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 Medicine Minnesota grant allowed us to determine if Phlpp inhibitors also promote human cartilage regeneration. 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, but could not enhance integration with native tissue in an ex vivo cartilage defect model. In our second year of funding, we developed an ex vivo cartilage explant model and used this model to demonstrate that Phlpp inhibit increases cartilage content. We performed whole transcriptome analyses (RNASeq) on these tissues and identified a novel gene of interest that is induced by Phlpp inhibition. Thus, these studies demonstrate that Phlpp inhibitors may promote cartilage regeneration and are promising disease-modifying OA drug candidates.