

Computational approaches - biology of Osteoarthritis

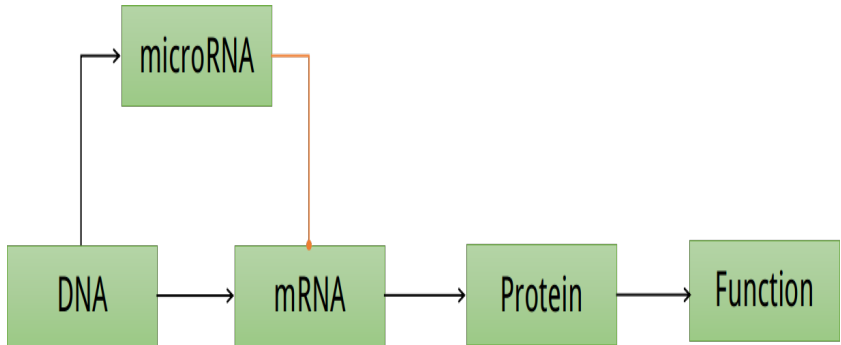
AG meeting: 22nd July

Krutik Patel

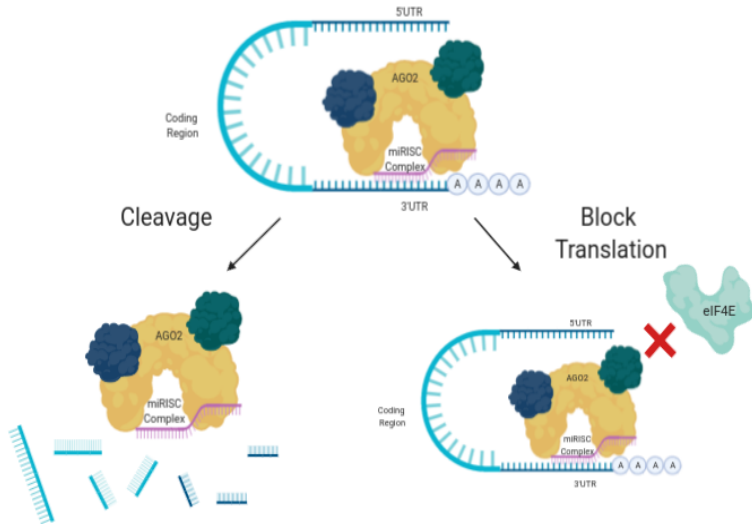
Newcastle University

22nd July 2020

microRNAs are important biological regulators



microRNAs down regulate target mRNAs



- Development :
 - 1 Neurogenesis
 - 2 Skeletogenesis
 - 3 Chondrogenesis
- Regulation of tissues :
 - 1 Epithelium
 - 2 Bone
 - 3 Cartilage
- Age related diseases :
 - 1 Cancers
 - 2 Huntington's disease
 - 3 Osteoarthritis (OA)

OA is a complex global debilitating condition

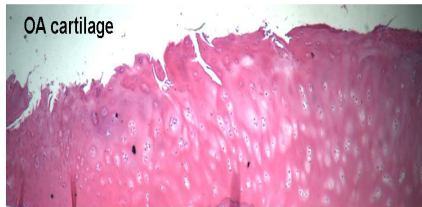
- WHO estimates 10% to 15% of all adults aged over 60 have some degree of OA, with prevalence higher among women than men.
- A UN report estimated by 2050, 15% of over 60s will suffer from OA, 1/3rd of which will be severe OA.
- Many factors contribute to OA and severity of the condition
 - 1 Age
 - 2 Obesity
 - 3 Gender
 - 4 Lifestyle
 - 5 Injury
 - 6 Genetics

Chondrogenesis could uncover mechanisms in OA

- Chondrogenesis is the process of mesenchymal stem cells differentiating into chondrocytes
- Chondrocytes form and maintain cartilage
- Over time changes in chondrocytes lead to molecular imbalances e.g. increase in catabolic factors, changes in miRNA levels
- These contribute to OA
- Better understanding chondrogenesis can give insights into OA

OA is the chronic loss of joint function

Histology of Human Normal and Osteoarthritic Cartilage

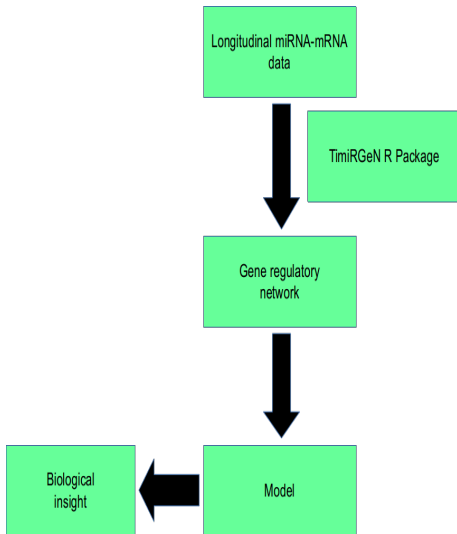


- Leads to pain, loss of movement, stiffness and in severe cases the formation of bone (osteophytes)
- No cure, only treatments such as surgery or pain relief drugs
- One obstacle for novel treatments is a lack of understanding in the basic biology

miRNA expressions patterns change between chondrogenesis and OA

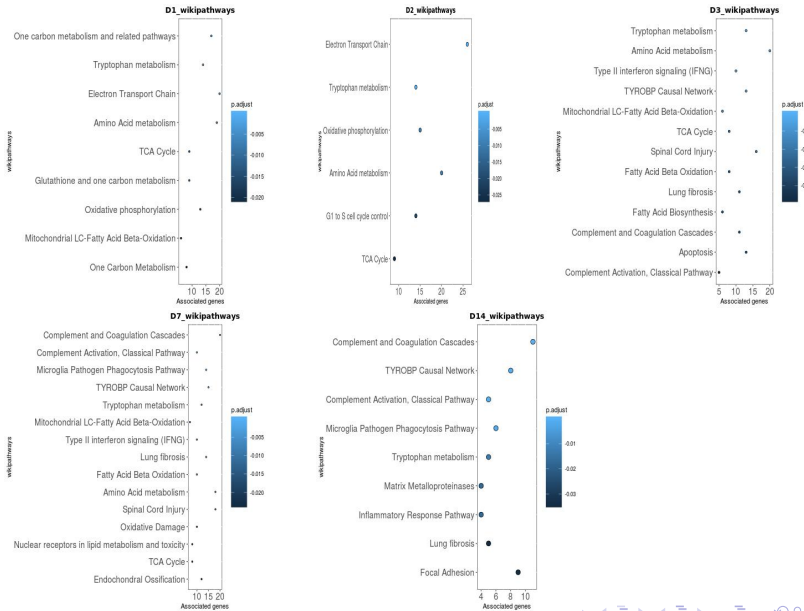
miRNAs	Chondrogenesis	Osteoarthritis
MIR-140-5p	↑	↓
MIR-140-3p	↑	↓
MIR-199a-5p	↓	↑
MIR-29a-5p	↓	↑
MIR-34a	↓	↑
MIR-455-3p	↑	↓

- Use computational approaches to better understand chondrogenesis
- Design a novel pipeline to automise big data analysis of multi-omic longitudinal data sets
- Generate a computational model which is of significance to chondrogenesis
- Work with collaborators to validate model

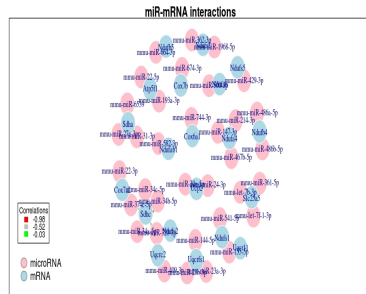
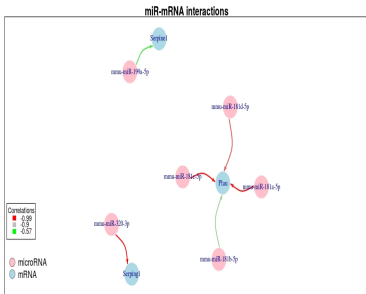
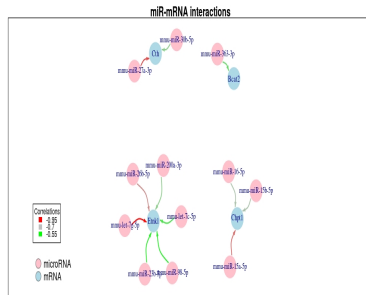
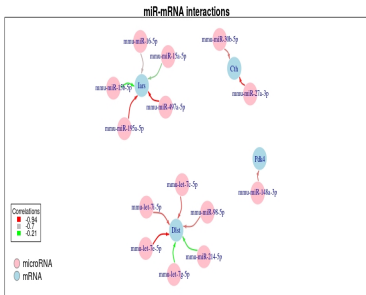


- R package which streamlines the process of finding models from longitudinal multi-omic data.
- Currently in review to become a Bioconductor package.
- Appeal from this in conferences in Europe and Japan.

TimiRGeN R package: Gene set enrichment



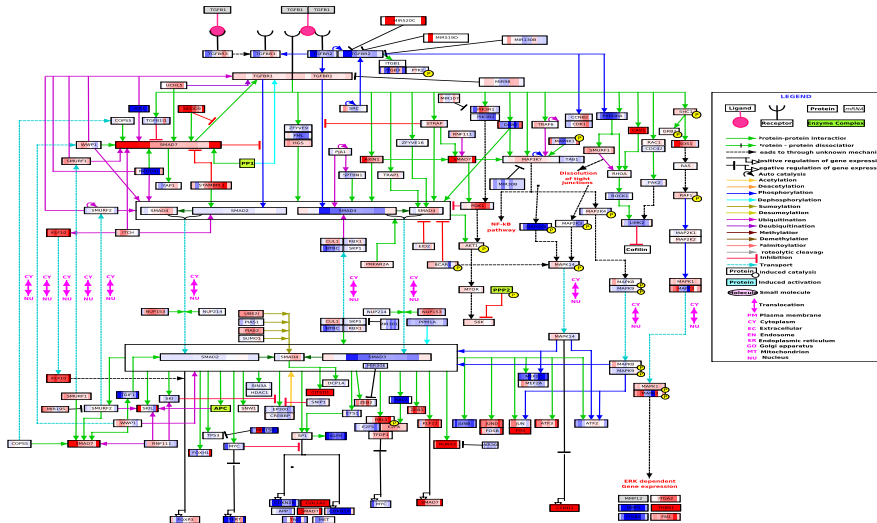
TimiRGeN R package: Network generation



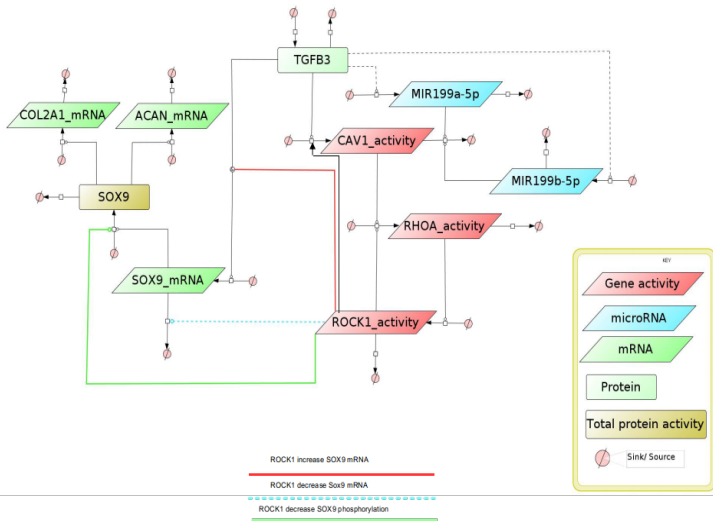
TimiRGeN R package: Export to Pathvisio

Title: TGF-beta Signaling Pathway
Availability: Freely available in
Organism: Homo sapiens

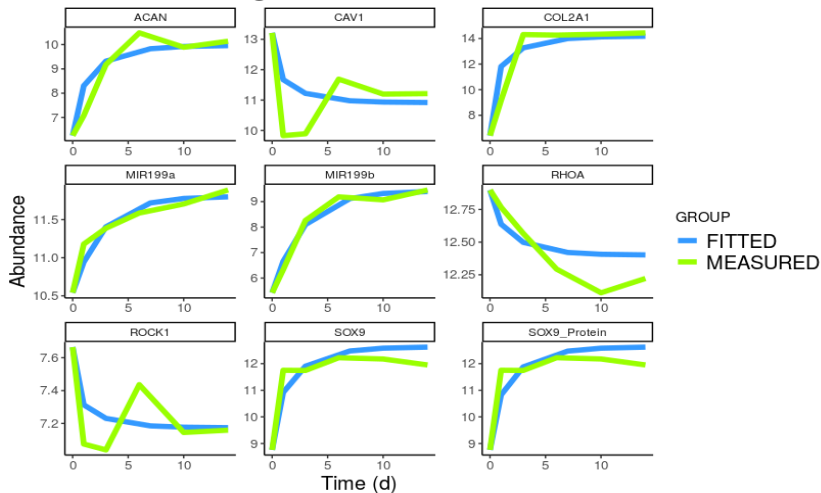
TGF beta Signaling Pathway



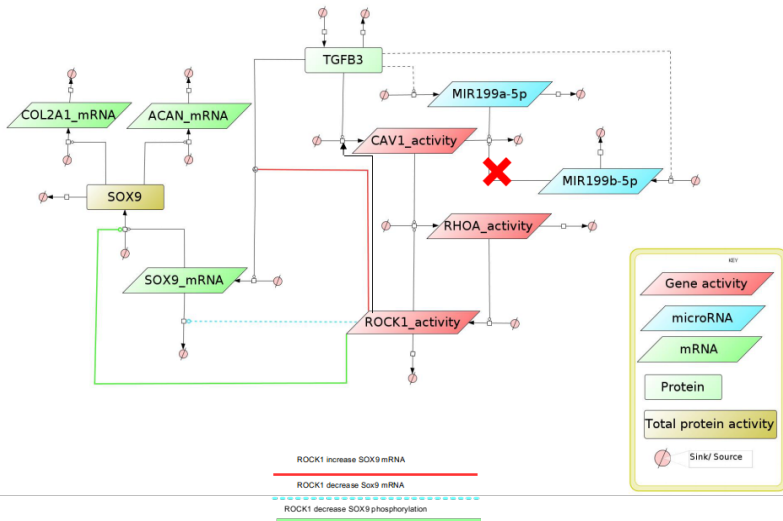
miRNA-mRNA model



Chondrogenesis Calibrated model

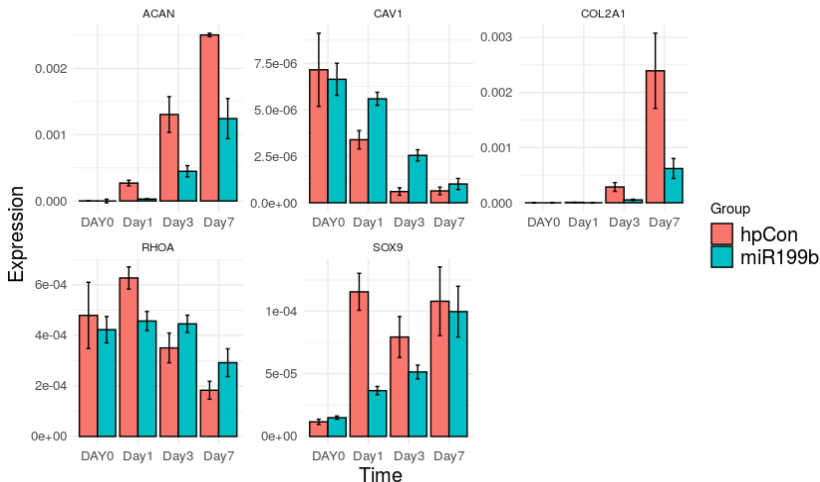


Validate model



miR199b-5p is important to chondrogenesis

miR199b Knockdown



- Have created a novel tool which can analyse longitudinal miRNA-mRNA data set to find biomarkers, create models or to better understand biological niches
- Have developed a miRNA-mRNA model which seems significant in chondrogenesis and OA

Further work to do

- Work on the TimiRGeN R package to have it accepted onto bioconductor
- Simulate validation results for the miRNA-mRNA model
- Add more to the model, to increase it's complexity and ability to make predictions