

Toward Early Treatment of OA: Joggle Between Engineering and Medicine

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Chronic Musculoskeletal Pain



**Sore/Swelling
/Pain/Numb/Stiff**

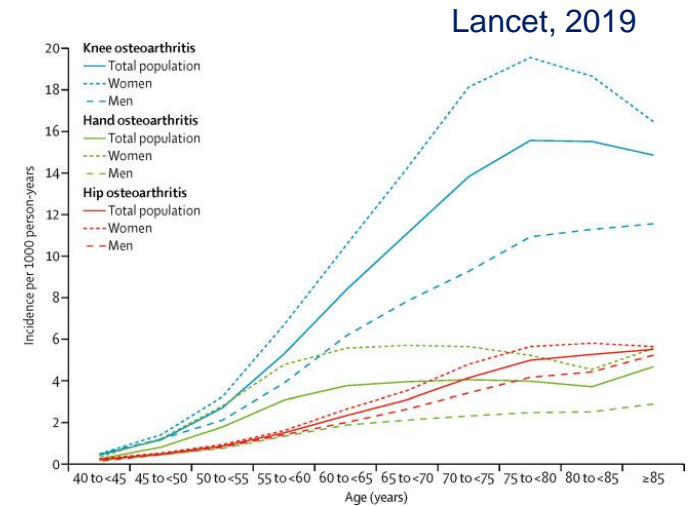
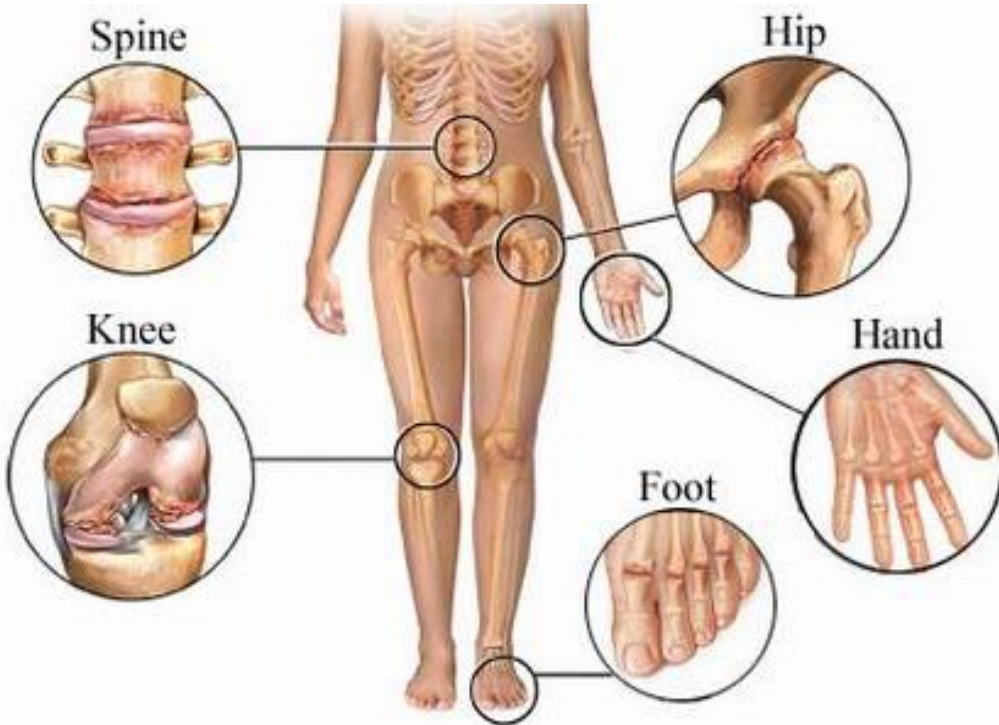


Arthritis is one of the main chronic musculoskeletal disorders

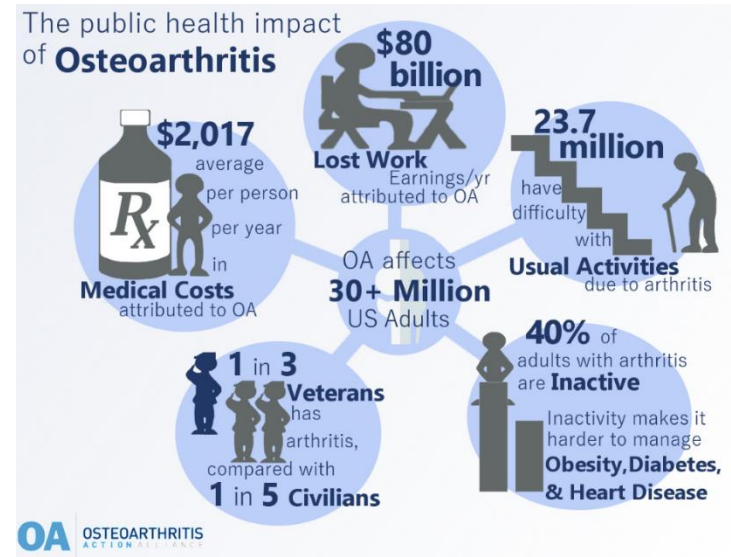


Osteoarthritis – A Clinical Problem

(Osteoarthritis can affect every Joints)

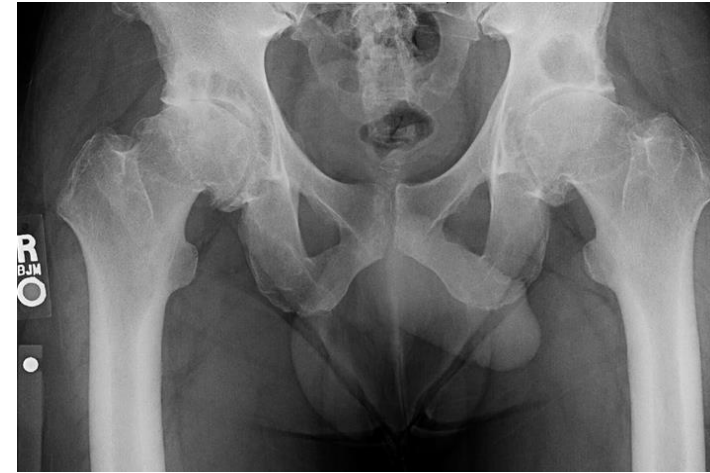
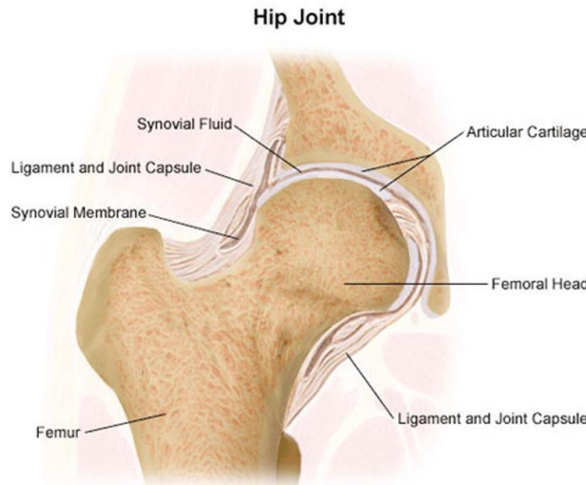


- ✓ Results in chronic pain and loss of mobility.
- ✓ Prevalence of 18% in over 45 in England.
- ✓ Over 6.5 million Hip and knee OA cases reported in England alone (2012, Versus Arthritis).
- ✓ By 2050, 400 million people will suffer from OA worldwide, of whom 40 million will be severely disabled by the disease.
- ✓ OA is likely to increasing due to the aging of the population and increasing rates of obesity.

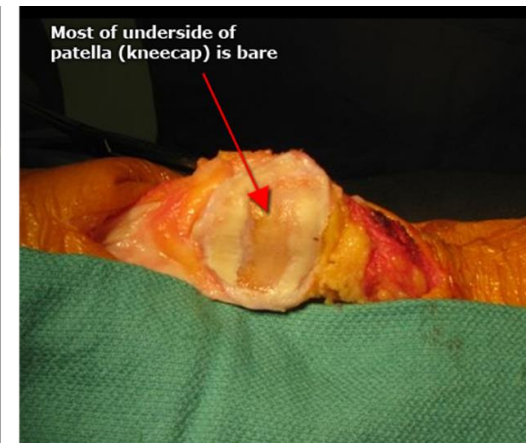
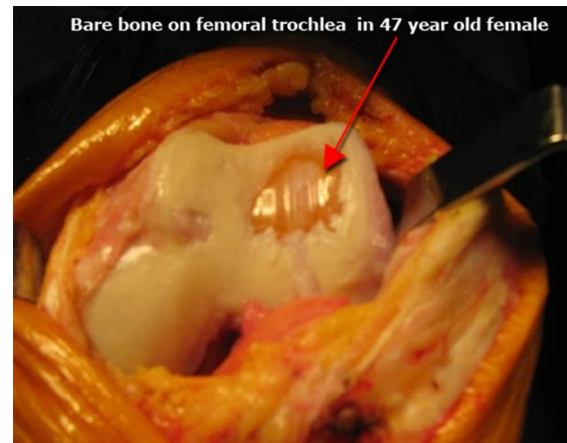


Osteoarthritis – A Cartilage Problem

- Distribute joint loads over wide area
- Allow relative movement of joint with minimal friction and wear



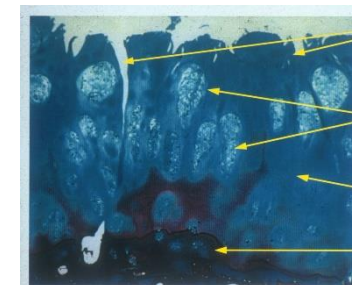
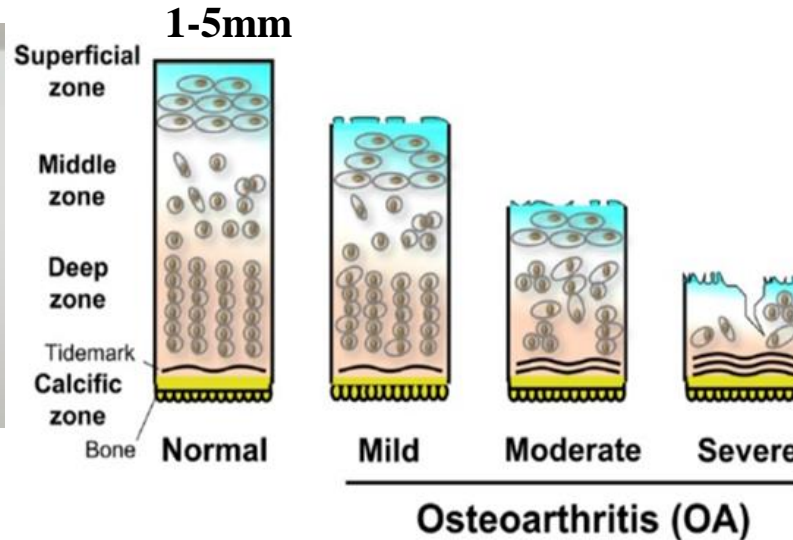
- (1) Joint space narrowing
- (2) Osteophytes
- (3) Subchondral sclerosis
- (4) Subchondral cysts
- (5) Structural damage



Osteoarthritis – A Cartilage Problem

Normal cartilage

OA cartilage



Fibrillation of articular surface

Stimulation of cell division

Loss of matrix components

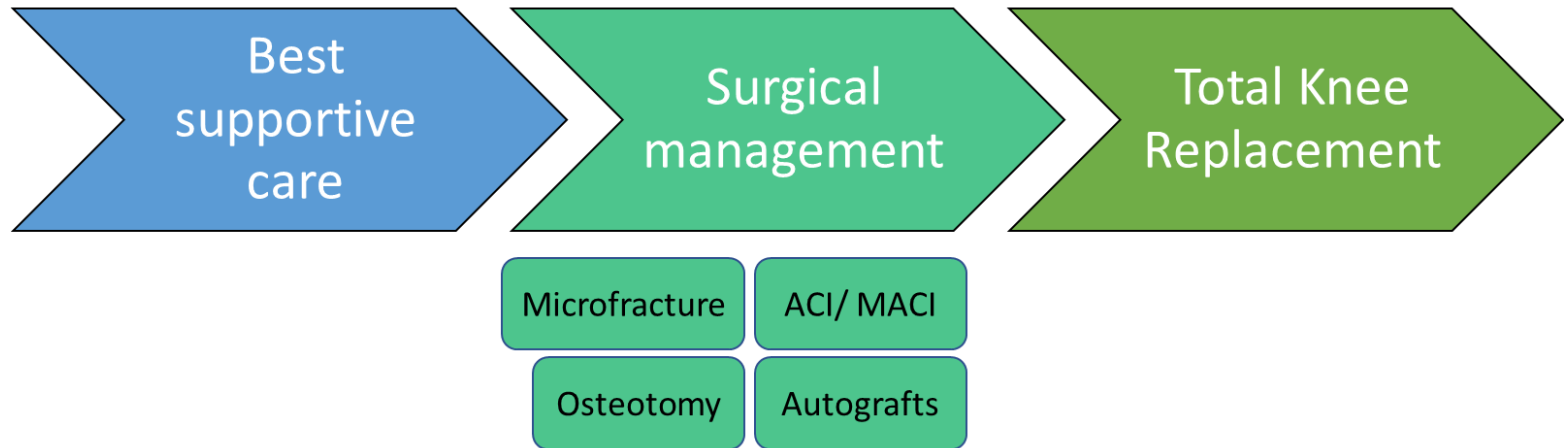
Advance of the subchondral bone

Disruption of cartilage and it is non-reversible

- More diagnosed and treated more frequently in young athletes.
 - ✓ Pain
 - ✓ Swelling / Joint locking
 - ✓ Stiffness / Clicking

Reduce quality of life

Osteoarthritis – Surgical Treatment



Joint replacements: Last resort in end-stage OA only when conservative management has failed:

- ✓ Non-reversible
- ✓ Big operation associated with life-time complications
- ✓ Implant failures



Implant Failure – An Unavoidable Problem



Fears Over Hip Replacement 'Poisoning'



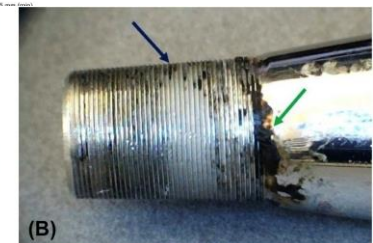
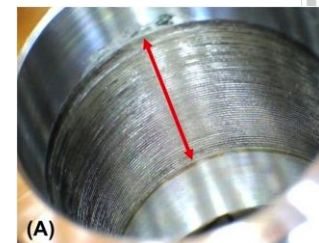
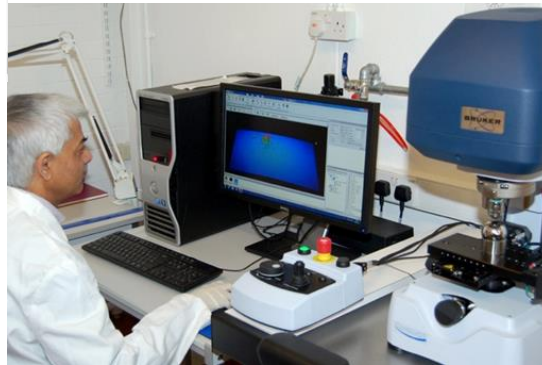
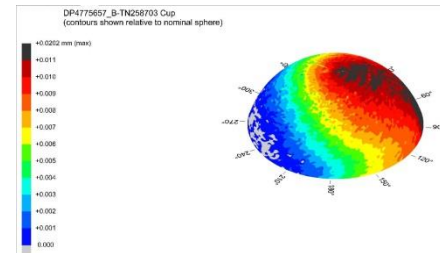
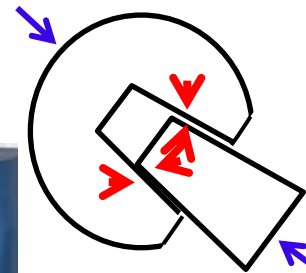
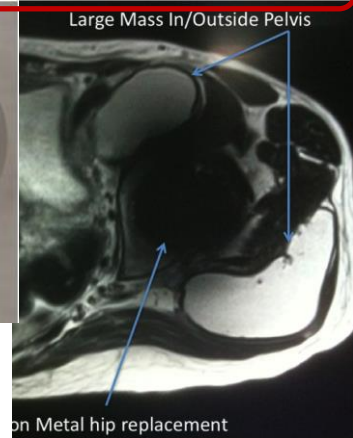
Surgeon related



Implant related

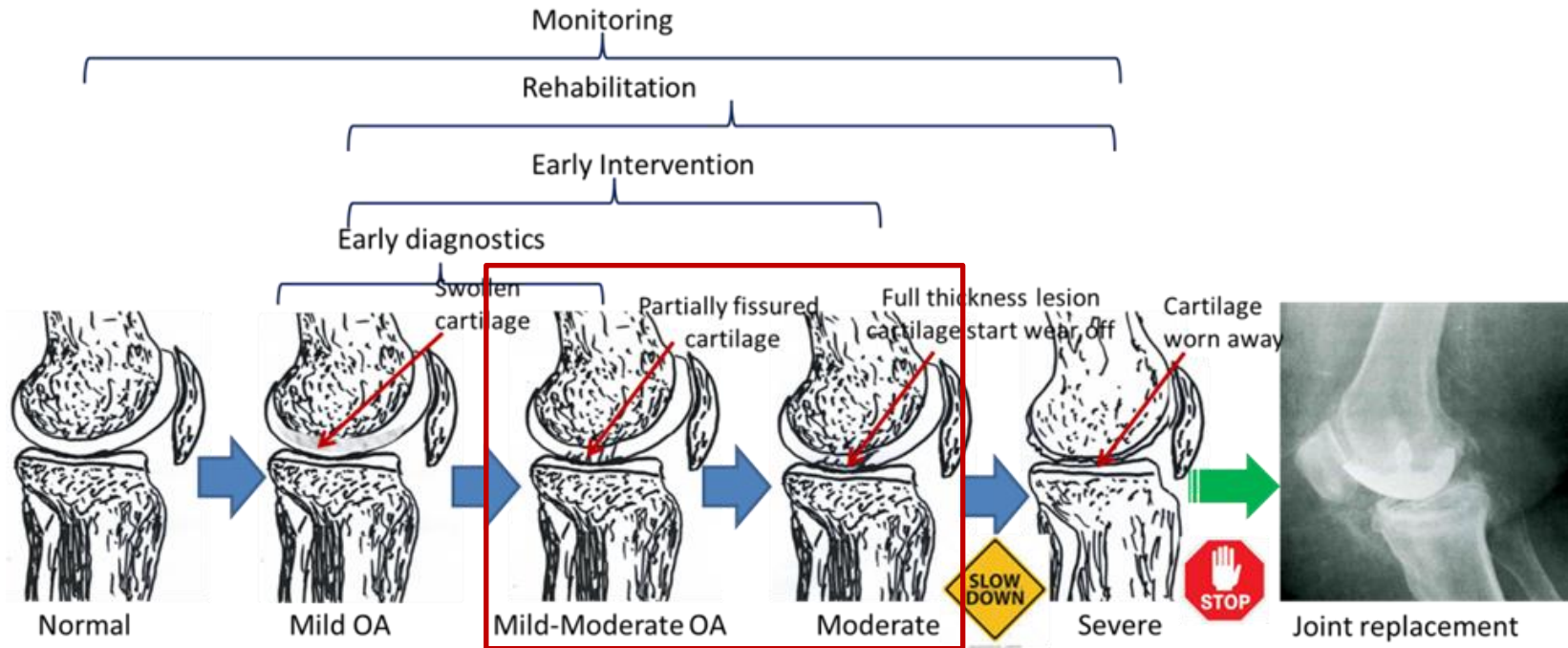


Patient related



Needs clinical and retrieval analysis

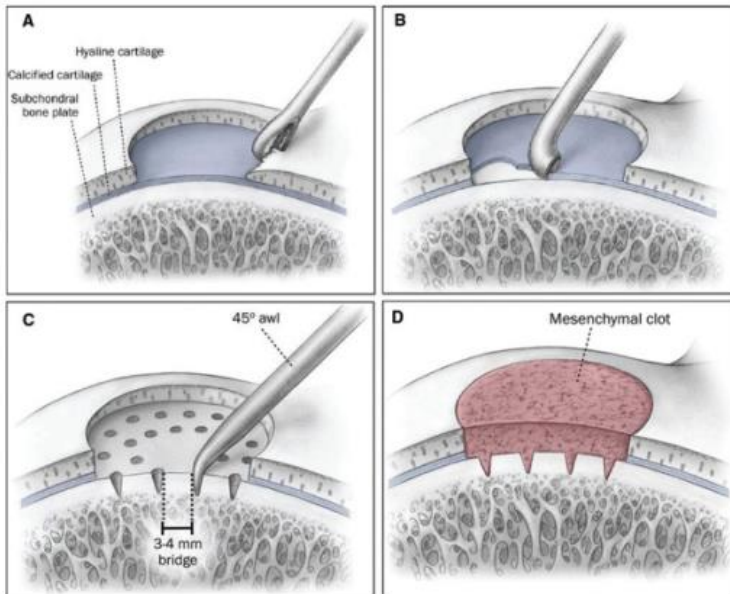
Osteoarthritis – Early Interventions



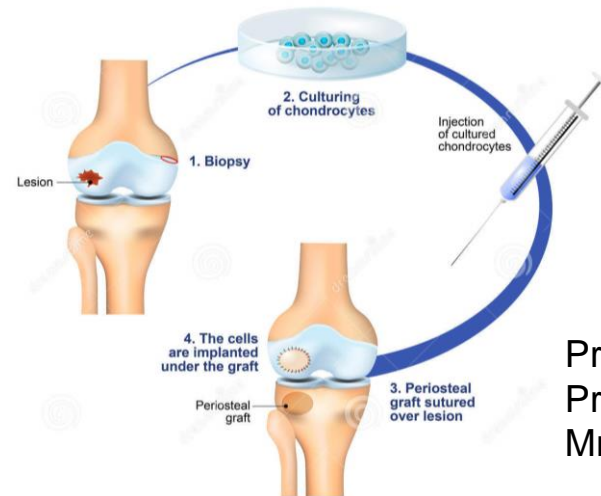
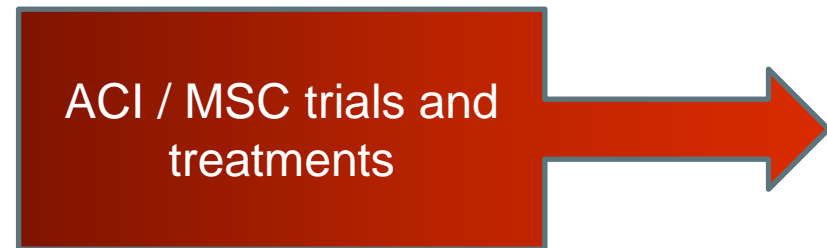
Mid OA

Intervention of OA at every stage of progression

Translational in Practice at UCL/RNOH



Microfracture



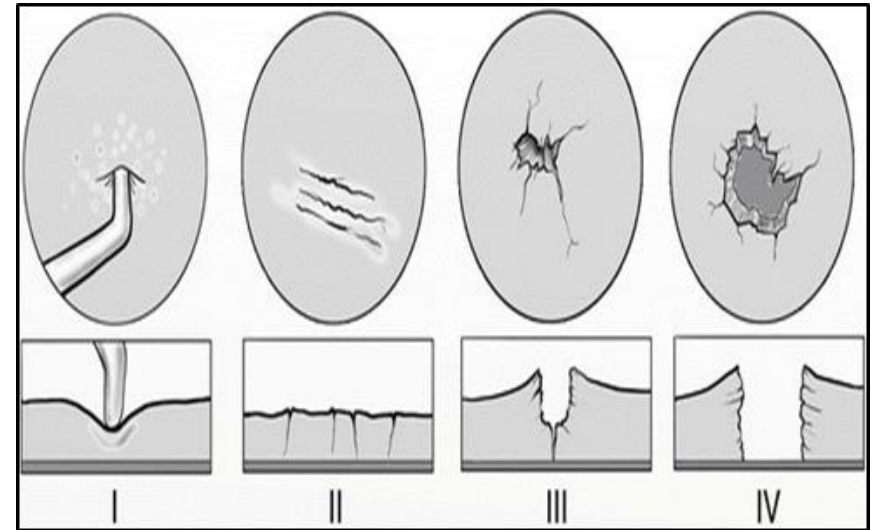
Prof George Bentley
 Prof John Skinner
 Mr James Donaldson

- Autologous chondrocyte implantation (ACI) / MACI
- Bone Marrow Stem Cell Therapy

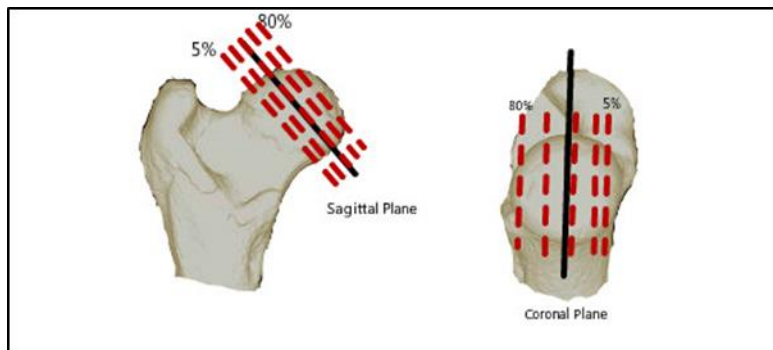
OA - Material Scientist's View



Femoral heads from total joint replacements: trauma and OA patients

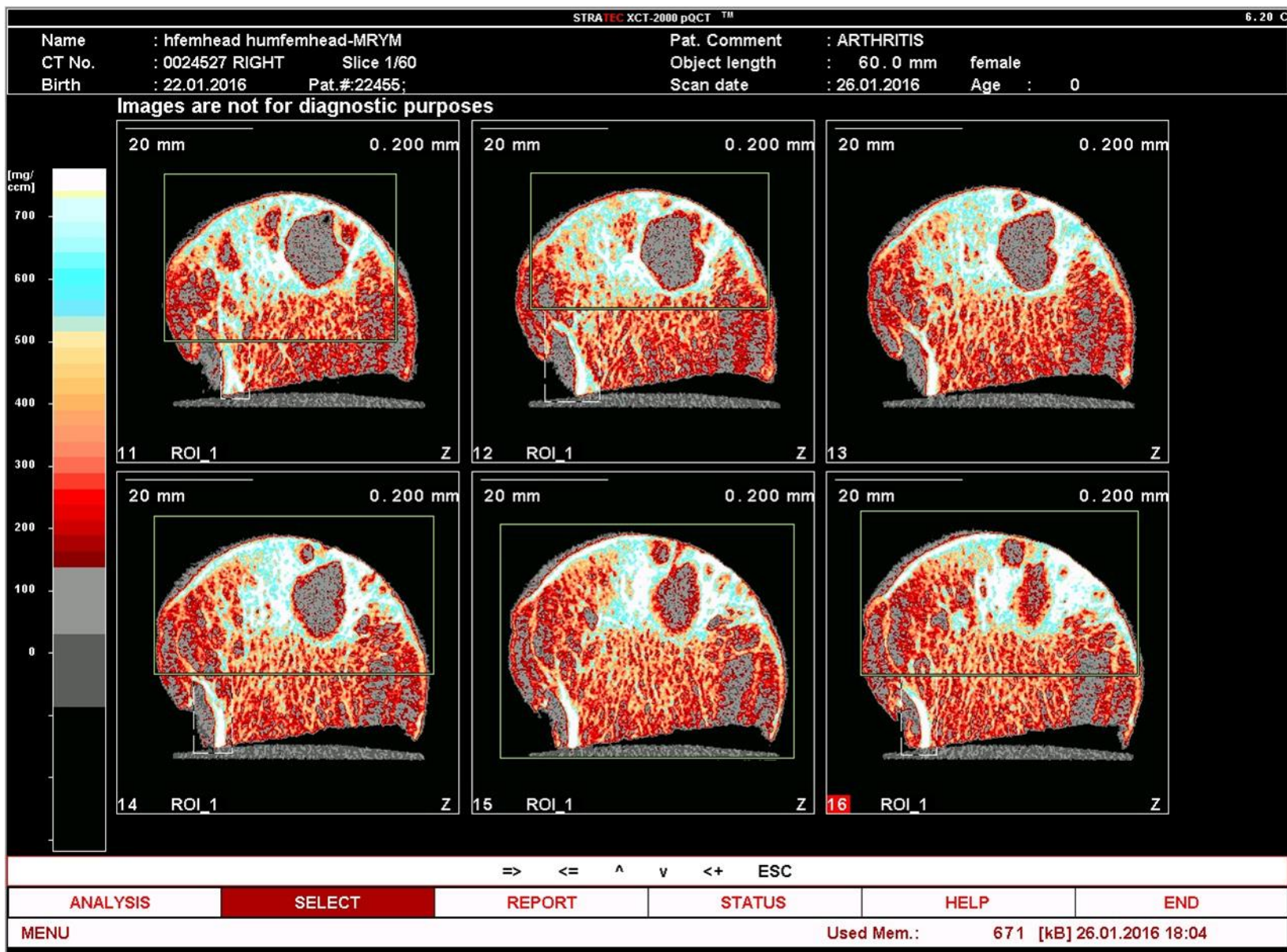


Outerbridge Classification(Wright 2014)

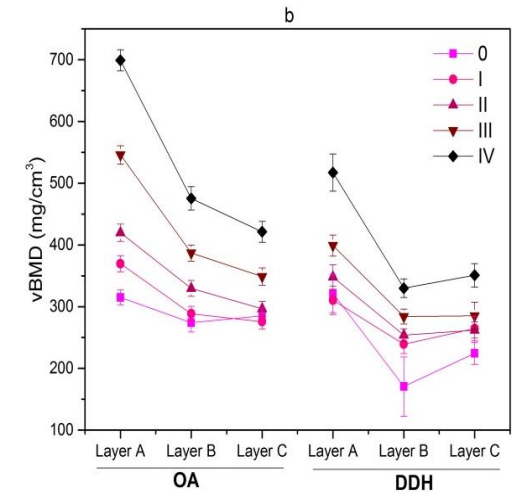
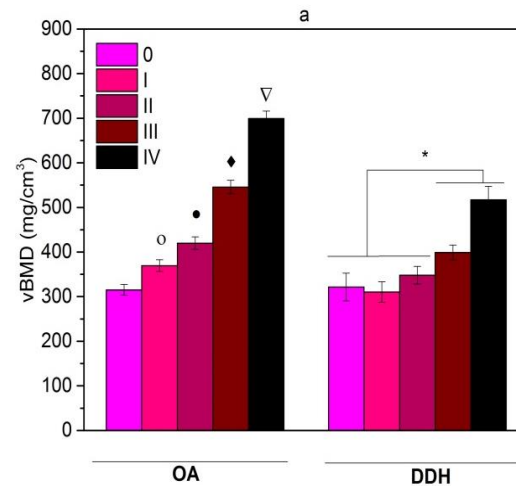
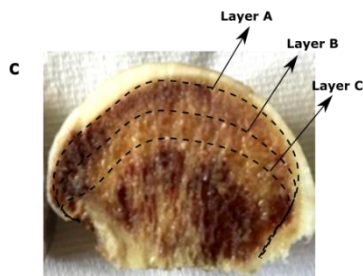
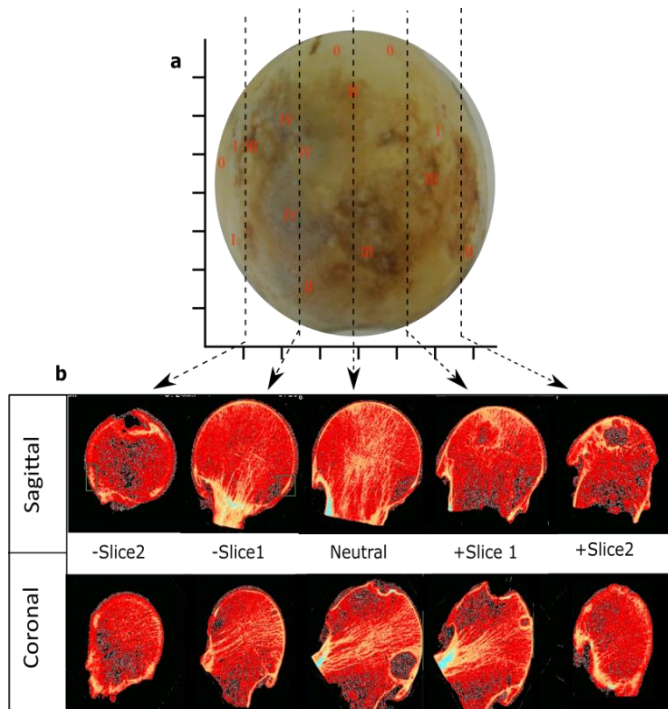


pQCT to measure the volumetric BMD (vBMD, mg/cm³) (Stratec XCT 2000, Germany)

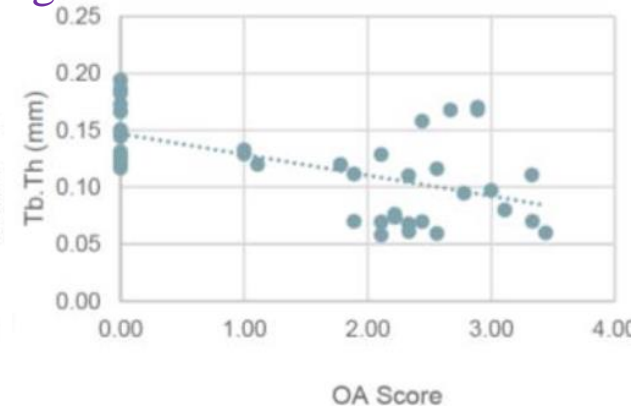
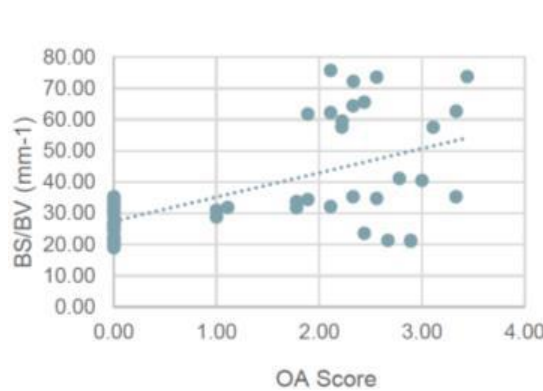
OA - Material Scientist's View



OA - Material Scientist's View



Positive association between local vBMD / bone remodelling and severity of cartilage damages

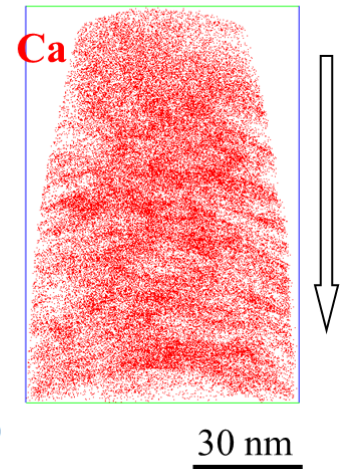
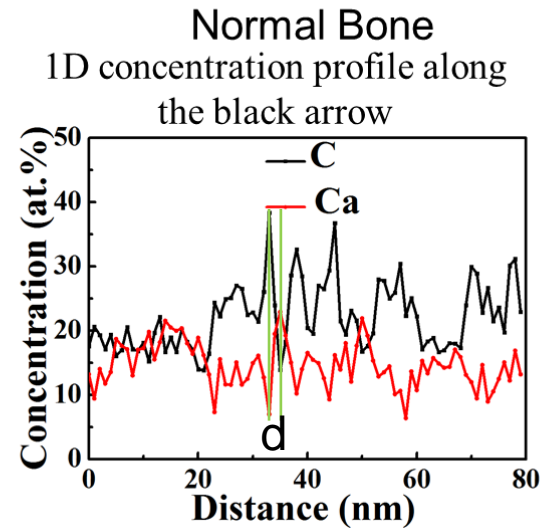
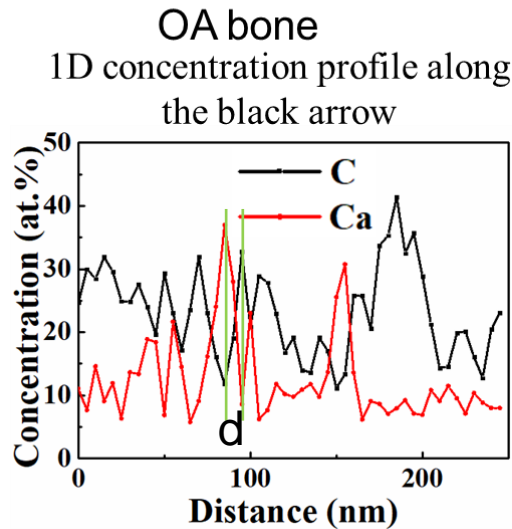
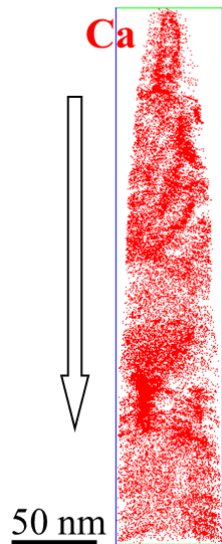


BS/BV and OA score ($r = 0.541, N = 52, P = 0.003$)

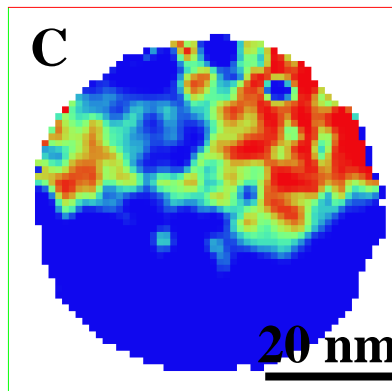
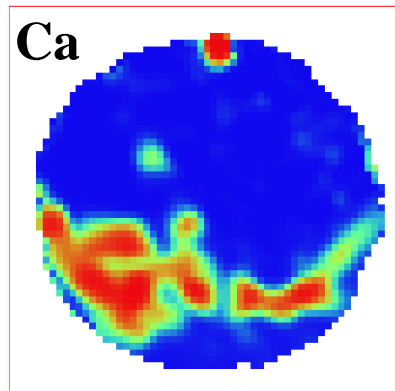
OA - Material Scientist's View

Subchondral bone Bulk composition (at.%)

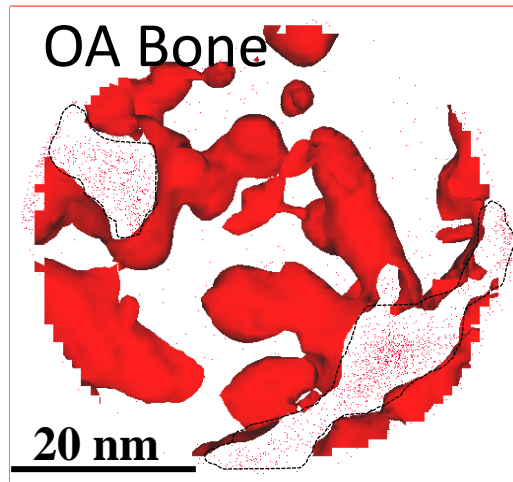
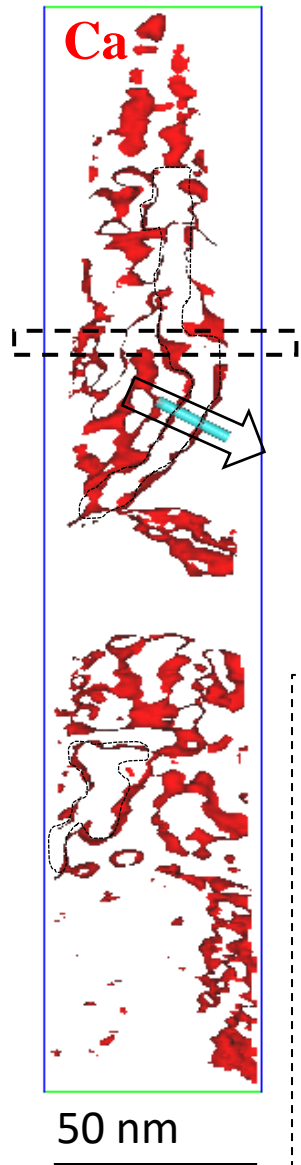
Info	O	Ca	C	P	Na	N	F	Mg
OA Bone	42.4±4.4	22.3±1.7	17.2±4.4	12.3±2.3	3.06±1.1	2.64±0.7	0.20±0.1	0.03±0.02
Normal	40.2	18.8	24.2	11.0	1.97	3.68	0.098	-



2D concentration contour map in the XY plane.

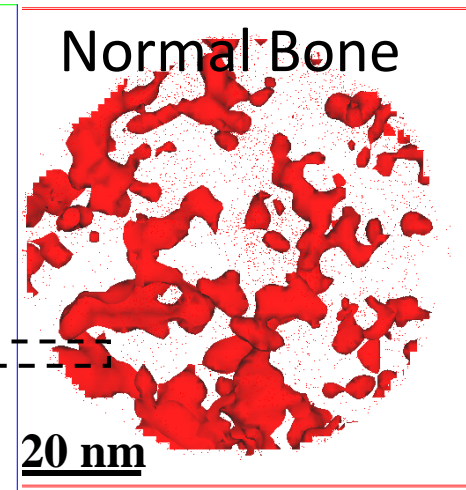
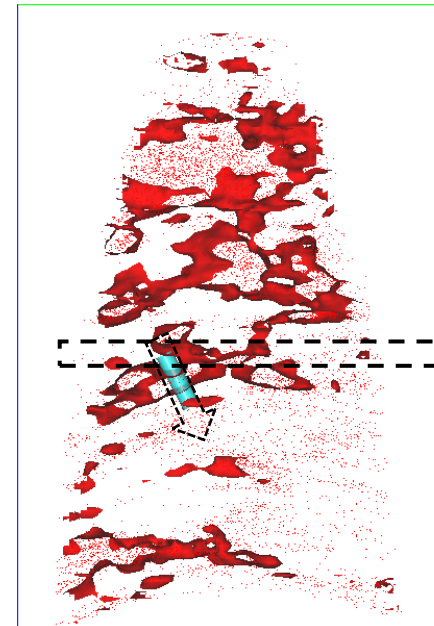
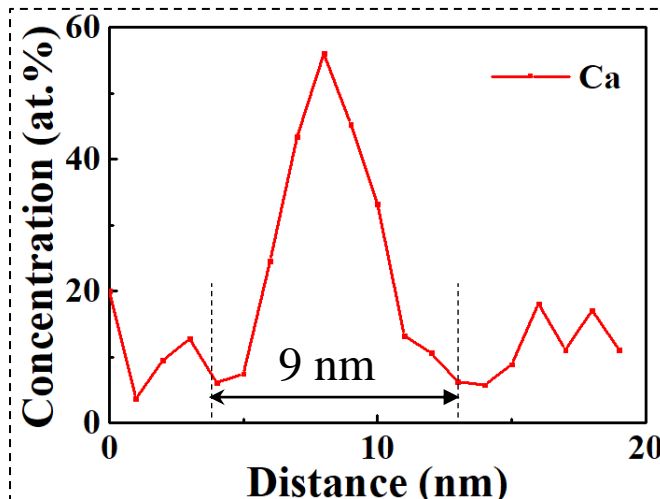


OA - Material Scientist's View

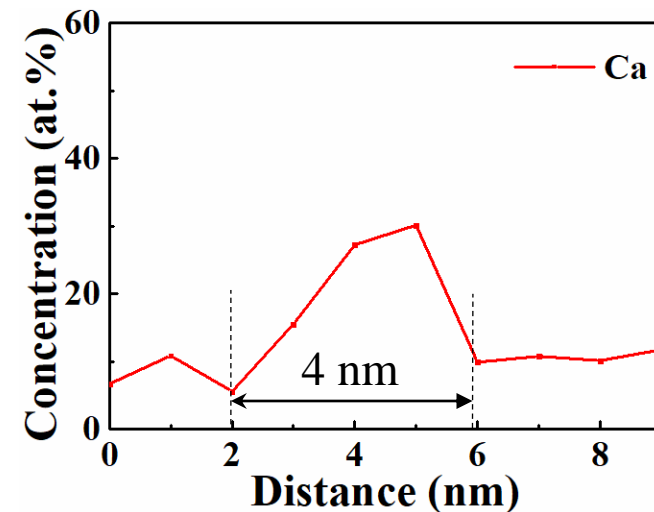


Isosurface of Ca at 17at.%

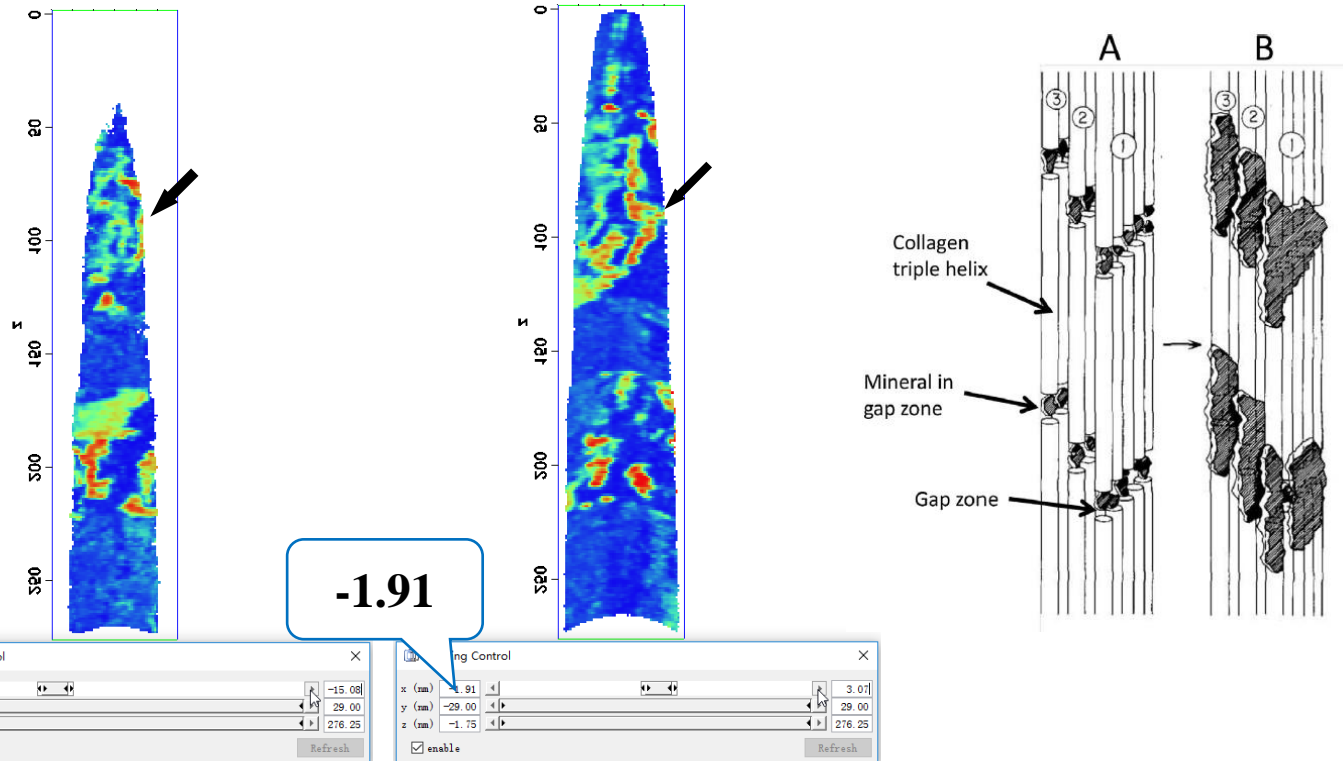
1D concentration profile along the black arrow



Isosurface of Ca at 17at.%



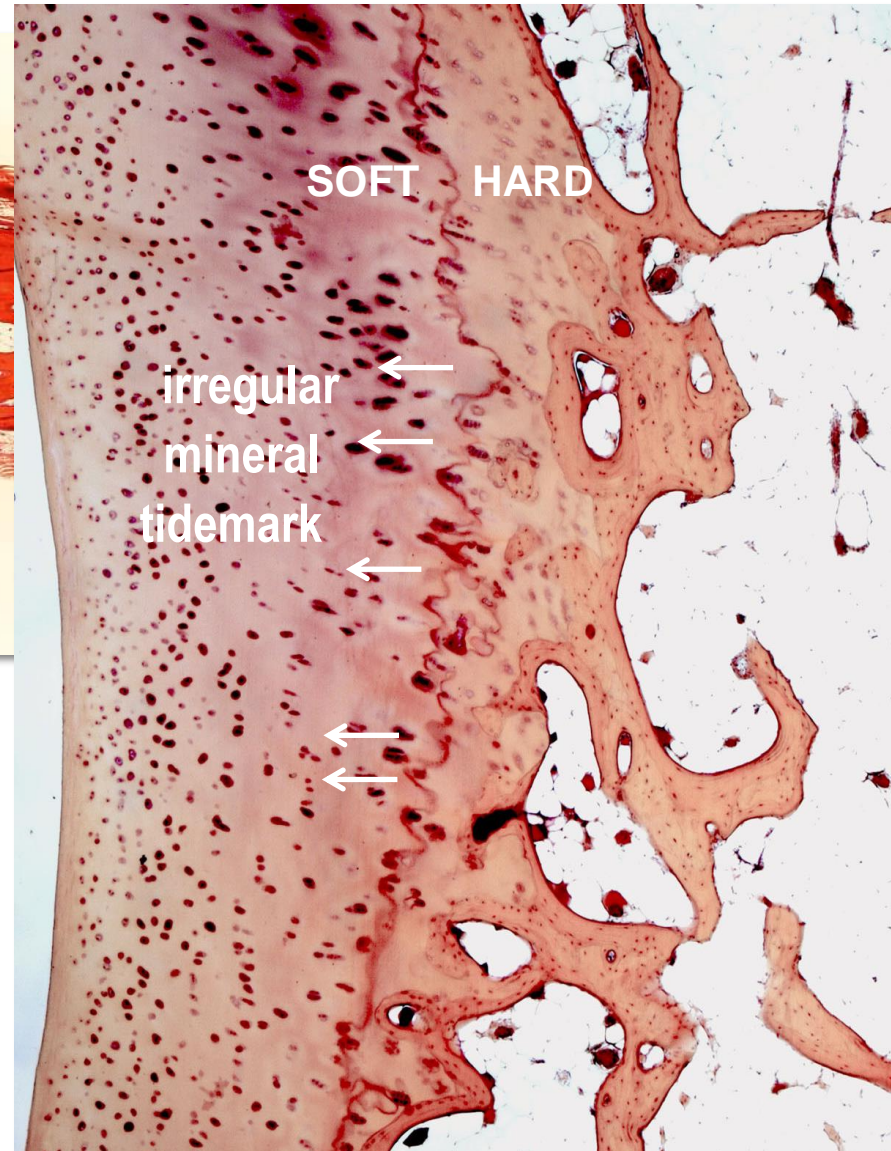
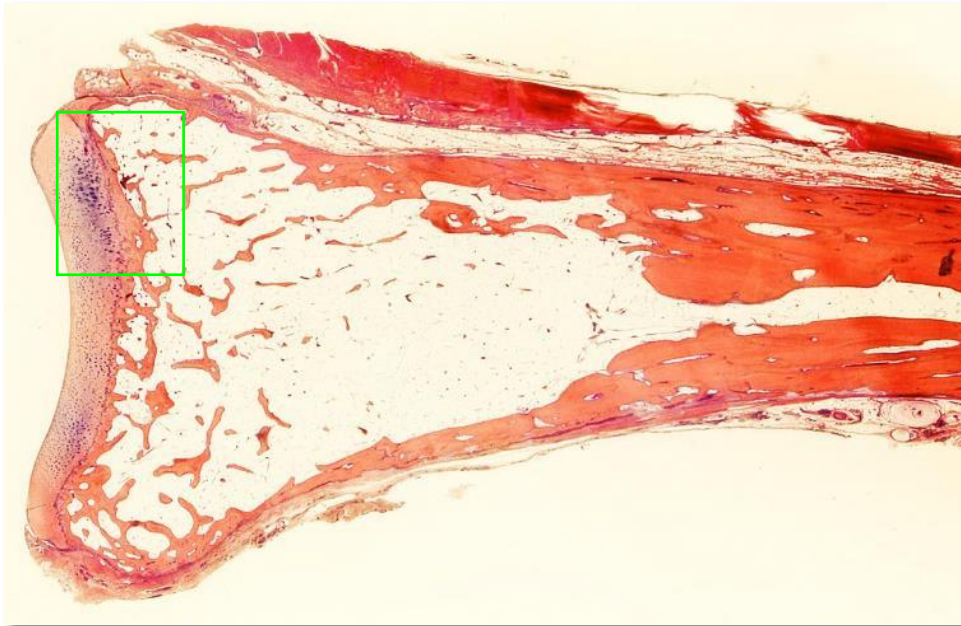
OA - Material Scientist's View



Concentration Volume Render of Ca

Hydroxyapatite crystals in OA bone are much bigger than that in non-OA samples, and in plate-like form.

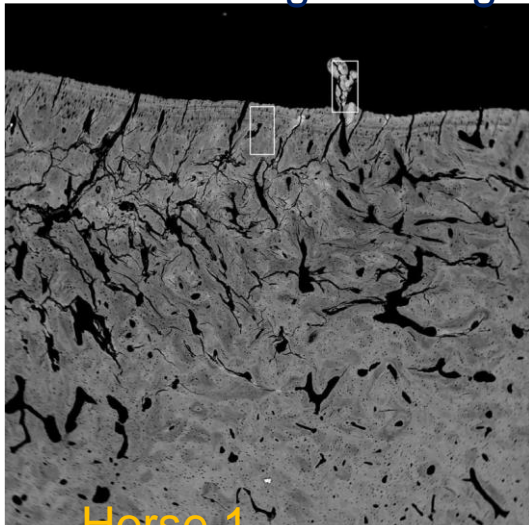
Tidemark-Interface Between Cartilage and Subchondral Bone



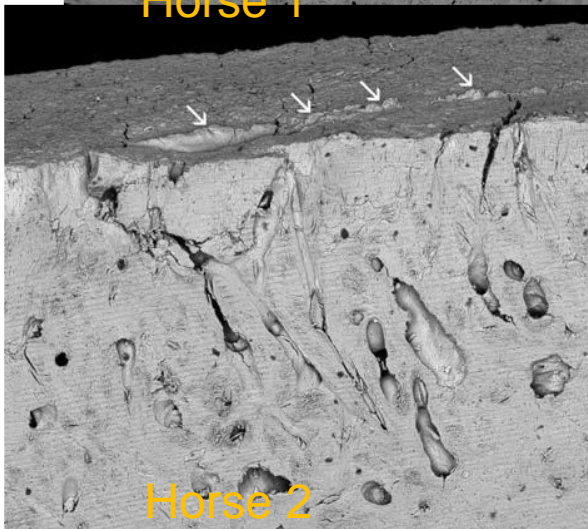
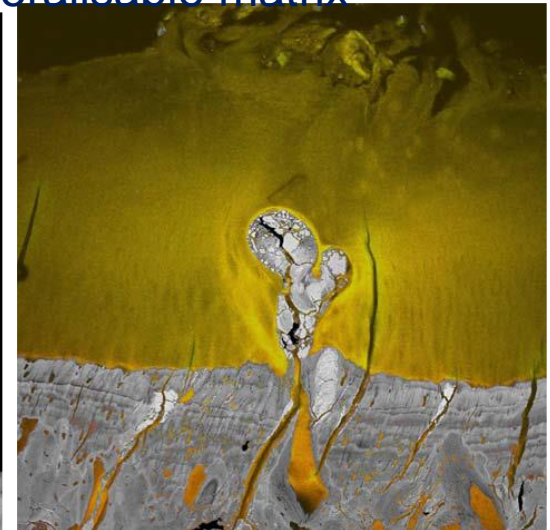
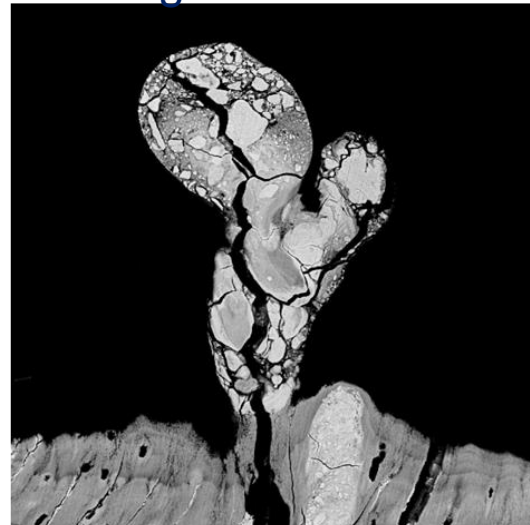
- Advancing, irregular mineral tidemark could act like buried 'cheesegrater', damaging soft cartilage as joint articulates...

Tidemark-Interface Between Cartilage and Subchondral Bone

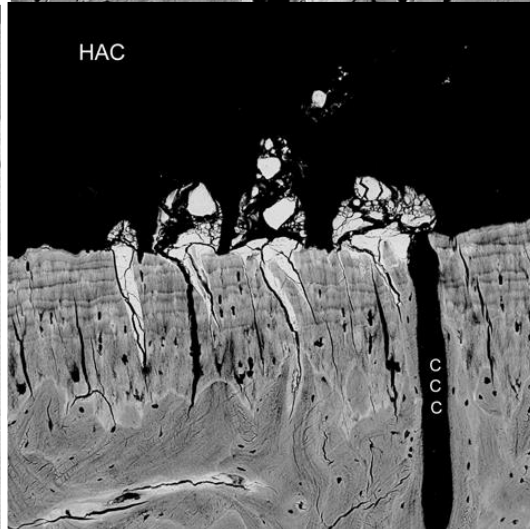
Cartilage damage involving extrusion of mineralisable matrix



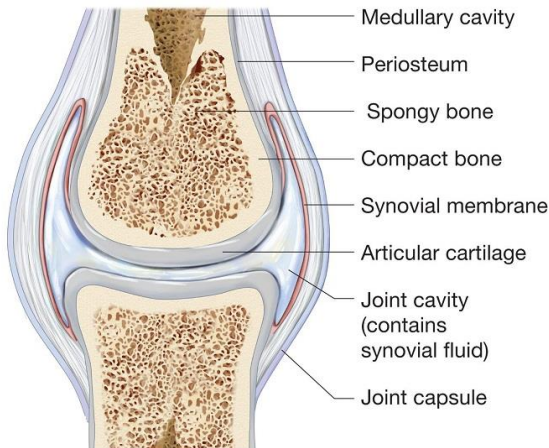
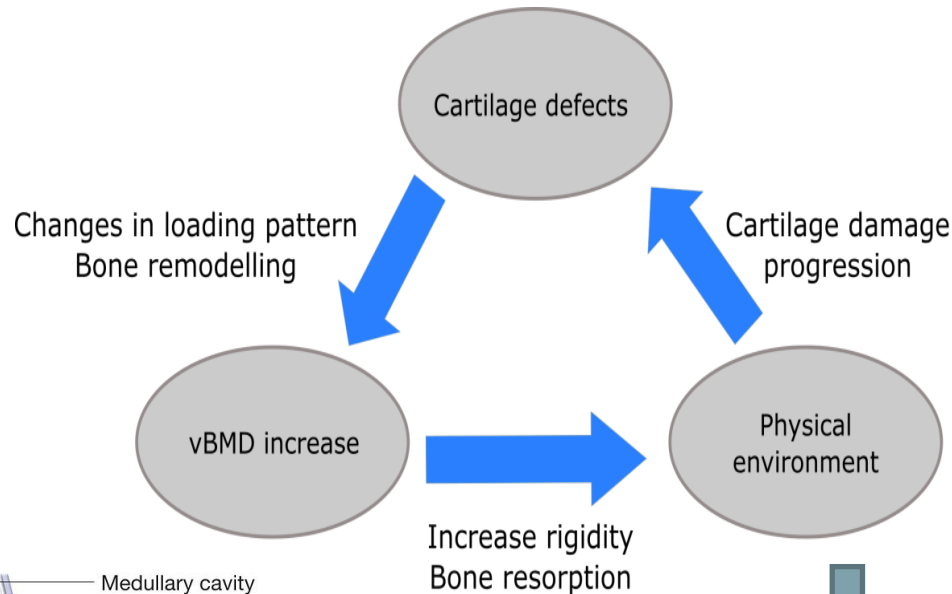
Horse 1



Horse 2



Paradigm for cartilage defect progression



- ✓ Can we change or control the physical environment of the OA joints?
- ✓ How?
- ✓ Can this enhance cartilage regeneration?

“COWALK” with Clinicians

**Osteochondral scaffold Innovation for
Early Repair of Cartilage Defect:**

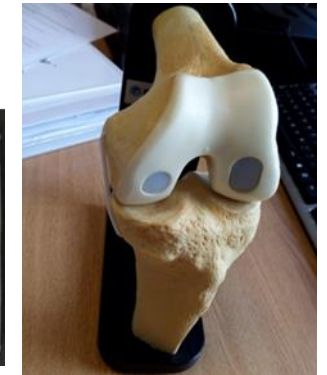
**Delay or Avoid the Use of Joint
Replacement**

Translational in Practice at UCL/RNOH



Cells / Environment / Scaffolds

OScaffold prototype



Bench to Bedside

Scaffold - Control the Physical Environment

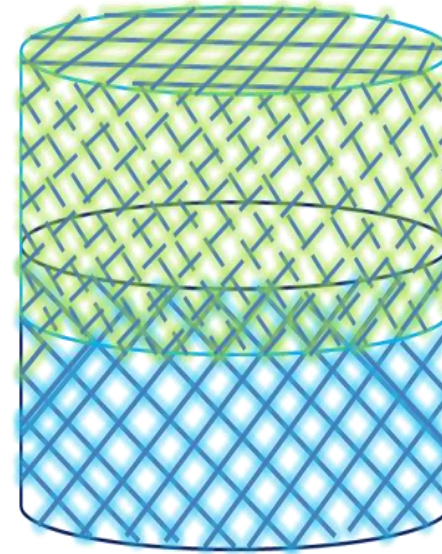
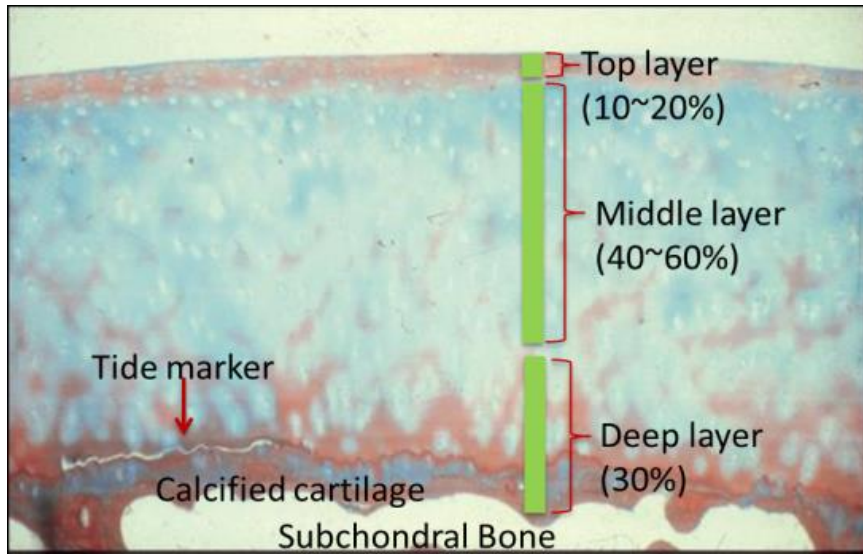
- ✓ Large cartilage defects / osteochondral defects
- ✓ Recruit cells
- ✓ Support cells growth and differentiation.
- ✓ Simultaneously repair cartilage and bone

“COWALK” – Start with Materials

(Biomimetic Osteochondral Scaffold)

EPSRC Feasibility Study 2014

Gradient structure



PLGA infiltrated
collagen layer

PLA Junction

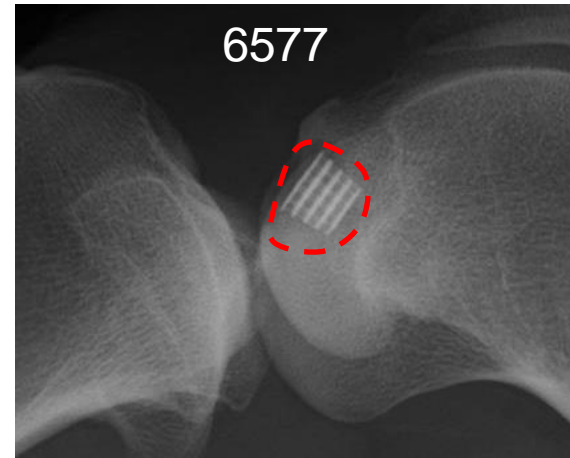
Titanium matrix

- **Structure gradient**
- **Mechanical property gradient**
- **Biological environment gradient**

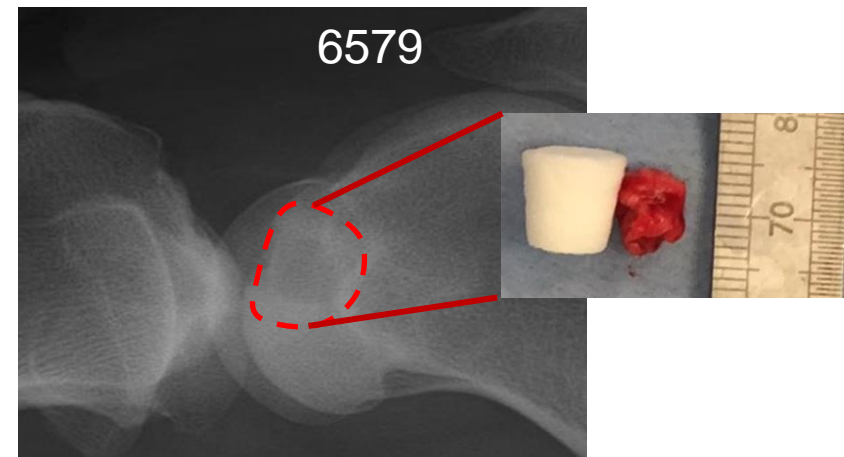
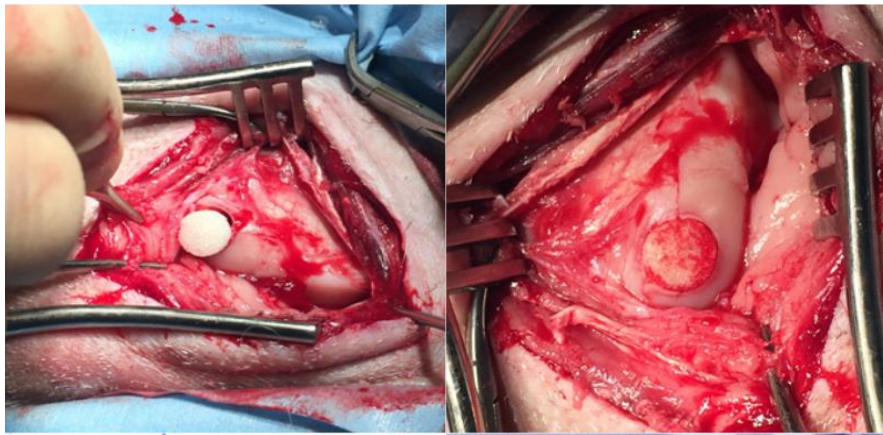
“COWALK” – POC

(ARUK-IKC PoC Project (grant no: A1184))

- Titanium/PLA framework reinforced collagen osteochondral scaffold
- Trilayered Collagen / hydroxyapatite scaffold as control



The scaffold form a stable fixation in the bone

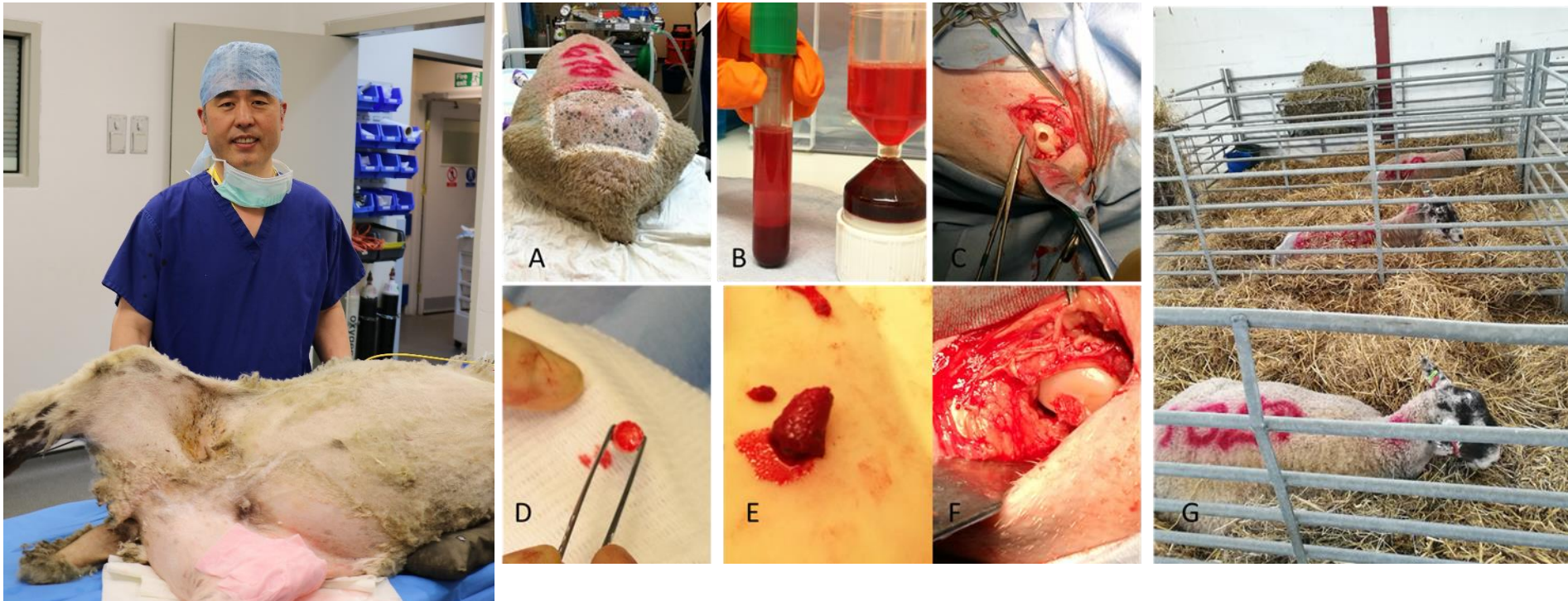


The control scaffold shrank upon contact with blood and form an incomplete fill in the joint

Scaffold was implanted in the sheep condyle

“COWALK” – Preclinical Study

(Innovate UK-MoST - 102872)



Scaffold was implanted in the sheep condyle

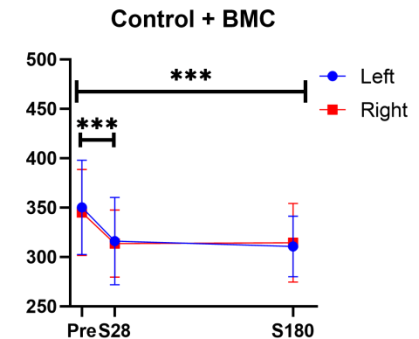
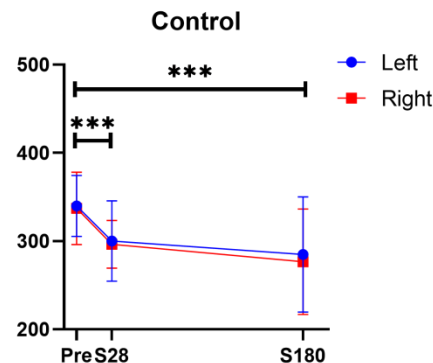
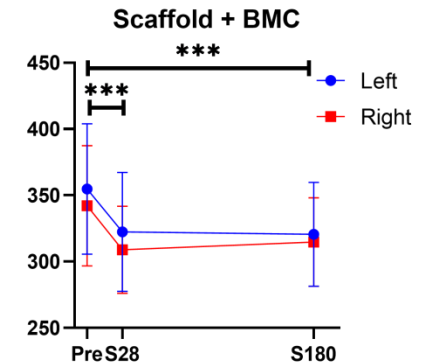
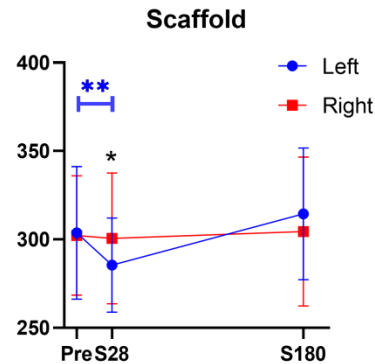
“COWALK” – Preclinical Study

(Innovate UK-MoST - 102872)

Walk the sheep on a pressure pad : pre-surgery, 1 months, 6 months



- No pain and limping was observed
- Scaffold group returned to pre-op gait
- Addition of BMC does not seem to affect the gait significantly

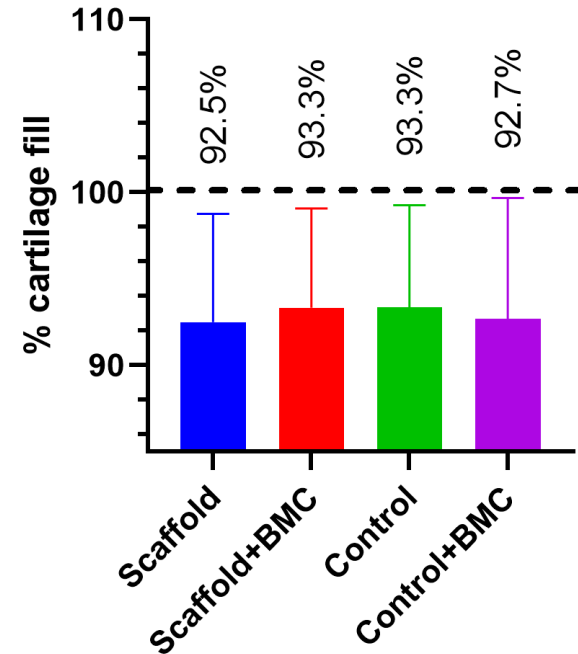
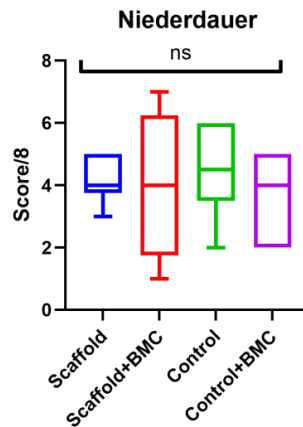
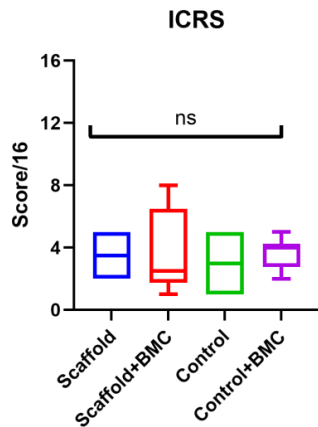
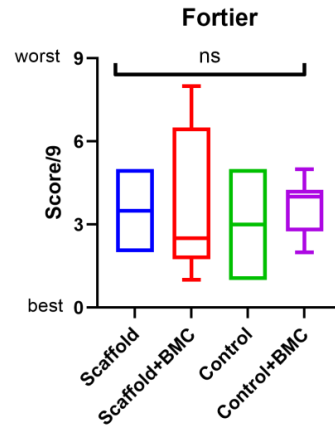
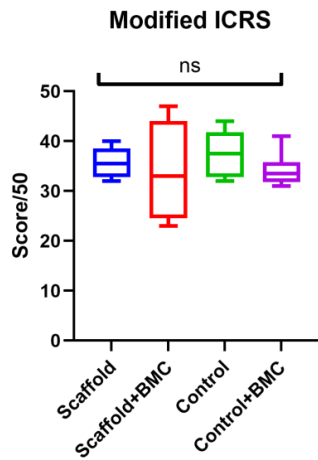


“COWALK” – Preclinical Study

(Innovate UK-MoST - 102872)

Analysed using : Fortier, Niederdauer, modified ICRS, ICRS and OAS systems

In Scaffold and Scaffold+BMC, we had over 92% cartilage fill

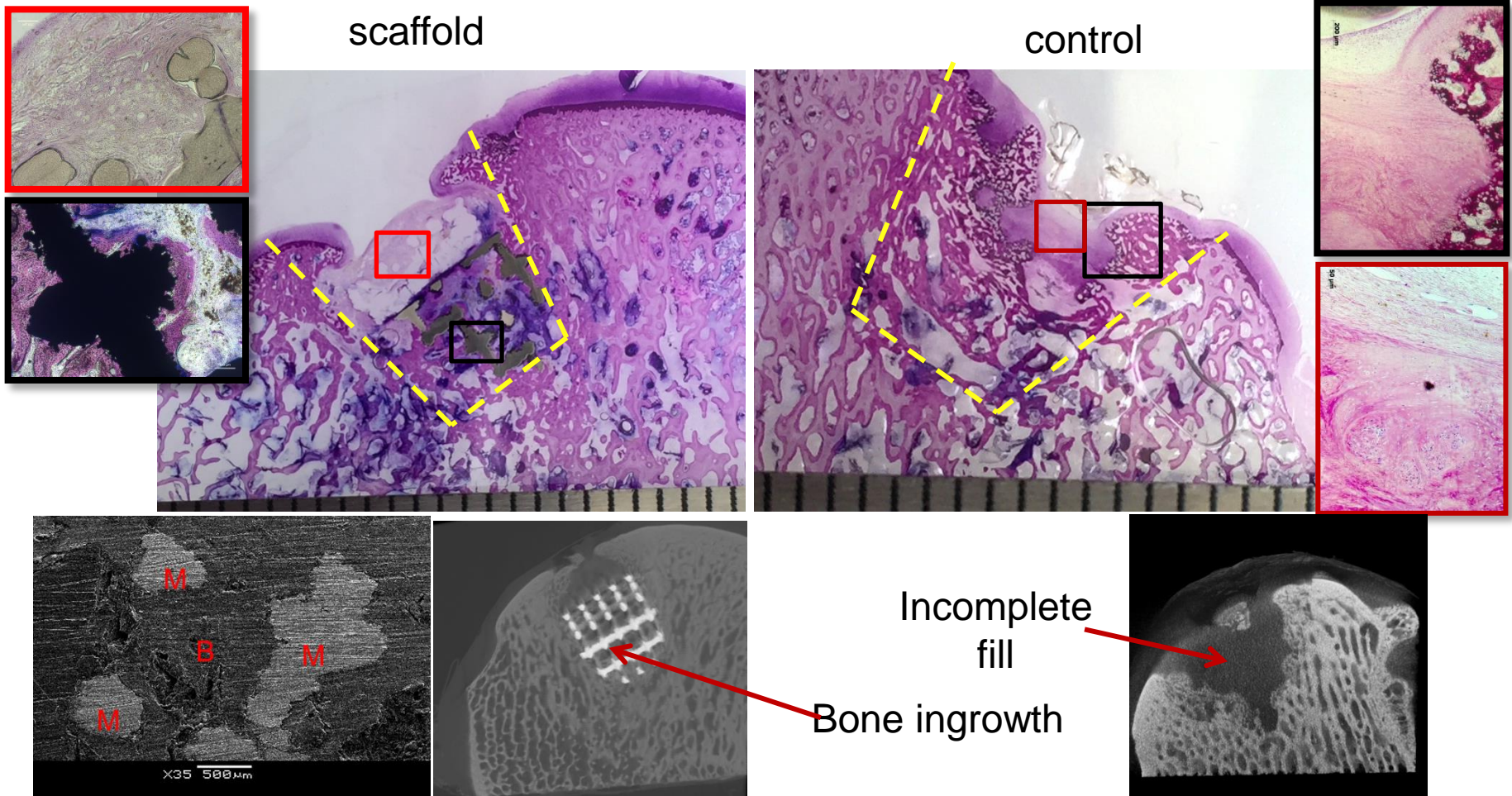


Cartilage Examinations - Macroscopic

“COWALK” – Preclinical Study

(Innovate UK-MoST - 102872)

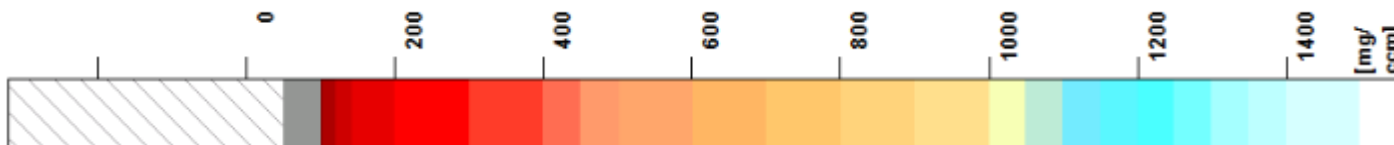
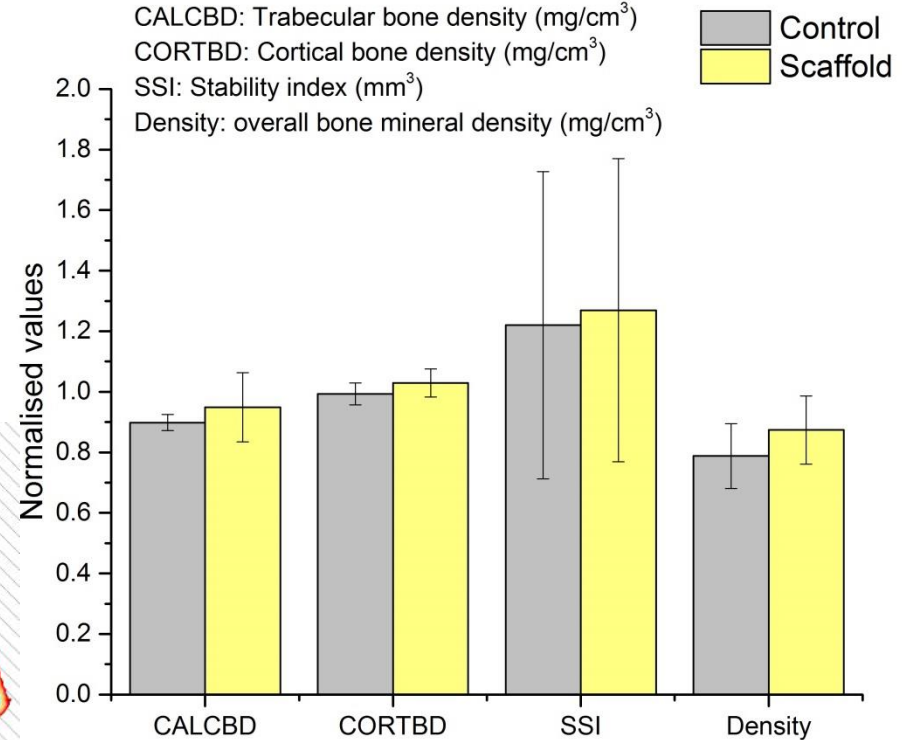
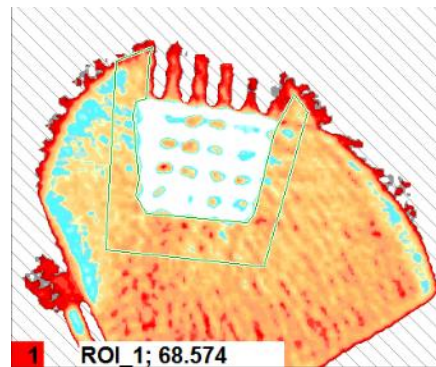
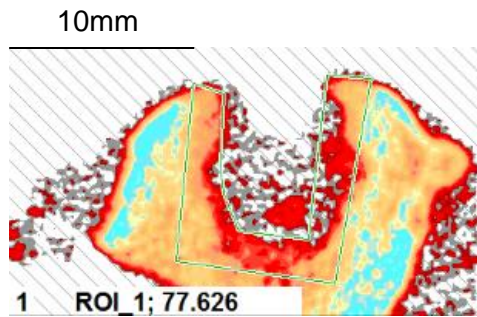
- Extensive bone ingrowth and integration in Ti layer, while fibrous tissue observed instead of bone in control



“COWALK” – Preclinical Study

(Innovate UK-MoST - 102872)

- Consistently higher values of bone mineral density in scaffold groups compared to control groups



“COWALK” – Preclinical Study

(Innovate UK-MoST - 102872)

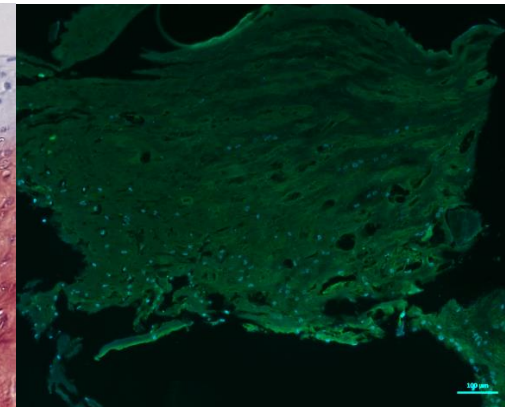
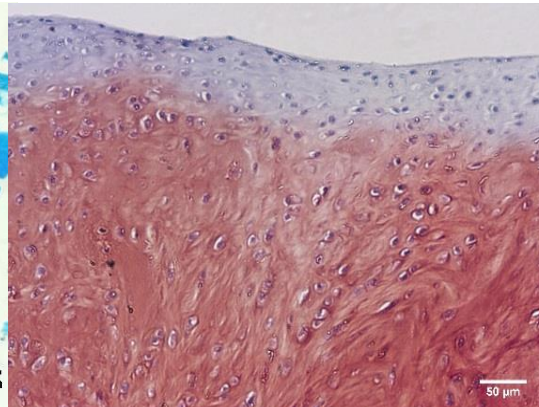
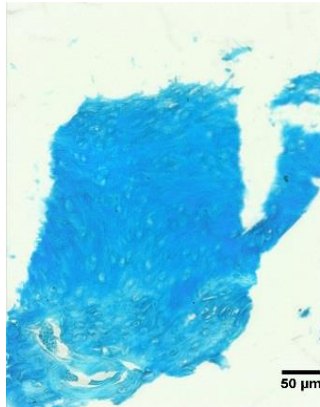
Formation of hyaline-like cartilage in scaffold group

Alcian Blue

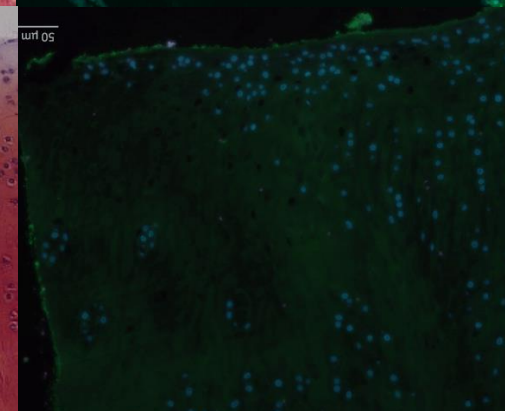
Safranin-O

Col-II

Scaffold

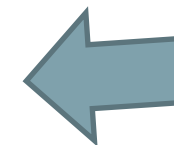
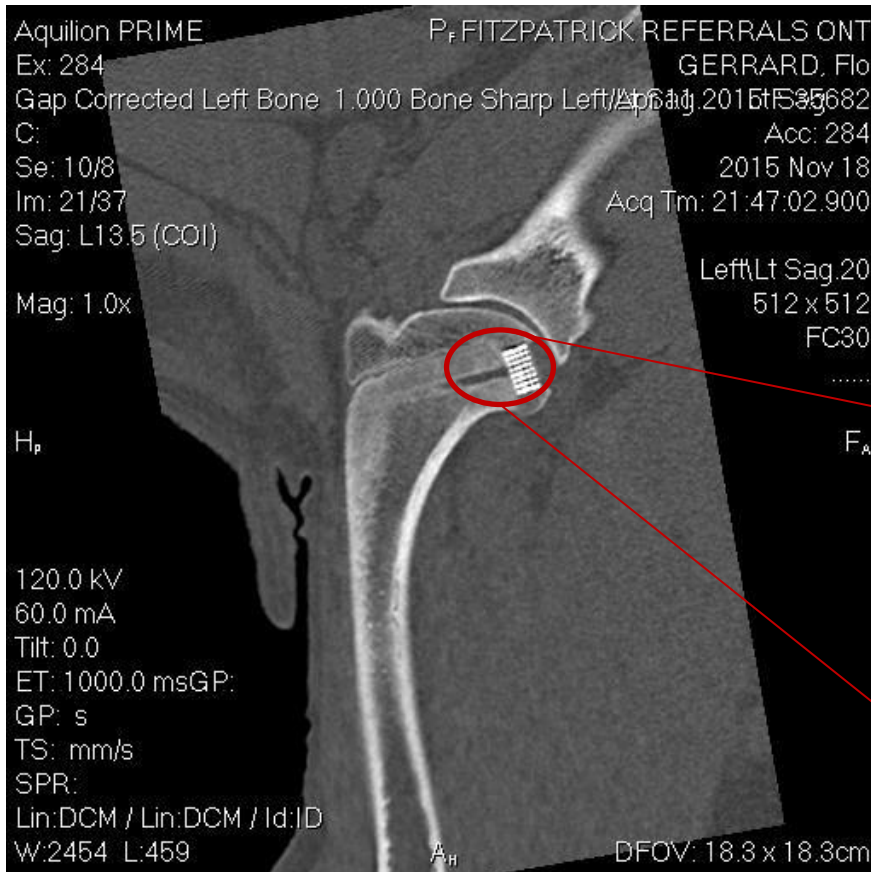


Control



“One Medicine” – For Human & Animal

- **Late stage OA**
- **Unable to walk**



18 Nov 2016

CNI7021219
Ex: 1922236-001785
LF_Shoulder_LAT
Se: 4/3
Im: 1/1

Fitzpatrick Referrals Ltd
GERRARD, FLO
O 35682
Acc: 1922236-001785
2016 Feb 18
Acq Tm: 13:23:57.603893

Mag: 1.0x
Lat: L



Lin:DCM / Lin:DCM / Id:ID
Default W:60673 L:30337
ERMF:

12 Week post operation

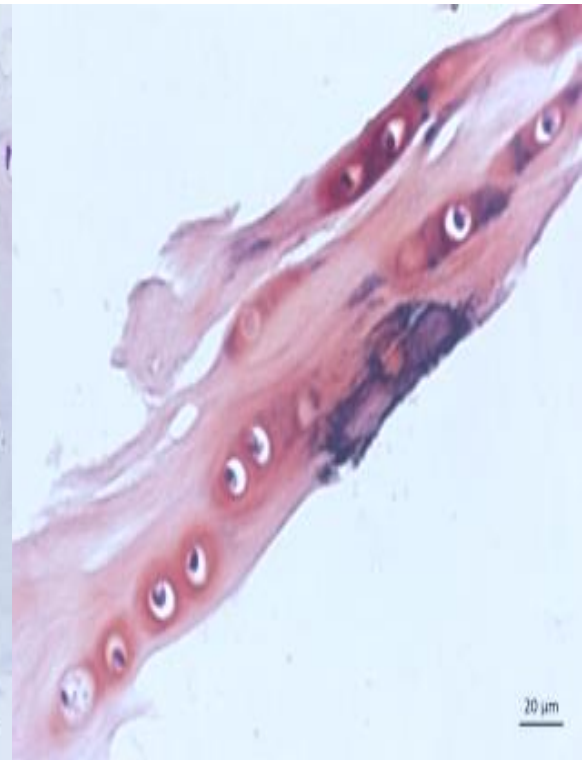
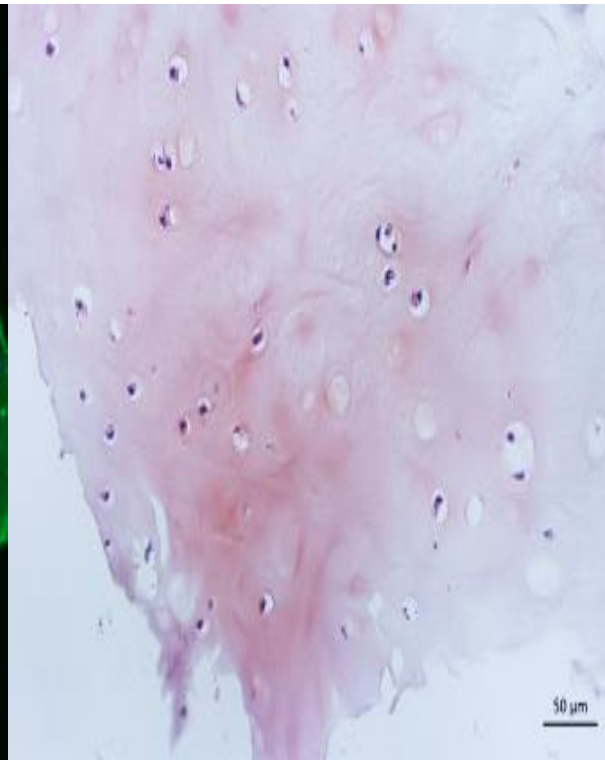
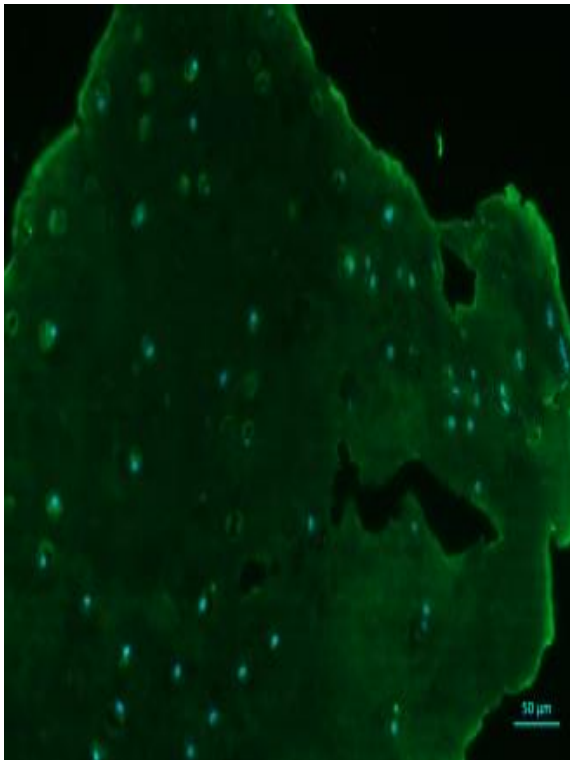
Before operation



12 weeks post operation

“One Medicine” – For Human & Animal

Collagen-II and Safranin-O staining - hyaline-like cartilage



Col-II

Safranin-O

**Cartilage biopsy post-2 years operation
Dog shoulder function is restored**

COWALK - From Animals to Human



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 St Mary's Court, St Mary's Gate,
 Chesterfield, Derbyshire S41 7TD

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 44 Portland Place,
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 t: 0100 790 0400
 arthritisresearchuk.org

24 October 2017

Ref: KP/21875

Dr Chaozong Liu
 Royal National Orthopaedic Hospital
 Brockley Hill, Stanmore
 London
 HA7 4LP

Dear Dr Liu

Outline application for an Arthritis Research UK Priorities in Clinical Research award

Thank you for your application to the priorities in clinical research call entitled 'A first-in-man study to assess short-term safety and efficacy of a novel osteochondral scaffold in early repair of cartilage defects'. Applications have now undergone review by the Arthritis Research UK Treatment Subcommittee. The purpose of the review is to identify at an early stage those proposals which the charity wish to invite to full application and those that will not be invited.

Outline applications were assessed on scientific quality, strategic relevance and merit, quality of the research design and feasibility of the work proposed.

I am pleased to inform you that after careful consideration the Treatment Subcommittee have recommended that your outline go through to a full application in this round.

The subcommittee were of the opinion that this was an exciting proposal with the potential to provide a novel intervention for a large number of patients and potentially provide good value for money for the health services. The panel members were impressed by the significant patient involvement in the development of the proposal and the plans described to disseminate the results following the completion of the study.



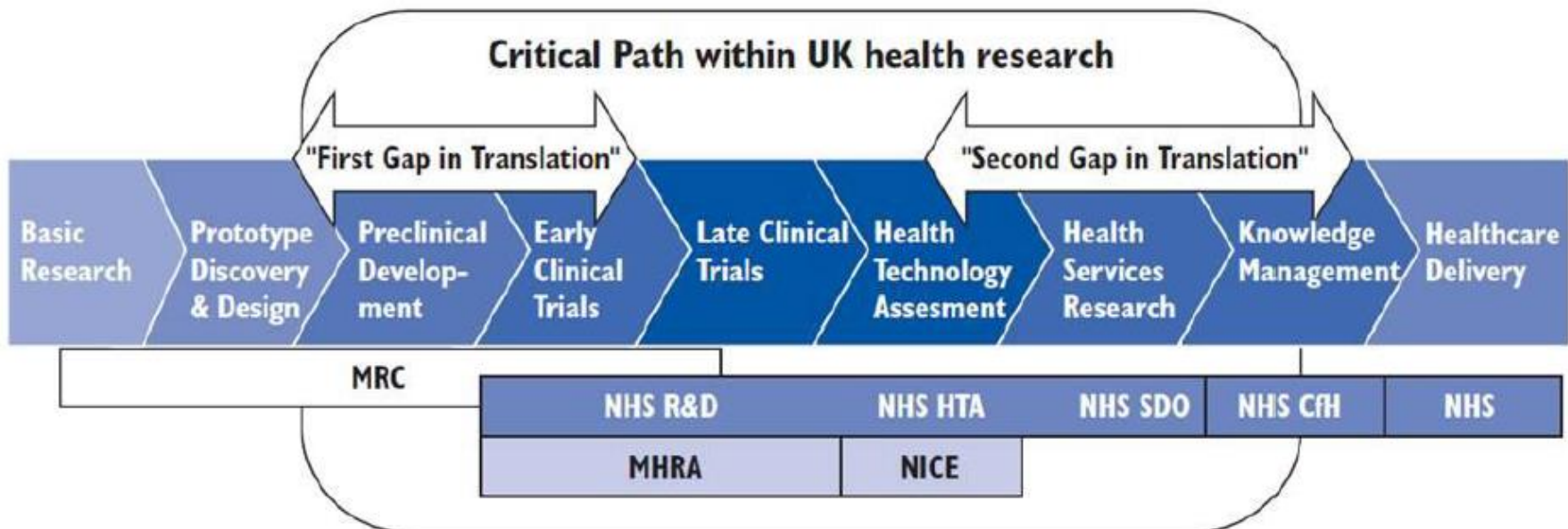
First in man study

- 20 Patients
- RNOH
- 01 Oct 2019 ~ 30 Sep 2023

The subcommittee were of the opinion that this was an exciting proposal with the potential to provide a novel intervention for a large number of patients and potentially provide good value for money for the health services. The panel members were impressed by the significant patient involvement in the development of the proposal and the plans described

But there are problems.....

Translational Research in the UK – ONE CYCLE



Acknowledgement:



Innovate UK

Shenzhen Science and Technology
Innovation Commission
深圳市科技创新委员会



Royal National Orthopaedic Hospital

NHS Trust



*Friends & Colleagues &
Collaborators*

A decorative graphic with the words 'THANK YOU' in a stylized, hand-drawn font. The text is surrounded by various leaves in shades of red, pink, and orange, along with small green berries. The word 'THANK' is on the top line and 'YOU' is on the bottom line. Small decorative marks resembling sunbursts are placed near the 'T' and 'U'.