Back pain—a clinical challenge addressed by Mesoblast using their Mesenchymal Precursor Cells

Mesoblast is a world leader in regenerative medicine, and has built a platform technology based on the immunoselection of adult mesenchymal precursor cells (MPCs). MPCs are perivascular cells found in all vascularized tissues in the body, including bone marrow, dental pulp and adipose tissue. MPCs are the precursors of all multi-potential fibroblastoid Colony Forming Units (CFU-F), suggesting that they give rise to all the mesenchymal lineage stem cells in the tissues they reside, and which can differentiate under appropriate stimuli into bone, fat and cartilage. MPCs have specific surface markers such as STRO-1, VCAM-1 (CD106), STRO-3, STRO-4 (HSP-90b) or CD146 that facilitates their extraction and purification using the principles of antibody immunoselection1–4.

Two important advantages of these cells are that they can be expanded to large numbers in culture while maintaining their undifferentiated phenotype, and can be used allogeneically since they are well tolerated when transplanted into unrelated recipients. Autologous mesenchymal precursor cells generally differentiate into osteoblasts, chondrocytes, tenocytes and fibroblasts upon implantation into the appropriate tissue. However, administration of allogeneic MPCs appears to predominantly result in the secretion by the MPCs of a broad range of cytokines, growth factors and chemotactant molecules which collectively act on endogenous cells to promote repair and regeneration of the affected tissue or organ. The mechanisms responsible appear to involve recruitment of the body’s own tissue specific precursor cells, induction of blood vessel formation, increase in cell survival, and reduction in deposition of fibrous scar tissue.

MPCs can also home in on sites of tissue injury where they release or transfer anabolic and regulatory factors to modulate and suppress the inflammatory and immunological pathways that inhibit the normal mechanisms of tissue repair6. Furthermore, factors secreted by MPCs are capable of suppressing the pro-inflammatory actions of monocytes and T cells, the key regulators of inflammation and immunity. As a consequence, we are now evaluating allogeneic MPCs in diverse medical fields, including cardiology, orthopaedics, inflammation and rheumatology, diabetes, and ophthalmological diseases.

Mesoblast’s MPCs are manufactured in a good manufacturing practice (GMP) environment according to stringent criteria set by regulatory agencies in each jurisdiction. By using well-defined purified cell populations, supported by both its MPCs technology platform and its patent positions, Mesoblast has established a proprietary manufacturing process that...

Figure 1 | Illustrates schematically the methodology used to isolate the Mesoblasts MPC from the bone marrow of healthy volunteers, and their culture expansion from a standard master cell bank. The competitive advantages of using this approach are also identified.
promotes reproducibility and batch-to-batch consistency for its allogeneic cell products. Mesoblast’s allogeneic MPCs are isolated from bone marrow aspirates from young healthy volunteers using antibodies that have been shown to interact with specific markers on the MPC surface. These immunoselected MPCs are culture-expanded under GMP conditions, and the final released “off-the-shelf” product aims to be as close as possible, phenotypically and biologically, to the naturally occurring perivascular MPCs as determined by specific product characterization release criteria and potency assays (Figure 1).

The use of MPCs in the treatments of back pain
Lower back pain is the leading cause of disability worldwide. Apart from the magnitude of human suffering, the socioeconomic and financial burden to healthcare providers is enormous. In the United States alone the direct and indirect costs of this problem has been estimated to be the order of $90 billion annually and is expected to increase as the population ages and becomes more obese.

The intervertebral disc has been implicated in the causation of back pain, both directly and indirectly as a pain generator through its pivotal role as the functional spinal unit (FSU). The disc is interposed and integrated with the vertebral bones of the spinal column to form the FSU that is located in close proximity to the spinal cord and its nerve roots. Anatomically, the disc is composed of a fibrocartilaginous outer ring, the Annulus Fibrosus (AF), which encapsulates a central hydrated gel, the Nucleus Pulposus (NP). The extracellular matrix of the gelatinous NP is rich in proteoglycans, which are negatively charged macromolecules that attract and immobilise large quantities of water molecules within this tissue. It is the presence of proteoglycans and their associated water molecules, constrained within the NP by the tough but flexible AF, that provides the unique biomechanical properties of the disc. These properties include its resilience and recoverability following the imposition of high axial loading of the spine while simultaneously allowing its flexion-extension and limited rotational movement. While the proteoglycans and collagens are the major structural units of the disc they still need to be constantly monitored and renewed throughout life. These roles are undertaken by the cartilage like cells residing in the NP, cartilaginous end-plate (CEP) and the fibrochondrocytes of the AF. Unfortunately, disc cells exist in a precarious nutrient environment, they are in fact located within the largest avascular structure of the human body. Oxygen and solute exchange of cells residing within the NP and inner AF occurs by the process of molecular diffusion across the CEP from capillary buds that extend from the blood supply of the vertebral body. The outer rim of the AF does have a limited blood supply but this is inadequate to also support the nutritional requirements of the cells of the NP. Figure 2 illustrates the main anatomical structures of a normal disc and

![Figure 2 | Photographs of a normal discs (A) showing the bulging central gelatinous Nucleus Pulposus (NP), and fibrocartilaginous lamellae of the Annulus Fibrosus (AF). Panel B is of an aged degenerate disc showing the loss and dehydration of the NP and structural disruption of the AF. Panels C and D are photomicrographs of a young disc stained with Masson Trichrom/fast green dyes to highlight the collagens of the AF (green) and bone of the vertebral bodies (VB)(red). Nutrition of the NP occurs exclusively via diffusion of oxygen and exchange of solutes across the cartilaginous end plate (CEP).]
shows the interface of the CEP with the vertebral body. Disc degeneration is a complex disease in which cell senescence, genetic, hormonal and environmental conditions, including micro-injuries to the AF and CEP, have all been shown to be contributing factors to varying degrees. These factors coupled with the aging process can lead to disc failure and the manifestation of symptoms. Figures 2 show examples of a normal (2A) and degenerate (2B) discs where the loss of the hydrated gel of the NP accompanied by disruption of the fibrous lamellar structure of the AF are clearly evident.

Loss of the hydrated NP gel and structural weakening of the restraining AF results in a decrease in disc height that is often accompanied by the protrusion of the AF on to the adjacent spinal cord or its nerves roots (see Figure 3). This interaction may promote an inflammatory response, can lead to difficulties walking, problems with fine motor activity, bowel or bladder dysfunction, weakness and pain. When this occurs, the diagnosis is usually straightforward, however for the many with isolated back pain the diagnosis is more complex. Nevertheless, the patient then seeks medical intervention.

The plethora of treatments for managing neck and back pain, both operative and non-operative, are generally aimed at relieving symptoms, but they do little to address the underlying pathology of disc degeneration which may be the root cause. Developing new strategies to reverse or slow down the degenerative processes that occur within the degenerate disc with aging and degeneration have the potential to change this paradigm thereby providing a solution to this urgent medical problem.

Mesoblast is advancing development of its cell-based therapies to provide such potential solutions. Mesoblast's capacity to consistently manufacture its patented MPCs to FDA regulatory standards coupled with its ability to rapidly translate preclinical studies into clinical trials have resulted in promising results in several key areas of clinical disease of the spine. Firstly, injection of MPCs into the NP of degenerate lumbar discs of a large animal model was shown to result in reconstitution of the disc matrix as evidenced by increased de novo synthesis of aggregating proteoglycans. This resulted in the restoration of disc height and reduced degenerative changes as determined by validated X-rays, MRI and histopathology scoring systems, without any evidence of adverse side effects. These encouraging preclinical findings supported commencement of a phase 2 multicentre clinical trial in patients with persistent chronic low back pain of discogenic origin. Interim results have been very encouraging. This clinical study is scheduled for completion by the end 2013 and depending on the outcome it may proceed to a phase 3 trial using the same category of patients with intractable chronic low back pain.

Secondly, Mesoblast have undertaken preclinical and clinical studies to evaluate the use MPCs to augment and possibly enhance current surgical treatments for patients who have more advanced disease that would exclude them from any attempt to restore the integrity of their degenerate discs and ameliorate symptoms by direct administration of MPCs. These patients may then become candidates for spinal surgery. This may involve decompression, a procedure that removes offending material, such as disc or bone, from impinging on neural structures. However, with such procedures fusion of the
vertebral bodies flanking the offending disc may also be required to stabilize the segment of the spine subjected to intervention.

Successful spinal fusion is reliant on the body's innate ability to mobilize its own bone marrow stem cells to facilitate the biological process of laying down new bone following injury. This is the same process that occurs in repairing a fracture of a long bone, however, in the case of spinal fusion the distance of the bone bridge is typically greater and requires grafts and other devices to maintain disc space and stability while the new bone forms. Experience has shown that the best grafts are from the patient’s own body and are as known as autografts, but obtaining this material can require harvesting viable bone from an alternate site, such as the hip which can lead to donor site pain and morbidity. A number of alternate grafts are often used to circumvent this problem, including synthetic matrices or cadaver grafts (allografts) that are normally non-osteoinductive and require augmentation to promote complete spinal fusion.

Unsuccessful spinal fusion, or non-union (also called pseudoarthrosis) may result in severe pain and require a second surgical intervention that is clearly an undesirable event. In an attempt to decrease rates of non-union and donor site morbidity recombinant bone morphogenetic proteins (BMPs) have been investigated as promoters of bone growth. Despite initial widespread use in spinal surgery, more recent concerns over the safety and efficacy of BMPs indicate that alternative approaches should be considered to biologic treatments for spinal fusion.

Mesoblast’s proprietary MPCs, when combined with an appropriate matrix, appear to be prime candidates for the enhancement of spinal fusion because of their ability to differentiate into osteoblasts or bone cells. In addition, they can secrete factors, such as BMPs, that induce resident cells to undergo osteogenic differentiation and neovascularisation as well as modulate inflammation at the site of injury. Moreover, since Mesoblast’s MPCs are immunoselected from the bone marrow of young healthy donors they are a homogenous population contrary to autografts from ageing patients that would be predicted to have diminished osteogenic potential.

In recent preclinical and clinical studies Mesoblast’s allogeneic MPCs were shown to produce a robust fusion equivalent to autograft, demonstrating the potential for the MPCs to eliminate the need for autograft harvest. Importantly, the MPCs did not promote any cell related adverse events. And MPC administration was not associated with any evidence of ectopic bone formation, nerve root entrapment, or neck swelling, as has been reported with recombinant BMPs.

Collectively, the preclinical and phase 2 clinical trials designed to evaluate the safety and efficacy of MPCs for spinal fusion at centres in the USA and Australia have shown that these cells are as effective as autograft in promoting robust fusion. Moreover, the amount of blood loss and operative time was reduced in the patients administered MPCs compared with autograft which is particularly advantageous to both the patient and the healthcare systems. These phase 2 trials will be used as templates for large, multicentre phase 3 clinical trials to be undertaken within the next 12 months.

Concluding remarks
Mesoblast’s patented MPC platform technology was specifically developed to create new biologic treatments based on well-characterized populations of cells and mechanisms of action. This has enabled Mesoblast to develop innovative products to address major unmet clinical needs of a variety of important medical problems including degenerative diseases of the spine, congestive heart failure, end-organ complications of type 2 diabetes, and disorders associated with both local and...
systemic immunological and inflammatory dysfunction. The progress achieved to date in identifying the safety and level of efficacy of MPCs in these diseases is reflected in the status of clinical development summarized in Figure 4. With respect to restoring the integrity of degenerate intervertebral discs and improving the outcomes of spinal fusion surgery, we anticipate that in the not-too-distant future MPC-based therapies for these intrinsigent spinal disorders will become available clinically.

References