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Promising data for CelGro® collagen rope for Anterior Cruciate Ligament reconstruction

- **Pre-clinical study data in rabbits indicate that a novel CelGro® collagen 'rope' is a viable alternative to conventional autologous tendon grafts for Anterior Cruciate Ligament (ACL) reconstruction**
- **CelGro® collagen rope promoted ligamentisation and exhibited tissue architecture that mimics native ACL**
- **CelGro® collagen rope integrated with the host bone tunnel and was biomechanically comparable to hamstring tendon autograft**
- **Results position CelGro® collagen rope as the potential first off-the-shelf biological device for ACL reconstruction**
- **In light of these results, Orthocell plans to advance development of this technology and will commence a larger animal study followed by first-in-human trials**

Perth, Australia; 15 September 2021: Regenerative medicine company Orthocell Limited (ASX:OCC, "Orthocell" or the "Company") is pleased to announce completion of its pre-clinical Anterior Cruciate Ligament (ACL) reconstruction study, which indicated that a novel CelGro® collagen 'rope' has potential to be the first off-the-shelf biological device capable of improving ACL reconstruction outcomes.

The pre-clinical study was led by Orthocell Chief Scientific Officer, Professor Ming-Hao Zheng, in conjunction with the University of Western Australia. Professor Zheng's team will present the findings at the 26th Australian and New Zealand Orthopaedic Research Society Annual Conference on 6 October 2021.

Orthocell Managing Director Paul Anderson said: *"We are extremely excited by the potential of this new application for the CelGro® platform. There are currently no biological off-the-shelf solutions that mimic native ligament to enable the optimal repair of ACL injuries and synthetic alternatives have proven to be disastrous for patients. An "off-the-shelf" biological device that augments ACL reconstruction and is biologically compatible is highly desired by the orthopaedic industry and Orthocell is ideally placed to deliver the CelGro® collagen rope in this rapidly growing and lucrative market."*

The study was designed to show that the CelGro® collagen rope was equal to or better than the gold-standard autograft – the patient's own tendon (usually hamstring) – for ACL reconstruction. Harvesting of tendon autografts is associated with significant pain at the donor site and weakens the donor tendon. In the study, 30 rabbits received CelGro® collagen rope and another 30 rabbits received hamstring tendon autografts in a standard model of ACL reconstruction. The performance of CelGro® collagen rope was compared to hamstring tendon autograft at 6, 12, 18, and 26-weeks post-ACL reconstruction, evaluated by histology, microCT and biomechanical testing.

The study provides encouraging pre-clinical evidence that CelGro® collagen rope is a potentially superior "off-the-shelf" alternative to current tendon autograft options in ACL reconstruction procedures. The data indicated CelGro® collagen rope can replace tendon autografts for ACL reconstruction. In particular, at 26-weeks post ACL reconstruction, the CelGro® collagen rope:

1. **Promoted ligamentisation** of the collagen rope into ligament-like tissue (Figure 1A);
2. **Exhibited comparable tissue architecture** to hamstring tendon autograft and, importantly, closely mimicked that of native ACL (Figure 1B);
3. **Promoted integration of the ligament into bone in the same fashion as normal ACL** (Figure 2); and
4. **Exhibited comparable biomechanical properties to human hamstring tendon grafts** (Figure 3).

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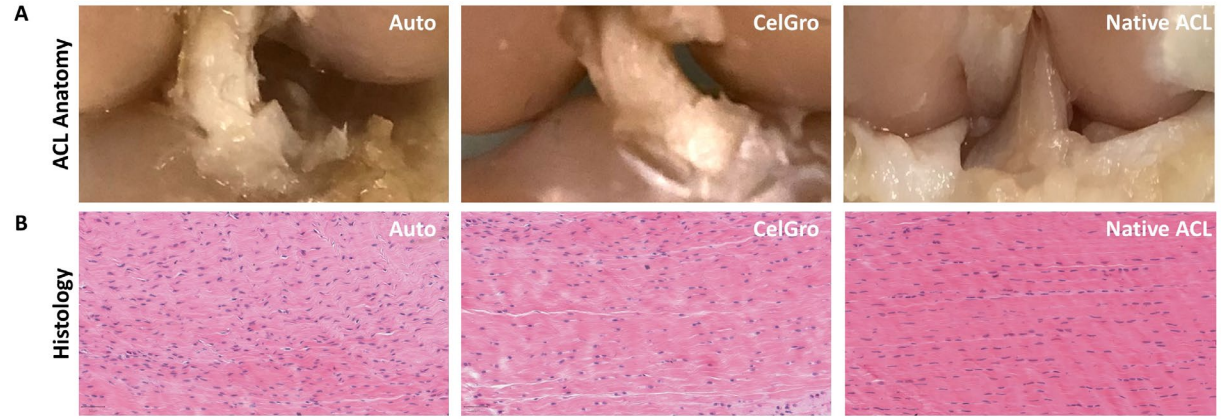
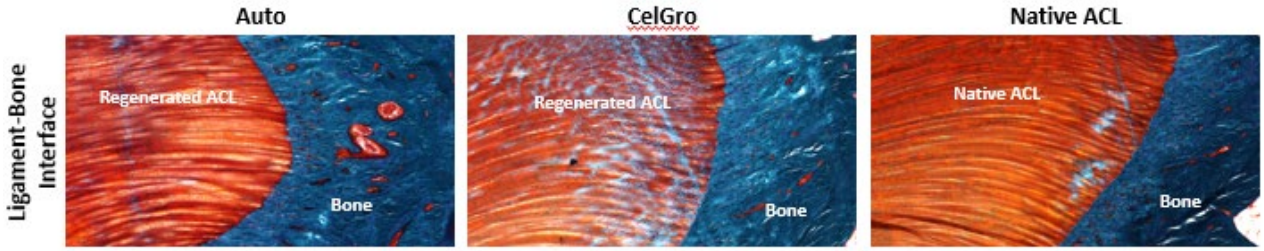
Figure 1: Remodeling and ligamentisation of collagen rope into ligament-like tissue



(A) CelGro® collagen rope supported host cell infiltration and subsequent remodelling of the collagen rope into ligament-like tissue (ligamentisation) with structural and biological properties approaching that of native ACL at 26 weeks post-surgery.

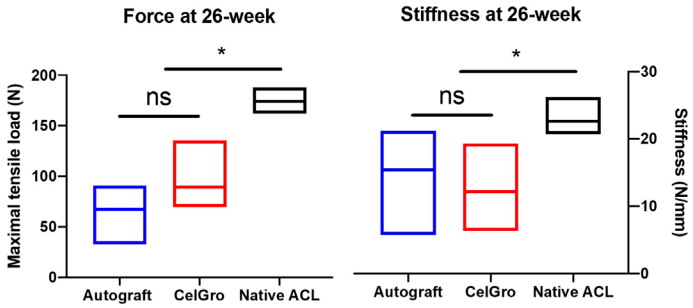
(B) Histological analysis showed cellular and collagen matrix alignment comparable to hamstring tendon autograft (Auto) and mimics native ACL.

Figure 2: Regeneration of ligament-bone interface and new bone formation



CelGro® collagen rope regenerated the ligament-bone interface predominantly composed of fibrocartilage similar to autograft (Auto) and native ACL.

Figure 3: Collagen rope was biomechanically comparable to hamstring autograft at 26-weeks



	Maximal Tensile Load	Stiffness
Autograft	67.2 ± 25.6 N	15.4 ± 6.9 N/mm
CelGro	89.2 ± 31.4 N	12.1 ± 6.2 N/mm
Native ACL	174.1 ± 11.8 N	22.6 ± 2.46 N/mm

Biomechanical testing of the CelGro® collagen rope showed a maximal tensile load of 89.2±31.4 N and stiffness of 12.1±6.2 N/mm, comparable to autograft at 26 weeks. Further improvement to return the ACL to native tensile load and stiffness is expected over time.

ACL injuries – growing health economic burden

The ACL is one of the key ligaments providing stability and mechanical support to the knee joint. A ruptured ACL is a common injury suffered by physically active individuals, usually requiring surgical intervention, with a long period of rehabilitation before returning to pre-injury activities. Approximately 15,000 ACL knee reconstructions are done annually in Australia and up to 200,000 per year in the United States, with up to a quarter of these patients needing additional or revision surgery [1]. The lifetime burden of ACL tears in the US alone is estimated to be more than $7.5 billion annually when treated with an ACL reconstruction and $17.5 billion when treated with rehabilitation [2].

Shortcomings of conventional treatment options

Current surgical ACL repair involves using either the patient's own tendon (hamstring or patellar) as an autograft to reconstruct the ACL or synthetic LARS ("Ligament Augmentation and Reconstruction System"). The limitations of current ACL repair options include:

- Tendon autografts - harvesting the patient's tendon significantly extends surgery time, introduces donor site pain, morbidity and potentially nerve damage. Tendon harvest can result in donor-site tendon tears and/or rupture during rehabilitation, prolonging recovery time. There is also a limited amount of healthy graft tissue available, which may compromise the repair or inhibit the opportunity for subsequent repairs.
- Synthetic LARS ligament - lacks clinically acceptable long-term outcomes due to poor durability, potential for foreign-body response from the generation of degradation products as the graft breaks down, mechanical mismatch (completely different tensile load and stiffness characteristics) and the very high incidence of fatigue failure. Failure rates of LARS ligaments have been reported in as many as 1 in 3 patients which not only causes further injury and requires further surgery, but distributes small plastic fragments throughout the body as the LARS ligament shreds[3].

The CelGro® collagen rope solution

To address the problems with current graft options available for ACL reconstruction, Orthocell has developed CelGro® collagen rope, fabricated from braided collagen fibres, as an alternative biological augment for ACL reconstruction (Figure 4).

CelGro® collagen rope has the potential to significantly improve treatment efficiency and effectiveness by simplifying repair techniques, reducing surgery time and mitigating the risks associated with autograft donor site morbidity. CelGro® collagen rope could also assist in returning patients to sport and normal activities sooner. CelGro® collagen rope provides a novel off-the-shelf solution to a common problem in a multi-billion dollar global market.

Figure 4: Stylised CelGro® collagen rope

[1] American Academy of Orthopaedic Surgeons "Promising ACL surgery outcomes of aging athletes" 8/21/2018
[2] Societal and Economic Impact of Anterior Cruciate Ligament Tears (2013) 1715-1759 Journal of Bone and Joint Surgery Oct 2; 95(19) Mather RC et al
[3] Histological analysis of ACL reconstruction failures due to synthetic-ACL (LARS) ruptures (2020) 136-145 Acta Biomed May 30; 91(4-S) Di Benedetto P et al

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Next Steps

Before human trials can begin, the Company plans to replicate the performance of CelGro® collagen rope for ACL reconstruction in a larger animal model such as sheep, which exhibit knee joint structure and dynamics that more closely mimics the human knee joint.

About CelGro®

Orthocell has secured 11 patent families covering its portfolio of breakthrough regenerative medicine products, comprising 110 separate patents/applications, of which 80 are granted. CelGro® is a customisable collagen medical device manufactured by the Company at its quality controlled (GMP) facility in WA, using the Company's proprietary SMRT™ tissue engineering process. The Company has validated that CelGro® has numerous competitive advantages over existing synthetic and biologic tissue repair devices, particularly in the areas of cell biocompatibility, tensile strength and the promotion of high-quality tissue repair. Use of CelGro® has shown to result in high quality outcomes in the repair of bone defects in the jaw, assist in the re-joining of severed or damaged peripheral nerves and augment repair of the rotator cuff tendon within the shoulder.

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About Orthocell Limited

Orthocell is a regenerative medicine company focused on regenerating mobility for patients by developing products for the repair of a variety of soft tissue injuries. Orthocell's portfolio of products include CelGro®, a collagen medical device which facilitates tissue repair and healing in a variety of dental, nerve and orthopaedic, reconstructive applications. Orthocell recently received FDA 510(k) approval for Striate+, the first application of the CelGro® platform for dental GBR applications. Striate+ is also approved in Australia (ARTG) and Europe (CE Mark) for the same. The Company's other major products are the cell therapies Autologous Tenocyte Implantation (Ortho-ATI®) and Autologous Chondrocyte Implantation (Ortho-ACI®), which aim to regenerate damaged tendon and cartilage tissue respectively. Orthocell is moving forward with Ortho-ATI® clinical studies designed to assist in the US (FDA) approval process and has completed its pre-IND meetings with the FDA.

For more information on Orthocell, please visit www.orthocell.com.au or follow us on Twitter **@Orthocellltd** and LinkedIn www.linkedin.com/company/orthocell-ltd

Forward Looking Statement

Any statements in this press release about future expectations, plans and prospects for the Company, the Company's strategy, future operations, and other statements containing the words "anticipate", "believe", "estimate", "expect", "intend", "may", "plan", "predict", "project", "target", "potential", "will", "would", "could", "should", "continue", and similar expressions, constitute forward-looking statements. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: the Company's ability to successfully develop its product candidates and timely complete its planned clinical programs and the Company's ability to obtain marketing approvals for is product candidates. In addition, the forward-looking statements included in this press release represent the Company's views as of the date hereof. The Company anticipates that subsequent events and developments will cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date hereof.