Unlocking Osteoarthritis (OA)

Transcriptomic and functional analysis of novel OA effector genes

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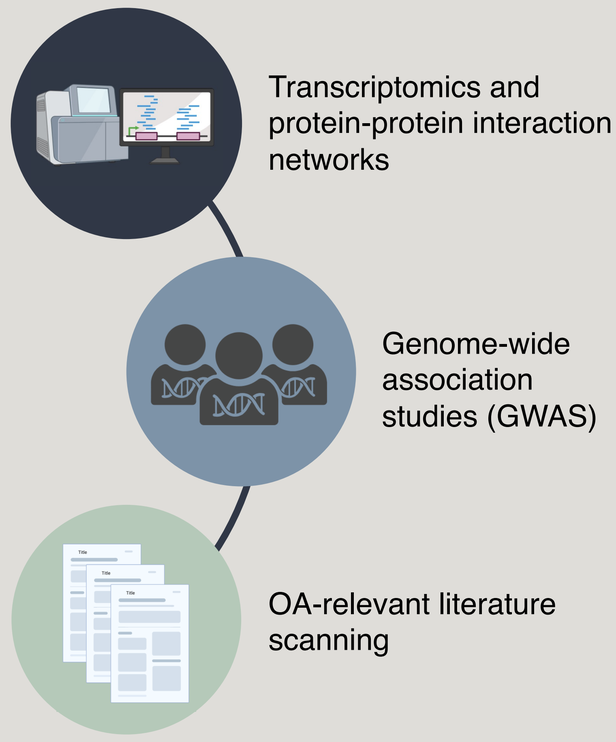
What is osteoarthritis (OA)?

OA is the **most common musculoskeletal disease**, affecting nearly 600 million individuals globally.

Patients with OA suffer **cartilage loss**, resulting in pain, reduced mobility and decreased quality of life.

Risk factors include **ageing**, obesity, and **genetics**.

No disease-modifying OA drugs (DMOADs), underscoring necessity to understand the molecular mechanisms underpinning OA.



Using a **machine learning** approach, we have developed a pipeline to identify novel and understudied OA effector genes

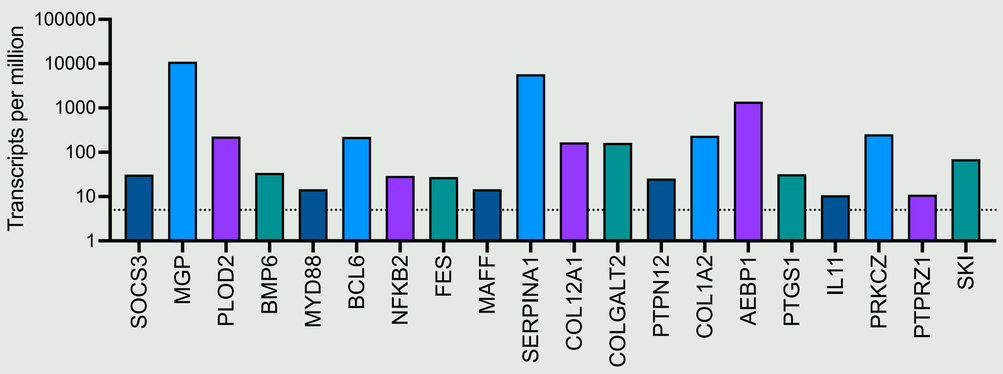
By characterising these genes, we aim to **enhance our understanding** of OA

Research proposal development

A **machine learning approach** ("OA Targets 2", under review) was used to rank understudied candidate OA effector genes for further investigation.

This list was intersected with the **largest pan-ethnic OA GWAS** to identify 20 candidates for transcriptomic screening.

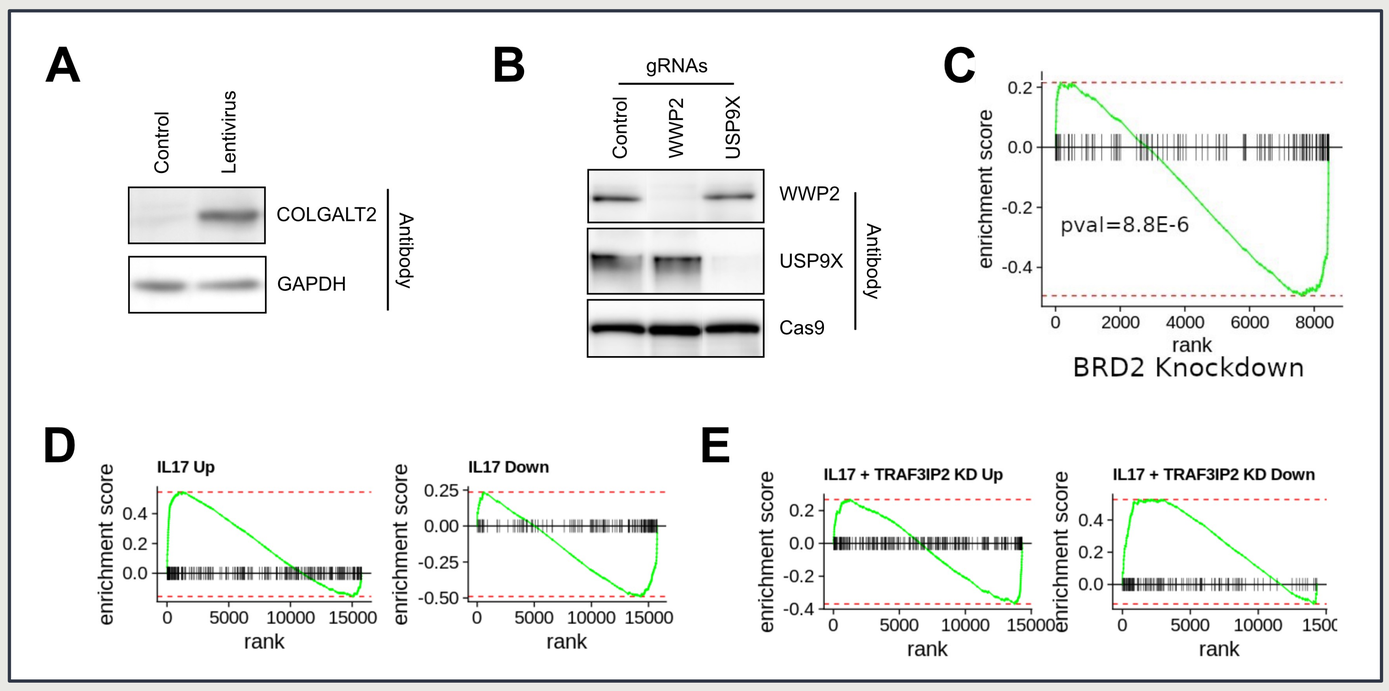
Each gene was identified to be **expressed in human knee OA cartilage**:



Our initial research proposal was refined following input from our **public and patient involvement network** (PIMS).

Three work packages (WPs) were designed:

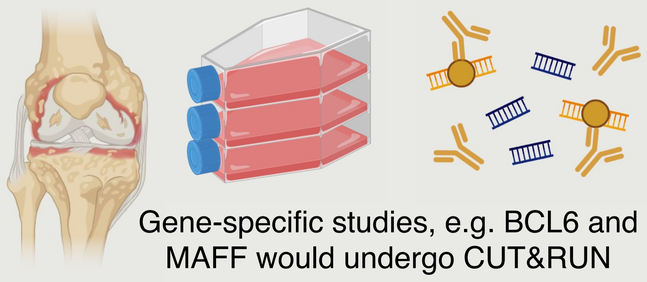
1. **Transcriptomic screening** of 20 candidates following gene perturbation
2. **In-vitro functional characterisation** of 3-5 candidates prioritized from WP1
3. **In-vivo murine OA studies** of the top candidate gene prioritised in WP1



Feasibility of transcriptomic screen (WP1)

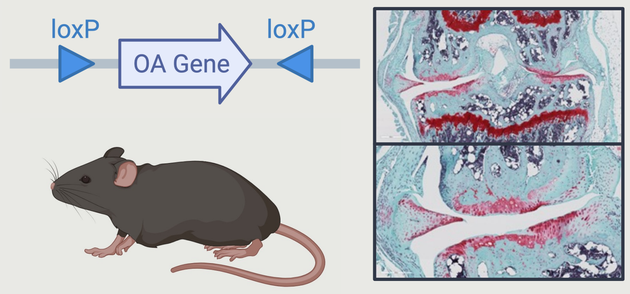
(A) Overexpression of COLGALT2 in chondrocytes following transfection of lentiviral constructs. **(B)** Knockdown of WWP2 and USP9X in chondrocytes following Neon NxT electroporation of Cas9 protein and targeting guide RNAs. **(C)** Gene Set Enrichment Analysis (GSEA) plot showing similarity (significant enrichment of BRD2 knockdown signature in comparison to upregulated genes associated with an "OA gene expression signature", concordant with BRD2's detrimental effect in OA models. **(D)** GSEA plots demonstrating IL17A stimulation in chondrocytes upregulates genes also enriched in the "OA gene expression signature" (left), while the converse is present for downregulated genes (right). **(E)** Depletion of predicted OA regulator TRAF3IP2 in chondrocytes reverses OA-like changes caused by IL17A stimulation. This demonstrates that we can prioritise OA regulators computationally ("OA Targets 2") and their depletion in chondrocytes can re-align OA gene expression to that of non-OA chondrocytes.

In-vitro characterisation (WP2)



Gene-specific studies, e.g. BCL6 and MAFF would undergo CUT&RUN

In-vivo OA studies (WP3)



Outputs and potential impact for individuals affected by OA

1. Extensive characterisation of novel and understudied OA genetic mechanisms
2. Identify druggable candidate genes and pathways
3. Build the foundations for future research to expand upon, ultimately translating into better patient outcomes