Recent advances in cell-based approaches to treat tendon and ligament injury have been exciting and fast moving[1]. With the many options available to treat the injuries in the hope of restoring normal architecture and function, it can be difficult to determine the best treatment plan. From earlier days when bone marrow aspirate alone was used, practitioners have moved toward bone marrow-derived mesenchymal stromal cells, the nucleated cell fraction from adipose tissue, and cultured adipose-derived mesenchymal cells. For some cases, platelet rich plasma may offer a viable, facile and cost effective treatment option[2]. Recent studies looking at using tendon-derived progenitor cells also offer hope to treat tendon lesions[3-5]. Collection of umbilical cord blood MSCs may also result in treatment options for a particular patient in the future[6]. Equine embryonic cell lines have also recently been developed and put to use in a clinical research cases[7-8]. While these therapies are in current use, controlled research studies and case-controlled randomized clinical trials are lacking. Characterization of these cell populations is underway by many laboratories but much more work needs to be done to better understand both what cell type is being used, and how best to prepare the cells for therapy. Additionally, combinatorial approaches using growth factors, a delivery vehicle or scaffold to support cell survival and proper differentiation, together with cells may actually offer the best approach to regenerating normal tendon after injury[1]. This article will focus on the background, rationale and research supporting the different cell-based approaches in regenerative medicine, including: bone marrow mesenchymal stromal cells, adipose-derived progenitor cells, and tendon-derived progenitor cells in relation to tendon injury.

In order to function properly, any given tissue must have specialized cells that build and maintain the structure of that tissue, and then perform additional homeostatic functions as needed. This process of specialization is termed differentiation. The differentiation process occurs during normal embryonic development. In an early embryo, the embryonic stem cells are capable of forming all of the cell types that make up the organism, and are therefore called totipotent. Prior to specialization, a cell that is capable of becoming many different cell types (i.e. multipotent) can be considered a “stem cell”, or a progenitor cell (which has a more limited capacity to form other tissues). In the postnatal organism, multipotent stem cells reside within the tissues, such as bone marrow, that are still capable of forming either the tissue type they reside in (progenitor cells) or multiple types of tissue that are related to each other, (e.g. mesenchymal stem cells) [9]. While it was once thought that some tissues did not have resident stem cells or progenitor cells, recent evidence has refuted this; progenitor cells have been isolated from cartilage, neuronal
tissue, liver and tendon [10-13]. Further research indicates that perivascular cells, called pericytes, may be the resident cells that contribute to healing of tissues [14]. Isolation of progenitor cells from different tissues demonstrate that they resemble mesenchymal stem cells from bone marrow, and are capable of differentiating toward multiple tissue types. However, progenitor cells or stem cells isolated from different tissues are not equivalent.

The definitions of mesenchymal stem cell and progenitor cell have been in flux, but in general, mesenchymal stem cells are characterized as having a specific set of cell surface markers, and the ability to differentiate into any mesenchymal tissues, while progenitor cells are thought to be more limited in how many different tissues they can become. More recent studies indicate that alternative sources of progenitor cells (adipose tissue, synovium, cartilage, and muscle) might also be beneficial for specific therapeutic applications [15-17]. The most prominent avenues of investigation have been directed at repair of bone, cartilage, myocardium, kidney, liver and nervous tissues [18].

Tendon injury in horses can result in prolonged rehabilitation with a high incidence of recurrence even after appropriate rehabilitation [19-20]. Factors that contribute to this include the abundant extracellular matrix in tendon that becomes damaged, and the high levels of degradative enzymes that can actually increase the level of matrix damage prior to reparative processes. The relatively low cellularity and vascularity in the tissue can impede healing, although ultimately for tendon to function properly, it is important for this low cellularity and low vascularity to return. The highly ordered organization of the extracellular matrix must also be restored.

While bone marrow derived cells have been tested in model species and used to treat tendon and ligament injury in horses, there is a low percentage of mesenchymal stem cells relative to the nucleated fraction obtained in aspirates [21]. Three to four weeks of cell culture are required to obtain sufficient cells to treat tendon lesions because numbers of mesenchymal cells are relatively low in bone marrow aspiration [5, 22]. In contrast, adipose tissue contains a significantly higher proportion of mesenchymal cells [15]. Adipose-derived cell populations are currently being used to treat tendon lesions [1, 23]. However, it is not known which mesenchymal cell type is best used for tendon regeneration, and early information has shown that there are differences in the ability of the cells to differentiate toward different lineages [24-25]. Since differentiation toward tendon is not as well characterized, comparisons between the adipose and bone marrow derived cells to differentiate toward tendon have not yet been reported.

Because incomplete information about how to drive tendon differentiation exists, it is possible that progenitor cells may differentiate toward an unwanted lineage such as bone, fibrocartilage or adipose tissue, once implanted. Indeed, phenotypic abnormalities noted within pathologic tendon and ligament include calcification, and fibrocartilaginous tissue [26-27]. Thus, abnormal repair mechanisms may involve de-differentiation of endogenous cells, and growth along non-tendon lineage pathways.
Because little is known about how to drive tendon differentiation, it might be preferable to use cells that are partially committed to differentiate toward tendon. Recently, tendon progenitor cells (TPCs) have been isolated. They compare favorably in an in vitro model of tendon injury to BMMSCs [4-5]. A proportion of the tendon progenitor cell population is similar to mesenchymal stem cells in that cells are able to differentiate along chondrocyte, adipocyte or osteocyte lineages [4]. TPCs produce more extracellular matrix and grow more rapidly than bone marrow cells in vitro. Rapid growth in culture is needed for timely use of cells to treat tendon lesions; production of appropriate extracellular matrix is critical for tendon function after healing[28].

Tendon-derived progenitor cells have been shown to differentiate toward multiple lineages; however, a quantitative analysis of this differentiation capacity has not been performed and improvements to the isolation technique have been made. In order to best use progenitor cells to treat injuries, it is critical to understand the capacity of the cells to become different tissues, whether it is cartilage, bone or tendon. A thorough analysis of the differentiation capability of tendon progenitor cells, compared with other commonly used stem cells, isolated from adipose tissue and bone marrow is currently underway, to help determine the best source of cells to treat injuries to tendon and ligament.