This presentation will summarize our laboratory’s work in developing a family of glycosaminoglycan (GAG)-based biomaterials with varying levels of affinity to positively-charged proteins. In particular, the versatility of these materials to modulate cellular response to soluble cues will be highlighted. Our in vitro results suggest that GAG biomaterials affect progenitor cell differentiation towards a chondrocytic phenotype, and that this may be exploited in controlled ways to direct differentiation of stem cells to achieve maximal healing of orthopaedic defects. Moreover, strong affinity interactions may be used to sequester endogenous signals and therefore better control timing of cellular differentiation. This presentation will also summarize the development of these materials as in vivo protein delivery vehicles, including how GAG sulfation pattern promotes tunability of release kinetics for a wide range of injuries. In particular, characteristics of rodent models of rotator cuff injury will be presented and the use of our biomaterials to treat joint degeneration will be discussed.