Nearly 10% of the population worldwide suffers from osteoarthritis (OA) in one or more joints. OA is a painful, disabling disease and currently cannot be cured. In a subset of OA patients, joint cartilage is replaced by bone via endochondral ossification. This is a natural process in growing long bones, where transient growth plate cartilage is replaced by bone. In contrast, healthy joint cartilage is permanent as it is protected against bone formation.

Stable joint cartilage is under control of master transcription factor SOX9, whereas bone formation is controlled by RUNX2. The processes that regulate the switch between a SOX9\(^+\) state and a RUNX2\(^+\) state are poorly understood, greatly hampering the development of successful therapies. We recently presented ANIMO (Analysis of Networks with Interactive Modeling), an intuitive software tool for modeling molecular networks for use by biologists\[1\]. Using ANIMO, we developed ECHO (Executable Chondrocyte), a computational model of the key processes that regulate expression and activity of SOX9 and RUNX2, based on a large-scale literature study \[2\]. In ECHO we predicted stimuli that prevent hypertrophic differentiation of articular cartilage, and tested this experimentally with FRAP using SOX9 and RUNX2 mobility as a read-out.

We tested the hypothesis that addition of WNT will change permanent into transient cartilage by inducing hypertrophy. Indeed, when we add WNT, a known regulator of bone formation, the permanent or SOX9\(^+\) state changes to a transient or RUNX2\(^+\) state. Addition of WNT3A to human chondrocytes transfected with SOX9-GFP resulted in a significant decrease of the immobile SOX9 fraction from 53% to 34% within 15 minutes after addition. However, we have found that the resistance of healthy cartilage to hypertrophy is probably due to the secretion of DKK1, FRZB and GREM1 \[3\]. Addition of nodes representing DKK1, FRZB and GREM1 stabilized the permanent cartilage or SOX9\(^+\) state even after addition of WNT to ECHO. Wet-lab experiments validated these in silico experiments.

References: