Nanoscale materials are the fundamental building blocks and functional subunits of cells, including subcellular organelles and extracellular matrix components. Currently, there is growing recognition of the importance of understanding and incorporating nanobiology into biomedical applications. This issue is of particular importance in the emerging field of regenerative medicine, the goal of which is to develop methods to repair, replace, and regenerate diseased, injured, or non-functional tissues. Towards this goal, stem or progenitor cells have been considered a highly desirable candidate cell type, because of their expandability and potential to be induced toward specific cell differentiation lineages. A key requirement in tissue engineering and regenerative medicine is that ultimately the “regenerate tissue” needs to be a three-dimensional structure. In weight-bearing musculoskeletal tissues, this requirement is particularly critical. Musculoskeletal disorders affect one out of seven Americans. This severe disease burden underscores the need to develop novel and effective treatment protocols. This seminar will present the excitement as well as the challenges in the field of skeletal tissue engineering and regeneration, specifically the application of adult stem cells and nanomaterial scaffolds. The biology of adult stem cells, particularly the mechanisms regulating their proliferation vs. differentiation into specific lineages, is intricately regulated by cell-cell interactions, signaling by extracellular bioactive factors, and transcriptional and epigenetic activities. More importantly, the extracellular matrix milieu provides critical cues, both architectural and structure-dependent, to guide cell-based tissue morphogenesis. We have developed biomimetic and biodegradable nanofibrous biomaterials to serve as scaffolds for cell-based tissue engineering. Information on the fabrication and biological basis of the scale-dependent bioactivities of the nanofibrous scaffold will be presented. Cell-nanofibrous constructs are currently being tested in animal models for their cartilage reparative potential in vivo. In conclusion, tissue engineering represents a unique, emerging inter-disciplinary research field that is a natural platform for life scientists, engineers, and clinicians working together to advance regenerative medicine.