

## Bradley – Year One Progress Summary

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability. Cartilage tissue has little intrinsic regenerative capacity; thus, identifying therapeutic targets that promote cartilage regeneration is of great interest. Phlpp1 (pronounced “flip”) is a phosphatase that functions as an inhibitor of tissue regeneration. We previously showed that Phlpp1 is highly expressed in articular cartilage from OA patients and that Phlpp1 genetic deficiency promotes murine neocartilage formation. This Regenerative Minnesota Medicine grant allowed us to determine if Phlpp inhibitors also promote human cartilage regeneration. To date, we have shown that Phlpp inhibition promotes cartilage regeneration by increasing expression of cartilage matrix genes and proliferation of cartilage cells isolated from patients with OA. We optimized the potential of stem cells derived from adipose tissue to generate cartilage cells and illustrated that Phlpp inhibition enhances the chondrogenic potential of these stem cells. In our second year of funding, we will fine tune our model to show that these fat-derived stem cells regenerate a cartilage defect. We also have preliminary data that demonstrates that Phlpp inhibitors increase cartilage content in explanted cartilage cultures from OA patients. Thus, these Phlpp inhibitors may promote cartilage regeneration and are promising disease-modifying OA drug candidates.