Poly(ethylene glycol) (PEG) based hydrogels are widely used in the field of tissue engineering. Biologically, these materials are a “blank slate” that can be designed to provide specific bioinstructive cues to cells, which has made them useful in both fundamental studies of cell-material interactions and translational applications for tissue regeneration. In most cases, the biochemical and biophysical properties of PEG hydrogels are predetermined according to the initial formulation. However, an emerging trend in the field is the implementation of chemical strategies to create hydrogels with tunable dynamic properties, as this approach has the potential to provide valuable new insights and capabilities for tissue engineering. In this seminar, highlights from our work in this area will be presented. The development of photoresponsive hydrogel systems will be emphasized in particular, and results from a project using photodegradable hydrogel substrates and photochemical patterning to study how extracellular signals (i.e., modulus, substrate topography) can drive aortic valve cells toward a diseased phenotype will be presented. Our work on using bioorthogonal tetrazine click chemistry to create a photoresponsive PEG hydrogel platform will also be presented, as the establishment of this system overcame some key challenges related to the photochemical patterning of 3D cellular microenvironments. In addition, a strategy for achieving tunable, sustainable release of peptide-drug conjugates from hydrogels using dynamic equilibrium reactions, which we used to direct the osteogenic differentiation of bone marrow stem cells, will be presented.