Stem cell therapy brings new life to musculoskeletal regeneration

Researchers Dr Khay-Yong Saw, Dr Caroline Jee, Ms Amal Dawam, and Ms Alisha Ramlan from the Kuala Lumpur Sports Medicine Centre, Malaysia, and Dr Adam Anz, Andrews Institute, Florida, USA, recently showed how stem cell therapy can be used as a pioneering treatment in articular regeneration of the knee. There is potential to apply this technology to other musculoskeletal damage where there is currently an unmet clinical need, including for patients with damaged articular cartilage, soft tissue, and bone. Now, in a series of case studies, the researchers show exactly how this innovative technology can power musculoskeletal regeneration, from cartilage and soft-tissue repair to the regrowth of heavily damaged bone, in less than a year.

The musculoskeletal system is vital; it protects critical organs, allows movement, and supports the body. However, contrary to its name, it doesn’t only consist of muscles and bones. Articular cartilage, as well as tendons and ligaments, are necessary for pain-free and smooth movement in joints such as knees, ankles, and hips. Articular cartilage forms a smooth and lubricated surface where bones meet. Fibrous connective tissue in the form of tendons and ligaments also play an important role, connecting muscle to bone, or bone to bone, respectively. Yet as with any complex system, the failing of just one component can have long-lasting and deeply felt effects. One example is damage of articular cartilage, either through injury or general wear and tear. In the knee, large cartilage defects can cause pain, swelling, and, in severe cases – loss of mobility. Traditional treatments have limitations. To close the gap on this unmet clinical need, a collaborative team including Dr Khay-Yong Saw, Dr Caroline Jee, Ms Amal Dawam, and Ms Alisha Ramlan from the Kuala Lumpur Sports Medicine Centre, Malaysia, and Dr Adam Anz, Andrews Institute, Florida, USA, demonstrated how stem cell therapy using peripheral blood stem cells (PBSC) can be used to regenerate articular cartilage in the knees, with safe and effective outcomes. So what exactly are PBSC and what is the potential of this innovative technology to treat patients with wide-ranging musculoskeletal damage?

REGENERATIVE POTENTIAL

PBSC are a type of stem cell – a basic and un specialised cell with the potential to develop (or differentiate) into other types of cells, such as bone and cartilage. PBSC have been shown to have potential to give rise to mesenchymal stem cells, which are especially relevant for musculoskeletal regeneration as they are already primed to differentiate into cartilage cells (chondrocytes) and bone cells (osteoblasts). Their regenerative potential, combined with the ability to readily harvest and process them, make PBSC an excellent candidate to aid musculoskeletal regeneration. What’s more, PBSC can be harvested in a large quantity in a single procedure from the same patient over several years, enabling repeat treatments many months after the initial therapy. Saw explains, “We believe that the pathway to repair and regeneration of the musculoskeletal system requires three key principles: Firstly, a fresh injury is created at the damaged site, using subchondral drilling or needling (Figure 1c). PBSC are then injected into the damaged site at repeated intervals, and again after several months, if needed. Finally, functional stimulation is applied to the affected joint. The potential of this innovative technology continues to be harnessed by Saw and collaborators to aid cartilage regeneration, ligament repair, and even bone regeneration following severe open fracture. In doing so, the researchers can address an unmet clinical need for patients with such conditions. ’With over 980 cases in the last 13 years, we have shown that PBSC can be used safely and effectively for the repair and regeneration of the major components of the musculoskeletal system,’ says Saw. Following years of clinical experience and a recent randomised controlled trial in patients with knee cartilage defects, three case studies illustrate the success and broad application of this technology.

FROM KNEE TO ANKLE

Similar to patients with large cartilage knee defects, patients with end-stage ankle arthritis suffer from severe pain, as well as a loss of function and mobility. This is caused by the progressive attrition of the joint’s articular cartilage and can ultimately lead to bone-on-bone grinding at the surface of the joint. Unsurprisingly, this has a severe impact on normal activities. However, current treatment options for patients with end-stage ankle arthritis are limited and not without complications. Total ankle replacement or fusion of the ankle joint (arthroscopic ankle arthrodesis or open ankle arthrodesis) can provide some respite, but around a quarter of patients experience complications and one fifth require further surgery. For younger patients in particular, these treatments can be deemed as sub-optimal given the patients’ longer life expectancy and expectation of a physically active life.

With better treatment options clearly needed, the researchers sought to apply their pioneering articular regeneration technology to patients younger than 60. In one example, a 58-year-old man suffered from advanced ankle arthritis precipitated by a motorcycle accident, resulting in 30 years of ankle pain (Figure 1). He initially underwent keyhole surgery to inspect and drill into the ankle joint to stimulate the bone marrow. PBSC were then harvested from the patient and injected into the joint alongside hyaluronic acid (HA), a natural fluid that acts as a joint lubricant. The patient then received four injections of PBSC and HA spaced a week apart as well as physiotherapy and joint mobilisation exercises over 12 months. These PBSC/HA injections were then given over the course of three weeks at 6-, 12-, 18-, and 24-months post-surgery.

The patient reported appreciable improvement, without adverse post-operative effects. Magnetic resonance imaging (MRI) scans clearly showed cartilage regeneration on both articular surfaces two years after the operation.

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Healing the Heel

Using a similar approach, Saw and colleagues addressed soft tissue damage in patients with chronic Achilles tendinopathy (CAT). Patients with CAT experience prolonged pain and even disability due to injury to the tendon that attaches the muscle in the lower leg to the heel bone.

In one example, a man aged 59 years underwent surgery to remove calcified loose bodies and a bony growth on the heel bone (Figure 2). During surgery, multiple needles were inserted into his inflamed Achilles tendon and HA mixed with PBSCs – harvested prior to surgery – were injected into the tendon. Four further identical injections were given at weekly intervals while the patient was isolated. Physiotherapy, electrical nerve stimulation, and joint mobilisation exercises followed directly after surgery. The patient undertook muscle strengthening exercises and stationary bike cycling after six weeks, once the ankles could bear full weight again. Repeat injections of PBSC and HA were also given three and six months after surgery.

Follow-up MRI scans showed regeneration of the tendon and six years after the treatment the patient was scored as asymptomatic. Jee explains, ‘we have shown that autologous PBSC therapy is a safe and effective approach for the repair and regeneration of CAT.

Bone Regeneration

Perhaps the most staggering example of musculoskeletal regeneration using PBSC is in the case of bone regeneration in a 16-year-old Grand Prix motocross rider (Figure 3). Following a high-speed collision, the middle third of the boy’s right tibia (shinbone) was severely fractured by damage from an occurring bike, resulting in fragmented bone as well as severe soft tissue damage. To treat the patient, bone fragments, foreign matter, and dead tissue were surgically removed and a brace (Ilizarov frame) was fixed to the leg to help lengthen the tibia bone via distraction osteogenesis or bone growth. Next, PBSC were harvested from the patient and injected into the near and far sites of the fracture. Unfortunately, the near site of the fracture became infected with an antibiotic-resistant infection which meant that bone lengthening could only be performed at the far end of the fracture. Five months of progressive bone lengthening followed until the ends of the bone were prepared for final healing. This involved drilling into the ends of the bone and injecting PBSC. The patient maintained the Ilizarov frame for a further five months, throughout which he underwent a physiotherapy regime, ultrasound, and soft tissue electrical stimulation, as well as joint strengthening and mobilisation exercises. Near-normal nerve activity was recorded 12 months after the injury. At this point, an additional procedure was needed to correct a deformity of the foot and ankle which had develop two months into the bone-lengthening procedure. However, just 15 months after his original injury, the patient resumed professional motocrossing.

During the ten months that the patient was supported by the Ilizarove frame, 1.3cm of bone was regenerated (Figure 4), resulting in a bone healing index (BHI) of 23 days per centimeters. This BHI is favorable compared with previous case studies that report longer BHI (52 days per centimeters), and highlights the effective regeneration seen with PBSC treatment. Saw and colleagues suggest that PBSC perform two vital roles during bone growth. Firstly, that the PBSC Paroxalvides differentiate into cells required for bone growth. Secondly, that they release factors that encourage mesenchymal stem cells from the bone marrow to move to the fracture site to aid repair of the musculoskeletal tissues.

PUSHING THE FRONTIERS

These case studies highlight the enormous potential of stem cell therapy for the safe and effective regeneration of musculoskeletal tissues. Patients with severe damage to articular cartilage, soft tissue, and bone have already hugely benefited from this regenerative technique. Using this innovative approach, it is becoming apparent that surgeons can push the frontier of medicine for the benefit of patients and bridge the gap for unmet clinical needs within orthopaedics.

References


Personal Response

Do you expect bone regeneration treatment with PBSC to become commonplace within the next decade?

We surely hope so! There are many cases of bone deformity, either due to accident or natural causes. There is currently no ideal treatment for these cases. When PBSC treatment for bone regeneration is commercialised and becomes widely available, these complex cases can be offered an alternative solution. This will lead to a significant improvement in the quality of life for many people.

How else do you foresee PBSC treatment being used?

PBSC treatment is not just limited to musculoskeletal applications. Based on in vitro (laboratory) studies, PBSC have been shown to yield cells from other tissue systems, given the right conditions. We believe that PBSC have regenerative potential that can be harnessed for the repair and regeneration of tissues outside the musculoskeletal system. We believe that there are applications for cardiovascular regeneration, skin repair, and also wound-healing enhancement.