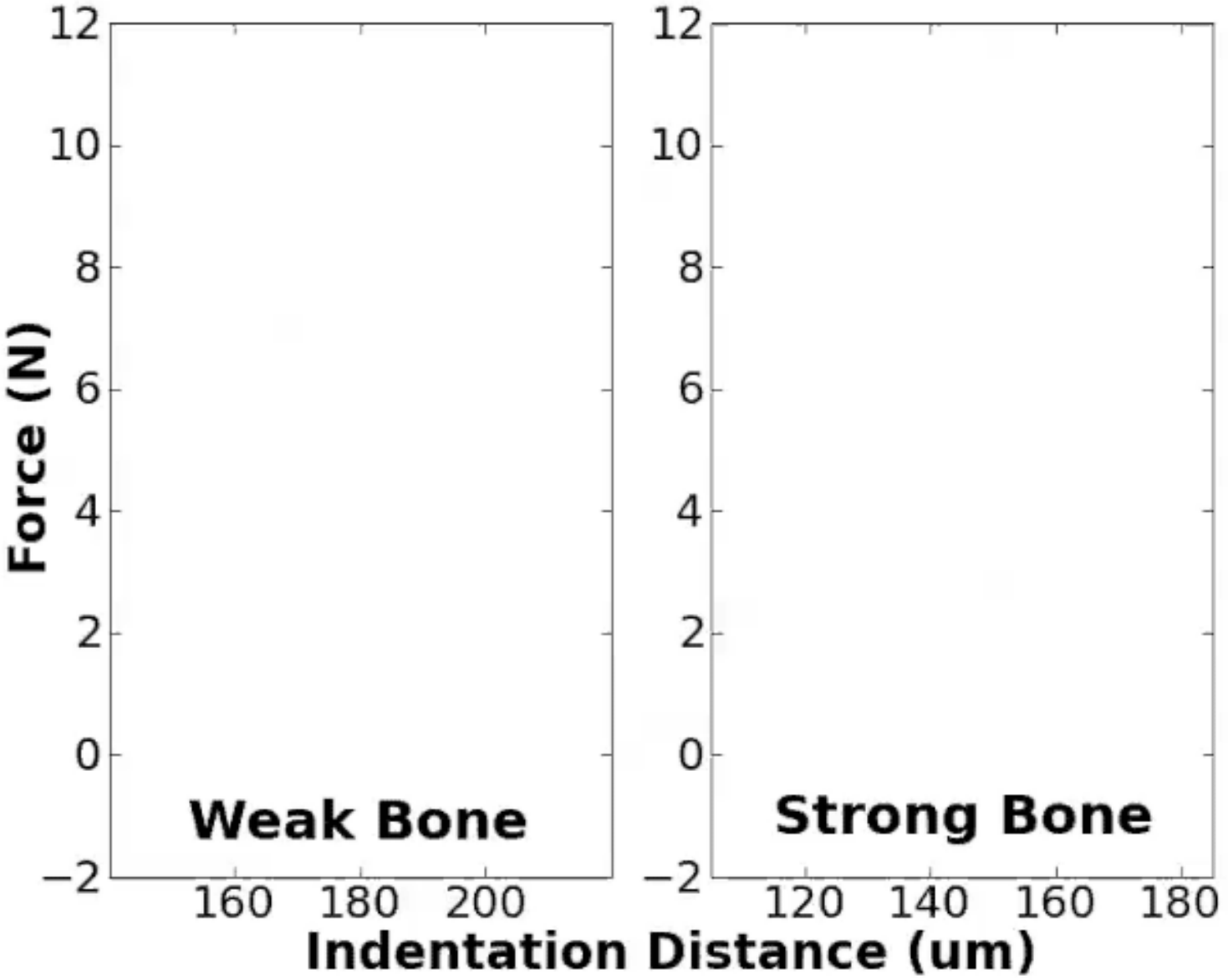


From Broida to Bedside

Alex Proctor and Davis Brimer win New Venture Competition.

Dr. Adolfo Diez Perez tests Davis Brimer with Alex Proctor in the backgrond.




12
10
8
6
4
2
0
−2
Force (N)
Weak Bone
160
180
200
12
10
8
6
4
2
0
−2
Strong Bone
120
140
160
180
Indentation Distance (um)

Patients with fractures had larger Total Indentation Distances than patients with no fracture.

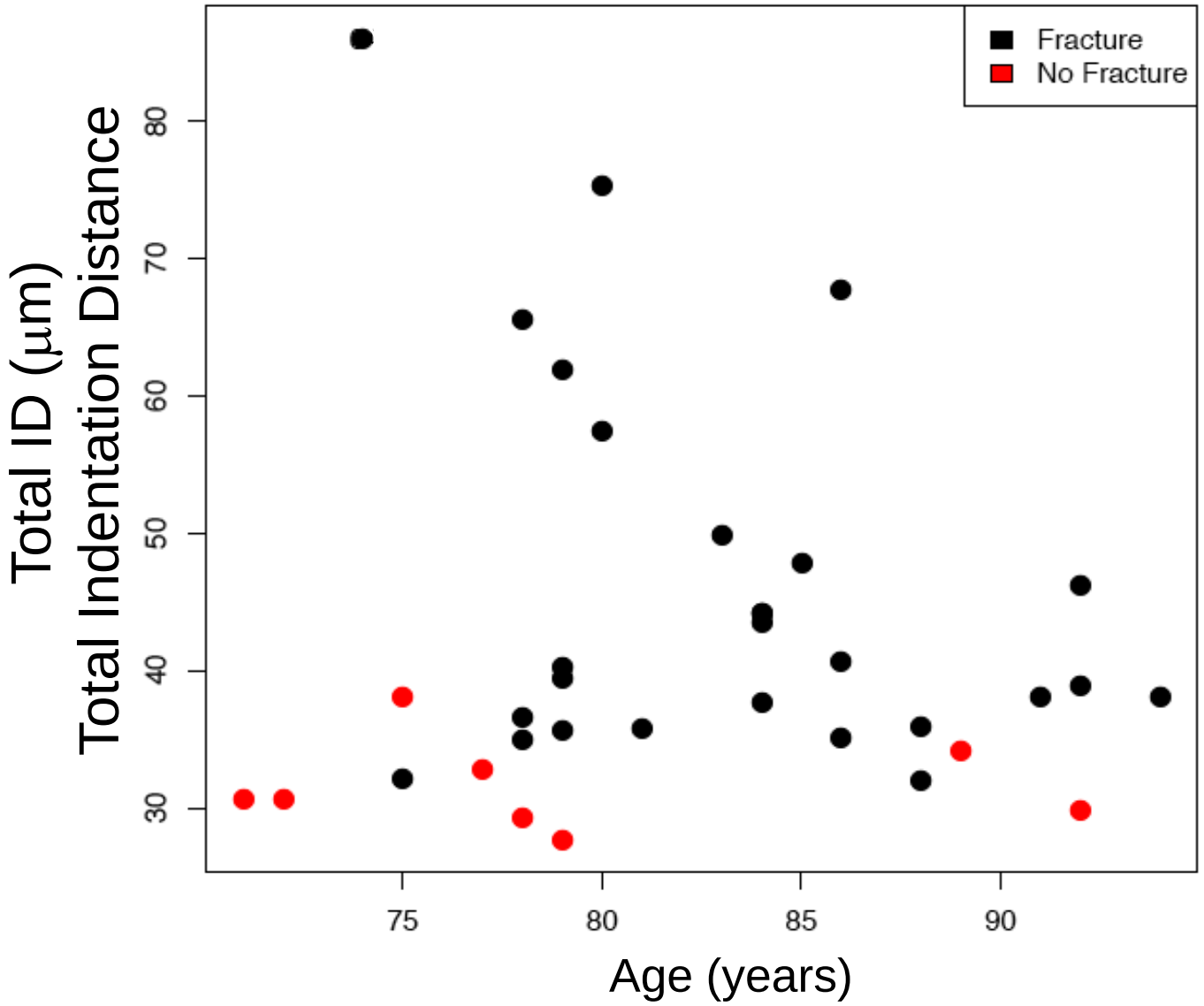
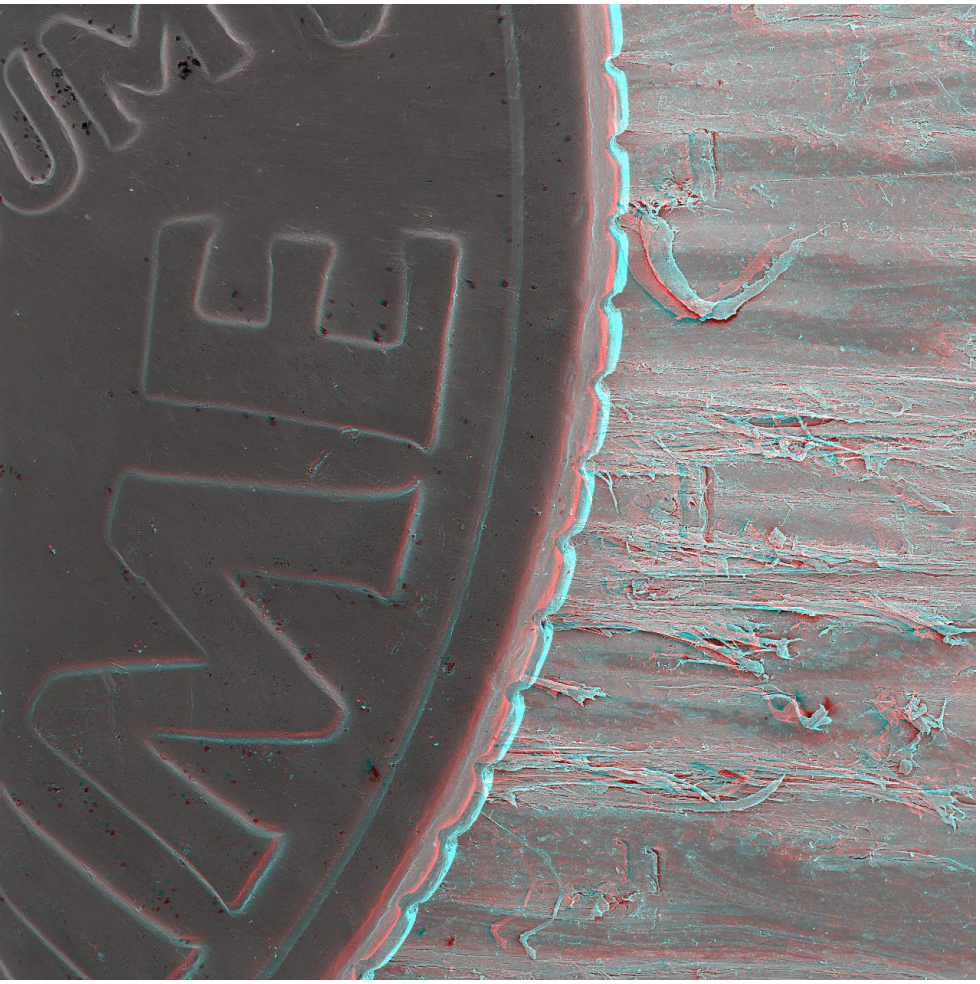
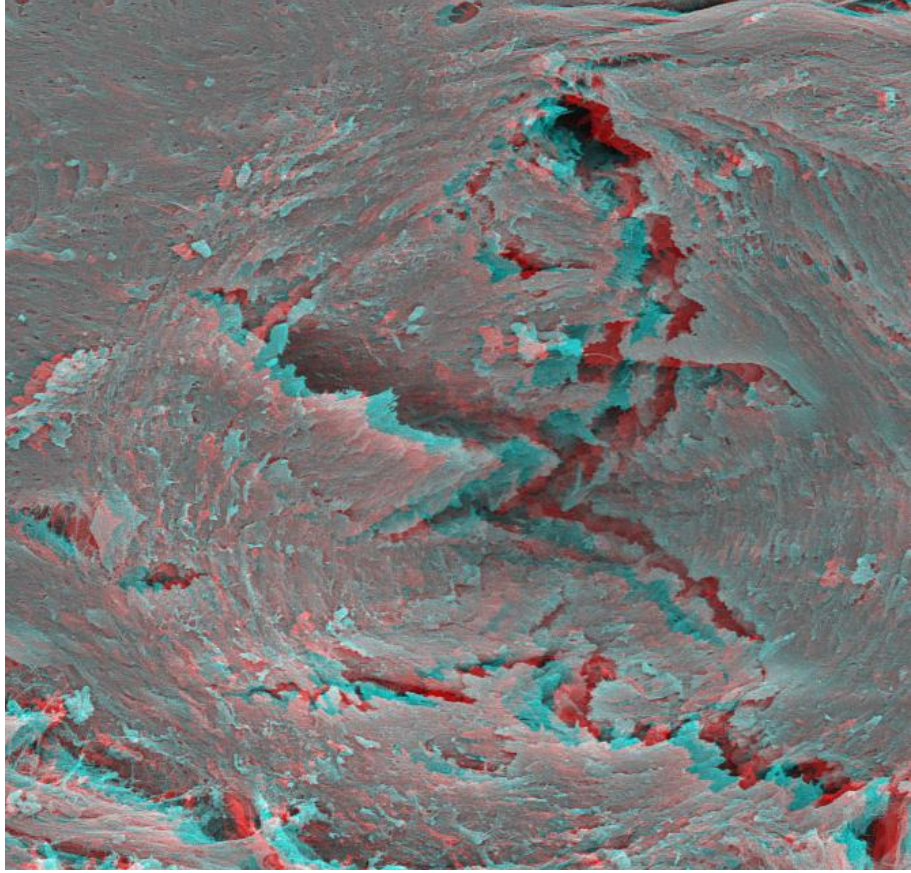


Image of an indentation compared to a dime

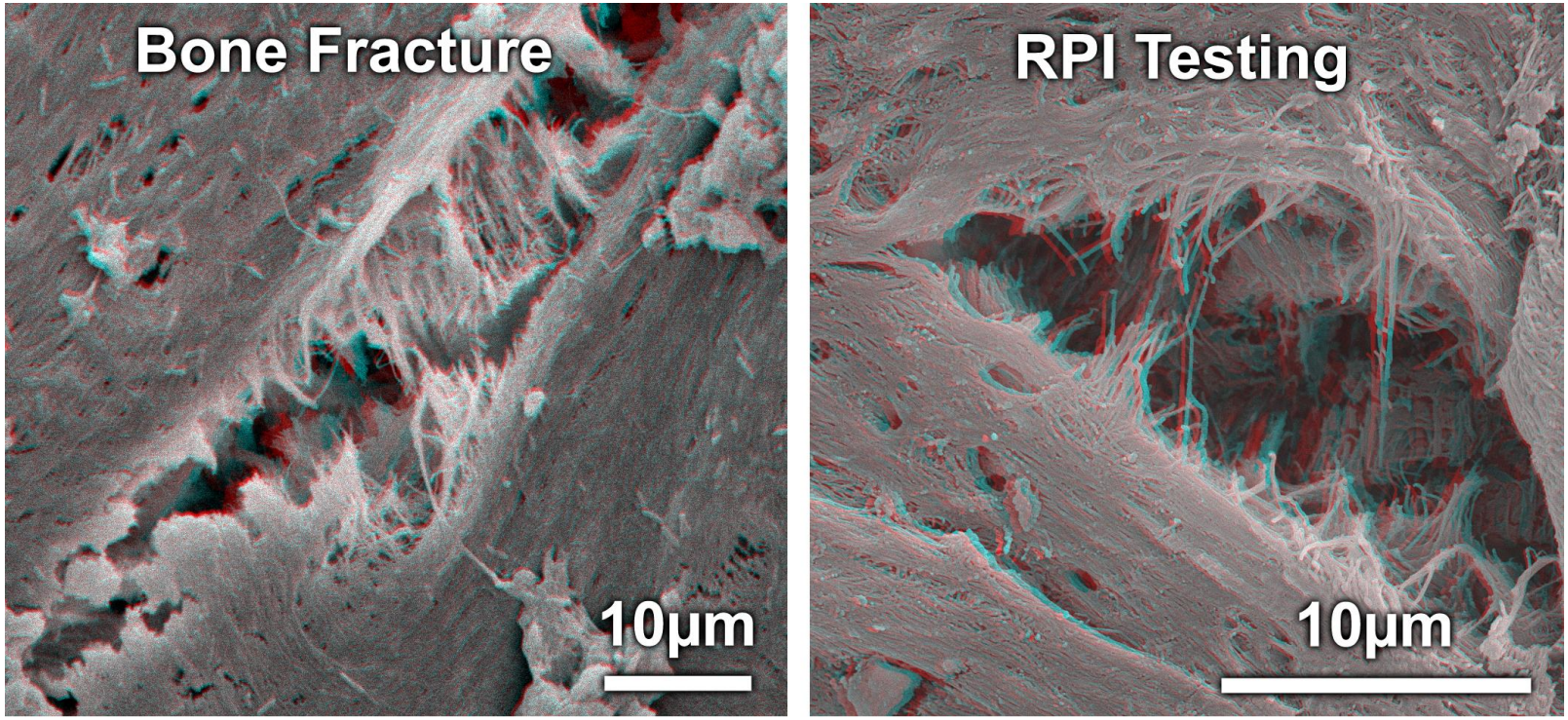




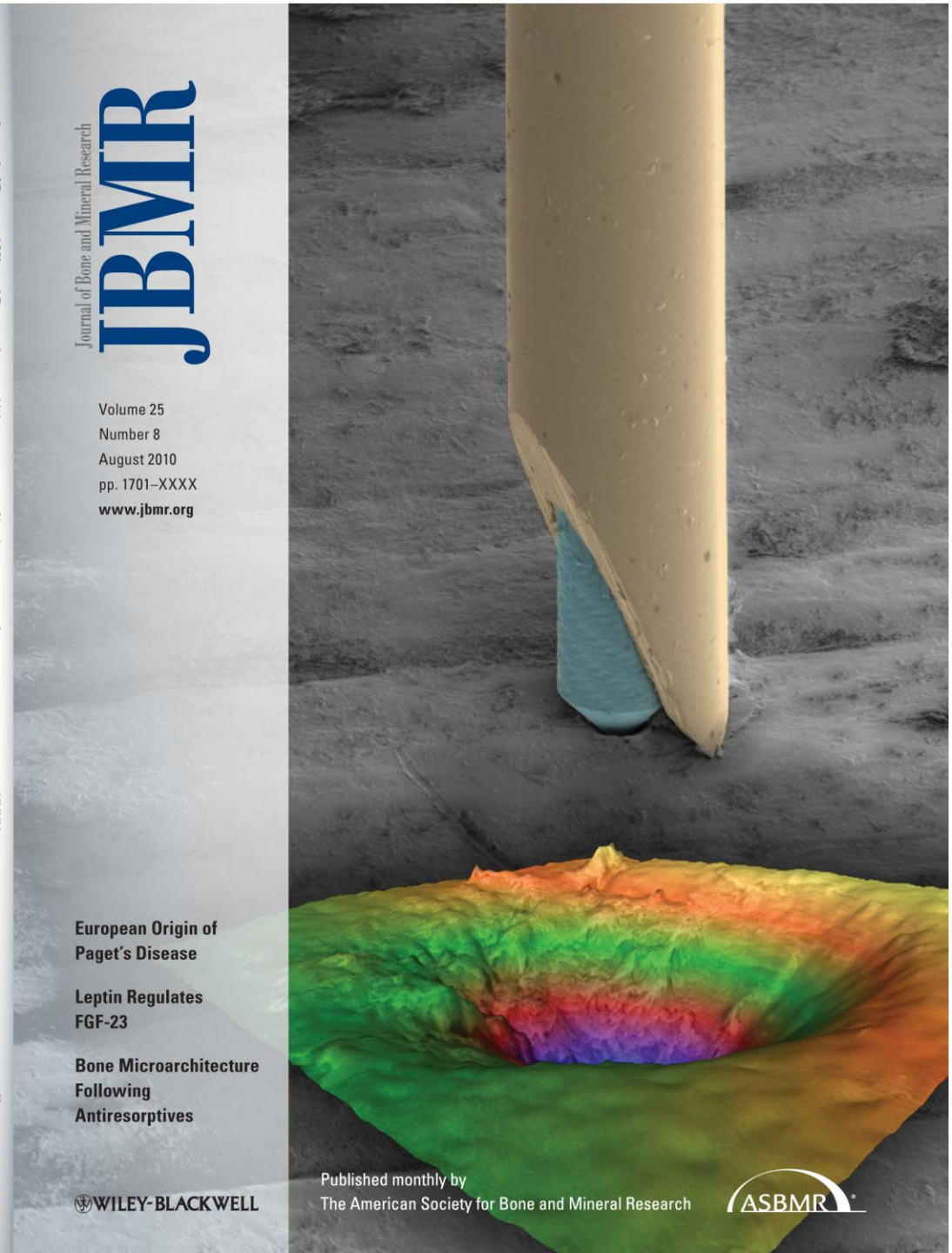
Close up view: indentation does not just compress the bone, it opens small cracks, just as in bone fracture

Discussion

• Bone fracture begins with the separation of mineralized collagen fibrils.



• Fracture resistance depends on the resistance to this separation of mineralized collagen fibrils.



Microindentation for *in vivo* Measurement of Bone Tissue Mechanical Properties in Humans

Adolfo Diez-Perez, Roberto Güerri, Xavier Nogues, Enric Cáceres, Maria Jesus Peña, Leonardo Mellibovsky, Connor Randall, Daniel Bridges, James C. Weaver, Alexander Proctor, Davis Brimer, Kurt J. Koester, Robert O. Ritchie, Paul K. Hansma

JBMR, 25, 1877-85 (2010)

From here there have been multiple new directions.

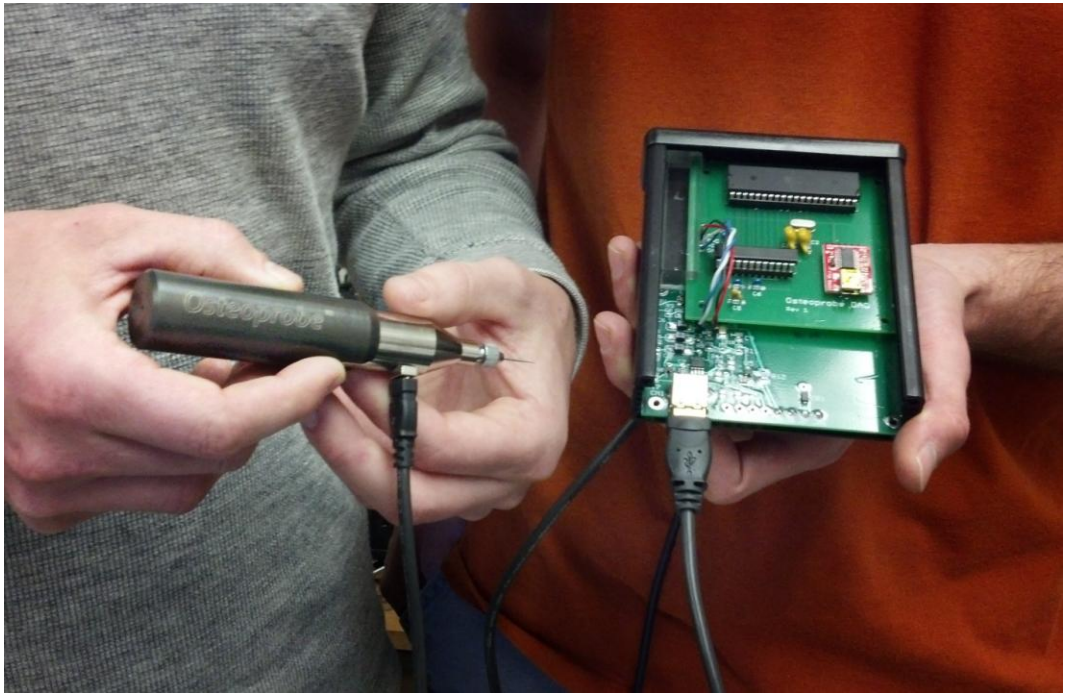
- A commercial version of our instrument is now being used in many institutions for basic research.
- A new type of Reference Point Indenter that is easier to use on patients and horses.
- A new, larger clinical study confirmed and extended the original study. Many new studies are already underway. Many more are planned.
- Theoretical work on modeling fracture processes.
- High resolution imaging of fractures and fracture processes.
- Experimental investigations of other tissues.

A commercial version of our instrument is now being used in many institutions for basic research

BioDent from Active Life Scientific, Inc.

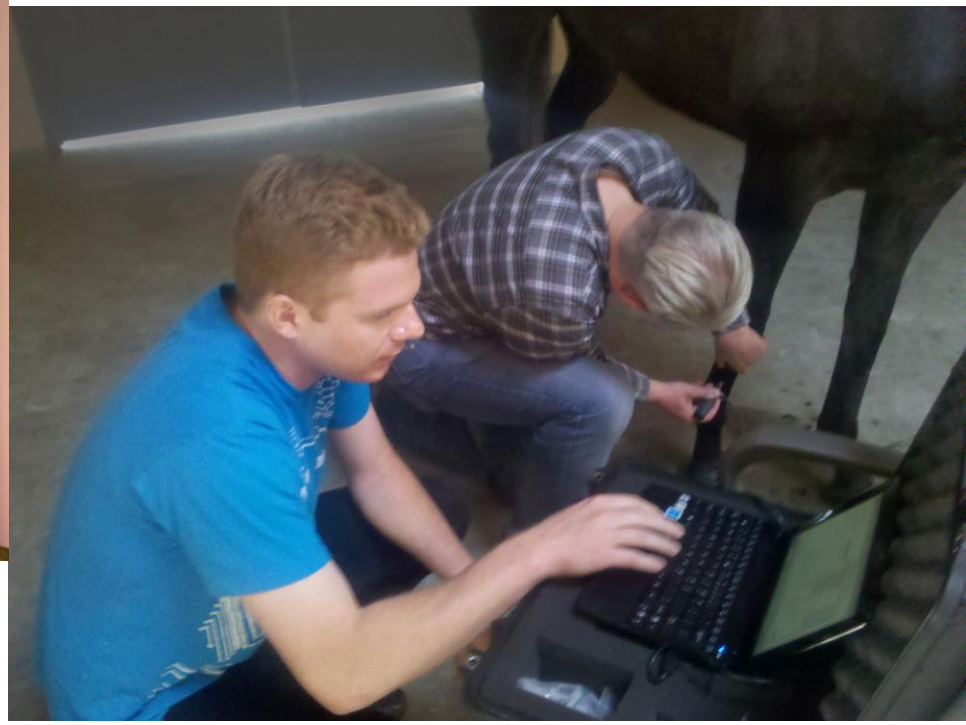
A new type of Reference Point Indenter that is easier to use on patients and horses: the Osteoprobe®

Connor Randall holding the Osteoprobe head.
Dan Bridges holding the electronics.



The Osteoprobe® went from a sketch on yellow lined paper to clinical applications in less than one year thanks to the excellence and hard work of Connor Randall and Dan Bridges.

Dr. Roberto Güerri-Fernández training a new operator on himself at Hospital del Mar, Barcelona, Spain



Kevin Hoffseth (one of Chancellor Yang's graduate students) with Doug Herthel, Alamo Pintado Equine Medical Center, Los Olivos, CA

Osteoprobe – Potential Research Areas

Active Life Scientific, Inc.
Creating New Tools For Life Scientists

Over 100 *known* diseases that can increase risk of bone fracture

BioDent™ Bio-Indenter

Acromegaly	Dent-Friedman syndrome	Liver disease	Peripheral neuropathy
Acroosteolysis neurogenic	Dentinogenesis imperfecta, type I	Lobstein disease	Perthes' disease
Adrenal Cortex Diseases	Depression	Lupus	Pituitary cancer
AIDS/HIV	Diabetes	Lymphoma and leukemia	Polio and post-polio syndrome
Allison atrophy	Dwarfism	Malabsorption syndromes	Poor diet, including malnutrition
Alpha-Mannosidosis	Dyskeratosis Congenita	Medication induced osteoporosis	Premature menopause
Ankylosing spondylitis	Eating disorders (esp. anorexia nervosa)	Medullary cystic kidney disease	Prostate cancer
Anorexia Nervosa	Familial Expansile Osteolysis	Megarbane-Jalkh Syndrome	Pseudophosphatasia
Arterial occlusive disease	Female athlete triad (incl. missing periods)	Metabolic disorders	Renal osteodystrophy
Autoimmune Lymphoproliferative Syndrome	Fibrous dysplasia	Multiple endocrine neoplasia type 1	Renal rickets
Biliary cirrhosis	Gastrectomy	Multiple Myeloma	Rheumatoid arthritis
Blood and bone marrow disorders	Gastrointestinal bypass procedures	Multiple pterygium syndrome lethal type	Rickets
Bone atrophy (from inactivity)	Gaucher Disease	Multiple sclerosis	Salvioli syndrome
Bone cancer	Gnathodiaphyseal dysplasia	Nephronophthisis, autosomal dominant	Scoliosis
Breast cancer	Grange syndrome	Neuropathy	Secondary Biliary Cirrhosis
Bruck syndrome 1	Grix-Blankenship-Peterson syndrome	Organ transplants	Secondary hyperparathyroidism
Bruck syndrome, 2	Hodgkin's Disease	Osteogenesis imperfecta	Spinal cord injuries
Calcium deficiency	Hyperhomocysteinemia	Osteomalacia	Stroke
Calvarial doughnut lesions	Hyper-IgE Syndrome	Osteomyelitis	Thalassemia
Chemical poisoning -- Aluminum	Hyperparathyroidism	Osteopetrosis	Thick skull syndrome
Chemical poisoning -- Ammonium Bifluoride	Hyperthyroidism	Osteopenia	Thyrotoxicosis
Chitty-Hall-Webb syndrome	Hypervitaminoses A and D	Osteoporosis	Vitamin D deficiency
Christian-Demyer-Franken syndrome	Hypophosphatasia	Paget's disease	Weight loss (incl. surgery like gastric bypass surgery)
COPD, including emphysema	Hypophosphatemic rickets	Panostotic fibrous dysplasia	Wilson's Disease
Cushing's syndrome	Inflammatory bowel disease (incl. Chron's disease)	Parastremmatic dwarfism	
Decreased serum phosphate	Juvenile hyaline fibromatosis	Parkinson's disease	

Also: Over 1,450 drugs with side effects *known* to increase risk of fracture

Davis Brimer, Active Life Scientific, Inc.

Current plans for Osteoprobe studies

Active Life Scientific, Inc.

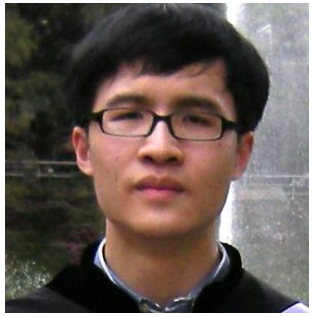
Translational Research Tools for the Life Sciences

Osteoprobe Study Proposals Include Researching How Bone Material Strength is Affected By ___:		
Post-menopausal osteoporosis	Diabetes – Type 1	Myastenia gravis
HIV/AIDS	Diabetes – Type 2	Chronic obstructive lung disease
Glucocorticoid steroid induced osteoporosis (GIOP)	Osteomalacia	Zoledronic acid (osteoporosis treatment)
Atypical femur fracture / long term use of bisphosphonates	Osteoporosis with and without hip fractures	Osteoarthritis
Knee replacement	Primary hyperparathyroidism	Van-Buchem disease
Post-organ transplant (kidney, liver)	Hyper- and Hypo-thyroidism	Paget's disease
Men (elder)	Multiple sclerosis	Osteogenesis Imperfecta
Fibrous dysplasia	Hypophosphatasia	Osteoporosis with and without vertebral fractures
Parathyroid Hormone (PTH) (osteoporosis treatment)	Vitamin D Deficiency	Weight loss after bariatric surgery
Obesity	Nutrition	Shoulder surgery/replacement

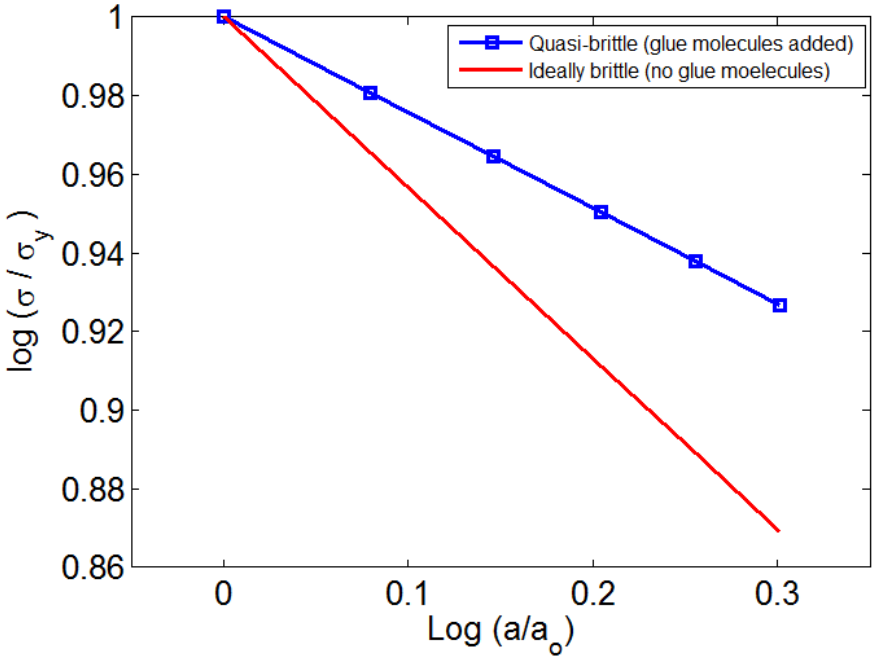
Davis Brimer, Active Life Scientific, Inc.

Theoretical work on modeling fracture processes: sacrificial bonds and hidden length increase resistance to crack propagation

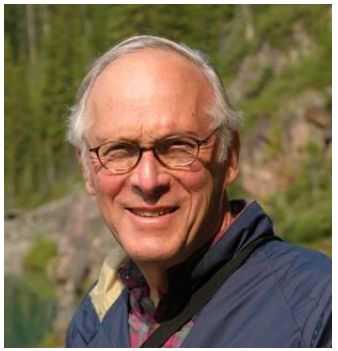
Ahmed Elbanna



Charles Lieou



Jean Carlson



Jim Langer

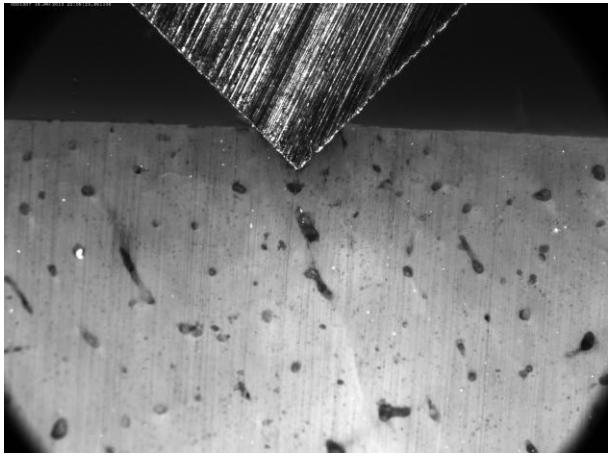
The "glue" with sacrificial bonds and hidden length increases the <u>flaw tolerance</u> in bone. That is, a larger stress is required to trigger a dynamic crack propagation (i.e. a catastrophic fracture) when the glue is present.

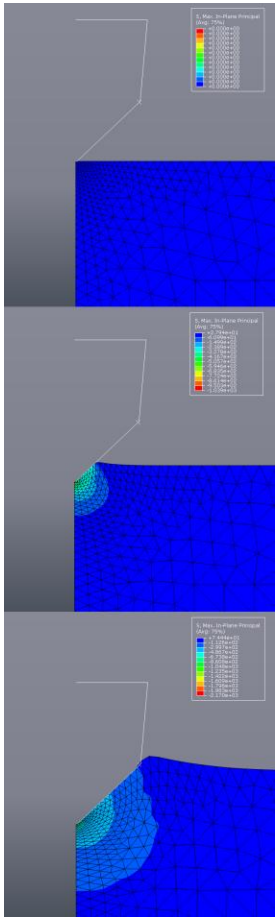
a	is the initial crack length
a_o	is the crack size below which the specimen fails by yielding rather than fracture.
σ	is the failure stress.
σ_y	is the yield stress.

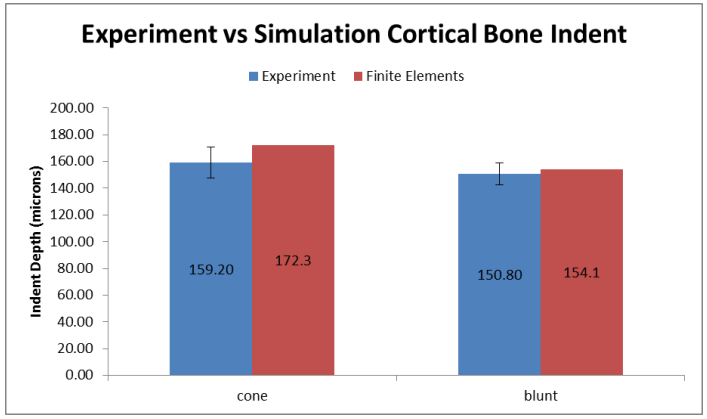
Theoretical work on modeling fracture: cortical bone plasticity and fracture

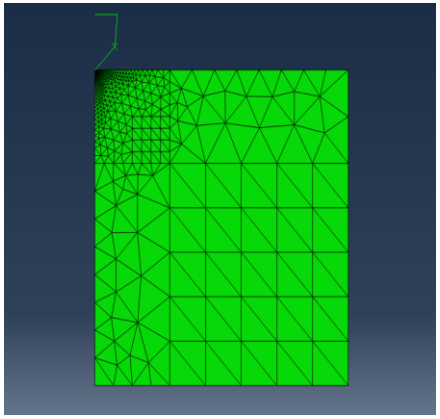
Kevin Hoffseth

Henry Yang



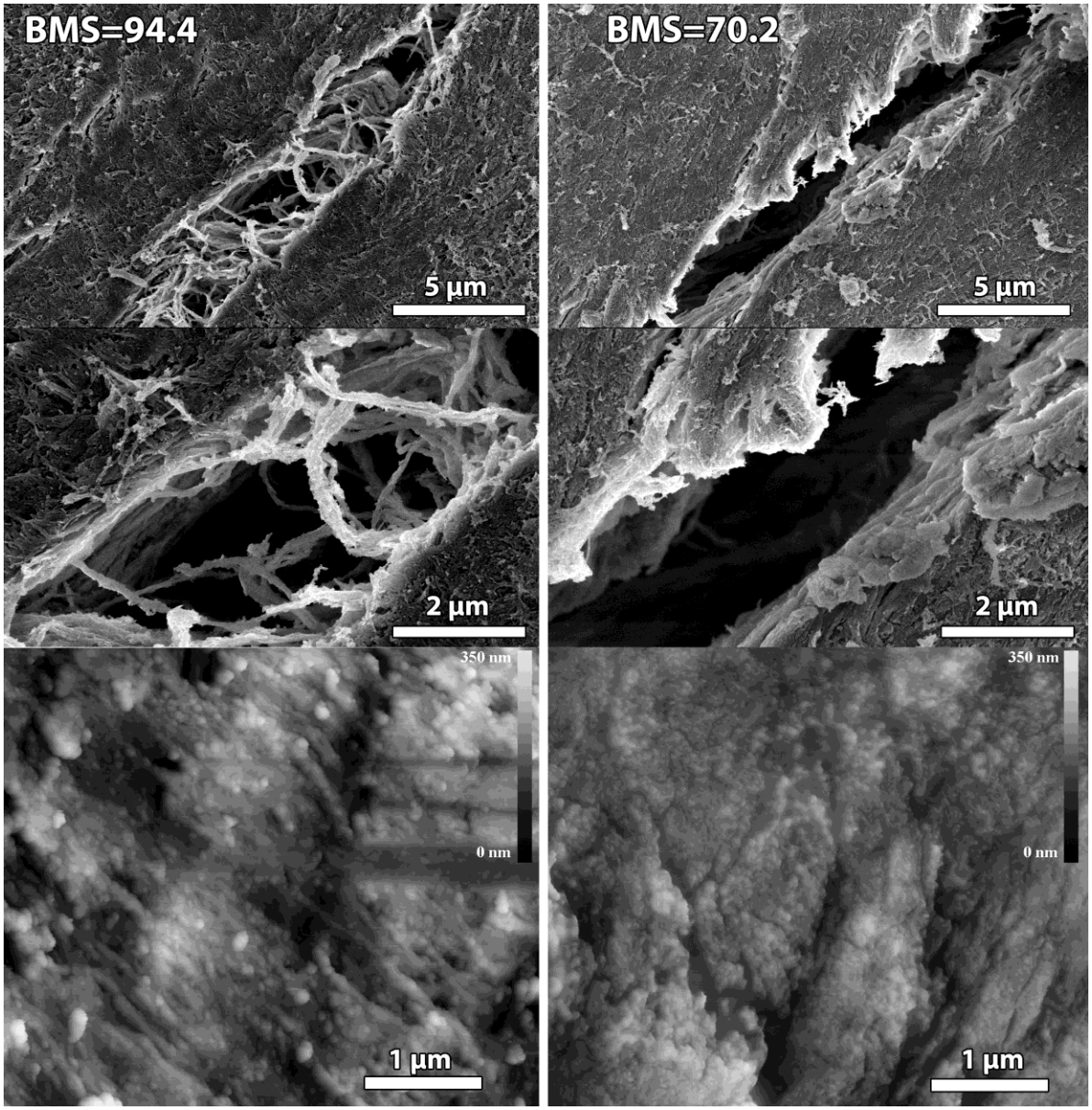






UC SANTA BARBARA engineering

High resolution imaging of fractures and fracture processes

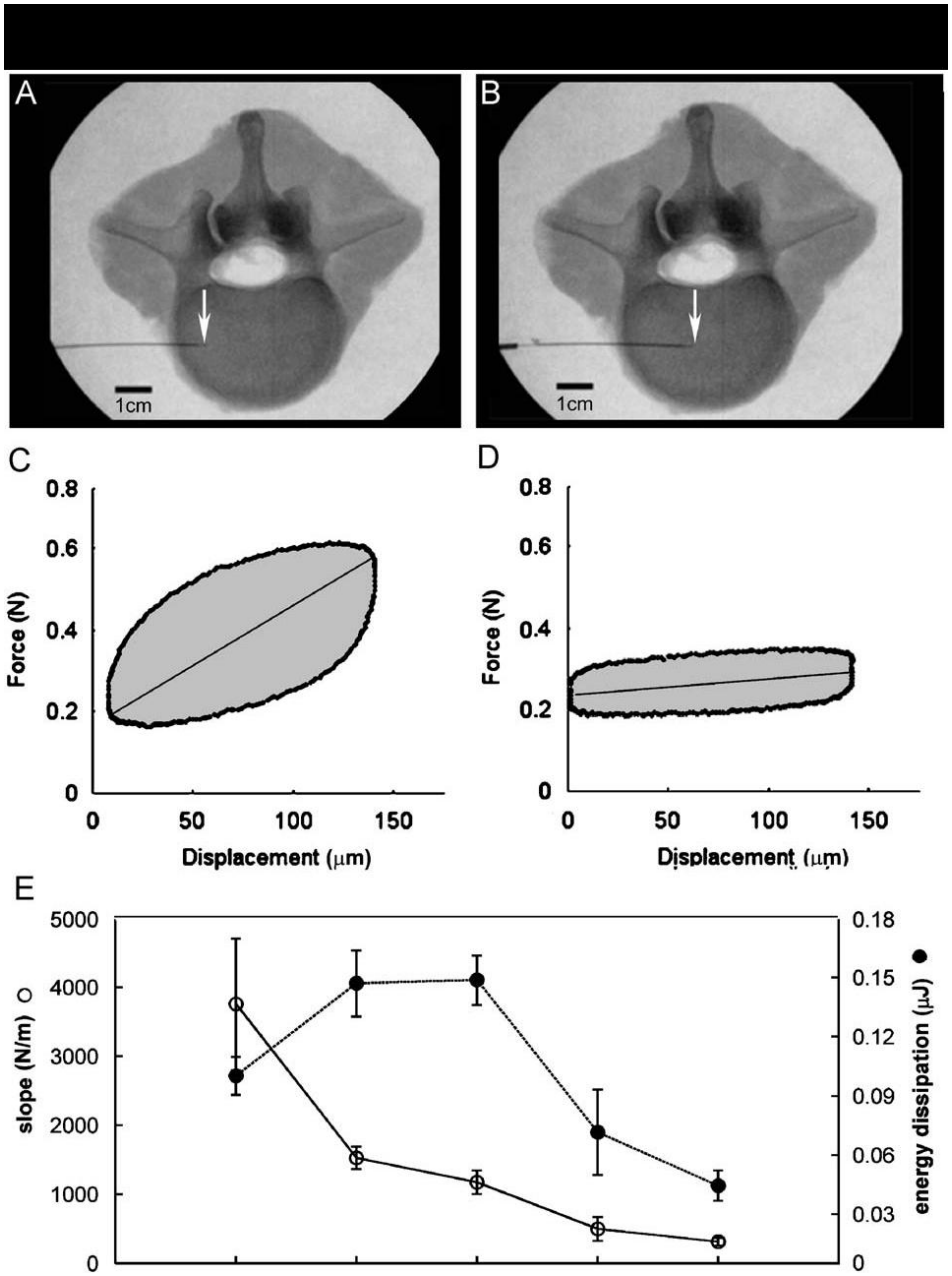


- **SEM and AFM imaging of fracture process.**
- **Strong bone showing bridging (left column)**
- **Diseased bone without bridging (right column)**

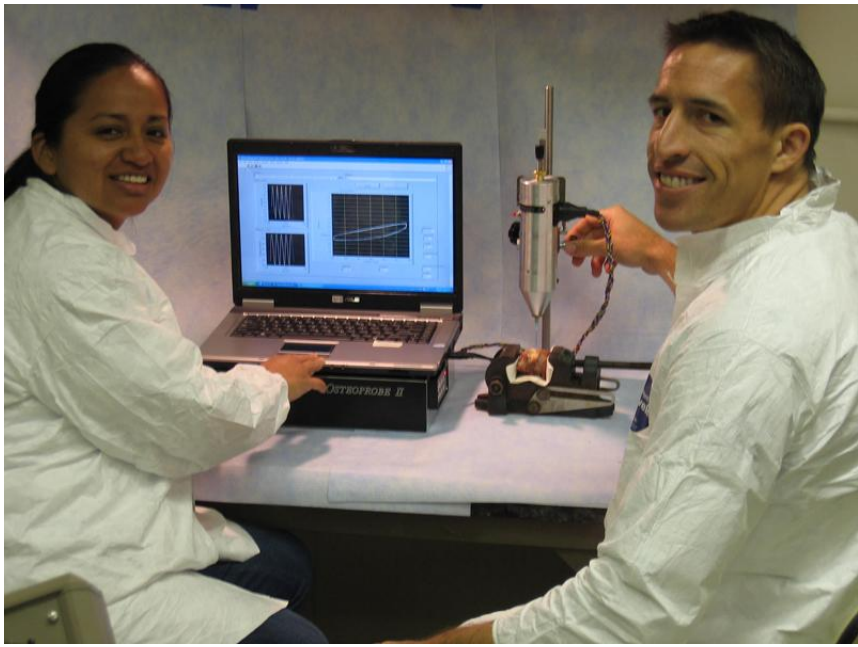
Connor Randall

Heather Barnard

Experimental investigations of other tissues



Mechanical profiling of intervertebral discs
Journal of Biomechanics 42 (2009) 1154–1157 Journal of Biomechanics



Azucena Rodriguez & David Schultz

In summary

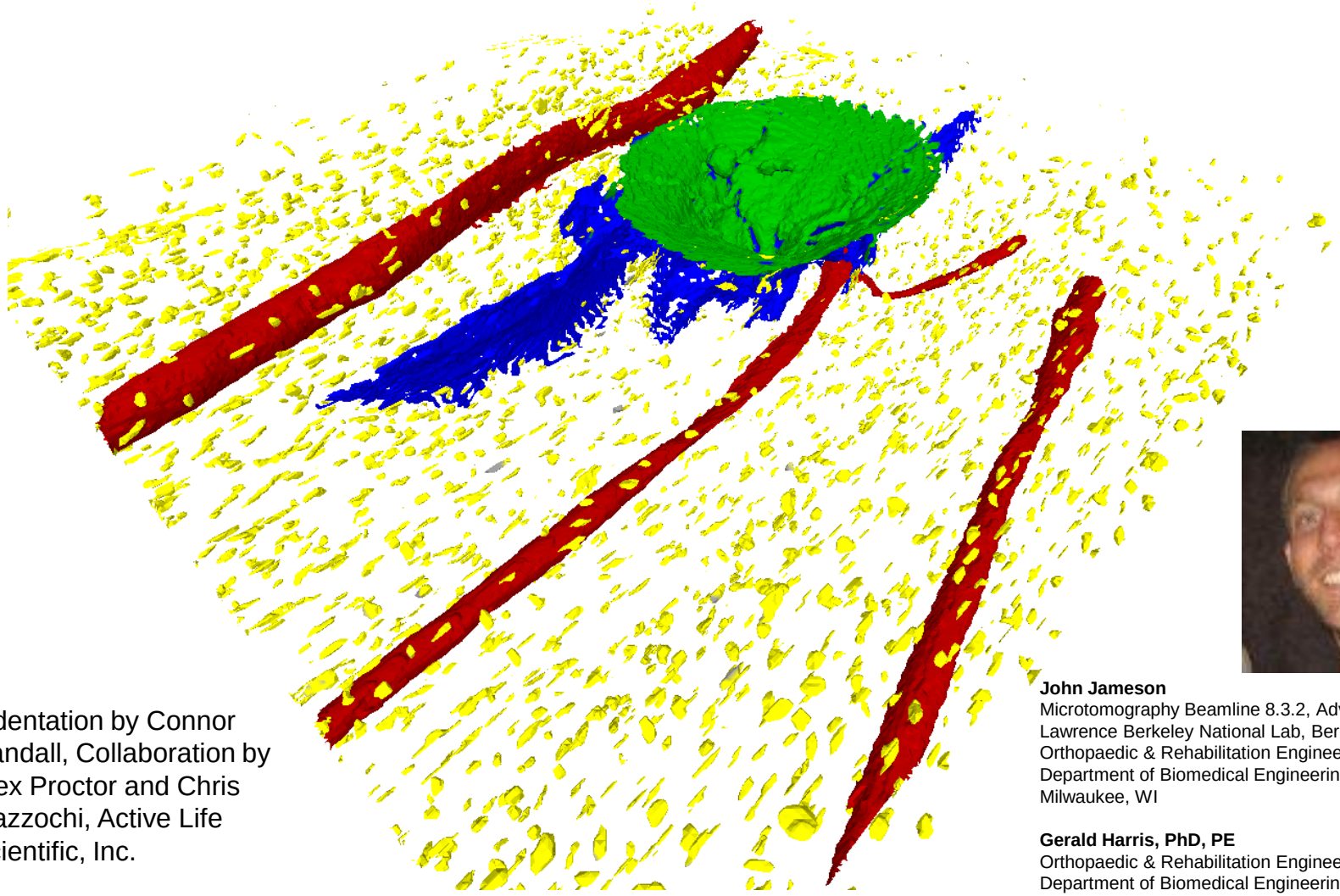
- Basic research on bone pointed to the need for a new clinical instrument.
- A Reference Point Indentation instrument can assess the contribution of materials properties to whole bone fracture risk in patients.
- Many human diseases are associated with changes in material properties of tissues.
- Now there is hope of measuring these changes in patients.

Acknowledgments

- Dan Morse, Galen Stucky, and Angela Belcher for collaboration on the abalone work that led to the bone work.
- Philipp Thurner , now School of Engineering Sciences, University of Southampton, Southampton, United Kingdom and Georg Fantner, now ETH, for the basic bone work.
- Connor Randall, Daniel Bridges, Doug Rehn, Bruce Murdock, Barney Drake, James C. Weaver, Georg Fantner, Philipp Thurner, Johannes Kindt, Eugene Yurtsev, and Ralf Jungmann for helping develop and test Reference Point Indentation at UCSB.
- Alexander Proctor, Davis Brimer and Dylan Cummings, Active Life Scientific, for commercializing Reference Point Indentation.
- Adolfo Diez-Perez, Roberto Güerri, Xavier Nogues, Lluis Puig, Elisa Torres, Enric Cáceres, Maria Jesus Peña, Oriol Diez-Ferrer, and Leonardo Mellibovsky, Hospital del Mar-IMIM, Autonomous University of Barcelona for the clinical research.
- Hal Kopeikin for statistical analysis of data from multiple sites and for helping make our user interface a teaching device.
- Ahmed Elbanna, Jean Carlson and Jim Langer for modeling the effect of sacrificial bonds and hidden length on fracture processes.
- Kevin Hoffseth and Henry Yang, UCSB, for modeling indentation processes with finite element analysis.
- Doug Herthel, Tim Lescun, S. Chandrasekar, Kevin Hoffseth and Henry Yang for the work on horses.
- NIH Grant RO1 GM 065354

Thanks for your attention!

High resolution imaging of fractures and fracture processes



Indentation by Connor Randall, Collaboration by Alex Proctor and Chris Mazzochi, Active Life Scientific, Inc.

John Jameson
Microtomography Beamline 8.3.2, Advanced Light Source, Lawrence Berkeley National Lab, Berkeley, CA
Orthopaedic & Rehabilitation Engineering Center (OREC), Department of Biomedical Engineering, Marquette University, Milwaukee, WI

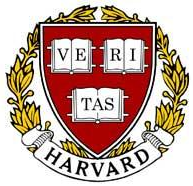
Gerald Harris, PhD, PE
Orthopaedic & Rehabilitation Engineering Center (OREC), Department of Biomedical Engineering, Marquette University, Milwaukee, WI
Shriners Hospitals for Children, Chicago, IL

Indenter Imprint **Microcracks** **Canal Network** **Osteocytes**

Active Life Scientific Collaborators

Active Life Scientific, Inc.

Translational Research Tools for the Life Sciences



Massachusetts Institute of Technology

The University Of Sheffield.

Imperial College London

UNIVERSITY OF Southampton

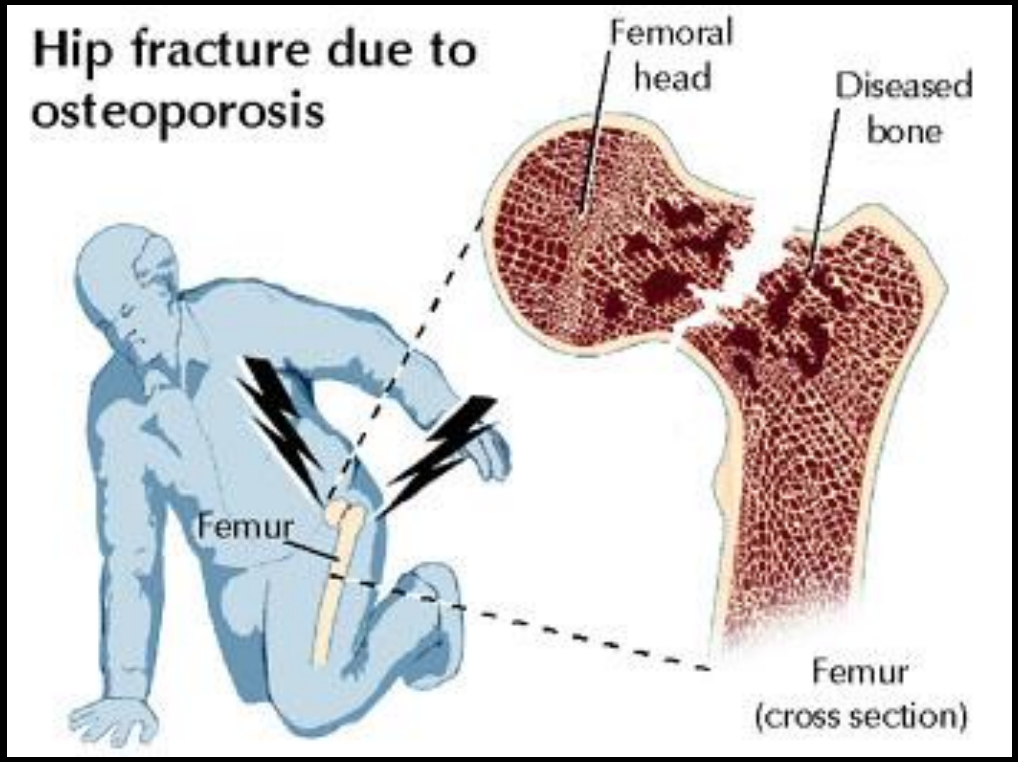
KATHOLIEKE UNIVERSITEIT LEUVEN

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

UNIVERSITÉ DE NANTES

Yale University

Hip Fracture: a serious problem

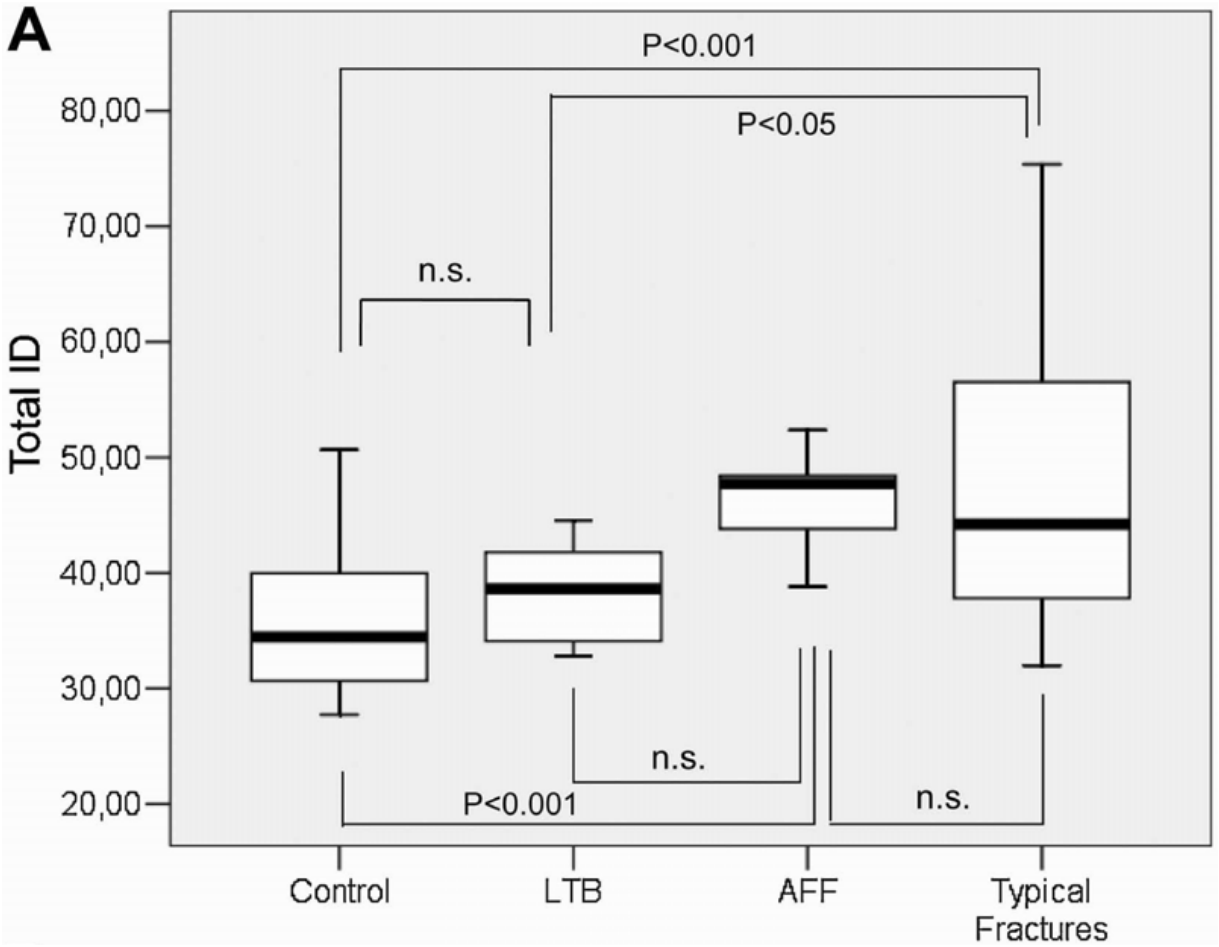


A person with a hip fracture has a greater chance of dying within one year than if they had a heart attack.

33% are totally dependent or in a nursing home in the year following a hip fracture

Pass around bone model

A new, larger clinical study that confirmed and extended the original study.



R Güerri-Fernández, X Nogués, JM Quesadabc, E Torresab, Ll Puig, N García-Giralt, G Yoskovitz, L Mellibovsky, PK Hansma, A Diez-Perez, JBMR 28, p162, 2013