

Orthopaedic tissue engineering and stem cells – an unfulfilled promise

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Despite being over thirty years since there was proof that the hypothetical osteogenic stem cell existed,¹ demonstration of any dramatic value for the use of such cells in orthopaedic clinical practice by tissue engineering approaches has not yet been realised. This is notwithstanding extensive studies concerning the likely nature and potentials of these cells in countless *in vitro* and *in vivo* investigations. In part, this is based on the confusion caused by exaggeration of claims by unreliable, or at best naïve, investigators and opportunistic entrepreneurs who have grossly misinterpreted data from many ill-conceived studies.^{2,3} This pseudo-science has been harmful, especially to the stem cell field, both academically and commercially.

But what can be salvaged from this debacle? Only when the exact nature of these stem cells at particular sites in the human skeleton,⁴ together with their physiological regulation in normal and pathological conditions is confirmed by careful and repeatable studies, will great progress for their significant practical use in orthopaedics be fulfilled. Cell populations that retain some capacity for osteogenesis are easily grown in cell culture from bone marrow, but these cells are variable in nature with significant loss of bone-forming ability on serial passaging in culture, and at best produce minimal amounts of skeletal tissue when reimplanted *in vivo*. Additionally, confusion has resulted from unsubstantiated claims that these innately or ‘determined’ osteogenic cells, that give rise to the bone, cartilage and some marrow adipocyte lineages by rigorous assays,⁵ are present in many connective tissues. Hence, such cultures of stromal fibroblastic cells have been given many other names, and all of those suggested are unsatisfactory as has been discussed previously.^{6,7} The most populist, albeit grossly inaccurate, term for these osteogenic stem cells has been “mesenchymal stem cells” for many years, although this term is now even rejected by its instigator.⁸ Over the years, numerous investigators have claimed that these cells can

regenerate cells outwith the osteogenic lineage such as skeletal muscle, intestine, brain, nerve, and cells of other organs. However, the evidence obtained from experimental data has been blindly misunderstood in relation to normal human physiology. That connective tissue cells in many organs of the body, including muscle, skin, lung, brain, and fat for example, can be induced into bone formation has been known for decades,⁹ but this process requires the presence of an inducer (such as a bone morphogenetic protein) that uniquely modifies gene expression. Whether osteogenic stem cells or purely proliferative osteoprogenitors are generated by these procedures is unknown.

Whatever the nomenclature of these cells, the basic physiological facts remain as emphasised by Friedenstein and others many years ago;¹ that is, that the osteogenic stem cells that are programmed inherently with the capacity to produce large amounts of bone reside predominantly close to all bone surfaces in normal individuals.⁶ These surfaces include the periosteal, endosteal, metaphyseal growth plate and the numerous vascularised channels throughout the bone tissue. These cells are normally quiescent and non-cycling during homeostasis in the adult but are activated as required during rapid bone growth and repair of major skeletal defects. This allows dramatic regeneration of bone after injury and confers the skeletal tissue at various physiological sites with extensive healing properties throughout life. As was shown initially, the bone marrow is a significant easily accessible source and has been amenable to extensive study over many years by *ex vivo* and *in vitro* methods. However, genetic controls and expression can be manipulated artificially under these conditions to activate transcription of a few non-lineage markers in cell populations and this may suggest possible transdifferentiation to another tissue type. Indeed, induced pluripotent stem cell technology that modifies chromatin¹⁰ has questioned whether

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such stem cells could be generated from differentiated somatic cells. But *in vivo* physiological environmental controls are supreme in maintaining and restricting phenotypic identity in the natural state. This does not preclude, however, that under diverse pathological conditions such controls may be altered.

To survive and perform their normal functions *in vivo* stem cells require localisation in precise, specific environmental niches.¹¹ These are characterised by physical and biological interactions with adjacent cells and matrices, together with integrated molecular signals from further afield, that are present in the milieu. In the adult, the constitution of the niches enables stem cells to remain quiescent, to be activated to self-renew and/or to produce progeny that will produce, when required, physiologically all the cell lineages characteristic of the tissue.¹²

In the present context, full knowledge of the biology of the stem cell niche, including the physiological mechanisms and factors that control stem cell maintenance, self-renewal and directed differentiation *in vivo*, is thus of paramount importance to be able to effectively design biomaterials to optimise translational research in this area. When knowledge of these major aspects are known more fully, biomaterials research will be able to promote optimal culture methods for retention of the essential self-renewal and full differentiation capacities of these osteogenic stem cells as seen in the natural state.

Fortunately, the above concerns are being considered by many current investigators^{7, 13} and the *in vivo* identification and detailed characteristics of these osteogenic progenitors and their environmental niches are now under intensive investigation. Although no single specific marker can identify the osteogenic stem cell, it is known that these cells occupy well defined positions in cartilage growth plate, bone periosteal and endosteal surfaces close to distinct areas of cell proliferation adjacent to cell differentiation and maturation zones, and surrounding blood vessels. Over the years, there has been some understanding of the cell and matrix characteristics present in these sites, but use of stem cell molecular markers and more complex characterisation of these stem cells *in situ* is required. Future molecular studies and *in vivo* identification *in situ* should allow detailed analysis of these cells and surrounding cell and matrix components by using, for example, the new, cutting edge 'omic' technologies of spacial proteomics, genomics and transcriptomics.^{14, 15} When the particular, likely dissimilar, niche characteristics of stem cells are established at distinct skeletal sites, the reproduction of environments preserving human stem cell activity will enhance capabilities for tissue engineering of skeletal components for orthopaedic use. The promise of stem cell technology applied to skeletal reconstruction in orthopedics may then be realized.

As emphasized by the contentious past history in this field, it is crucially important for all investigators and peer reviewers to be ultra-critical in their assessments of submitted papers. This, as well as compliance with normal publication standards, will ensure that all alternative explanations of presented data can be indicated and considered objectively before any acceptance for publication. I trust that this will be considered as a continuing aim of submissions to this exciting new journal, *Biomaterials Translational*.

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Data sharing statement

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