In contrast to bioreactors that produce single cells, tissue engineering bioreactors have supported the development of large 3D tissue grafts. To produce large (centimeter-sized) viable grafts, these systems often use convective flow to provide crucial mass transport regimes, overcome the diffusional limitations of nutrients and oxygen, and prevent the accumulation of metabolic waste products that otherwise induce starvation and death of the cells in the inner regions of the construct. Tissue engineering bioreactors can also enhance the functional- ity of grafts through the application of biomimetic physiological stimuli as well as the incorporation of sensors that give real-time feedback of culture conditions. After incubation, the mature, functional cellular constructs can be transplanted in vivo to regenerate damaged tissues. Tissue engineering bioreactors will likely play a significant role in translating engineered grafts to the clinic as the potential automation renders them economically efficient and amenable to mass production for larger populations of patients. Cutting-edge research in this field continues to focus on the improved application of biophysical stimuli to optimize functional tissue assembly30–35 and computational modeling to improve predictability of the outcomes19,36,37–40. Addition- ally, notable efforts to enhance the clinical applicability of these grafts have focused on engineering grafts that are similar in size to critical-sized bone defects in humans and are tailored to the patient20,41,42. Nguyen et al. recently demonstrated the ability to culture a 200 cm3 cell-based construct in vitro without the development of necrotic centers20,42. In this approach, bone marrow-derived mesenchymal stem cells were encapsulated in hydrogel beads and placed in a tubular perfusion bioreac- tor. Three-dimensional-printed molds that could be anatomi- cally shaped were used to direct the flow through the hydrogel beads. The space between the hydrogel beads enhanced mass transport to the cells throughout the entire construct, allowing the stem cells to remain viable and undergo osteogenic differentia- tion. Although this approach represents a critical advancement in the culture of clinically sized constructs, it remains limited by the use of hydrogel beads that minimize cell–cell interactions and inhibit paracrine signaling between cells, which are impor- tant factors in bone formation. In contrast, Bhumiratana et al. directly seeded adipose-derived stem cells into the pore spaces of anatomically shaped, porcine temporomandibular joint scaffolds41. They cultured the adipose-derived stem cell-seeded scaffolds in perfusion bioreactors for 3 weeks in vitro before using the bioreactors to maintain their viability during transport to an on-site animal facility. The grafts—customized for each pig—were implanted and cultured for up to 6 months in vivo. This was a foundational, proof-of-concept study and clearly demonstrated the feasibility of using this strategy as a treatment for humans. However, in general, there remains a huge gap in the growth of 3D engineered .tissues in bioreactors and demonstration of in vivo functional integration and potency