



GENEVA 2018



PROFESSOR DEREK A MANN



**Fibrogenic-Inflammatory Cross-Talk in Post-Total Knee Arthroplasty
- A Human Model of Induced Chronic Fibrosis**

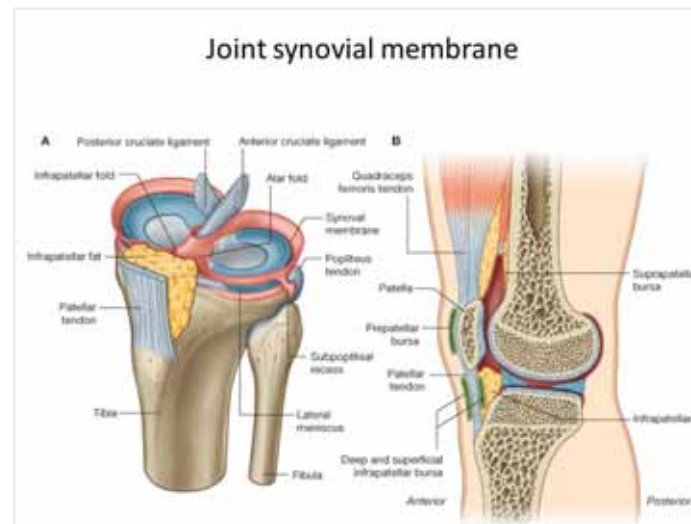


Total Knee Arthroplasty (TKA)

- TKA is a surgical procedure in which the diseased knee joint is replaced with an artificial joint.
- Osteoarthritis is the most common condition for which TKA is used therapeutically.
- 100,000 primary TKAs carried out in UK annually.
- 15-30% of patients express dissatisfaction with outcome.
- Pain, stiffness, 'grinding', swelling/tightness and impaired mobility are the most common complaints.

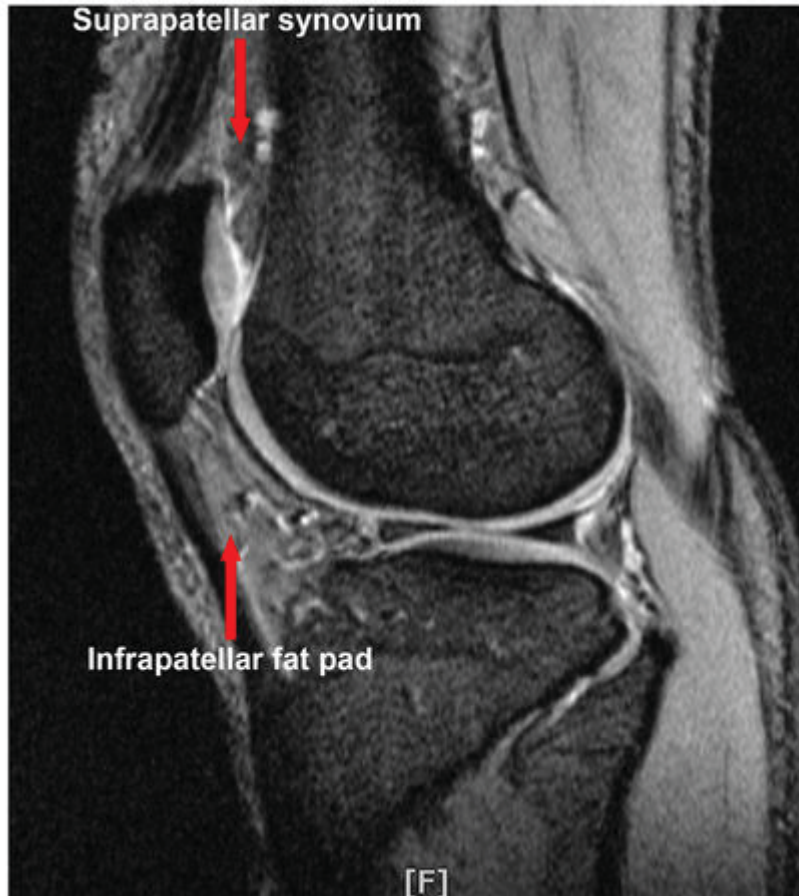
Athrofibrosis

- Up to 10% of TKA develop post-operative stiffness (athrofibrosis)
- Joint structures affected by athrofibrosis include the synovial membrane and infrapatellar fat pad.

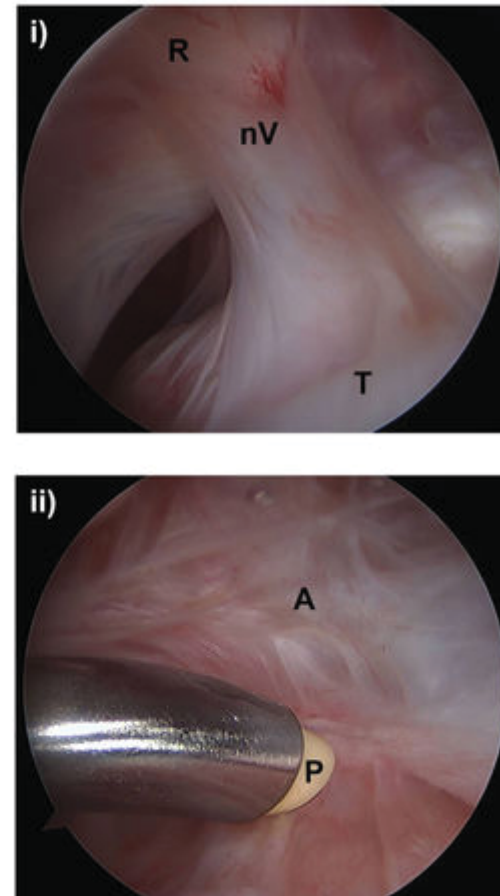


- Athrofibrosis is an ‘induced’ human pathology that can provide new mechanistic insights into fibrogenesis.

a)



b)



Severe atrophyfibrosis

R = suprapatellar pouch roof

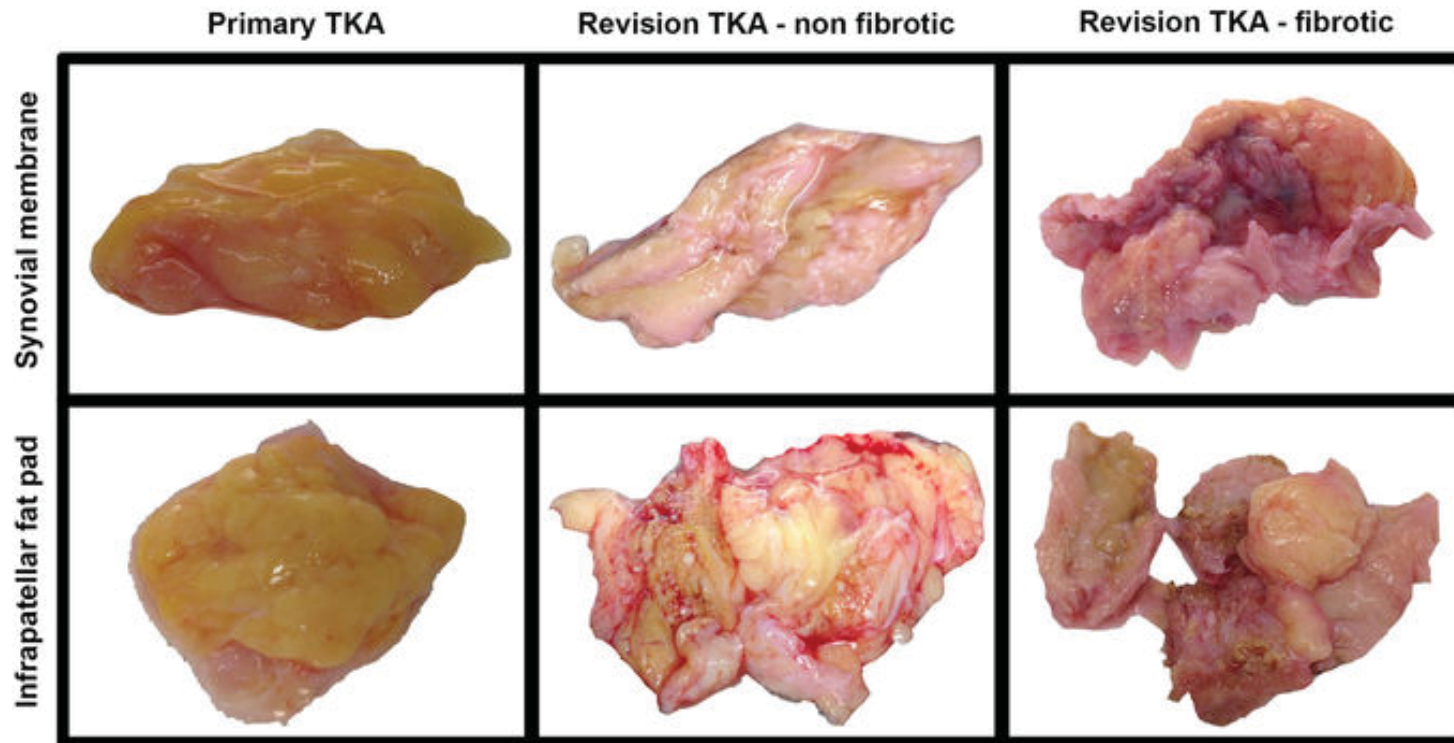
nV = neovascularisation

T Trochlea

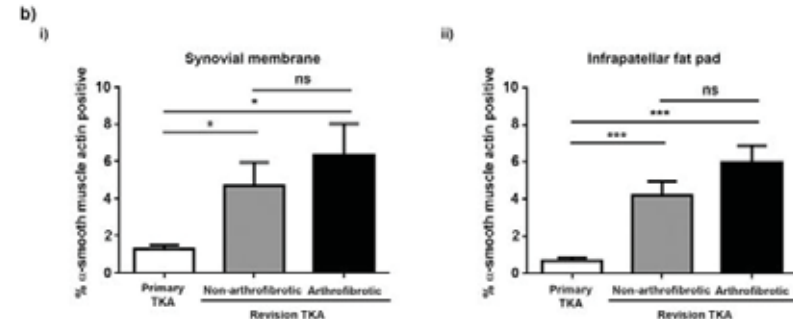
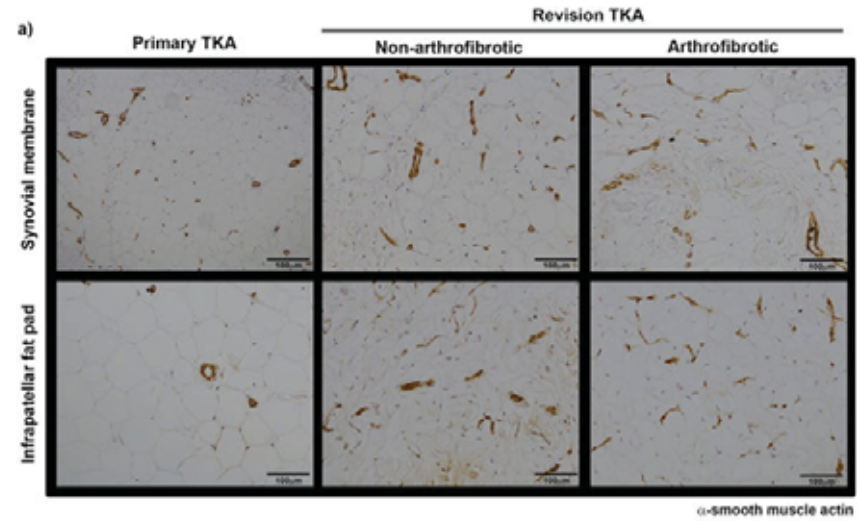
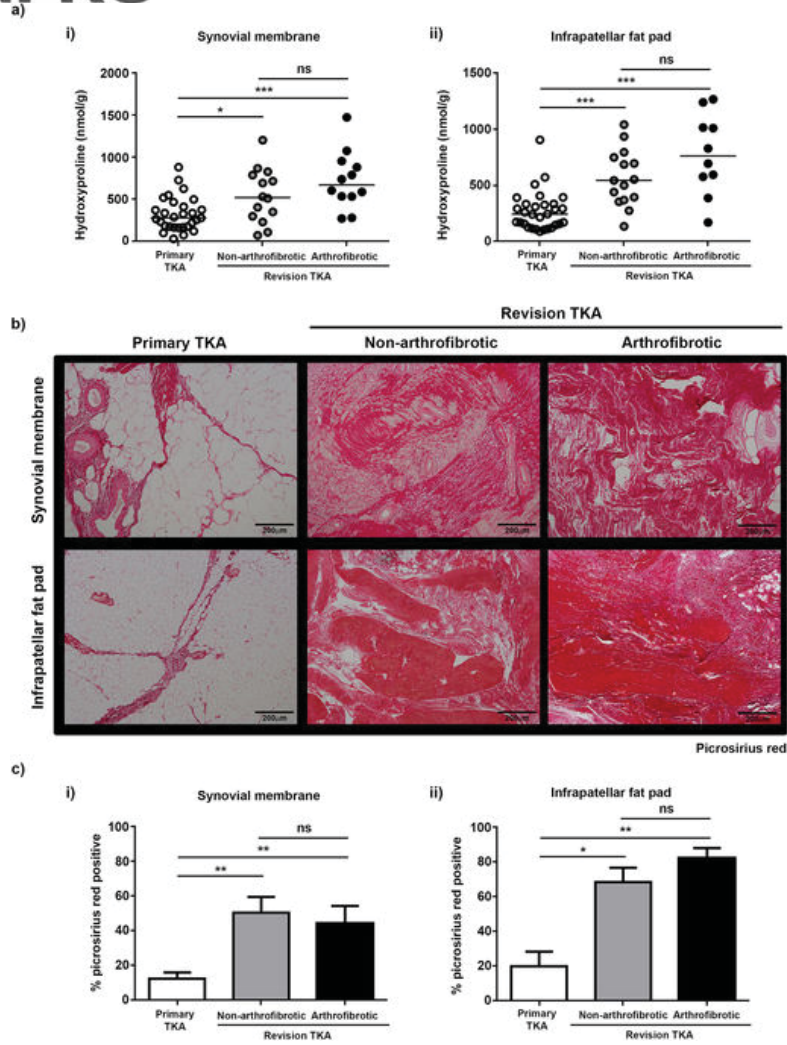
A = dense layered adhesions

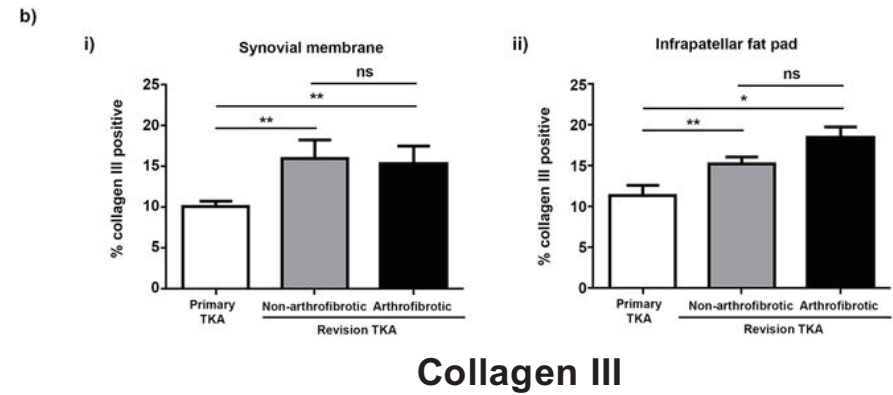
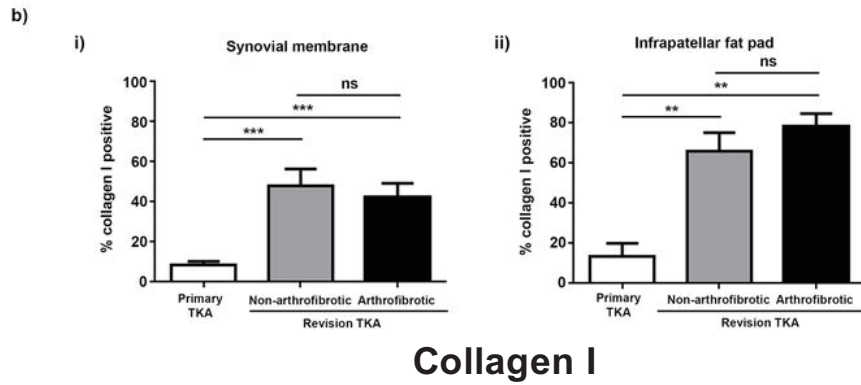
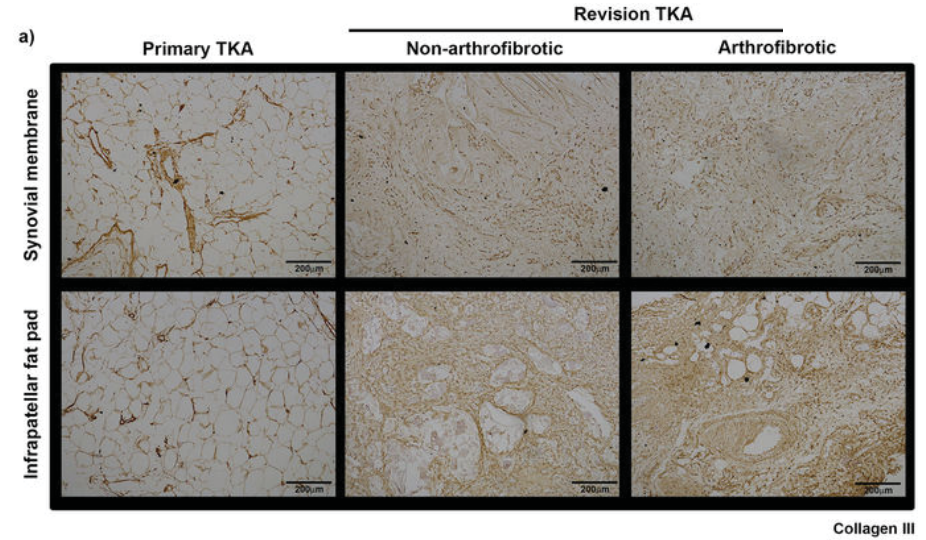
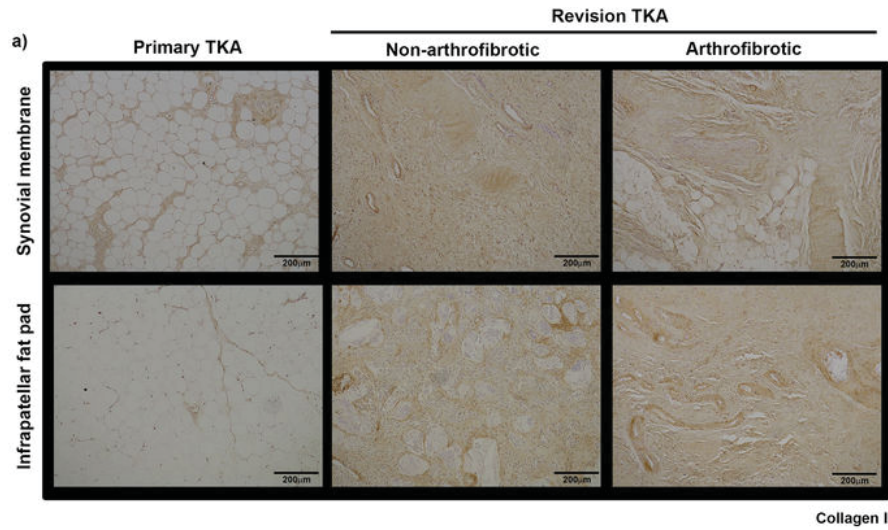
P = probe

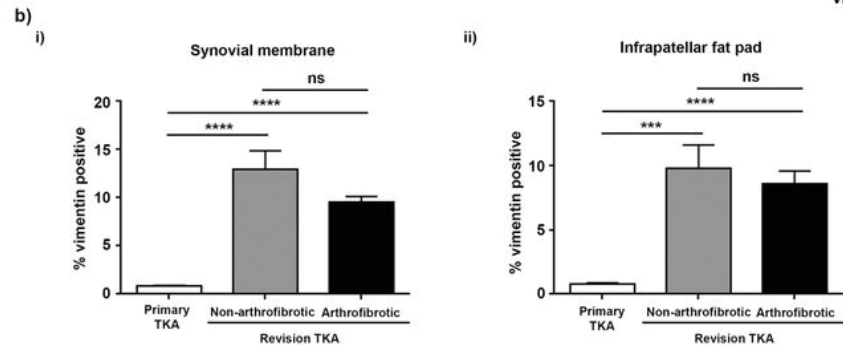
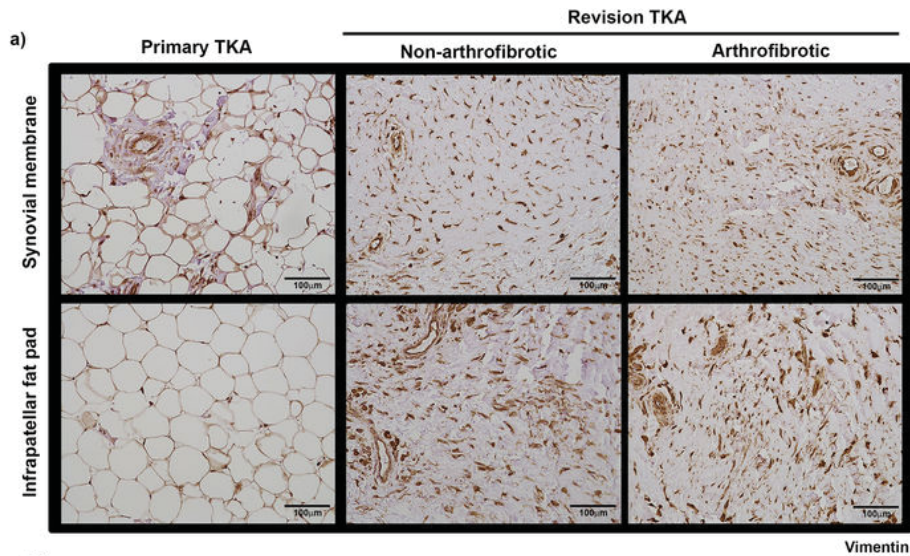
Macroscopic Images of post-TKA Fibrotic Joint Structures



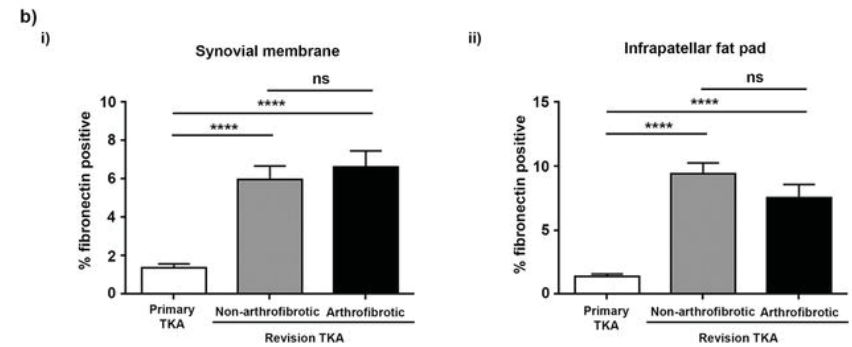
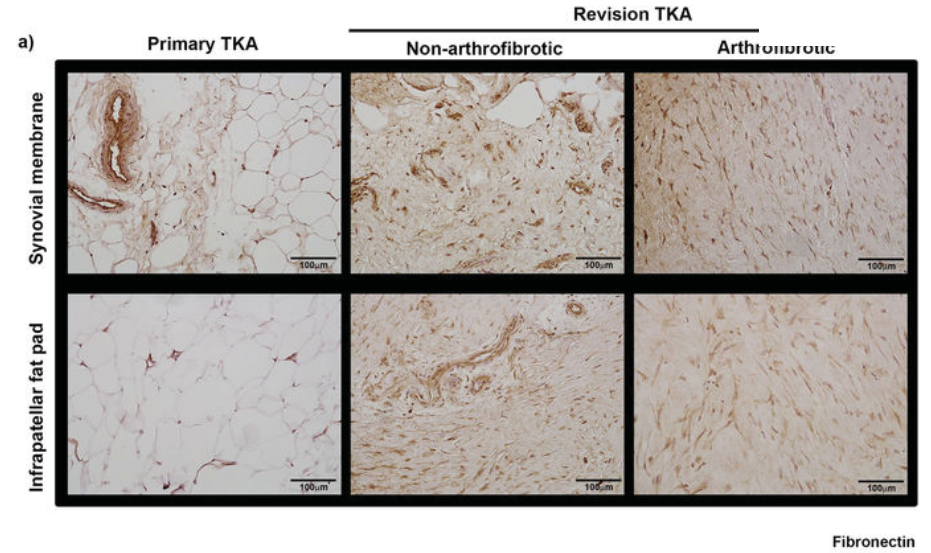
Fibrosis is a feature of the majority post-TKA joints





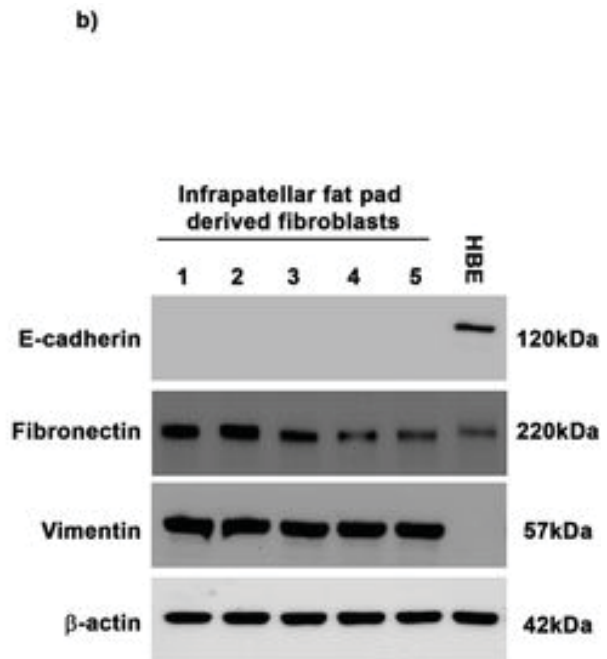
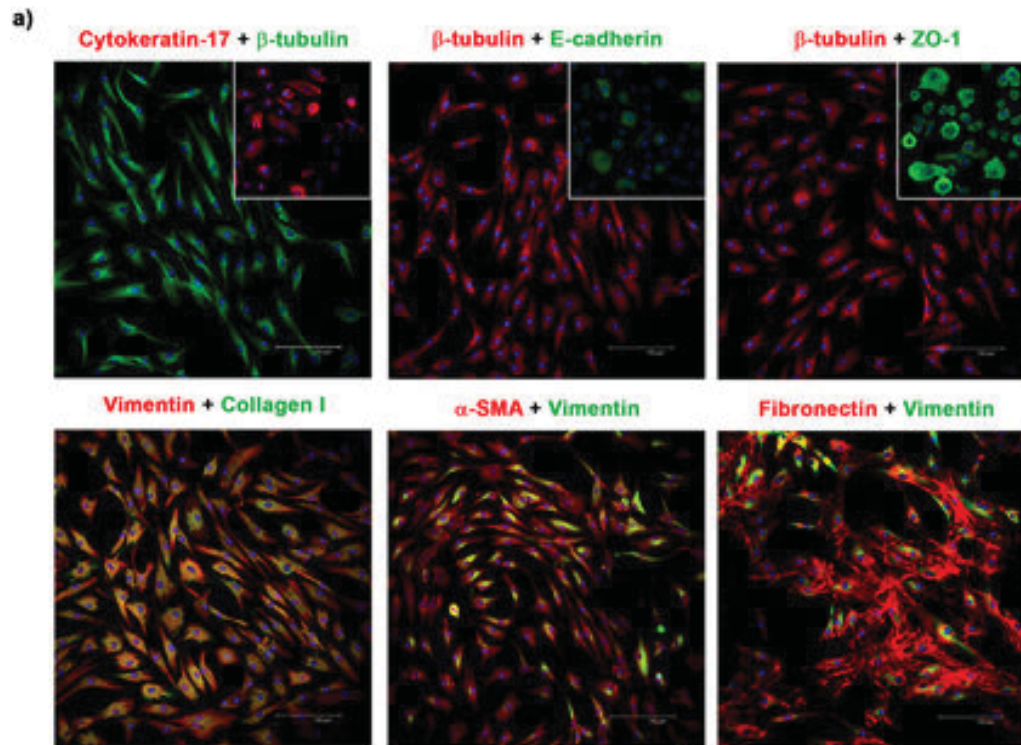


VIMENTIN

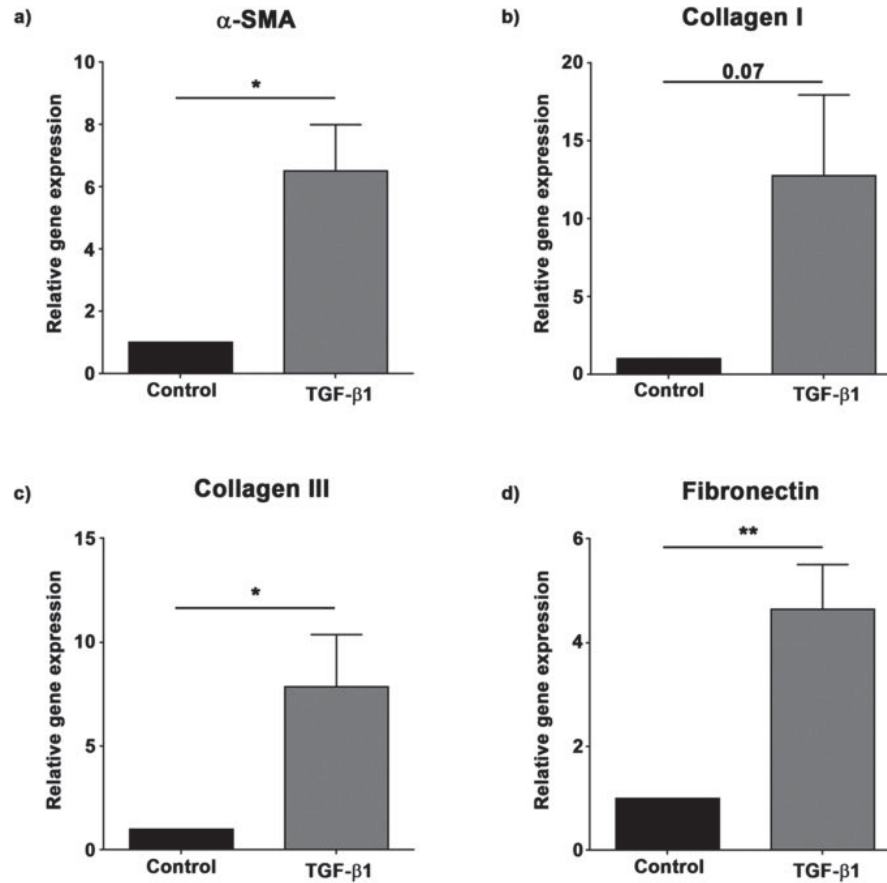


FIBRONECTIN

Cells isolated from the post-TKA fat pad are fibroblastic



Fat pad-derived fibroblasts are responsive to TGFβ1

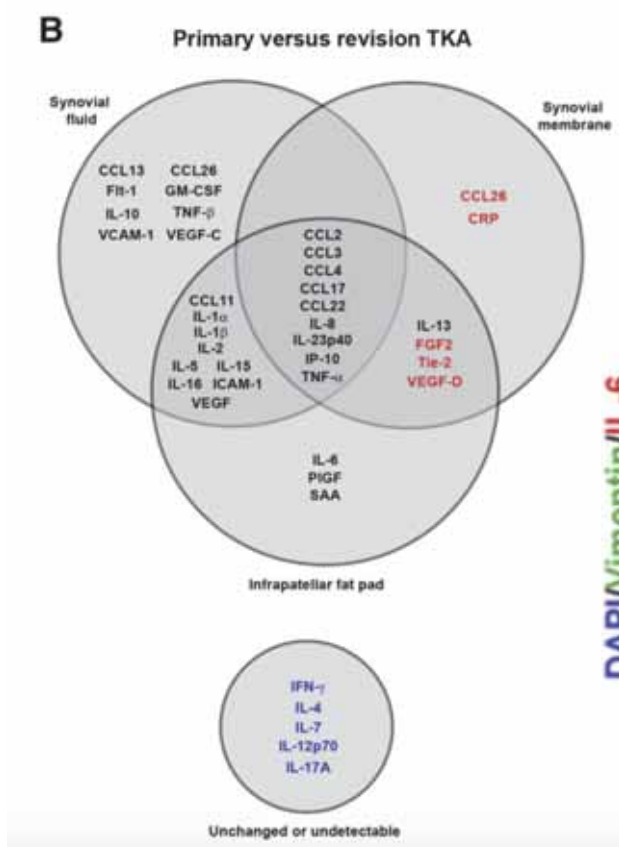


Summary 1

- Despite its success TKA can be associated with pain, swelling, stiffness and poor motion/mobility.
- Gross and histological analysis reveals fibrosis in all post-TKA joints.
- The post-TKA synovial membrane and fat pad exhibit dramatic collagen deposition and become populated with activated myofibroblasts.
- Fibroblasts isolated from the TKA fat pad are responsive to the main fibrogenic mediator TGF β 1.

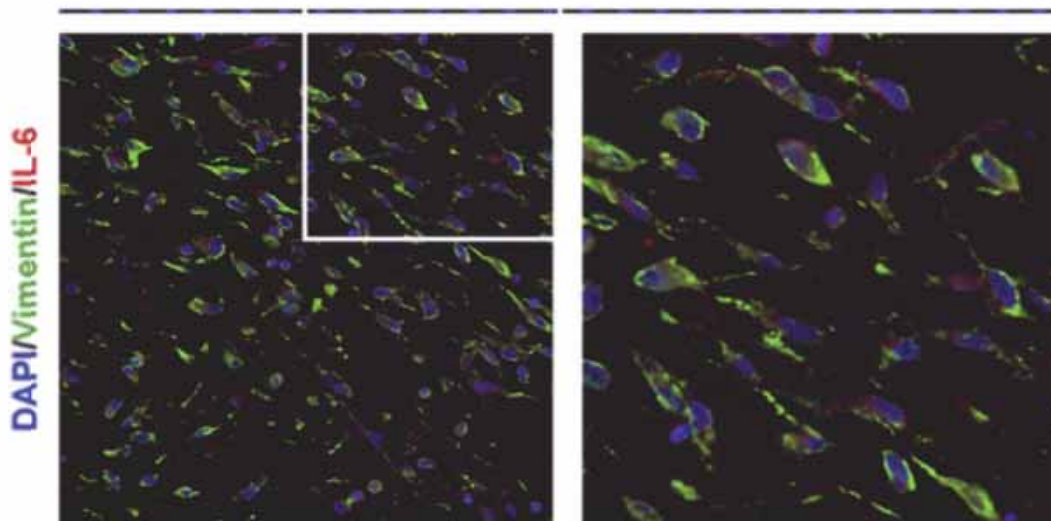
Is the post-TKA joint in a state of chronic inflammation?

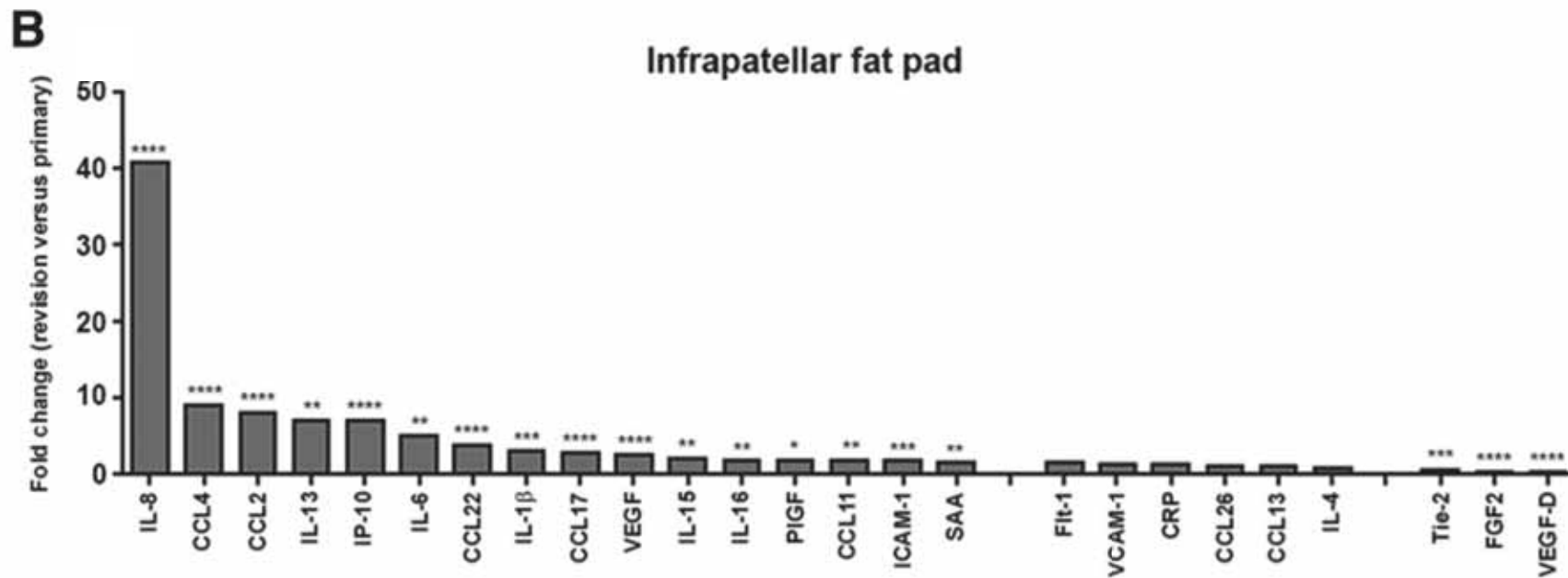
Study of inflammatory mediators in primary (n = 29) vs revision TKA (n=33)



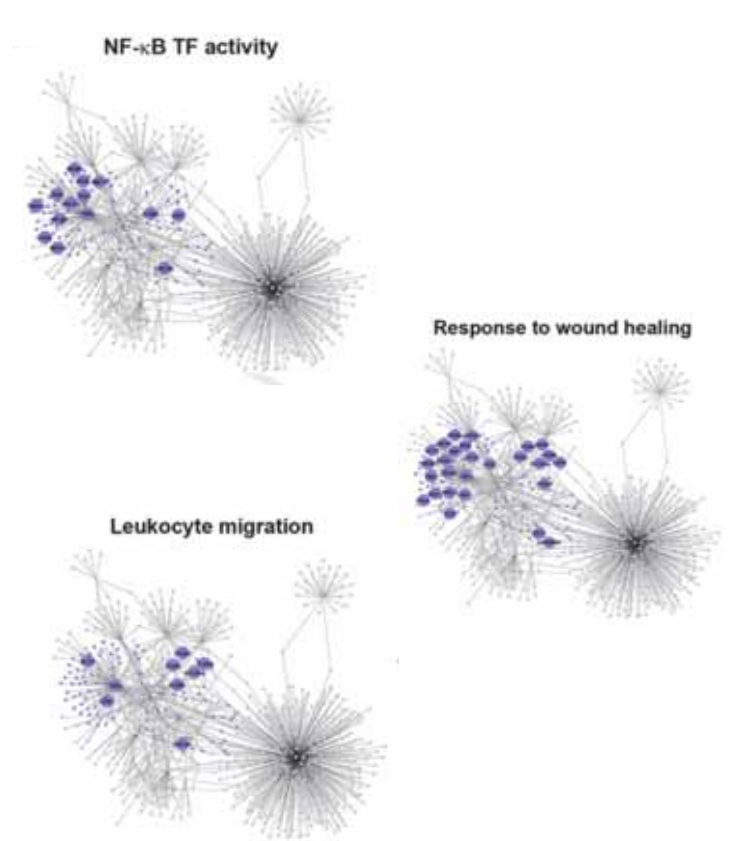
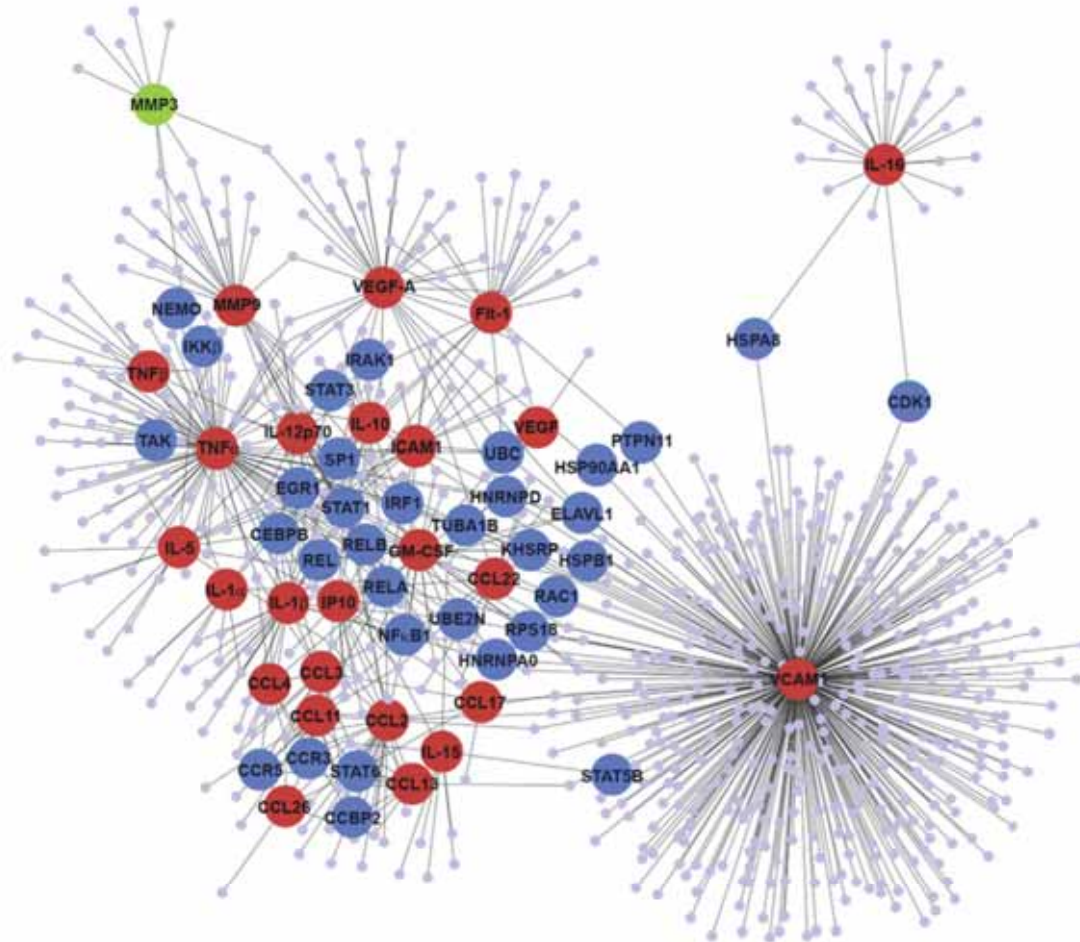
Aseptic inflammation is evident post-TKA and maps to fibroblasts

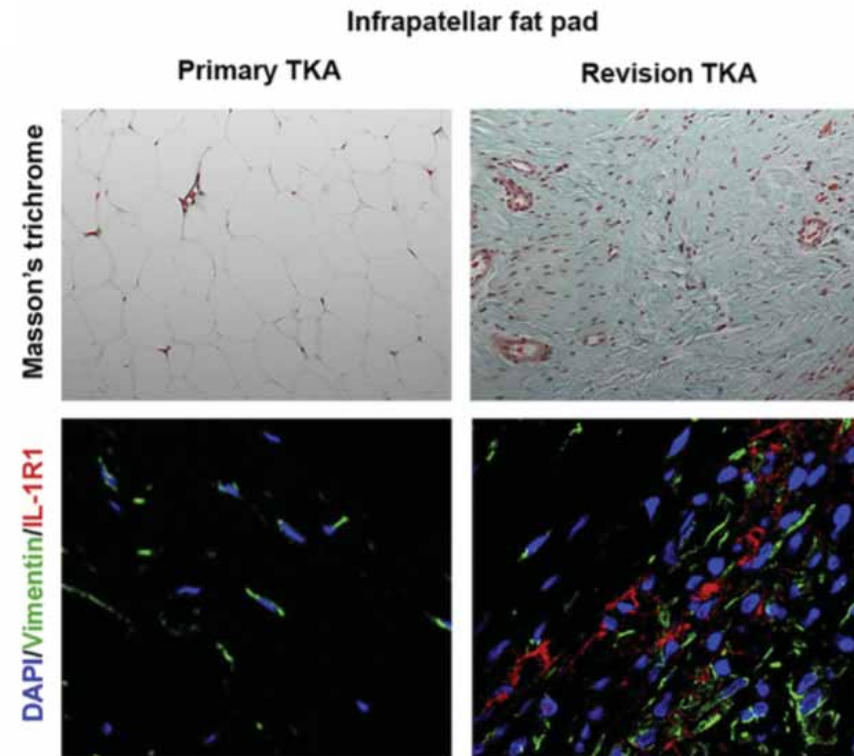
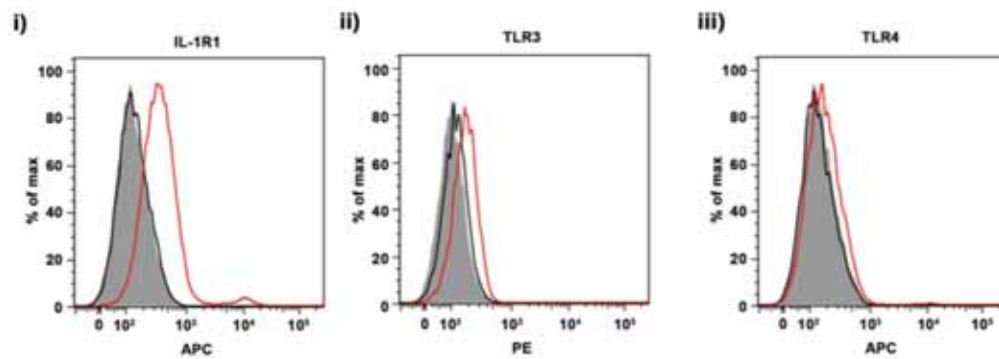
Revision TKA - infrapatellar fat pad





TKA fat pad protein-protein interaction network



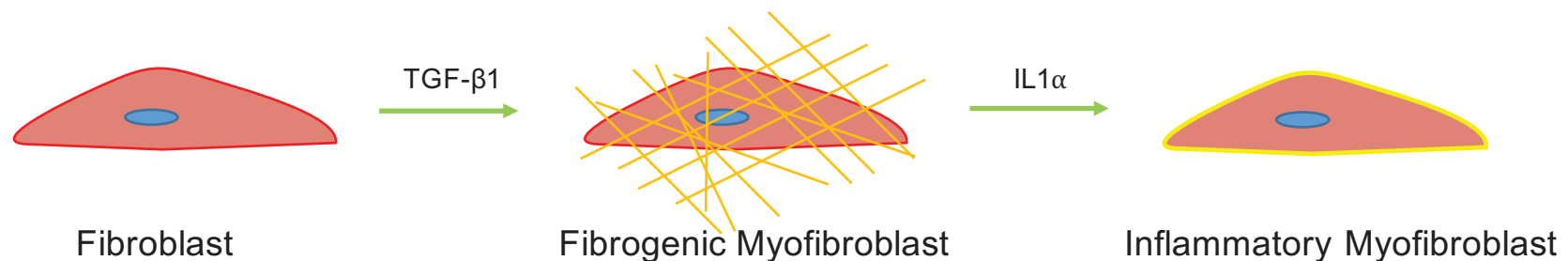


IL-1 α released from damaged epithelial cells is sufficient and essential to trigger inflammatory responses in human lung fibroblasts

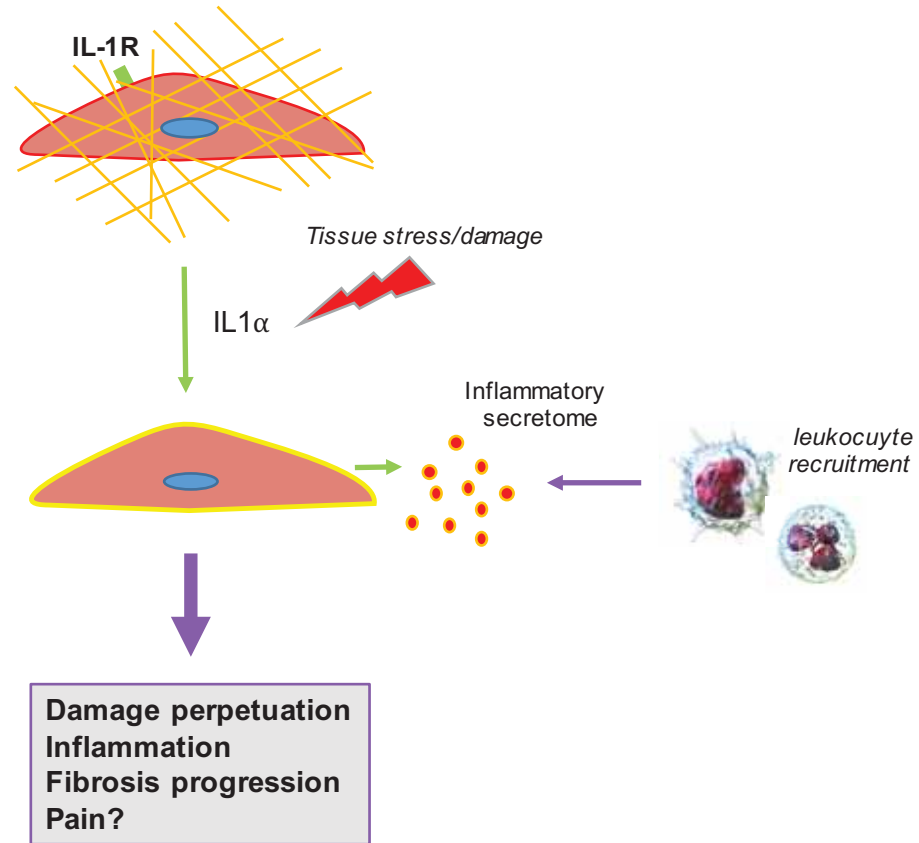
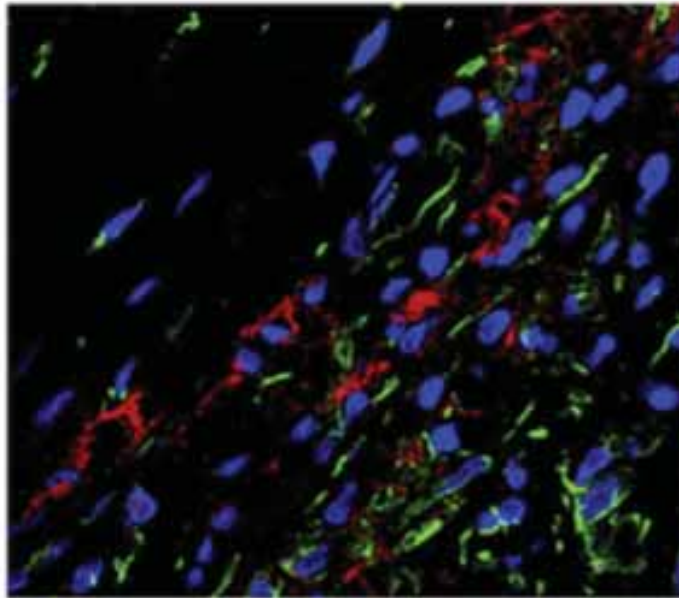
MI Suwara¹, NJ Green¹, LA Borthwick¹, J Mann¹, KD Mayer-Barber², L Barron², PA Corris¹, SN Farrow³, TA Wynn², AJ Fisher¹ and DA Mann¹

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Fibroblast Heterogeneity and Polarization



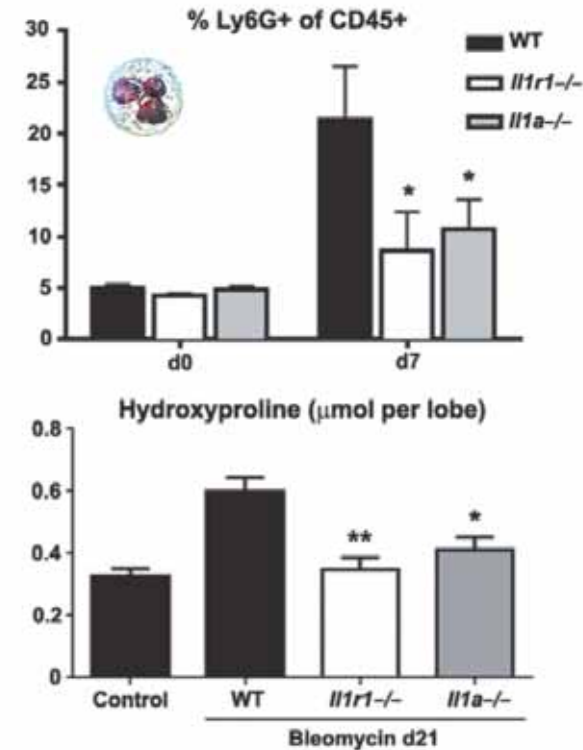
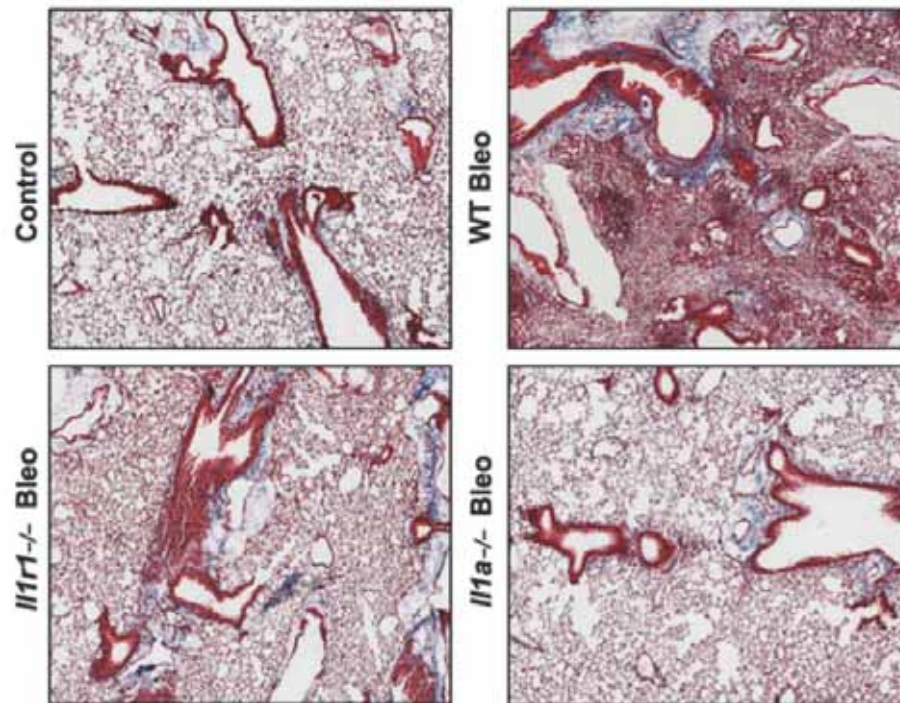
IL-1R-expressing fibroblasts and inflammatory priming



IL-1 α /IL-1R signaling required for lung inflammation and fibrosis

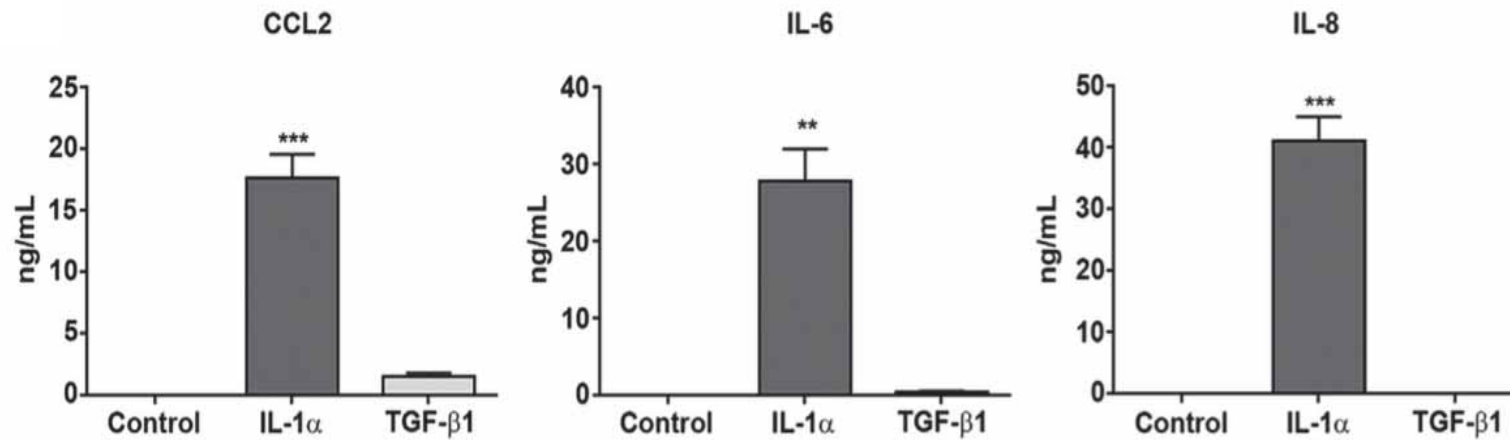
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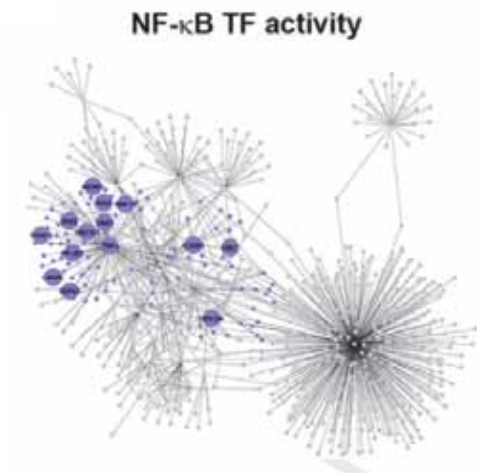
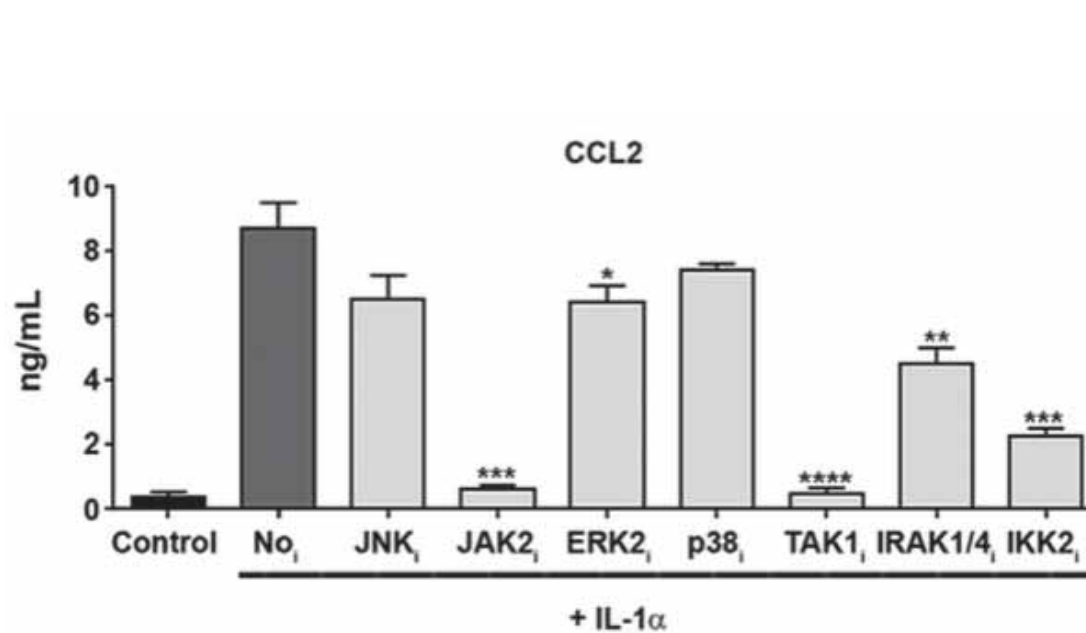


Coming next: *Il-1R1* ^{Δ Fib}

IL-1 α (but not TGF- β 1) induces inflammatory polarization of human infrapatellar fat pad fibroblasts

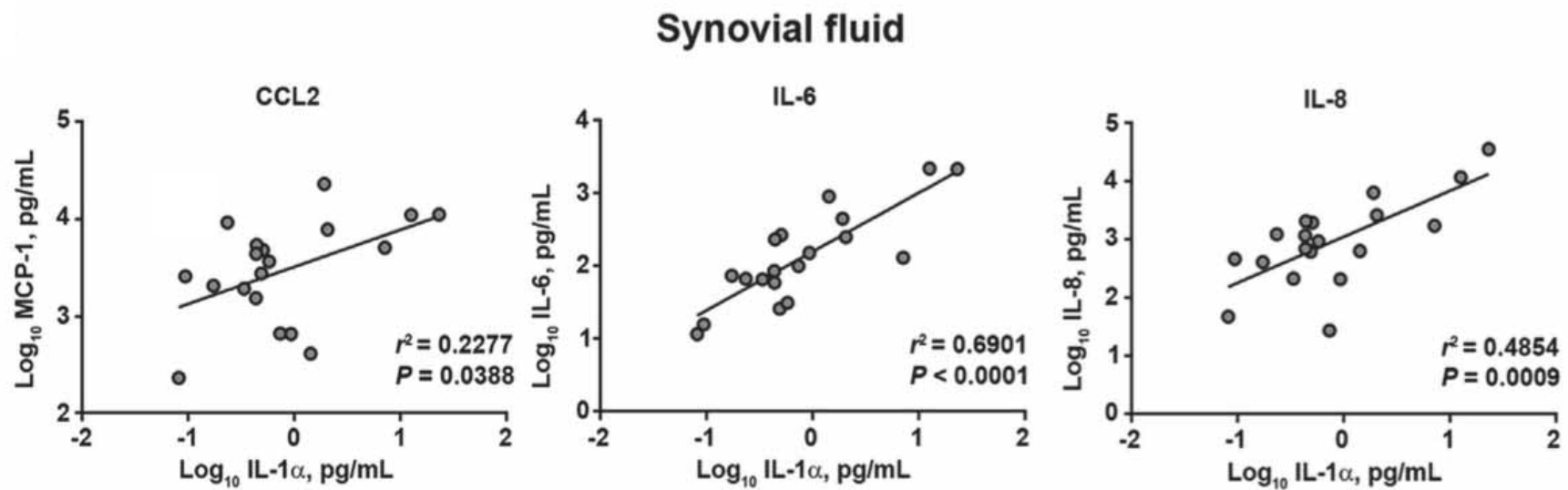


IL-1 α -induced polarization requires NF- κ B signaling

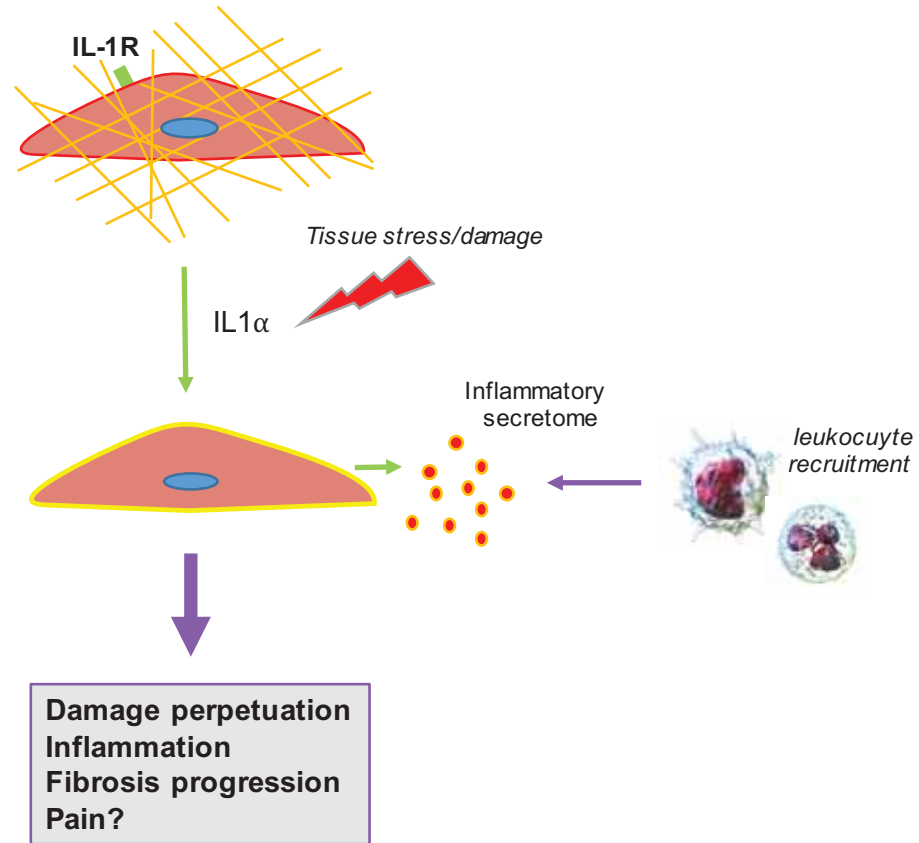
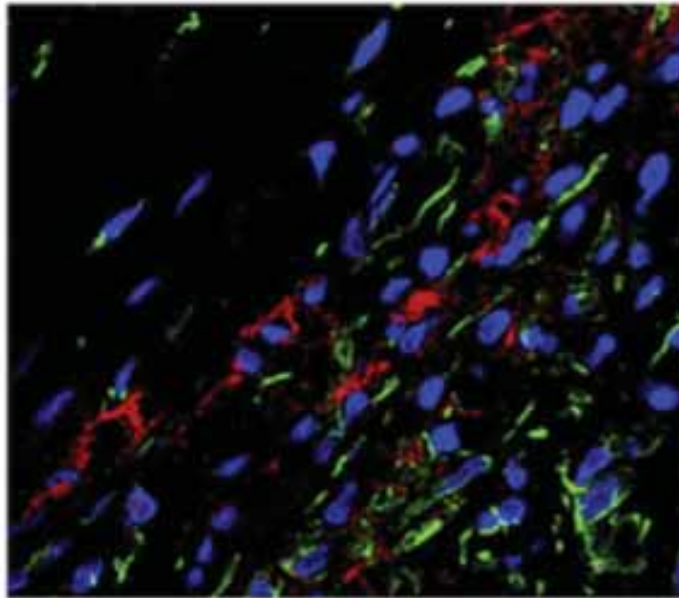


IL-1 α expression in TKA joint correlates with increased CCL2, IL-6 and IL-8.

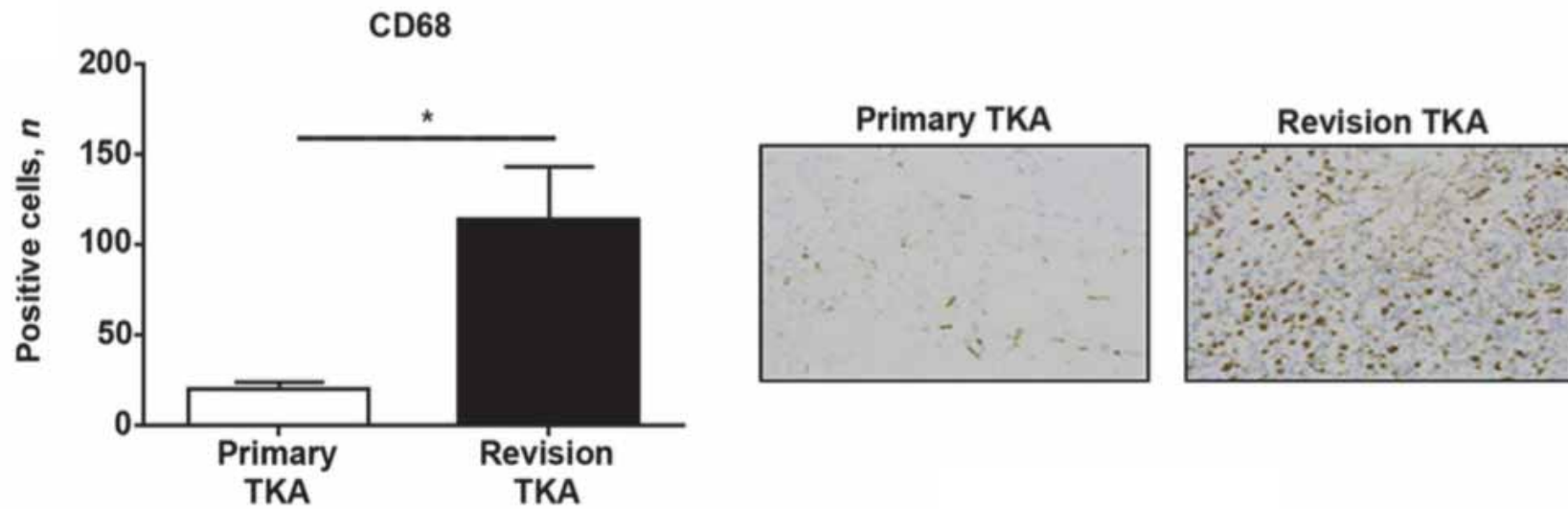
Linear regression analysis on individual patient samples



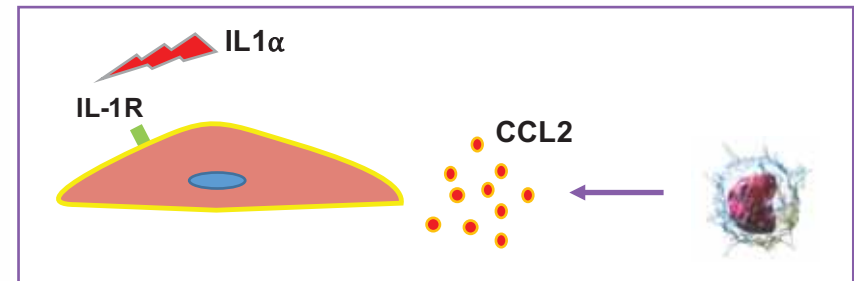
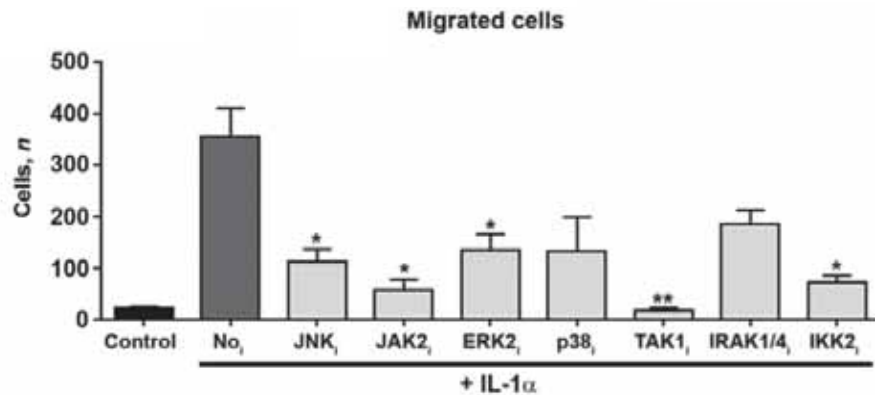
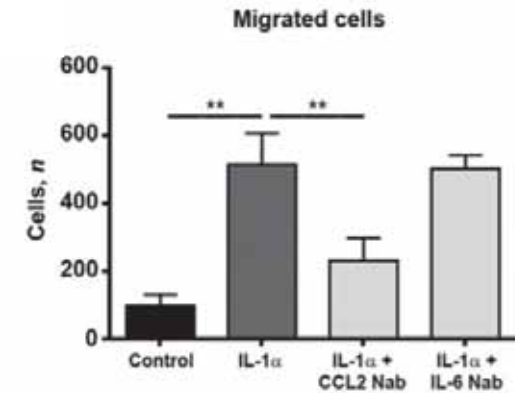
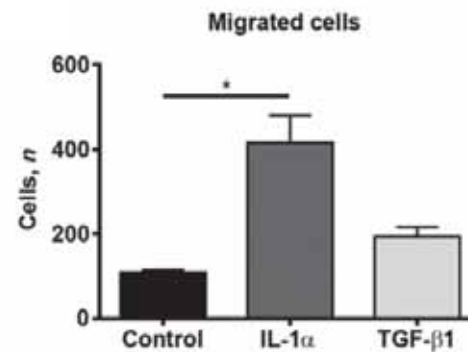
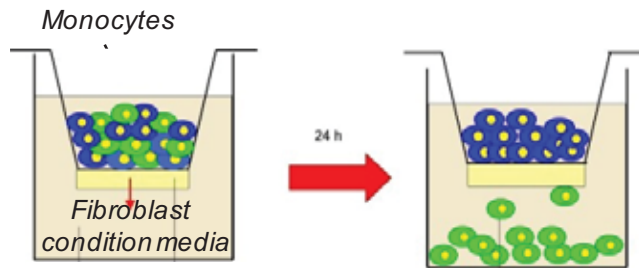
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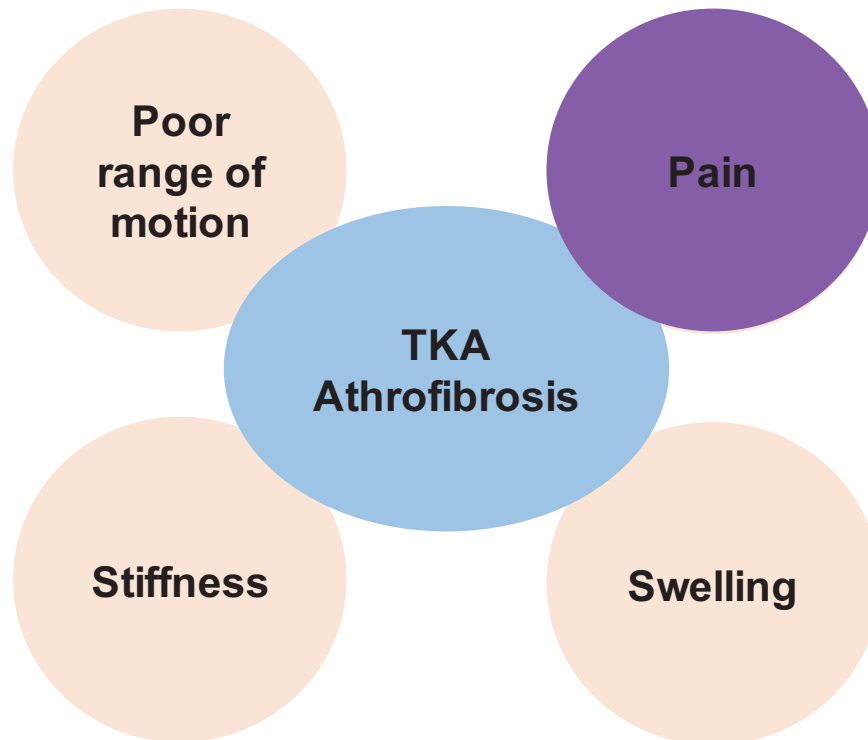
Monocyte numbers are increased in TKA revision fat pad



IL-1 α induces monocyte recruitment via NF- κ B dependent CCL2 secretion by IL-1R1 expressing fat pad fibroblasts



Translational Opportunities?

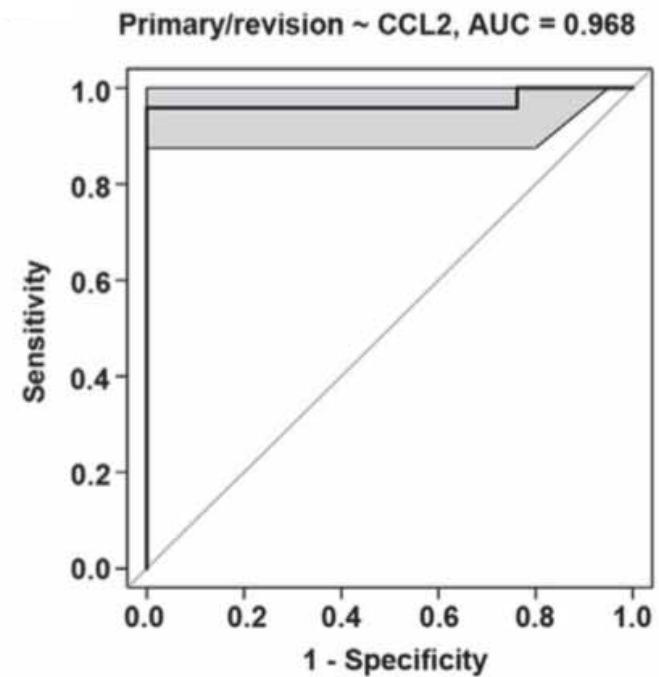
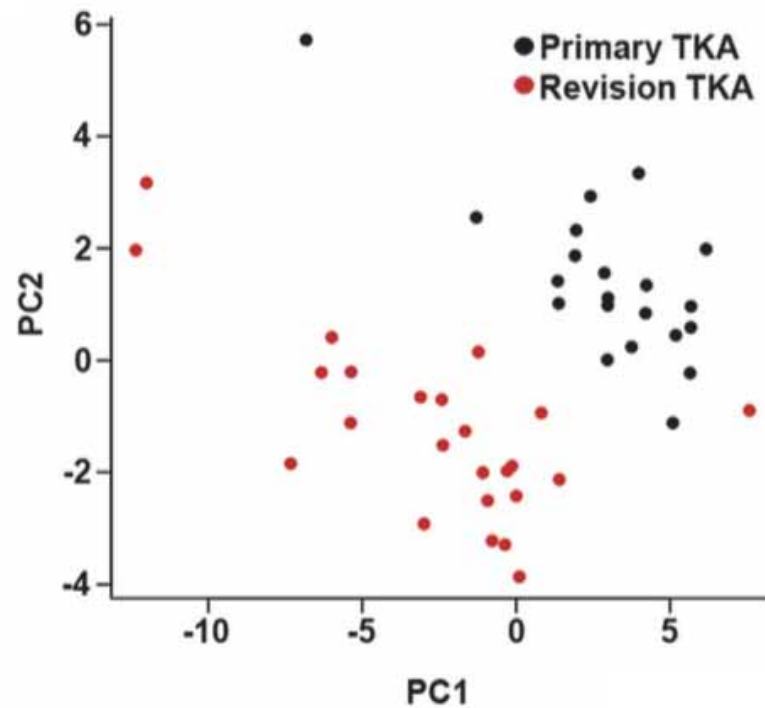


IL-1R antagonists (Anakinra)

CCR2 antagonists (AZ, GSK etc)

CCL2 inhibitors (Bindarit)

Post-TKA chronic pain correlates with synovial CCL2



Summary 2

- Replacement knee joints requiring revision display a characteristically chronic inflammatory profile.
- Fibroblasts in the fibrotic TKA joint display an inflammatory phenotype that is 'primed' by IL-1 α .
- TKA fibroblasts recruit innate immune cells through IL-1 α /IL-1R/NF- κ B/CCL2 intercellular cross-talk.
- Levels of the monocyte chemoattractant CCL2 in the TKA joint correlate with patient-reported pain .
- IL1 α , IL-1R, CCL2 and CCR2 antagonists have potential for therapeutic use in TKA.



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Biomedical Research Centre

Etc etc

