Osteoarthritis is a painful joint condition which is becoming increasingly prevalent as a result of an aging population. Loss of protective cartilage from a lifetime of wear-and-tear and its ectopic replacement with bone matter causes the rubbing of bone-on-bone which can make normal movements – getting out of bed or putting the kettle on – very painful experiences. While twin studies have demonstrated a strong genetic component to osteoarthritis, the identity and effects of these genes are only recently being examined. Using zebrafish as a vertebrate model, the Hammond lab aims to understand more about this condition suffered by tens of millions of people worldwide.

The onset of osteoarthritis in many ways resembles the normal embryonic process of endochondral ossification, whereby bones develop from a cartilage template. The cartilage cells proliferate, turn hypertrophic then die, leaving gaps for the bone cells to migrate into. Wearing-away of cartilage reinitiates this process as a repair mechanism, but the death of the cartilage cells and infiltration of bone exacerbates osteoarthritis. Understanding the genetic causes of the normal development is an important step in understanding how to terminate it at the hypertrophic stage – maintaining the benefits of the cartilage repair while ensuring it doesn’t get replaced with bone matter.

The popularity of the zebrafish as a model organism really took off in the 1980s. It was chosen for its convenient small size and low maintenance living conditions, genetics which are easy to modulate and, crucially, transparent embryos making in vivo visualisation of tissues as they develop incredibly easy. Work done by the Hammond lab has helped establish the zebrafish as a valid and advantageous model organism to use in the study of osteoarthritis.

The initial proof-of-principle came when the lab ran a genetic screen on zebrafish displaying phenotypic characteristics of osteoarthritis such as reduced joint mobility, loss of cartilage and bony spur formation. One of the genes which came up was chst11, the human homologue of which (CHST11) was subsequently identified as an osteoarthritis susceptibility gene. The lab is now working to understand how changes to this cartilage matrix protein lead to changes in cell signalling.

Since then, the lab has used zebrafish to study a number of other genes which have been implicated in human osteoarthritis, including one called mcf2l. The Mcf2l protein is known to cause migration of some cell types including breast cancer and Schwann cells, but what role it could play in osteoarthritis is unknown. Utilising the transparent bodies of the embryos and mRNA in situ hybridisation, the changing patterns of mcf2l expression during development was shown for the first time in any animal model. The lab found mcf2l highly expressed in developing jaw cartilage. Following the establishment of normal expression patterns, future work will involve overexpression and knockdown studies of genes like mcf2l to see what effect this has on joint development. The lab also seeks to understand the communication between cell types important in cartilage and bone development, and what effect physical activity and strain may have at a genetic and cellular level.

Osteoarthritis is suffered by 40% of people over 70 years old and can progress to a debilitating extent. While symptoms can sometimes be managed or prevented, there is no known cure. The origins of the condition need to be better understood. The Hammond lab’s work towards identifying and characterising the genes responsible for cartilage and bone development aims to reveal some targets which may lead to a much-needed pharmaceutical cure.