Large tissue defects and repairs remain a challenge to restore in terms of structure and function, as options for tissue regeneration with retention of tissue volume remain very limited. To address this challenge, we have been pursuing silk protein-based biomaterial systems. These systems have been studied in various formats, including injectable gels, implantable sponges, shape-change materials, chemically modified systems and dense devices. The design, characterization and utility of these silk-based biomaterials will be discussed in the context of materials science and engineering and tuning mechanics and degradation lifetimes to match structure-function relationships and clinical needs. The systems discussed are all based on the unique, slow degrading, silk protein-based biomaterials which offer biocompatibility and versatility in terms of processing, chemistry, formulations and properties.