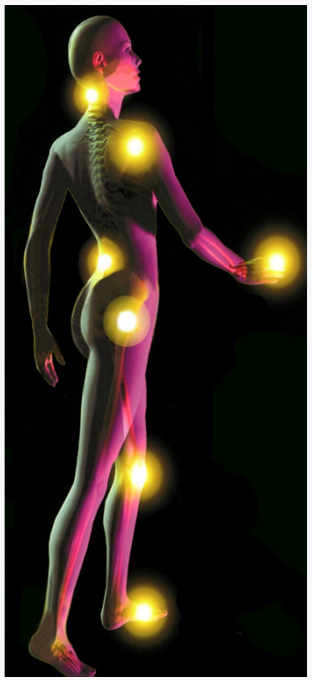
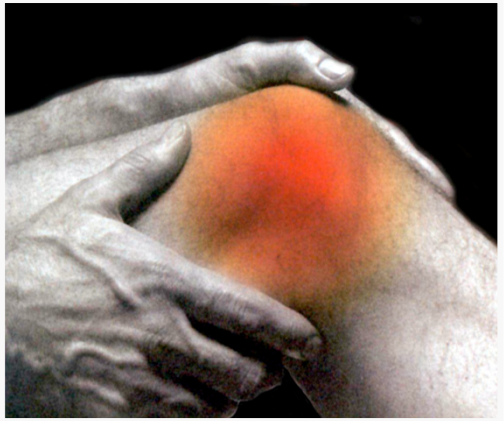
Small Animal models of Osteoarthritis: Testing Emerging treatments, drug delivery and mechanisms of action"



Dr. Mohit Kapoor

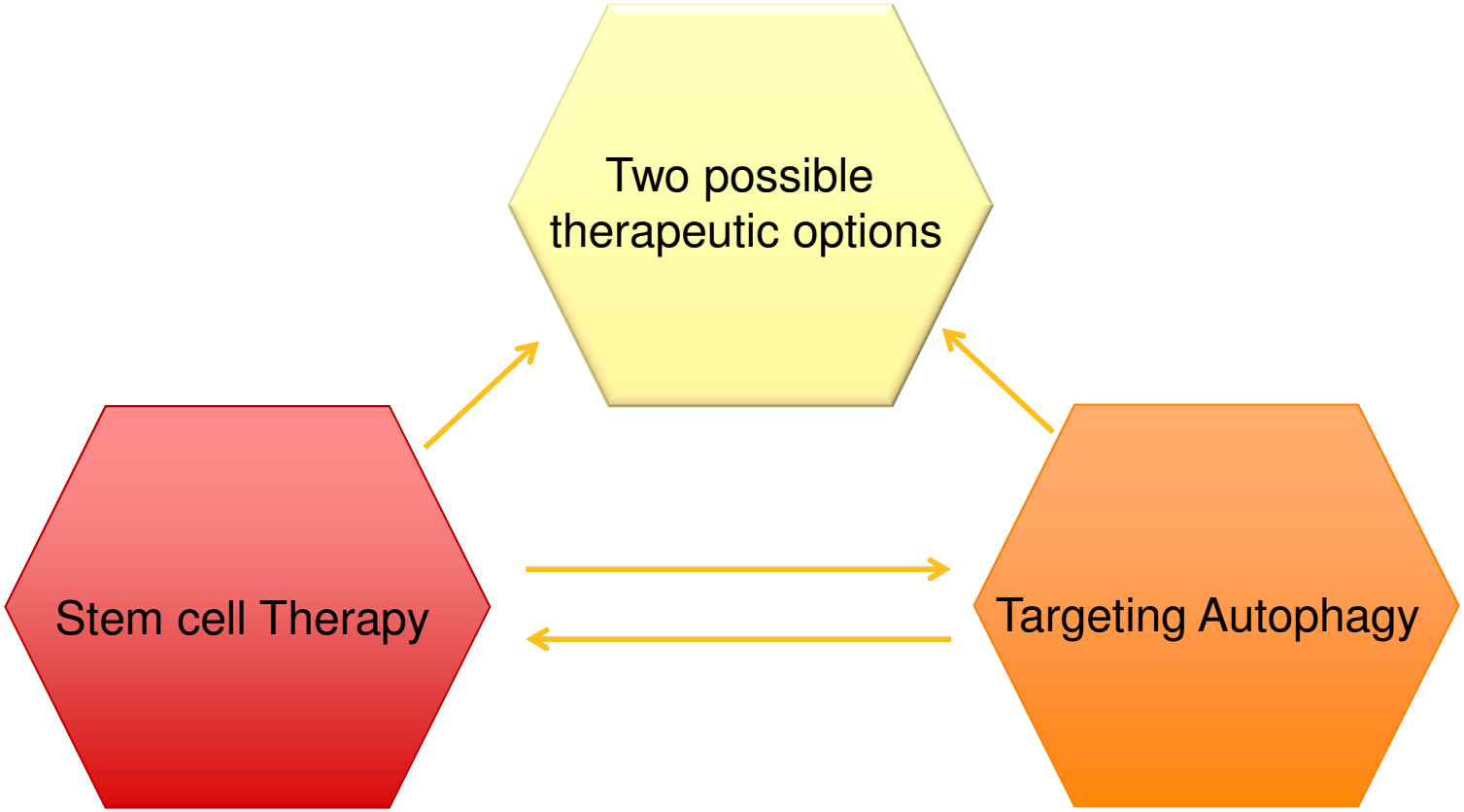
Head, Cartilage Biology Research Group
Co-chair, Arthritis Program Biobank
Toronto Western Hospital

Associate Professor
Department of Surgery
University of Toronto
Toronto, Canada



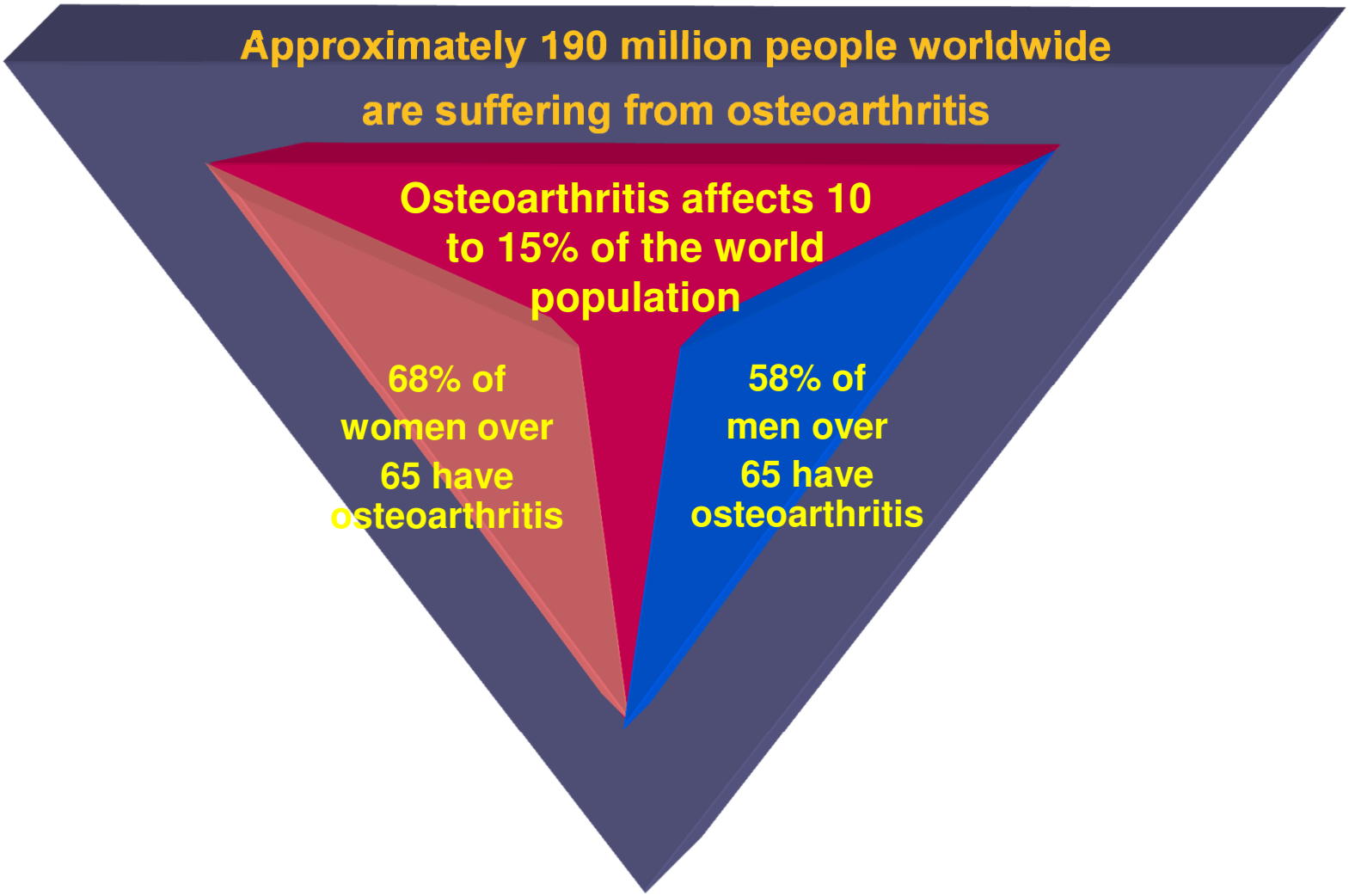


UHN Orthopaedics
Toronto Western Hospital


Two possible therapeutic options
Stem cell Therapy
Targeting Autophagy

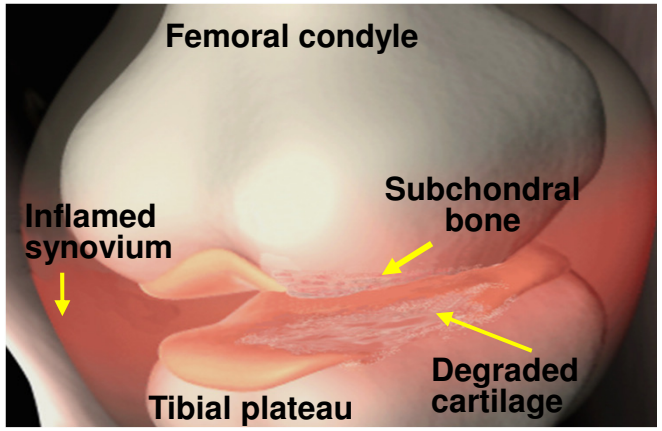


Osteoarthritis

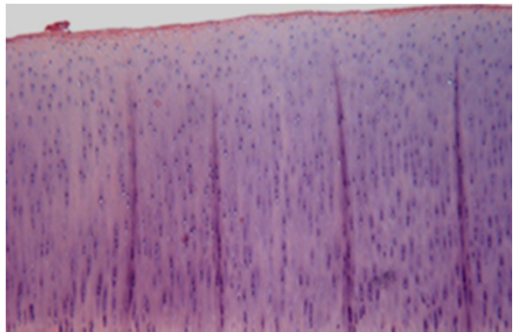


Joint Structures affected in OA

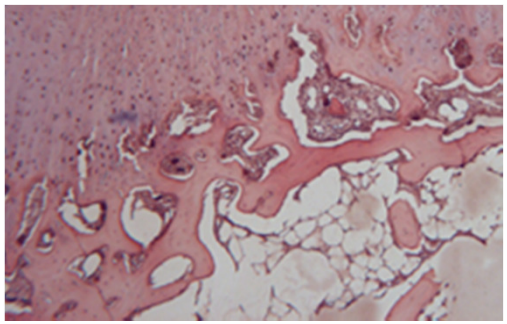
OA Joint



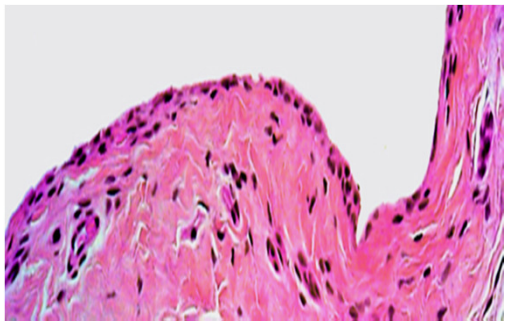
Normal Human Cartilage



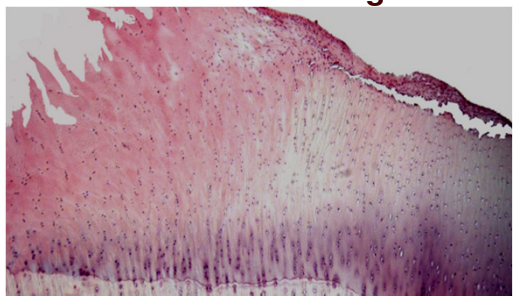
Normal subchondral bone



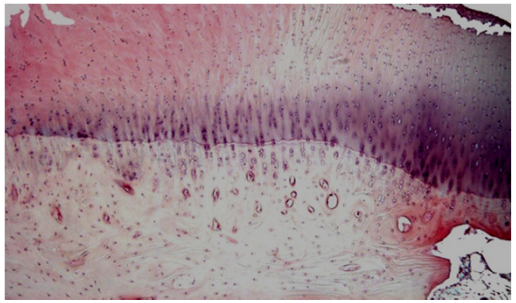
Normal Synovium



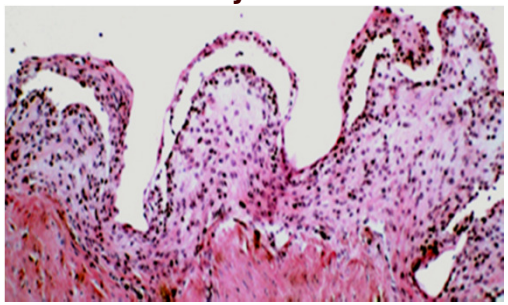
Human OA Cartilage



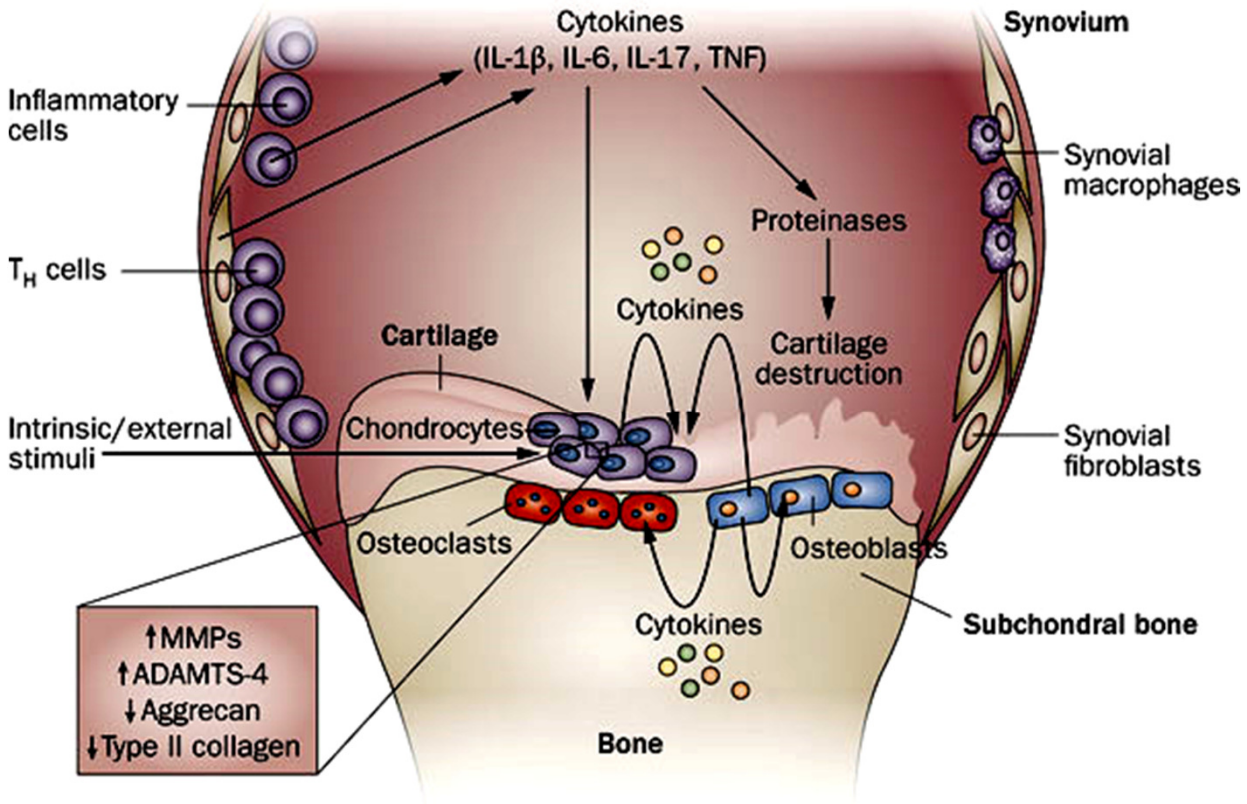
OA Subchondral bone



OA Synovium



Pathophysiology of Osteoarthritis



Kapoor M, et al. (2011) *Nature Review Rheumatology*

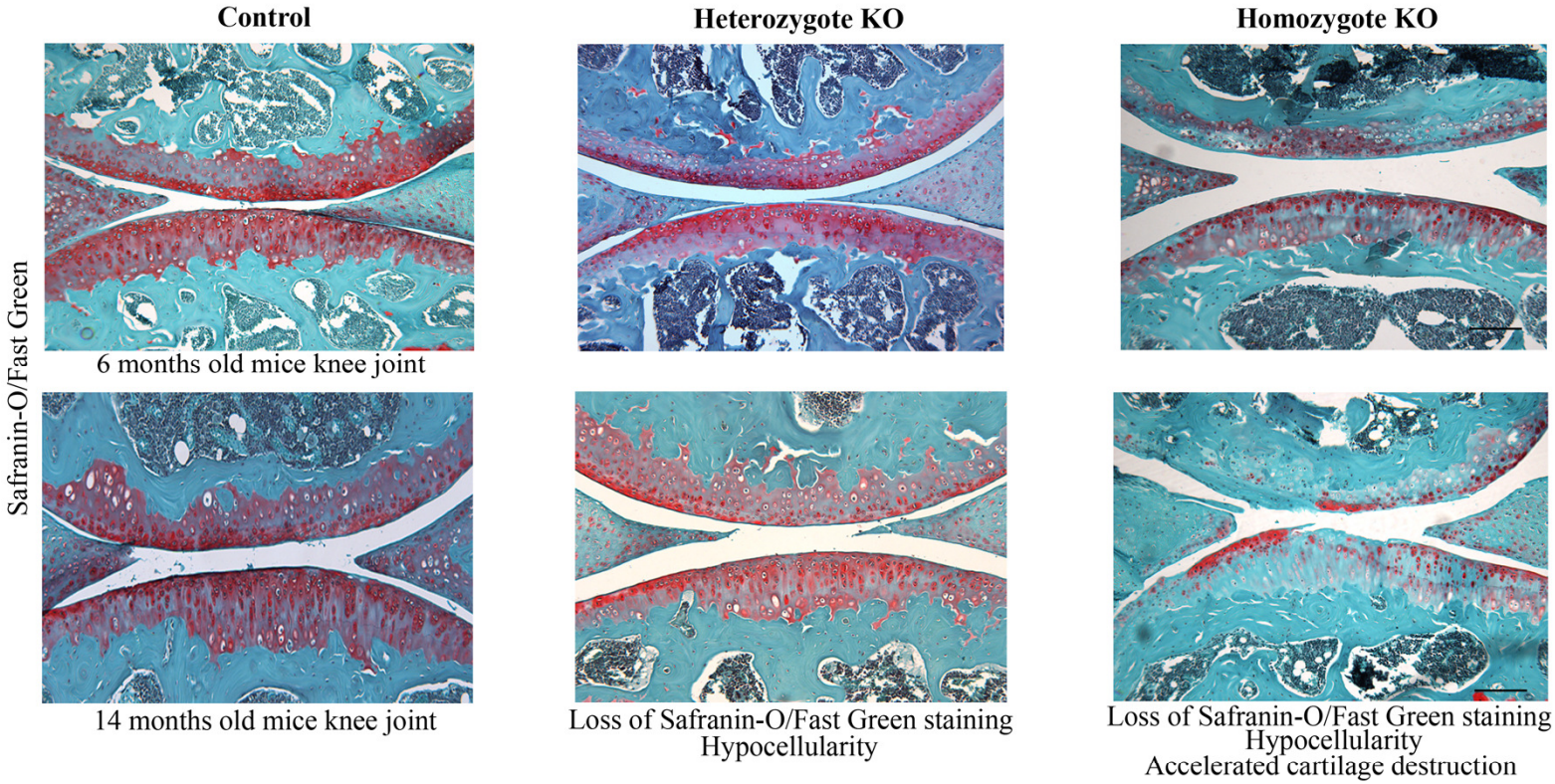
Small Animal models of Osteoarthritis

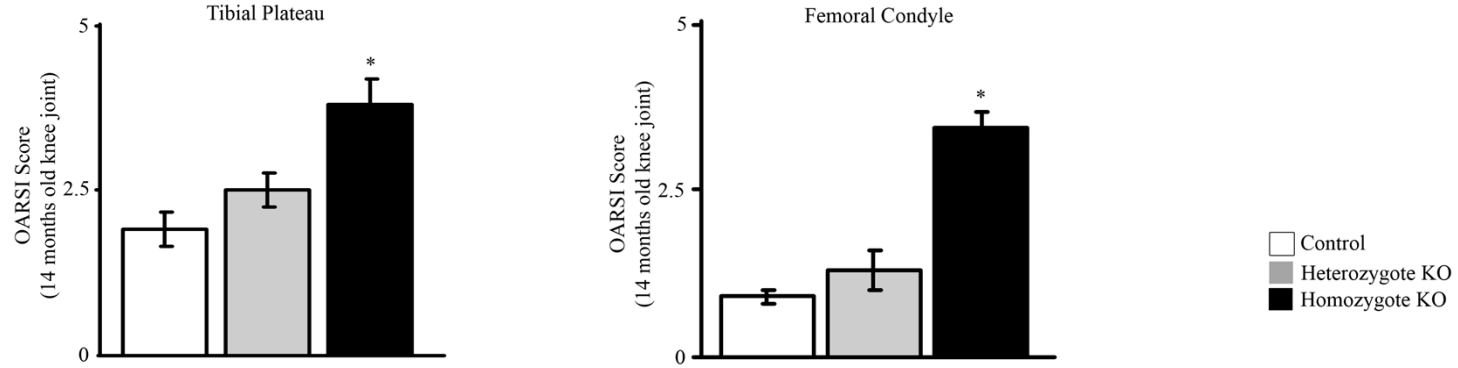


Spontaneous OA model

Cartilage-specific PPARγ KO mice exhibit spontaneous OA phenotype.

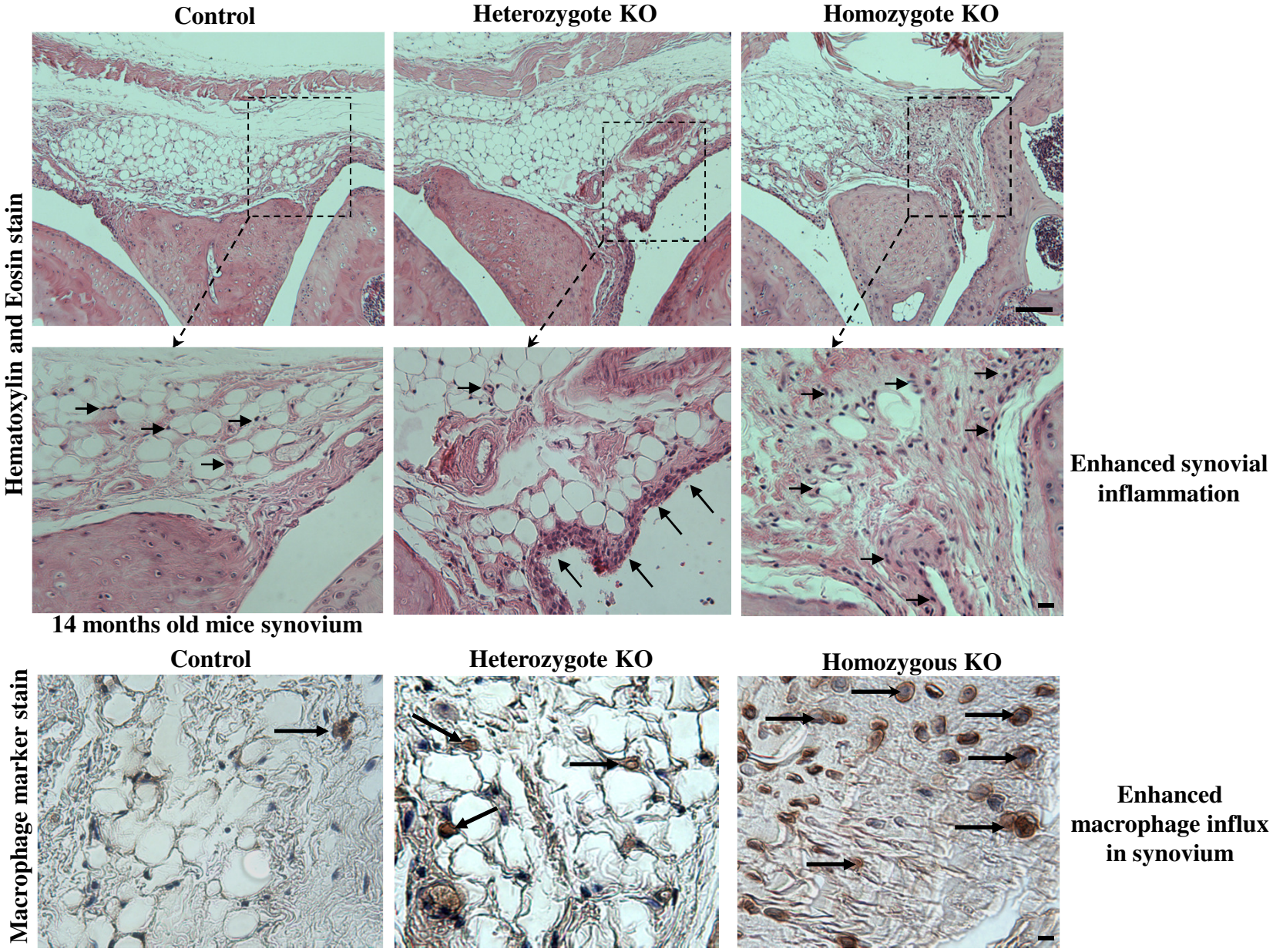
Cartilage-specific deletion of PPARγ results in acceleratedOA like characteristics during aging





Vasheghani et al., Am J Pathol (2013), Monemdjou et al Arthritis and Rheumatism (2012), Vasheghani et al, Annals of Rheumatic Diseases (In revision)

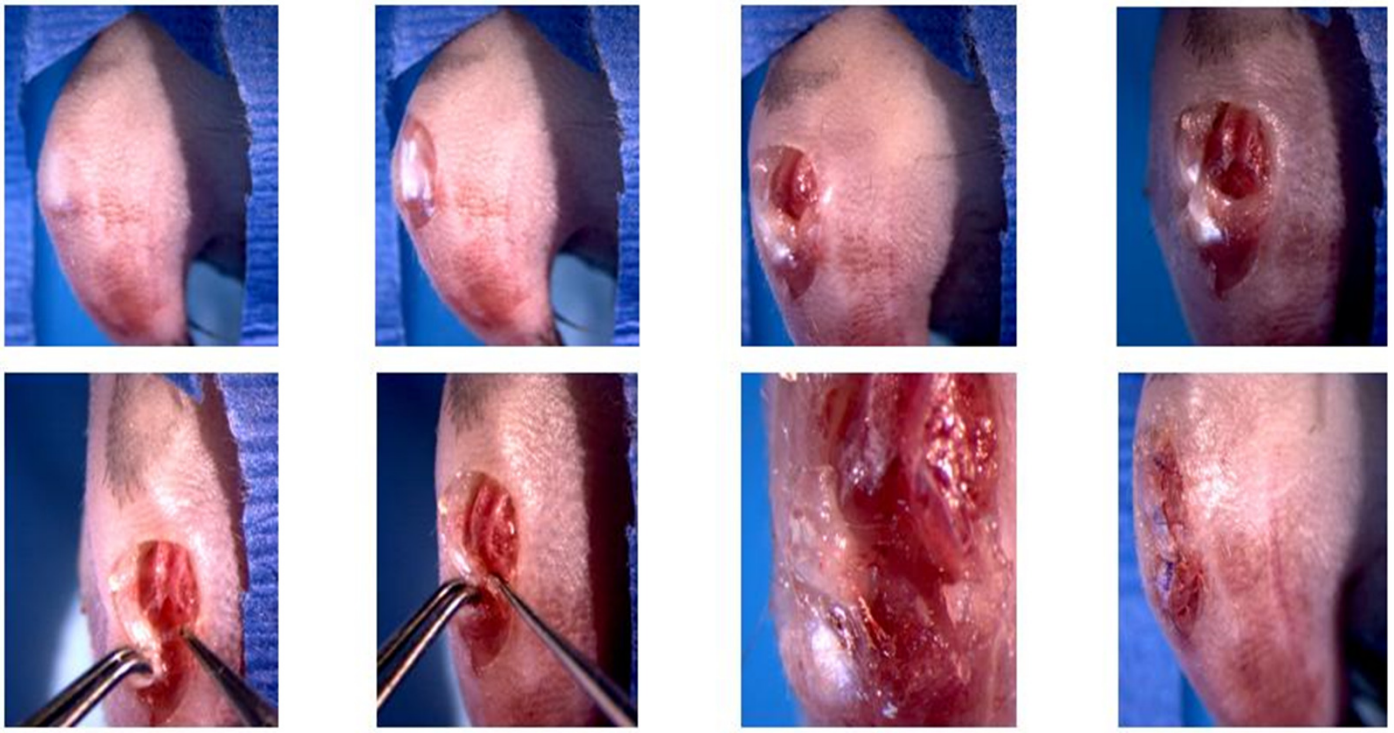
Aged PPARγ KO mice exhibit increased synovial inflammation and macrophage influx



Destabilization of Medial Meniscus OA model

Surgical Model of Osteoarthritis in Mice

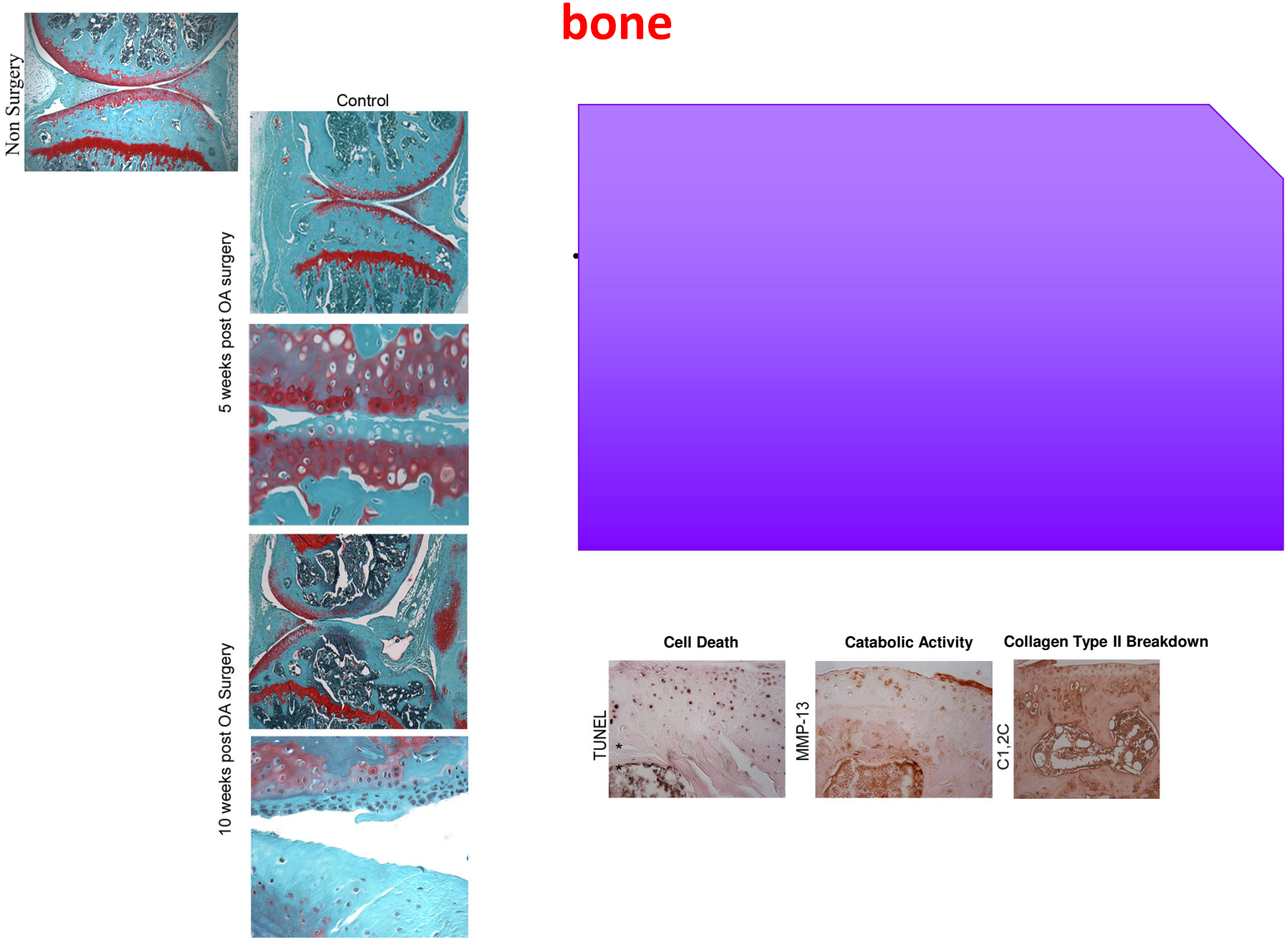
DMM Model of OA



Zhang et al…..Kapoor M. Annals of Rheumatic Diseases 2014
Kapoor M, Nature reviews rheumatology, 2012.

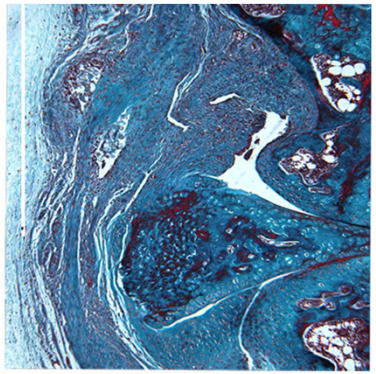
- Destablization of medial meniscus: Resulting moderate OA-like phenotype
- This surgery results in a modest degree of OA (partial cartilage erosion and fissures, proteoglycan depletion, synovial inflammation, synovial fibrosis as well as some degree of subchondral bone remodeling.
- This model of relatively slow progression of OA is more reflective of human pathogenesis.

DMM model: Effects on articular cartilage and subchondral bone

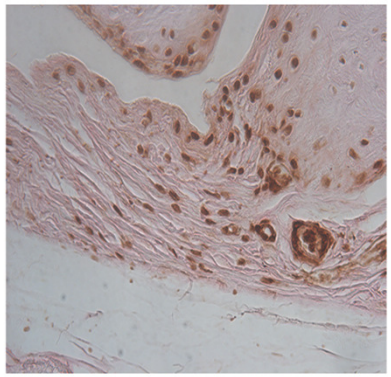


DMM model: Synovial Inflammation and Fibrosis

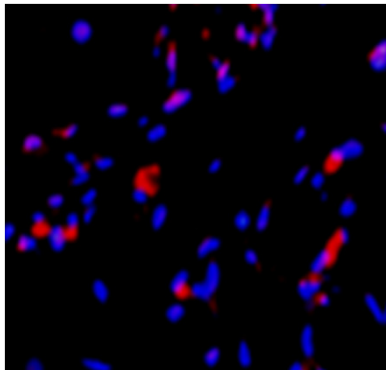
Trichrome Stain
5 weeks post OA

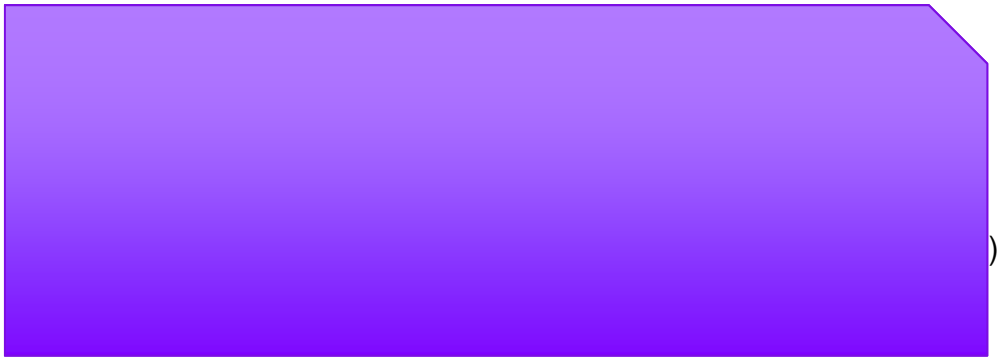


p-SMAD3



Monocytes/macrophages



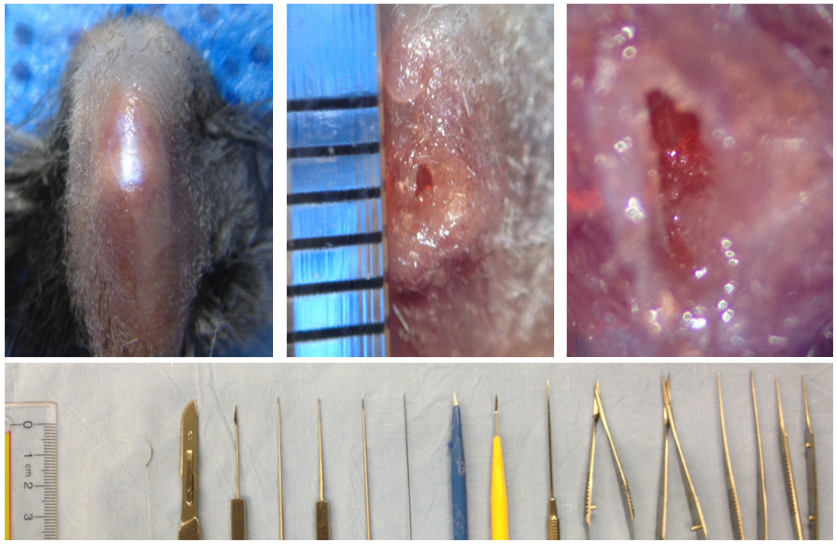


MIDMM (Minimally Invasive Destabilization of Medial Meniscus) Model of OA In Mouse

- This model closely resembles human OA by limiting surgical exposure to minimum.
- There is a learning curve associated with the technique.
- MMTL transection is carried out using micro-surgical techniques under direct vision.
- This model results in mild OA at 8 weeks post surgery.
- Application in transgenic mice & evaluation of DMOADs.

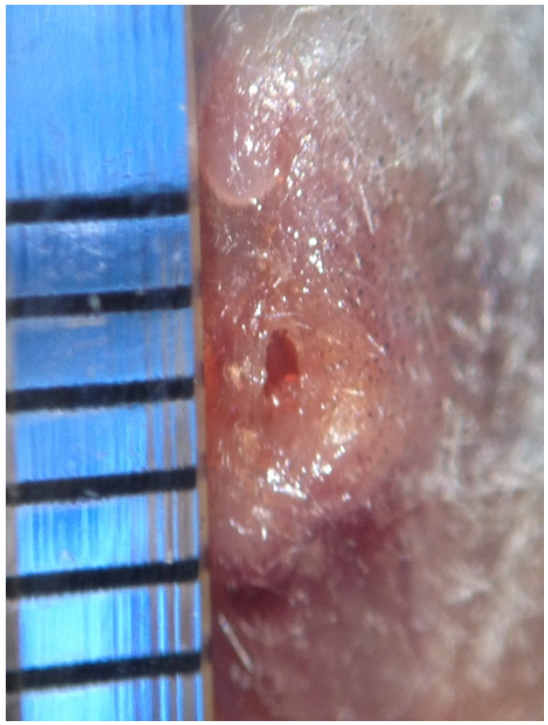
Method

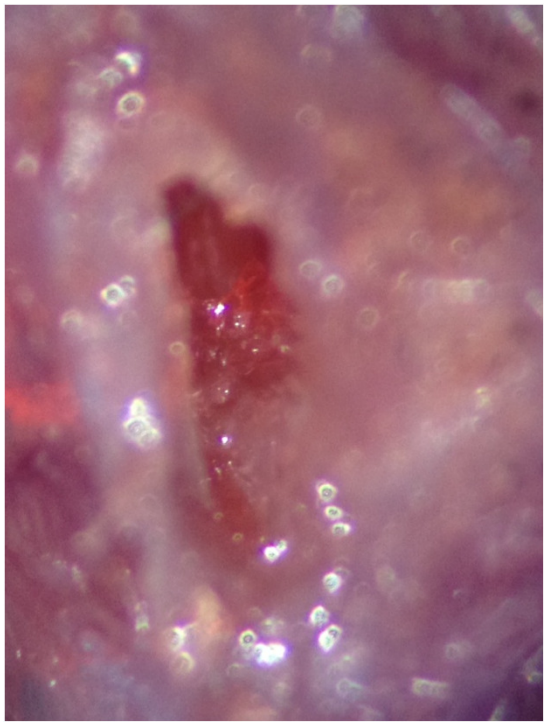
- 1mm skin incision is made over antero-medial region of knee.
- Arthrotomy is carried out and fat pad over medial meniscus dissected.
- MMTL is identified and transected under direct vision with special micro-surgical knife.
- Joint irrigation and closure is done.

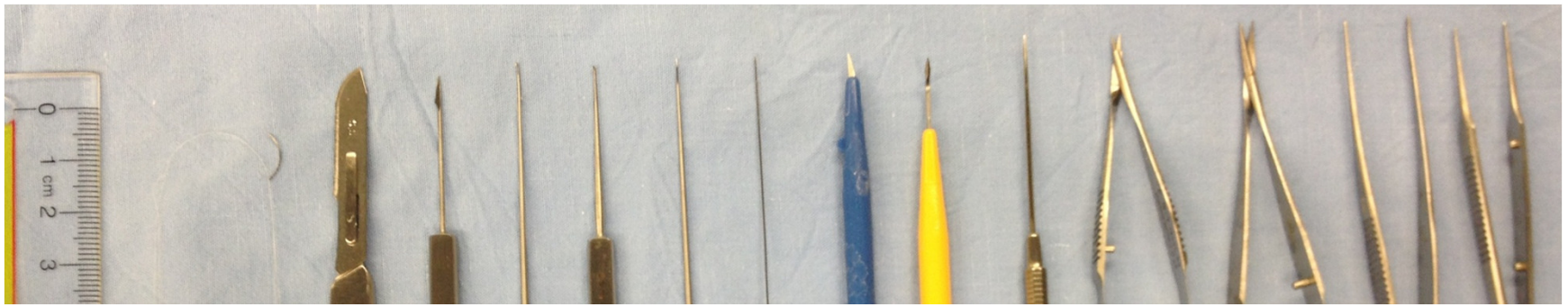


Minimally Invasive Model







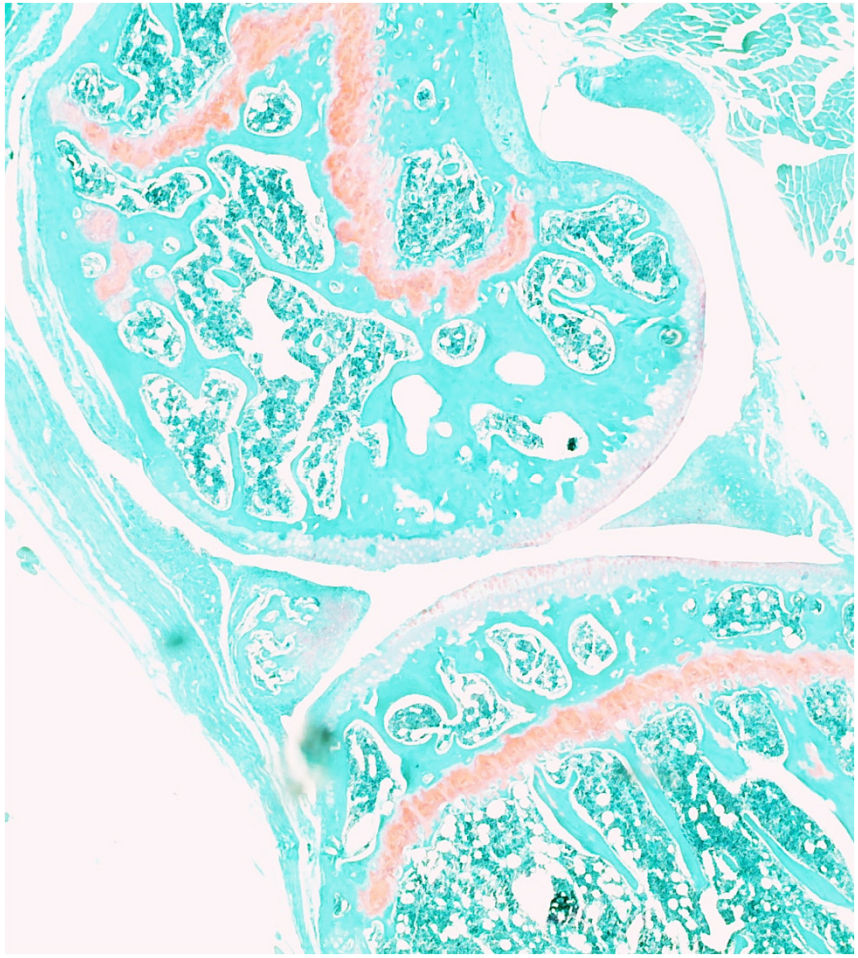


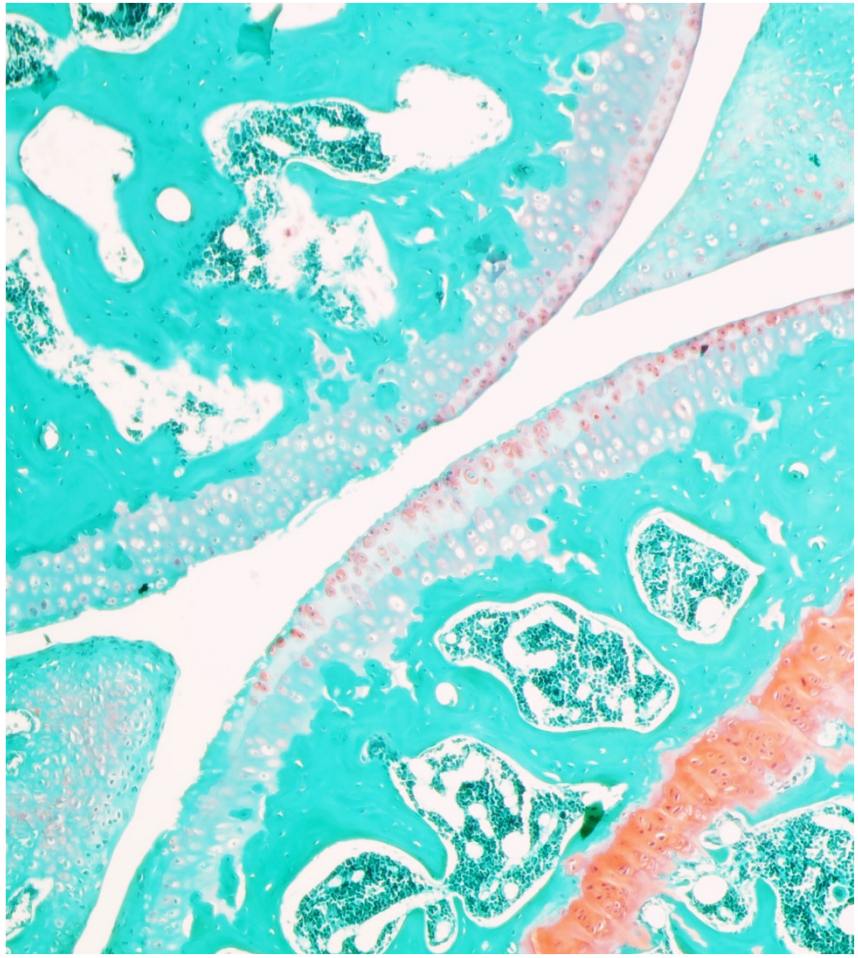
Notes

- The technique utilized an in house custom knife with blunt tip to reduce surgical trauma.

- To our knowledge, this is the only mouse OA model with:
  - minimum surgical trauma
  - early mouse weight bearing

Histopathology

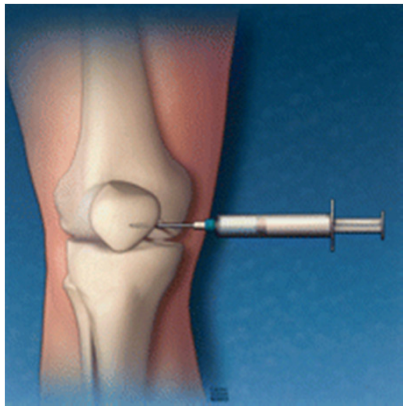




Cell Therapy: Small animal models of OA Feasibility and challenges

Characterization of Cells

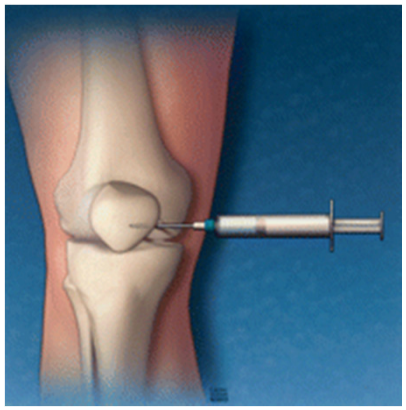
Type, amount, route of administration

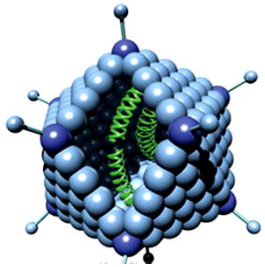


Intra-articular injection (DMM Model)

Ongoing testing of new therapies to treat Osteoarthritis
In my lab

Deliver autophagy specific gene ULK1 in mouse OA cartilage (intra-articularly)

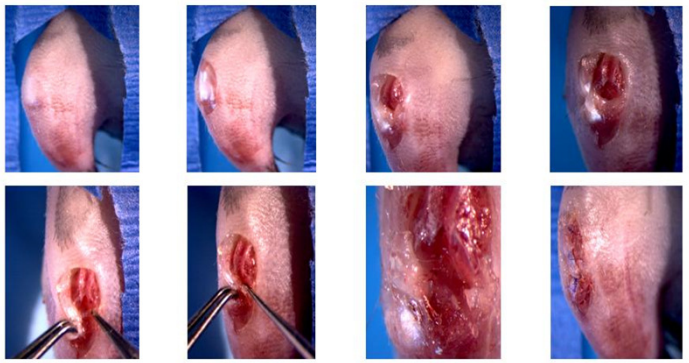




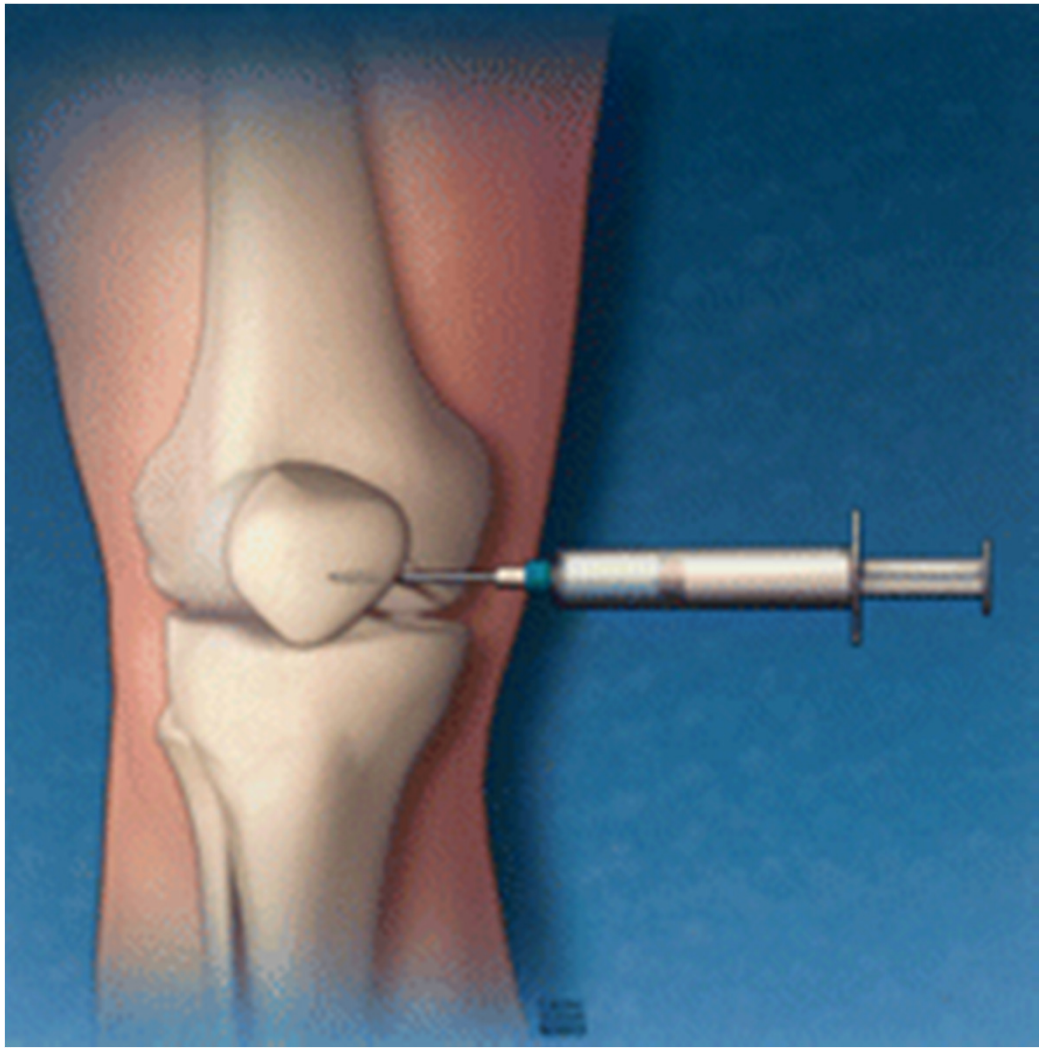
ULK1 adenovirus
Intra-articular injection

(Concentration 50 MOI, 5ul injection, 2 times)
1st injection: 10 days post surgery
2nd Injection: 20 days post surgery
Evaluate severity of OA 10 weeks post surgery

OA surgery



Deliver bone marrow derived MSCs intra-articularly



Stem cell therapy

Animal Models
Clinical trial

MK Research Team

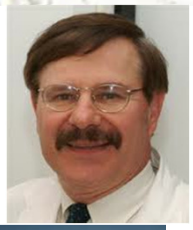


Department of Orthopedics and Rheumatology TWH















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Fondation canadienne pour l'innovation

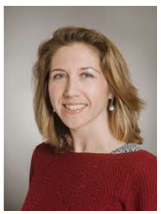

Dr. M Hurtig


Dr. F Beier

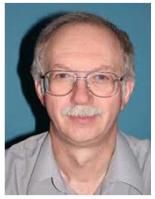

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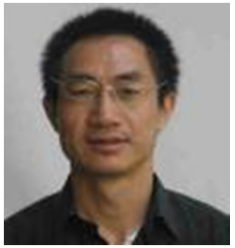
Unité de recherche en ARTHROSE

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