designed for tissue engineering (Hern and Hubbell 1998; Burdick and Anseth 2002; Nuttelman et al. 2005; Salinas and Anseth 2008). Adhesion to the RGD motif also facilitates cell migration and vasculogenesis (DeForest et al. 2009; Phelps et al. 2012; Mann et al. 2001; Zisch et al. 2003; Lee et al. 2015b) and enhances osteogenic differentiation of mesenchymal stem cells (MSC) in 3D hydrogels (Shin et al. 2002; Burdick and Anseth 2002; Yang et al. 2005; Alsberg et al. 2001). The addition of collagen-mimetic peptides and recombinant fragments of fibronectin have similarly been used to stimulate osteogenesis (Lee et al. 2008; Reyes and García 2003; Connelly et al. 2011; Petrie et al. 2008). In addition to adhesive peptides and proteins, bio-functionalization can be used to regulate ECM deposition and new tissue formation. For example, functionalization of PEG hydrogels with chondroitin sulphate promotes MSC chondrogenesis and deposition of a cartilaginous ECM (Varghese et al. 2008), while cross-linking of synthetic polymers with MMP-degradable peptides facilitates matrix remodelling (Lutolf et al. 2003; Mann et al. 2001). Finally, covalent binding of growth factors or growth factor binding proteins is a powerful approach to regulating cell fate and function within engineered constructs (Martino et al. 2011; Martino et al. 2013; Watarai et al. 2015). Tethering of epidermal growth factor (EGF) to synthetic scaffolds improves cell survival and is actually more effective than saturating concentrations of EGF in solution (Fan et al. 2007; Mehta et al. 2010; Platt et al. 2009). Moreover, the incorporation of growth-factor binding domains derived from fibrinogen allows multiple growth factors to be simultaneously activated and significantly improves wound repair (Martino et al. 2011; Martino et al. 2013). Together, these studies demonstrate how bio-functionalization of hydrogels can be used to direct cell fate and function and improve their use in regenerative medicine applications.

Bioengineering Functionality with Spatial Control

As described above, hydrogels can be synthesized through different molecular mechanisms and tuned to exhibit specific bioactive properties. However, the successful application of these materials in medical applications requires significant control of both physical and chemical properties in both space and time (Tibbitt et al. 2015; Webber et al. 2016). For example, the ECM plays a crucial role in our body regulating cell adhesion, migration, and differentiation; cell-cell communication, mechanostransduction; tissue development, regeneration, and degeneration; and in general our body's functionality and homoeostasis. This ECM can be thought of as a hydrated matrix material capable of optimizing molecular presentation and providing structural hierarchy, chemical anisotropy, selectivity, and adaptability. Therefore, hydrogels for biomedical applications that are designed to replace, recreate, interact with, or stimulate elements of the ECM, would require a high level of tuneability of their properties, including the ability to exhibit specific signalling capabilities hierarchically and with spatial control.

Anisotropic hydrogels

Most human tissues, like skeletal muscle or liver lobules, as well as evolving biological environments present an anisotropic organization with distinctive chemical (i.e.,