



NDF RESEARCH

Providing independent research coverage of ASX-listed Life Science companies

Orthocell (ASX: OCC)

Initiation of Coverage – Tuesday 20 March 2018

Growing with CelGro®

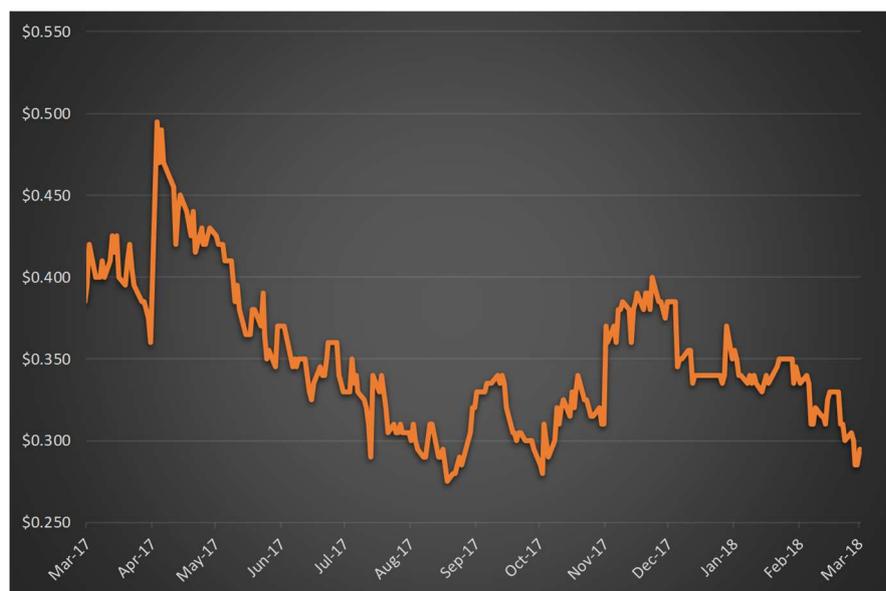
Orthocell is an emerging player in the multi-billion-dollar field of regenerative medicine. Its unique foundation products (Ortho-ATI® for tendon repair and Ortho-ACI® for cartilage repair) provide early commercial opportunities with large addressable markets. But, the big payday may occur this financial year with European approval (CE Mark) achieved for CelGro® and US approval to follow. CelGro® is the company's collagen scaffold that facilitates rapid tissue regrowth across a range of indications. We regard CelGro® as a potential breakthrough product due to its mechanical strength, natural collagen structure and versatility. CelGro® could also enjoy rapid initial revenue in dental and orthopaedic markets - potentially accelerated by commercial partnerships with large healthcare companies. CelGro®'s potential market is well in excess of US\$2bn. Orthocell has further related and ground-breaking opportunities including its 'Cell Factory' project to harness stem cell growth factors. Our target price for the company is A\$1.75 per share (midpoint of base case: A\$0.89 and optimistic case: A\$2.63).

Rating
Buy

Risk
Speculative

Current price
\$0.29

Target price
\$1.75



Stock details

Daily Turnover: ~A\$36,000
Market Cap: A\$32.4m
Shares Issued: 110.0m
52-Week High: \$0.26
52-Week Low: \$0.49

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Please note: This report has been commissioned by Orthocell and NDF Research has received payment for its preparation. Please refer below for risks related to Orthocell as well our General Advice Warning, disclaimer and full disclosures. Also, please be aware that the investment opinion in this report is current as at the date of publication but that the circumstances of the company may change over time, which may in turn affect our investment opinion.



About NDF Research

NDF is an independent equity research firm based in Sydney, Australia. It focuses on Life Science companies that are publicly traded on the Australian Securities Exchange (ASX), most of which are headquartered in Australia and New Zealand. ASX hosts one of the world's premier equity markets for biotech and medical device companies, and is home to world-beating companies such as CSL and ResMed and emerging pioneers such as Mesoblast and Impedimed.

NDF's Founder and Senior Analyst, Stuart Roberts, has been involved in Life Sciences since 2002 as a sell-side analyst as well as an executive of two ASX-listed immuno-oncology drug developers.

NDF believes that ASX-listed companies have been largely overlooked in the global Life Sciences boom that began in late 2008, partly because of insufficient quality research. NDF's goal is to provide such research, and introduce investors around the world to potential future billion-dollar companies from 'Down Under'.

To learn more about the Life Sciences sector on the ASX and our firm, please visit ndfresearch.com.



Ferry at the end of a rainbow on Sydney Harbour, August 2014



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Introducing Orthocell, ASX: OCC

Orthocell is a commercial-stage regenerative medicine company with a focus on cellular therapies and collagen medical devices for the repair of soft tissue injuries and musculoskeletal disorders.

Orthocell's portfolio of products include the TGA-licensed cell therapies Autologous Tenocyte Implantation (Ortho-ATI®) and Autologous Chondrocyte Implantation (Ortho-ACI®), which aim to regenerate damaged tendon and cartilage tissue. Orthocell's market leading tendon regeneration product is attracting interest from global health care companies. For example, Orthocell is recruiting patients for a clinical trial of Ortho-ATI®. The objective of this study is to assess the safety and effectiveness of Ortho-ATI® compared to corticosteroid injection in the treatment of rotator cuff tendinopathy and tear. The trial is being undertaken in collaboration with DePuy Synthes Products, Inc., part of the Johnson & Johnson Medical Device Companies.

The company's other major product is CelGro®, a collagen medical device which facilitates tissue repair and healing in a variety of orthopaedic, reconstructive and surgical applications. Orthocell recently received European regulatory approval (CE Mark) for CelGro®. The collagen medical device can now be marketed and sold within the European Union for a range of dental bone and soft tissue regeneration procedures and is being readied for first approval in the US.

At the early research stage are the 'Lab-Grown Tendon' project, where human tendons grown in a bioreactor may be used in tendon repair; and the 'Cell Factories' project in which growth factors from stem cells are used for allogeneic therapies.

What is regenerative medicine and why is it significant in today's healthcare setting? Regenerative medicine is the use of drugs and medical devices to harness the power of stem cells and related growth factors for repairing damaged tissues and organs. This is regarded as significant because up until recently there was no way for physicians to easily repair damaged soft tissue and bone, such as hearts, joints and spinal cords. Regenerative medicine promises to be the tool to make this possible. For musculoskeletal conditions in particular, the potential is for the first ever disease-modifying therapies. Where, for example, hyaluronic acid and steroids simply provide some pain relief, tissue repair using scaffolds and/or stem cells can repair the damaged tissue responsible for that pain. By being minimally invasive, and focused on the pathology not just the symptoms, such therapies can be highly cost-effective. For example, 12% of all osteoarthritis is due to traumatic joint injury¹. Proper joint repair will significantly lower the incidence of osteoarthritis in these patients.

How is Orthocell a serious regenerative medicine player? One of Orthocell's most notable achievements in the regenerative medicine field to date is the development of Ortho-ATI®, the first autologous therapy in the world for the treatment of tendon damage. Orthocell have demonstrated that Ortho-ATI® has significant clinical and commercial potential. On 9 November 2017 the company announced regulatory approval (CE Mark) for the marketing and distribution of CelGro® in various dental bone and soft tissue regeneration procedures in the EU.

**ORTHOCELL
RECENTLY
RECEIVED CE
MARK FOR
CELGRO®**

¹ See Int J Clin Exp Med. 2011; 4(4): 285-298.



This is the first product of a diverse suite of collagen medical devices to be commercialised from Orthocell's CelGro® platform. CelGro® is arguably one of the best tissue repair scaffolds yet invented. Further down the track, Orthocell could potentially be the first company to develop 'cell factories' for allogeneic tissue repair.

Why is CelGro® a potential 'breakthrough' product for Orthocell? Often in tissue repair, biocompatible scaffolds are used in order to allow new tissue to grow into place. CelGro®, which consists of high-purity natural collagen, is unique in that it is completely acellular, has ideal mechanical properties and the right 'integration profile' to hasten in-growth of tissue at the site of the scaffold. It also has a tunable 'degradation profile' once the new tissue is in place. Orthocell argues that the result is high-quality tissue repair in a range of applications, with numerous clinical studies currently ongoing expected to verify this.

Why is the CE Mark so important? The CE Mark allows CelGro® to be sold within EU countries and provides a strong foundation for additional dental bone and soft tissue regeneration regulatory applications in other key markets such as the US. Orthocell has a clear commercialisation strategy in place to drive initial sales of CelGro® and the company is in discussion with strategic commercial partners for product distribution in Europe and other key regions. Orthocell is also currently in discussions with selected Key Opinion Leaders in the dental and bone regeneration fields, who play an important role in driving broader market adoption. The CE Mark also validates the potential of the entire technology platform by endorsing CelGro®'s clinical performance and quality manufacturing, and by enabling other potential future indications, including peripheral nerve repair and hernia repair.

What are autologous and allogeneic therapies, and which is more important in the regenerative medicine field? In autologous therapy, a patient's own tissue is engineered and given back to them. Autologous therapies tend to be expensive because of the need to individually manufacture each dose. By contrast allogeneic therapies, where recipients receive tissue or stem cells from unrelated donors, will be lower-cost because they can be marketed 'off-the-shelf'. However allogeneic therapies are, at this stage, not suitable for every indication in regenerative medicine. In tendon repair, for example, allogeneic cell sources are very difficult to achieve where typically Mesenchymal Stem Cells will not engraft into the tendon and will only act as a stimulus². Orthocell's autologous therapies are cost-effective because they are 'fit for purpose' and work better than current commercially-available alternatives.

If Orthocell is so good, why is it currently capitalised at only US\$24.9m (A\$31.9m)? We believe that most publicly traded biotech and medical device companies in the regenerative medicine field are undervalued because of historical debates over the ethical use of stem cells in medicine and because of the fact that most stem cell therapies are still in clinical development. We believe the recent encouraging article in the *New England Journal of Medicine* from FDA commissioner Scott Gottlieb and his colleague Peter Marks, director of the FDA's Center for Biologics Evaluation and Research, on stem cell regulation³ will help change public perceptions on the sector. Meantime, for Orthocell, its second breakthrough product has achieved regulatory approval in Europe and its tissue-engineering processes are non-controversial. The recent achievement of the CE Mark approval has derisked CelGro®. We expect further regulatory approvals of CelGro® in other jurisdictions (such as the US) and across

² See, for example, *J Shoulder Elbow Surg.* 2012 Feb;21(2):278-94.

³ *N Engl J Med.* 2018 Mar 8;378(10):954-959.



other indications (such as nerve, tendon and ligament) to provide key catalysts for the stock, by validating the Orthocell platform and providing more understanding of its many big-market applications.

Ten reasons to look at Orthocell

- 1) **Regenerative medicine is becoming big business.** With International health authorities focusing on accelerating the introduction of regenerative medicine through accommodating policies; with sophisticated stem cell products performing well in late stage clinical trials; and with products like CelGro® gaining their first regulatory approval, we believe we are in the early stages of a boom in regenerative medicine.
- 2) **The market for repairing damaged tissue is significant.** Injuries such as tennis elbow and ACL rupture are commonplace not just in sport⁴ but in life and work. Musculoskeletal conditions accounted for approximately 8% of the global disease burden in 2010⁵ so there are multi-billion-dollar opportunities for the best, most cost-effective therapies. The acquisition of LifeCell by Allergan in February 2017 for US\$2.9bn, and Rotation Medical by Smith & Nephew for US\$125m upfront in October 2017, illustrates the upside for companies that are successful in this field.
- 3) **Orthocell's Ortho-ATI® is a market-leading product,** as the only regenerative-medicine-based product currently available for the repair of damaged tendons.
- 4) **Orthocell has received its first regulatory approval for CelGro®, with other major markets to follow.** CelGro® is a platform technology with multiple applications including bone, tendon, nerve and cartilage repair. The product has performed well in numerous clinical studies since 2015.
- 5) **The upside for CelGro® in the dental field is particularly significant,** with advances in dental implant technology driving the need for membranes that can work with bone graft substitutes.
- 6) **Orthocell's portfolio of regenerative medicine technologies are attracting interest from global health care companies.** For example, Orthocell is recruiting patients for a clinical trial of Ortho-ATI®. The objective of this study is to assess the safety and effectiveness of Autologous Tenocyte Injection (Ortho-ATI®) compared to corticosteroid injection in the treatment of rotator cuff tendinopathy and tear. The trial is being undertaken in collaboration with DePuy Synthes Products, Inc., part of the Johnson & Johnson Medical Device Companies.
- 7) **Ortho-ACI® has been a dependable foundation product,** with considerable advantages over earlier chondrocyte injection therapies. Ortho-ACI® has been marketed by Orthocell since 2010, with over 480 patients treated to date.
- 8) **Orthocell is working on allogeneic products.** The company's 'Lab-Grown Tendon' and 'Cell Factories' projects have the potential to become the Next Big Things in tissue engineering.

**WE BELIEVE
WE ARE IN THE
EARLY STAGES
OF A BOOM IN
REGENERATIVE
MEDICINE**

⁴ Around 5% of the US population is physically active every day of the week – source: Sports and Fitness Industry Association, 2013 Sports, Fitness and Leisure Activities Topline Participation Report.

⁵ See Ann Rheum Dis. 2014 Aug;73(8):1462-9. Epub 2014 Mar 3. This estimate covers all musculoskeletal disorders as estimated by the Global Burden of Disease 2010 study investigators, but removing osteoarthritis, Rheumatoid Arthritis, gout, low back pain and neck pain.



- 9) **Orthocell has a solid management team.** Founder and CEO Paul Anderson has built the company over ten years into a regenerative medicine contender with autologous products on the market and allogeneic projects in the pipeline. We are backing Anderson and the executive team as they have skills and previous success in building revenue-stage Life Sciences companies.
- 10) **Orthocell is undervalued, on our numbers.** We value Orthocell at A\$0.89 per share (base case) and A\$2.63 (optimistic case) using a probability-weighted DCF-based valuation of the lead products. Our A\$1.75 per share price target sits at about the midpoint of our valuation range.

Ortho-ATI® – A world-first tendon repair product

Tendon repair is an area of unmet medical need. Tendons are the fibrous connective tissues in the body, mostly made from collagen, which attach muscles to bone and help those bones to move⁶. Tendons are easily injured because they bear much of the stress when the muscle contracts, and they are less vascularised than muscle, making them slower to heal when damaged. Consequently, tendon injury, called tendinopathy, is commonplace in advanced industrial countries. And yet, in spite of this, 'the ideal treatment for tendinopathy', as one reviewer recently put it, 'is still nebulous'⁷.

- **Tendinopathy is a large market opportunity.** There are no exact figures on the prevalence of all tendinopathies however it could be >6% of the adult population⁸.
- **Standard of care for tendinopathy is still being worked out.** Traditionally tendinopathy has been treated in the first instance with anti-inflammatories such as corticosteroids, with only short-term benefit⁹, and if the injury is slow to heal, with surgery¹⁰. Two more recent trends have been 'needling' and 'platelet-rich plasma' (PRP), where a common aim in each case is to harness growth factors that will prompt tissue regeneration. In needling, a special needle is thrust into the tendon to make it bleed and bring about the influx of growth factors¹¹. PRP takes advantage of the fact that the platelet-derived growth factors in such a blood product can do likewise¹², although there is a paucity of controlled, randomised studies on duration of effect¹³.

**6% OF THE
ADULT
POPULATION
MAY HAVE
TENDINOPATHY**

Orthocell clinical data suggests its Ortho-ATI® is a superior tendon repair product. Ortho-ATI®, initially developed in 2006¹⁴, is Orthocell's Autologous Tenocyte Implantation treatment for tendinopathy. In an Ortho-ATI® procedure, a sample of healthy tendon tissue is biopsied from the patient (usually from the patellar tendon near the knee), with the tenocytes from those cells expanded in Orthocell's laboratory in the Australian city of Perth over a 4-to-6 week period, after which they are returned to the patient. The product grew out of an insight

⁶ Tendons also connect muscles to other structures such as the eyeballs.

⁷ Ortop Traumatol Rehabil. 2013 Mar-Apr;15(2):109-16.

⁸ See, for example, J Rheumatol. 2007 May;34(5):1076-82. Epub 2007 Mar 1.

⁹ Clin J Sport Med. 2011 Nov;21(6):540-1.

¹⁰ Clin Orthop Relat Res. 2008 Jul;466(7):1539-54. Epub 2008 Apr 30.

¹¹ Phys Sportsmed. 2015 Feb;43(1):80-6. Epub 2015 Jan 22.

¹² See, for example, Blood Transfus. 2014 Oct;12(4):533-40. Epub 2014 Jun 19.

¹³ J Stem Cells Regen Med. 2015 May 30;11(1):7-17.

¹⁴ See *Tenocyte cell culturing method*, WO/2007/106949, priority date 23 March 2006.



from Orthocell founder Professor Ming-Hao Zheng that tenocytes, the characteristic cells in tendons¹⁵, were slow growing but that phenotypically stable tenocytes could nonetheless be cultured in therapeutically relevant numbers and in a reasonable time-frame in a culture medium. Once these new tenocytes were in place they could pump out the right kind of collagen¹⁶ and other non-collagenous matrix proteins that would restore a cohesive tendon with normal structure and function. Orthocell's clinical data suggests Ortho-ATI[®] is a superior tendon repair approach to needling, PRP and other therapies because no other approach can put these important building blocks of tendons in place. This insight led to a global regenerative medicine breakthrough – in 2010 Ortho-ATI[®] became the first approved cell therapy for tendon repair in the world, and the clinical evidence behind Ortho-ATI[®] has grown considerably since then.

The data on Ortho-ATI[®] has been very good so far. Five main human studies have borne out the clinical effectiveness of Ortho-ATI[®] in tendinopathy to date¹⁷. An original clinical study in 2008 in tennis elbow established the product's early clinical effectiveness and durability, while an as-yet-unpublished study from 2015 in severely-affected tennis elbow patients showed that Orthocell's product could work after everything else had failed.

THERE HAVE BEEN FIVE SUCCESSFUL CLINICAL STUDIES OF ORTHO-ATI[®]

- **A Phase 1 study in Lateral Epicondylitis, 2008-2015.** This study, which commenced in 2008, tracked 17 patients in Perth with Lateral Epicondylitis after they received Ortho-ATI[®]¹⁸. Lateral Epicondylitis is commonly called 'tennis elbow'. Orthocell's tennis elbow patients, whose condition was over six months old at the time of treatment, registered a statistically significant ($p < 0.001$) reduction in pain scores (86% mean reduction over 12 months¹⁹), an improvement in grip strength (85% mean increase over 12 months²⁰), an improvement in overall elbow function (94% mean increase over 12 months²¹), and an improvement in the grade of tendinopathy, as measured by MRI. This data was published in the *American Journal of Sports Medicine* in September 2013²². The *American Journal of Sports Medicine* also published, in April 2015²³, long-term follow up data with average duration of 4.5 years showing that Ortho-ATI[®] was genuinely disease-modifying. This data, which first became available in August 2014, showed that, over time, the patients' grip strength continued to improve (from 85% over baseline at 12 months to 207% over baseline at 4.5 years) while the initial reduction in pain scores and improvement in elbow function were maintained (83% versus 86% and 87% versus 94% respectively)²⁴. The data set for this study was one of the longest assembled for a cellular therapy up to that time.

¹⁵ Even though most of the cells in tendons are fibroblasts, endothelial cells, synovial cells and chondrocytes.

¹⁶ In tendons, most collagen is type I. Ruptured Achilles tendons contain a significantly greater proportion of type III collagen - see *Am J Sports Med.* 2000 Jul-Aug;28(4):499-505.

¹⁷ One study which has yet to read out data is a double-blind, placebo controlled trial in Achilles tendinopathy which commenced in 2011 at Erasmus Medical Center in the Dutch city of Rotterdam (see NCT01343836 at www.clinicaltrials.gov). The study recruited 90 patients with Achilles tendon injuries who had failed a prescribed exercise regime. Half the patients received Ortho-ATI[®] and half received saline injections. The study had completed recruitment by December 2013. The primary endpoint of the trial was a reduction in the severity of Achilles tendinopathy, as measured by a questionnaire-based ratings scale called 'VISA-A' (Victorian Institute of Sports Assessment – Achilles). Data has been expected to read out in mid-2015 however we understand a suitable journal in which to publish is being sought. In America there are over 200,000 Achilles tendon sports injuries – see *Orthop J Sports Med.* 2014 Sep 18;2(9):2325967114549948. eCollection 2014 Sep.

¹⁸ The ANZCTR trial ID for this study is ACTRN12607000402448 – see www.anzctr.org.au.

¹⁹ Using Visual Analog Scale.

²⁰ Measured by how many kilograms worth of weight the patient can pick up.

²¹ QuickDASH.

²² See *Am J Sports Med.* 2013 Dec;41(12):2925-32. Epub 2013 Sep 25.

²³ *Am J Sports Med.* 2015 Jul;43(7):1775-83. Epub 2015 Apr 23.

²⁴ See the company's market release dated 25 August 2014 and headlined 'Clinical study shows long-term effectiveness of Orthocell's Ortho-ATI[®] for treatment-resistant tennis elbow' and the company's 2 September 2014 Investor Presentation. The data also showed a 64% improvement in UEFS at the 4.5 year mark.



- **Phase 1 study in gluteal tendinopathy, 2010-2017.** This study, which commenced in 2010, evaluated 12 patients with serious gluteal tendinopathy where the average symptom duration had been 33 months and where patients had failed all previous therapies²⁵. Damage to the gluteal tendons affects hip and thigh movement. Orthocell reported in 2014 that 8 of the 12 patients reported that they were 'satisfied' or 'highly satisfied' with the treatment after 12-months²⁶. In November 2014, the company disclosed two-year data from the 12 patients showing statistically significant reductions in pain scores (VAS), an improvement in hip function (Oxford Hip Score) and an improvement in quality of life (SF36 PCS)²⁷. In December 2016 Orthocell indicated that the average quality-of-life increase had been 148%²⁸. The data was finally published in the *Orthopaedic Journal of Sports Medicine* in February 2017²⁹. Gluteal tendinopathy may affect >23.5% of women and >8% of men over the age of 50³⁰.
- **Case study in rotator cuff injury, 2011-2013.** In 2011 Ming-Hao Zheng and his colleagues administered Ortho-ATI® to a 20-year-old elite gymnast with a rotator cuff tendon injury. Damage to these tendons impacts the ability of a person to rotate their shoulder, something vitally important to gymnasts. At the 12-month timepoint after receiving Ortho-ATI®, Zheng's gymnast was reporting substantial improvement of clinical symptoms and was back in competition. This favourable outcome was reported in the journal *BMJ Case Reports* in January 2013³¹.
- **Study in severely-affected Lateral Epicondylitis patients on Workers' Compensation, 2015.** Orthocell reported in October 2015 that Ortho-ATI® had proved effective in the treatment of 25 people with work-related Lateral Epicondylitis where the injury had inhibited their ability to work, where those patients had failed other modes of therapy, and where the symptoms had persisted for an average of 22 months. Ortho-ATI® was able to return 88% of these patients to work, most within 1-3 months, with a return to pre-injury productivity by a little over five months³². Orthocell has indicated that it intends to publish this retrospective data in a suitable journal.
- **Case study in rotator cuff injury, 2017.** In this case study an elite swimmer returned pain-free to full training, and international-level competition only four months after treatment³³. This favourable outcome was reported in the *Physical Therapy in Sport* journal in October 2017.
- **Study in Lateral Epicondylitis patients comparing Ortho-ATI® to conventional surgery – data to come.** Orthocell announced in July 2016 a study at The Avenue Hospital in Melbourne that will compare Ortho-ATI® with surgery in Lateral Epicondylitis, with 25 patients in each treatment arm³⁴. Recruitment to this study is expected to be completed in mid-2018.

**ORTHO-ATI®
HAS HELPED
INJURED
WORKERS
RECOVER
FASTER**

Collaboration with DePuy Synthes Products, Inc., part of the Johnson & Johnson Medical Device Companies.

Orthocell is recruiting patients for a clinical trial of Ortho-ATI®. The objective of this study is to assess the safety

²⁵ The ANZCTR trial ID for this study is ACTRN12612000383864 – see www.anzctr.org.au.

²⁶ Source: Orthocell May 2014 prospectus, page 26.

²⁷ See Orthocell's 24 November 2014 Annual General Meeting presentation.

²⁸ See Orthocell's December 2016 corporate presentation slide 15.

²⁹ *Orthop J Sports Med.* 2017 Feb 21;5(2):2325967116688866. eCollection 2017.

³⁰ *Arch Phys Med Rehabil.* 2007 Aug;88(8):988-92.

³¹ *BMJ Case Rep.* 2013 Jan 11;2013 (full text available for free online).

³² See Orthocell's 28 October 2015 market release headlined 'Ortho-ATI® tendon treatment positive in Workers' Compensation study'.

³³ *Phys Ther Sport.* 2018 Jan;29:19-25. Epub 2017 Oct 13.

³⁴ See Orthocell's 12 July 2016 market release headlined 'Orthocell receives ethics approval for pivotal Ortho-ATI® tendon study'. The ANZCTR trial ID for this study is ACTRN12616000458437 – see www.anzctr.org.au.



and effectiveness of Autologous Tenocyte Injection (Ortho-ATI®) compared to corticosteroid injection in the treatment of rotator cuff tendinopathy and tear. The trial is being undertaken in collaboration with DePuy Synthes Products, Inc., part of the Johnson & Johnson Medical Device Companies. The study recruited its first patient in September 2017. We expect, if the study is successful, this may roll over to become a pivotal study.

The two big indications – tennis elbow and rotator cuff injury. Possibly 2-3% of the adult population has rotator cuff tendinopathy³⁵ and around 1-2% each have Lateral Epicondylitis as well as a related condition called Medial Epicondylitis (commonly called 'golfer's elbow')³⁶. We argue below that tennis elbow and rotator cuff alone can create sizeable commercial opportunities for Orthocell and whoever chooses to partner with the company to take Ortho-ATI® forward.

Orthocell has optimised its manufacturing for Ortho-ATI® over the last seven years. Orthocell brought Ortho-ATI® onto the Australian market in 2010 via the then-prevailing local regulations that licensed manufacturers of human tissue rather than approved individual human tissue products³⁷. In Orthocell's case, the company set up an ISO-146441 compliant GMP manufacturing facility on the campus of Murdoch University in Perth's southern suburbs for which a license was granted in January 2010. In 2011, the Therapeutic Goods Administration (Australia's version of the FDA) changed the regulations so that individual biologicals had to be approved, but grandfathered products such as Ortho-ATI® so long as the manufacturers filed a design dossier³⁸, which Orthocell did in 2013. Orthocell is continuing with its application for the inclusion of Ortho-ATI® on the Australian Register of Therapeutic Goods (ARTG), the official list of the country's approved medical products, as a 'Class 3 biological'³⁹. We believe this transition has eased the path towards gaining FDA and CE Mark approvals for Ortho-ATI® given the heavy emphasis that drug and medical device regulators are now placing on GMP manufacturing as part of their overview of product safety in the regenerative medicine field⁴⁰.

Ortho-ATI® is starting to go global. Currently Ortho-ATI® is available only in Australia and New Zealand, and, since 2015, in Hong Kong⁴¹, but Orthocell now has big plans for the product in multiple new markets.

- **Australia/New Zealand, with the help of a contract sales force:** Locally, the patient numbers to date have been relatively small – around 450 over the last seven years⁴². That said, the Australian business has proved a valuable testbed. Orthocell charges A\$3,200 per injection for Ortho-ATI®, which it argues makes the product highly cost effective. Up until recently Orthocell itself handled marketing of Ortho-ATI® to radiologists, sports medicine specialists and physiotherapists in conjunction with select distributors. In October 2017 the company announced that a local medical device distributor called Surgical Specialties would handle distribution of Ortho-ATI® in the markets in which it is currently available, as well as the foundation Ortho-ACI® product we discuss below. We think this move is a good

**ORTHOCELL
HAS BIG
PLANS FOR
ORTHO-ATI®**

³⁵ See Am J Epidemiol. 2005 May 1;161(9):847-55 and BMC Musculoskelet Disord. 2010 Jul 20;11:165.

³⁶ Rheumatology (Oxford). 2012 Feb;51(2):305-10. Epub 2011 Oct 22.

³⁷ The product gained an early use among various Australian athletes including AFL players – see *Tendon relief hope in store* by Daniel Hoy, Herald Sun, 22 August 2011.

³⁸ Source: TGA, Australian Regulatory Guidelines for Biologicals, June 2011.

³⁹ Class 2 biologicals as per the TGA's classification criteria are minimally manipulated products while Class 3 and 4 are higher-risk, higher manipulation products - see Pathology. 2011 Oct;43(6):627-34.

⁴⁰ See Methods Mol Biol. 2015;1283:93-107.

⁴¹ See Orthocell's 9 February 2015 market release dated 9 February 2015 and headlined 'First patients in Hong Kong treated with Ortho-ATI® therapy'.

⁴² See Orthocell's October 2017 corporate presentation, slide 17. At the time of Orthocell's 2014 IPO the number of Ortho-ATI® implants was closer to 200 – see Orthocell's May 2014 prospectus, page 22. Orthocell announced in November 2017 that the 1,000th patient for Ortho-ATI® and Ortho-ACI® had been treated.



one since it allows better training of surgeons and treating physicians, and allows Orthocell to learn about distribution ahead of the global roll-out of CelGro®.

- **The US:** Orthocell flagged in December 2016⁴³ that it is preparing for a pre-IND meeting with the FDA ahead of a planned Phase 2 study in Lateral Epicondylitis. Orthocell now expects this meeting to take place in the second quarter of 2018 and the study to initiate shortly thereafter.
- **Japan:** Orthocell will likely seek to leverage the abridged approval process that currently applies in Japan for new regenerative medicines⁴⁴.

Rotator cuff is a US\$6.5bn market opportunity for Ortho-ATI®. Assume

- 1.5% of the population will suffer a rotator cuff injury in any one year⁴⁵;
- 35% of these patients are symptomatic and will therefore seek treatment options⁴⁶;
- 15% of the symptomatic patients will undergo arthroscopic rotator cuff surgery⁴⁷ and the other 85% 'conservative treatment', such as steroids, hyaluronic acid injections⁴⁸ and physical therapy;
- For the surgery patients, 33% of the procedures will not work⁴⁹;
- For the non-surgical patients, 25% will not have satisfactory outcomes⁵⁰.

Assume further that the surgery and non-surgery treatment failures then became candidates for Ortho-ATI®. Across the billion people in the four major markets that Orthocell wishes to address⁵¹, this would represent 1.4 million patients. At US\$4,500 per patient, a price that would likely be cost-effective given our estimate of US\$15,000 for rotator cuff repair costs in the US⁵², Ortho-ATI® is a US\$6.5bn opportunity.

Lateral Epicondylitis is a US\$1.5bn market, at least. Assume

- 0.3% of the population will suffer a from tennis elbow in any one year⁵³.
- 10% of cases will prove refractory to conservative treatment and may transition to surgery⁵⁴.

Assume further that patients that who would ordinarily be referred to surgery become candidates for Ortho-ATI®. At US\$4,500 per treatment, this would represent a US\$1.5bn opportunity⁵⁵. US\$4,500 is cost effective here because around one in five patients with Lateral Epicondylitis still need care a year after first diagnosis⁵⁶. Ortho-ATI® has potential to markedly cut the cost of this care.

LATERAL EPICONDYELITIS IS A US\$1.5BN MARKET, AT LEAST

⁴³ See the company's December 2016 Corporate Update presentation, slide 17.

⁴⁴ In November 2013 the Japanese Diet passed amendments to Japan's Pharmaceutical Affairs Law defining new medical products which contain stem cells as 'regenerative medicine products'. This will allow the Japanese Ministry of Health to give conditional approval to such products if their safety is confirmed after Phase 2.

⁴⁵ Estimated from Muscles Ligaments Tendons J. 2014 Jul-Sep; 4(3): 309-314.

⁴⁶ J Orthop. 2013 Feb 26;10(1):8-12.

⁴⁷ J Bone Joint Surg Am. 2012 Feb 1;94(3):227-33. There are at least 320,000 surgeries in the US market.

⁴⁸ Muscles Ligaments Tendons J. 2016 Feb 13;5(4):270-5.

⁴⁹ Am J Sports Med. 2011 Oct;39(10):2099-107. Epub 2011 Aug 3.

⁵⁰ J Orthop Sci. 2013 Mar;18(2):197-204. Epub 2013 Jan 12.

⁵¹ US 327 million, EU 516 million, Japan 127 million, and Australia and New Zealand 28 million.

⁵² Estimated from J Shoulder Elbow Surg. 2007 Mar-Apr;16(2):181-7, adjusted with BLS inflation data.

⁵³ Am J Sports Med. 2015 May;43(5):1066-71. Epub 2015 Feb 5. This contrasts with other estimates such as '1% to 3% of the adult population each year' (Am J Sports Med. 2015 Sep; 43(9): 2133-2137) and reflects the fact that it is a population-based study rather than an estimate based on patient flow at a specialist clinic.

⁵⁴ Br J Sports Med. 2007 Nov; 41(11): 816-819.

⁵⁵ That is, ~340,000 patients at US\$4,500 each.

⁵⁶ Lancet. 2002 Feb 23;359(9307):657-62.



Ortho-ACI® – The most advanced Autologous Cartilage Implantation product available

Ortho-ACI® was Orthocell's foundation product. Ortho-ACI®, Orthocell's cartilage repair product, was what enabled the company to be started in 2006. Autologous Chondrocyte Implantation, similar to Autologous Tenocyte Implantation, involves biopsying a sample of cartilage tissue from the patient, extracting and then expanding the chondrocytes from the cartilage, and returning them to the site of cartilage injury.

Ortho-ACI® is a superior third-generation ACI product. Orthocell did not invent Autologous Chondrocyte Implantation - it had been pioneered in the mid-1990's by a group at the University of Göteborg in Sweden⁵⁷ and then commercialised by a German company called Verigen. That company gained FDA approval for the product, which it called MACI and is now called Carticel, in 1997. The major US biotech company Genzyme acquired Verigen in 2005. Around that time Paul Anderson and Ming-Hao Zheng, who had brought Verigen's product to Australia, set out to create a better ACI solution. What they ended up with, and were able to market from 2010 after the manufacturing facility was licensed, could best be described as 'third generation' ACI:

- The first generation ACI approach saw the chondrocytes kept in place at the site of the defect by way of a flap made out of periosteum, the outermost layer of bone. This was an effective therapy but had the problem of graft hypertrophy, where scar tissue formed around the edges of the periosteal flap.
- Second generation ACI solved the problem of keeping the chondrocytes in place through the use of bioengineered collagen or synthetic membranes as the placement agent. A recently approved second generation ACI, which is now marketed as MACI, was originally developed, as we noted above, by Verigen and Genzyme and is now a product of the US regenerative medicine company Vericel⁵⁸. MACI (Matrix-induced Autologous Chondrocyte Implantation), is cultured chondrocytes on a porcine collagen membrane for the treatment of full-thickness cartilage defects of the knee⁵⁹.
- Third generation ACIs such as Ortho-ACI® took the membrane idea a step further and used three-dimensionally constructed scaffolds that could grow cells faster and could be quickly fitted into place using fibrin glue. Ortho-ACI® uses a porcine-derived collagen scaffold. Typically for Ortho-ACI® the cell expansion process takes only 4-5 weeks versus closer to 8 weeks for first and second-generation approaches.

**ORTHO-ACI®
WORKS FASTER
THAN ITS
COMPETITORS**

Ortho-ACI® has a long history of clinical use now. As with Ortho-ATI®, Ortho-ACI® was able to be used clinically in Australia without specific product approval through the tissue manufacturer regulations that existed prior to 2011. The product was included on the ARTG in May 2017. By then >380 patients had been treated⁶⁰. Orthocell reported retrospective data on 38 patients with articular cartilage defects in October 2015 showing 89% 'good to

⁵⁷ N Engl J Med. 1994 Oct 6;331(14):889-95.

⁵⁸ Ann Arbor, Mi., Nasdaq: VCEL, www.vcel.com. Vericel, formerly Aastrom Biosciences, acquired Sanofi's cell therapy and regenerative medicine business in June 2014. Sanofi had inherited that business with its acquisition of Genzyme in 2011. Aastrom/Vericel paid US\$6.5m.

⁵⁹ See www.maci.com.

⁶⁰ See Orthocell's December 2016 corporate presentation, slide 19.



excellent' outcomes on MRI assessment and 83% on arthroscopic assessment⁶¹. In Australia, Orthocell markets Ortho-ACI® at A\$6,500 per injection⁶². The company started offering Ortho-ACI® in Singapore in November 2015.

Ortho-ACI® is a valuable product, but Orthocell now has bigger fish to fry. In itself, Ortho-ACI® is not as valuable as Ortho-ATI® because there are competing ACI approaches for cartilage repair. That said, we expect there will be partnering opportunities for Ortho-ACI® given the market need and the treatment outcomes that have been demonstrated to date. The real utility of Ortho-ACI®, however, is the collagen scaffold that was developed for it, which became Orthocell's CelGro® product.

Ortho-ACI® will compete in a >US\$300m market globally. Vericel estimates that the annual US incidence of full-thickness cartilage defects of the knee is 46,000 patients but that MACI's market is only 11,000 patients once age (age 18-55 – the pivotal studies didn't evaluate patients over 55⁶³), insurance status and level of physical activity is taken into account⁶⁴. That said, at US\$10,000 per procedure with Ortho-ACI® there is probably a US\$300m-350m opportunity across Orthocell's target market.

**ORTHO-ACI®
CAN ATTRACT
STRONG
PRICING**

CelGro® – Possibly the best tissue engineering scaffold invented

Tissue repair often just needs a decent scaffold, like Orthocell's. Scaffolds are a vital part of the stem cell and tissue engineering field today. As we've seen with Ortho-ACI® above, generally if one wants to grow new tissue at the site of a wound or tissue defect, it's not sufficient to lay down new cells at the site. These cells often need to be scaffolded with a device that can mimic the natural three-dimensional environment in which those cells would ordinarily grow, with the scaffold eventually being replaced by the extracellular matrix. The last fifteen years has seen a lot of development activity around new scaffolds. Orthocell argues that it has one of the best, with a collagen scaffold that can encourage natural tissue regeneration with or without the use of stem cell implants.

CelGro® has an ideal structure to promote rapid cell proliferation at the site of tissue repair. Around 2008 or 2009 Professor Ming-Hao Zheng, experimenting with the collagen-based scaffold that he had earlier developed for Ortho-ACI®, came up with one that he argued had the ideal properties of a scaffold⁶⁵. CelGro® is simply a bio-derived collagen membrane comprised predominantly of type I collagen. Type I collagen is the type most commonly used in medicine, being the most abundant collagen type in higher-order organisms. It is a fibrillar collagen with high tensile strength and is a key component of tendons, skin, ligaments, fascia, bones and cornea⁶⁶. Zheng and his collaborators were able to harness type I to a membrane manufacturing process he developed, and that was later trademarked, called SMRT™. As a result of this proprietary process, which Orthocell performs at its quality-controlled GMP facility in Perth, CelGro® scaffolds retain the natural collagen structure from the source

⁶¹ See Orthocell's 15 October 2015 market release headlined 'Orthocell technologies and data to be presented at key orthopaedic conferences'.

⁶² See Orthocell's 24 November 2014 Annual General Meeting presentation.

⁶³ Am J Sports Med. 2014 Jun;42(6):1384-94. Epub 2014 Apr 8.

⁶⁴ See the Vericel August 2017 corporate presentation, slide 16.

⁶⁵ See *A collagen scaffold for cell growth*, WO/2010/009511, priority date 24 July 2008.

⁶⁶ See Adv Drug Deliv Rev. 2003 Nov 28;55(12):1531-46 and Adv Drug Deliv Rev. 2003 Nov 28;55(12):1699-721.



material. The scaffold has one rough and one smooth surface. The rough surface enhances cell attachment and infiltration, while the smooth side repels fibrous adhesions that would form damaging scar tissue. CelGro® is arguably one of the best tissue repair scaffolds yet invented. The structure of the scaffold gives it mechanical strength and pliability as well as the right porosity so that cells infiltrating the scaffold can feel at home. The high purity of the collagen, the fact that collagen is a biocompatible (and bioresorbable) natural product, and the fact that CelGro® comes without cross-linking or chemical additives, all help avoid the problems that can come with synthetic scaffolds such as toxicity and cell incompatibility. Orthocell was able to make CelGro® under GMP by about 2012⁶⁷.

CELGRO® IS ARGUABLY ONE OF THE BEST TISSUE REPAIR SCAFFOLDS YET INVENTED

The clinical evidence so far for CelGro® has been encouraging. As with Ortho-ATI®, Orthocell has tested CelGro® clinically in multiple indications over the last three years. The evidence suggests that CelGro® can work in both soft tissue repair as well as bone regeneration:

- In November 2015, Orthocell reported favourable results for the first two patients in a study evaluating the use of CelGro® as a barrier membrane in dental implant procedure called 'guided bone regeneration'⁶⁸.
- In June 2016, the company announced that CelGro®, was safe and tolerable⁶⁸, as a tool for the surgical repair of rotator cuff tears in three study patients.
- In February 2017 Orthocell reported similar safety and tolerability from three patients in a study of CelGro® to promote regeneration in severed peripheral nerves⁶⁹ while in January 2018 Orthocell reported that the positive safety and tolerability profile had extended to ten patients⁷⁰.

There is plenty of data to come. There are currently four clinical studies of CelGro® ongoing which are expected to read out data over the next couple of years:

- **Guided dental bone regeneration.** The study designed to show that CelGro® is a good barrier membrane will recruit 30 patients in all. It gained ethics approval in March 2015⁷¹.
- **Rotator cuff surgery.** Another 30-patient study is designed to show that CelGro® can speed the rate of surgical rotator cuff repair, thereby lowering the re-tear rate. The study was unveiled in December 2015⁷².
- **Osteochondral defects in the hip.** 'Microfracture' is a common treatment for chondral defects in various joints including the hip. It involves making holes in the underlying bone, which brings a new blood supply to the surface, carrying with it marrow progenitor or stem cells that can repair the chondral defect. A 25-patient study, announced in May 2016, will see CelGro® used as the scaffold for the microfractures⁷³. This approach has proven safe and tolerable for the first three patients⁷⁴.

CELGRO® MAY BE A GOOD TOOL TO IMPROVE ROTATOR CUFF SURGERY

⁶⁷ See *Method for producing a collagen membrane*, WO/2013/185173, priority date 12 June 2012.

⁶⁸ See Orthocell's market release dated 10 November 2015 and headlined 'Orthocell reports initial clinical results using CelGro® in dental study'.

⁶⁹ See Orthocell's market release dated 22 February 2017 and headlined 'Initial results positive for CelGro® in human nerve regeneration'.

⁷⁰ See Orthocell's market release dated 2 January 2018 headlined 'Orthocell achieves 50% patient treatment milestone in human nerve regeneration trial'.

⁷¹ The ANZCTR trial ID for this study is ACTRN12615000027516 – see www.anzctr.org.au.

⁷² See Orthocell's market release dated 16 December 2015 and headlined 'Orthocell receives approval for human tendon study using CelGro®'. The ANZCTR trial ID for this study is ACTRN12615001065583 – see www.anzctr.org.au. One paper has estimated that massive tears of the rotator cuff, after surgical repair, will re-tear in 57% of cases over ten years - see *J Bone Joint Surg Am.* 2008 Nov;90(11):2423-31.

⁷³ See Orthocell's market release dated 4 May 2016 and headlined 'Orthocell receives approval for human hip study using CelGro®'. The ANZCTR trial ID for this study is ACTRN12616000464460 – see www.anzctr.org.au.

⁷⁴ See the Orthocell market release dated 6 September 2017 and headlined 'CelGro® positive safety and performance in human hip study'.



- **Nerve regeneration.** The 20-patient study evaluating CelGro® in the repair of severed peripheral nerves of the hand and upper limb was announced in October 2016⁷⁵.

Orthocell has achieved its first approval for CelGro®. On 9 November 2017 the company announced regulatory approval (CE Mark) for the marketing and distribution of CelGro® in various dental bone and soft tissue regeneration procedures in the EU. This is the first product of a diverse suite of collagen medical devices to be commercialised from Orthocell's CelGro® platform.

The CE Mark also validates the potential of the entire technology platform by endorsing CelGro®'s clinical performance and quality manufacturing, which will ultimately enable new applications, including:

- neurological: peripheral nerve repair;
- orthopaedic: tendon, ligaments, cartilage and bone; and
- other: general surgery (including hernia repair) and urogynecology.

For the 510(k) filing, Orthocell is using data from its guided bone regeneration and tendon repair studies and will use various existing scaffolds for its predicate device.

Why Orthocell believes CelGro® can be better than the alternatives. CelGro® will not be the only scaffold on the market when it gains approval. Indeed, there are multiple scaffolds already on the market:

- Bio-Gide, from a Swiss company called Geistlich Pharma⁷⁶, and BioMend Extend, from the US medical devices company Zimmer Biomet⁷⁷, are dental barrier membranes;
- TissueMend, from Stryker⁷⁸, and GraftJacket from Wright Medical⁷⁹ are routinely used in tendon repair;
- AxoGuard, from a US biotech company called Axogen⁸⁰, and Neuroflex from Stryker are nerve repair scaffolds.

Orthocell believes that CelGro® is superior to these products. As we noted above, it can retain the natural collagen structure from the source material but doesn't have the associated baggage of lipids, DNA and other non-collagen components. Moreover, it has mechanical strength without the need for cross-linking that can reduce pore size and thereby impede cell infiltration into the scaffold. Given that many large and emerging orthopaedic device companies have approved scaffolds, we see potential for CelGro® to gain licensing interest from other major medical device companies looking to enter this space.

The early indications – multiple opportunities for this versatile platform. Obviously, there are multiple indications that Orthocell can pursue with CelGro® once it gains approval. We see five in particular:

- **Dental implants.** A big problem in dental implants is that once a tooth disappears from gums, the bone that formerly anchored that tooth in place disappears over the next few months. When the dentist then puts an implant in place, he needs to place a bone graft substitute at the site of the implant to regenerate that bone. Trouble is, non-bone tissue will invade the area as well, hence the need for a barrier

**THERE ARE
NUMEROUS
CELGRO®
APPROVALS
COMING**

⁷⁵ See Orthocell's market release dated 18 October 2016 and headlined 'Orthocell receives approval for human nerve regeneration study using CelGro®'. The ANZCTR trial ID for this study is ACTRN12616001157460 – see www.anzctr.org.au.

⁷⁶ Wolhusen, Switzerland, privately held, www.geistlich-pharma.com.

⁷⁷ Warsaw, In., NYSE: ZBH, www.zimmerbiomet.com.

⁷⁸ Kalamazoo, Mi., NYSE: SYK, www.stryker.com.

⁷⁹ Amsterdam, The Netherlands, Nasdaq: WMGI, www.wright.com.

⁸⁰ Alachua, Fl., Nasdaq: AXGN, www.axogeninc.com.



membrane. If Orthocell can show that CelGro® is a superior barrier membrane, the commercial upside is significant – more than 500,000 dental implant procedures are carried out every year in the US⁸¹.

- **Rotator cuff repair.** We noted above the massive market opportunity for this indication.
- **Pelvic organ prolapse.** In this female health condition, the organs inside the pelvis protrude into the vaginal wall. Prolapse is treated via a pelvic floor reconstruction where scaffolds would be ideal to speed up healing. Possibly 6% of women over the age of 40 have experienced prolapse⁸².
- **Bone regeneration.** In America, there are estimated to be >500,000 fractures p.a. where union of the bone is delayed or where there is no union⁸³.
- **Nerve regeneration.** Annual US incidence of nerve injury is around 1.4 million, of which 0.9 million will require surgical intervention⁸⁴.
- **ACL replacement.** Anterior Cruciate Ligament injury is a common orthopaedic problem with annual US incidence of >20,000 cases⁸⁵.

**POSSIBLY 6%
OF WOMEN
OVER 40 HAVE
EXPERIENCED
PROLAPSE**

Six trends that can make CelGro® a significant commercial success. We believe that six factors that are becoming significant in modern medicine can help to grow the market for CelGro®:

- 1) **The rise of stem cells.** Since the first embryonic stem cells were isolated in 1998 there has been a significant amount of academic and applied clinical research devoted to identifying stem cells of all kinds, including autologous and allogeneic adult stem cells and, more recently, induced pluripotent stem cells, that are capable of either differentiating into specific tissue types or producing growth factors that could facilitate tissue regeneration. As this work translates into approved therapies – and companies like Mesoblast⁸⁶ and TiGenix⁸⁷ are now close to the market with their leading products – interest will grow in scaffolds that can place those stem cells at the required regeneration sites for optimal treatment outcomes⁸⁸.
- 2) **The rise of growth factors.** While more and more stem cells are being identified and characterised, the individual growth factors many of these cells produce are being isolated and harnessed for clinical use. An early example was bone morphogenic protein, a product commonly used for the last 15 years in an orthopaedic procedure called spinal fusion⁸⁹. As with stem cells, growth factor products are likely to be employed alongside scaffolds⁹⁰.
- 3) **The push towards allogeneic therapies.** We noted previously that, as a general rule, autologous therapy means 'higher cost' and allogeneic therapy 'lower cost'. Given the cost pressures in First World healthcare

⁸¹ Source: American Academy of Implant Dentistry, Dental Implants Facts and Figures.

⁸² See *Obstet Gynecol.* 2007 Jun;109(6):1396-403.

⁸³ A common assumption in orthopaedics is that around 5-10% of fractures will be delayed union or non-union - see Praemer, Furner and Rice, *Musculoskeletal Conditions in the United States* (Rosemont, Illinois: American Academy of Orthopaedic Surgeons, 1999). In 2006 there were around 5.6 million fractures in the US, 1.6 million resulting in hospital admissions from the Emergency Department, the other 4 million being treated in the ED and then discharged (source: HCUP Statistics on Emergency Department Use).

⁸⁴ Source: Axogen.

⁸⁵ Estimated from *Am J Sports Med.* 2016 Jun;44(6):1502-7. Epub 2016 Feb 26.

⁸⁶ Melbourne, Australia, ASX: MSB, www.mesoblast.com.au.

⁸⁷ Leuven, Belgium, Euronext Brussels: TIG, www.tigenix.com.

⁸⁸ For some recent *in vivo* work on the combination of mesenchymal stem cells and scaffolds in rotator cuff repair see *PLoS One.* 2017 Apr 3;12(4):e0174789.

⁸⁹ The Bone Morphogenetic Proteins or BMPs are a group of naturally occurring growth factors that are 'osteoinductive', that is, able to induce the formation of bone and cartilage. They have been important in spinal fusion since 2002 when the FDA approved a BMP-based spinal fusion product called INFUSE, from Medtronic.

⁹⁰ *Tissue Eng Part A.* 2014 Aug;20(15-16):2077-87. Epub 2013 Dec 18.



systems we think the economics of regenerative medicine will converge on scaffold-type therapies that can be delivered 'off-the-shelf' and draw the endogenous stem cells and growth factors to the site of tissue repair⁹¹.

- 4) **The interest of orthopaedic device companies at moving into biologicals.** The orthopaedic devices sector is dominated by around a dozen large, mostly US companies, including Medtronic, Stryker and Zimmer Biomet⁹². In recent years the orthopaedic majors have become very interested in developing or acquiring 'orthobiologic' products that would improve patient outcomes, as well as help them grow faster in an environment where there is less emphasis, and therefore less growth, in new 'hardware'. Platelet-Rich Plasma is an example of this trend, as is hyaluronic acid.

Company	Location	Code	Market cap (USDbn)	Web
Johnson & Johnson	New Brunswick, NJ	NYSE: JNJ	358.7	www.jnj.com
Medtronic	Minneapolis, Mn.	NYSE: MDT	110.2	www.medtronic.com
Stryker	Kalamazoo, Mi.	NYSE: SYK	62.8	www.stryker.com
Zimmer Biomet	Warsaw, In.	NYSE: ZBH	23.7	www.zimmerbiomet.com
Smith & Nephew	London, UK	LSE: SN	16.2	www.smith-nephew.com
Globus Medical	Audubon, Pa.	NYSE: GMED	5.0	www.globusmedical.com
Integra LifeSciences	Plainsboro, NJ	Nasdaq: IART	4.5	www.integralife.com
Nuvasive	San Diego, Ca.	Nasdaq: NUVA	2.7	www.nuvasive.com
Wright Medical	Memphis, Tn.	Nasdaq: WMGI	2.2	www.wmt.com
Orthofix International	Lewisville, Tx.	Nasdaq: OFIX	1.1	www.orthofix.com

- 5) **Greater understanding of what works in bioscaffolds.** It's fair to say that understanding of the *in vivo* microenvironment that would allow optimal tissue regeneration is still sketchy⁹³. As the science builds up around issues such as biomaterial-host interaction, the role of the immune system in tissue repair, and the mechanisms of stem cell recruitment, growth, and differentiation, we expect that better kinds of scaffolds with, say, a tunable pore size will be developed.
- 6) **Greater interest in natural product implants.** For a long time, the orthopaedics companies used synthetic materials in various implantable devices. There is now greater interest in natural products, where the material is biodegradable, in the expectation that these materials would better promote natural healing as against man-made polymers⁹⁴. Collagen is a natural beneficiary of this trend given its important role in tissue structure throughout the body⁹⁵, and the ease with which medical-grade collagen can be sought.

**CELGRO®
BENEFITS
FROM THE
TREND
TOWARDS
NATURAL
MATERIALS IN
SCAFFOLDS**

Nerve repair is a >US\$500m market for Orthocell. A HCUP search⁹⁶ suggested that in the US around 200,000 peripheral nerve repairs are performed annually⁹⁷. Assume a similar rate of nerve procedures per head of

⁹¹ Tissue Eng Part A. 2017 May 12. [Epub ahead of print]

⁹² Other companies in this space include the privately held Arthrex, Conmed and DJO Global.

⁹³ J Clin Invest. 2010 Jan;120(1):60-70.

⁹⁴ Natural scaffolds have been made out of collagen, alginate, agarose, hyaluronic acid derivatives, chitosan, and fibrin. Man-made polymers such as polyglycolide (PGA), polylactides (PLLA, PDLA), poly(caprolactone) (PCL), and poly(dioxanone) (PDS) have also been tried as scaffolds.

⁹⁵ Biopolymers. 2008 May;89(5):338-44.

⁹⁶ HCUP is the Healthcare Cost and Utilization Project, a hospital use databased maintained by the US government's Agency for Healthcare Research & Quality. We used HCUP to search for all procedures that had the ICD-9 code starting with '04', which encompasses 'Operations on cranial and peripheral nerves'.

⁹⁷ Axogen's research has suggested a market of more like 900,000 procedures – see the page headed 'About the nerve repair market' on the Axogen web site.



population across Orthocell's target markets, and further assume that only 50% of those procedures are successful⁹⁸, allowing Orthocell to address the other 50% with CelGro[®]. At US\$1,500 per procedure for CelGro[®], this suggests a market opportunity of >US\$500m.

Dental implants are a >US\$600m market for Orthocell. We noted above the estimate of 500,000 new dental implants in the US every year. The American Academy of Implant Dentistry doesn't release annual figures but assume that 500,000 is a reasonable estimate. Assume a similar rate of implants per head of population across Orthocell's target markets. At US\$400 per procedure for CelGro[®], this suggests a market opportunity of >US\$600m.

Orthocell is growing its pipeline of regenerative medicine opportunities

In addition to developing Ortho-ATI[®] and CelGro[®], Orthocell has also seeded two other intriguing early-stage opportunities:

- **'Lab-Grown Tendons'**. In November 2014 Orthocell announced that it had been part of a collaboration⁹⁹ in which human tendons had been grown in a bioreactor¹⁰⁰ without the need for scaffolds. Orthocell has filed for patent protection over this work¹⁰¹. This opens up the potential for a future allogeneic tendon repair product. A grant worth A\$430,000 was received in July 2015. Lab-Grown Tendons could potentially be a new treatment solution for many tendinopathies.
- **'Cell Factories' - Orthocell's move into the allogeneic space.** Led by Orthocell director Lars Lidgren, who is Professor Emeritus in the Department of Orthopaedics at Lund University in Sweden, Orthocell has built a solid body of knowledge that tissue-specific growth factors from cultured cells can work as off-the-shelf therapies for tissue repair. The company, along with a network of academic collaborators¹⁰², showed *in vitro* in July 2015 that such growth factors would work in cartilage repair¹⁰³ while in April 2016 came *in vivo* evidence that the product would also work in bone repair (although the scaffold used wasn't CelGro[®] but a gelatin-based scaffold¹⁰⁴). In October 2016 the Cell Factory researchers generated further *in vitro* evidence of bone repair, this time with muscle as the scaffold¹⁰⁵.

'CELL FACTORIES' COULD BE IMPORTANT IN THE FUTURE OF TISSUE REPAIR

⁹⁸ Plast Reconstr Surg. 2005 Aug;116(2):484-94.

⁹⁹ Partners in the collaboration alongside Orthocell were groups at the University of Western Australia, Curtin University, Griffith University and the University of Auckland.

¹⁰⁰ See Orthocell's market release dated 6 November 2014, and headlined 'First human tendons grown in laboratory'.

¹⁰¹ See *Collagen construct and method for producing the collagen construct*, WO/2016/054686, and *Sutureless repair of soft tissue*, WO/2016/054687, priority date in each case 10 October 2014.

¹⁰² From Indian Institute of Technology Kanpur, the University of Copenhagen, Oxford University, and University of Western Australia.

¹⁰³ Gupta et. al., *J Tissue Eng Regen Med*. 2015 Jul 14. [Epub ahead of print].

¹⁰⁴ See *ACS Appl Mater Interfaces*. 2016 May 4;8(17):10775-87. Epub 2016 Apr 25.

¹⁰⁵ See *Bone Joint Res*. 2016 Oct;5(10):500-511.



Obviously both projects are early stage. However, we think that the novelty of both will find commercial appeal given the large market opportunities and, in the case of Cell Factories, the opportunity to be able to sell product 'off the shelf'.

Valuing Orthocell

	Base	Optim.
Ortho-ATI (A\$m)	70.4	160.8
Ortho-ACI (A\$m)	16.9	51.3
CellGro (A\$m)	63.0	199.0
Value of Orthocell technology	150.4	411.1
Value of tax losses	5.9	5.9
Corporate overhead	-46.0	-46.0
Cash now (A\$m)	4.9	4.9
Cash to be raised (A\$m)	10.0	10.0
Option exercises (A\$m)	9.0	9.0
Total value (A\$m)	<u>134.2</u>	<u>395.0</u>
Total diluted shares (million)	<u>150.4</u>	<u>150.4</u>
Value per share	\$0.892	\$2.626
Valuation midpoint	\$1.759	
Share price now (A\$ per share)	\$0.290	
Upside to midpoint	506.6%	

We valued Orthocell at \$0.89 per share base case and \$2.63 per share optimistic case using a probability-weighted DCF approach. Our A\$1.75 per share price target sits at about the midpoint of our valuation range. Our valuation approach was as follows:

- We modelled payoffs for Ortho-ATI®, Ortho-ACI® and CelGro® involving upfront and milestones payments from licensing deals but allowed no value for the Cell Factories or Lab-Grown Tendon programmes given their relatively early stage of development. We believe *in vivo* and clinical data will allow us to gradually add value from these emerging technologies.
- We assumed a 96% probability of clinical success for Ortho-ATI® and Ortho-ACI®, since the history of clinical use of these products, and the data on effectiveness that have been gathered to date, suggests no great impediment to their being approved in new markets such as the US and Europe. For CelGro® we allowed a 71% probability of success, since this is, in effect, a 'Phase 3' opportunity.
- Our WACC was 11% (Medium risk).
- We assume another ~US\$12m in expenditure for Orthocell to mature the three product lines.
- We model around 14 years of commercial exclusivity in each case.

Why we assumed high probabilities of clinical and regulatory success. Historically, large molecules at Phase 3 had a high probability of succeeding in the clinic and subsequently gaining regulatory approval. For our valuation



purposes we took the historical success rate for large molecule drugs as per the figure below and applied it to Ortho-ATI®, Ortho-ACI® and CelGro®.

<i>Historical probabilities of success in drug developments¹⁰⁶</i>		
LARGE MOLECULES	Probability of Phase success	Probability of gaining approval
Phase I	84%	32%
Phase II	53%	38%
Phase III	74%	71%
Filing for approval	96%	96%

Why we used an 11% WACC. A key question in developing a DCF model is the cost of capital. At NDF Research we use the following approach:

- **Risk-Free Rate.** We use the Australian Ten-Year Bond Rate, which is currently 2.8%.

Market Risk Premia. We use three basic MRPs for Life Science companies - 7.5% for 'medium risk' companies¹⁰⁷, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies. We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'. We regard Orthocell as 'Medium Risk'.

Ungearred beta. We use an ungearred beta of 1.1.

This approach suggests a discount rate for Orthocell of 11% at the present time.

Elements of the commercial payoff for the Ortho-ACI® and CelGro® programmes – pre-launch. We estimated, for each of the three products, a base case and an optimistic case for the following elements:

- Level of expenditure required prior to a licensing deal;
- Timing of a prospective licensing deal;
- Level of upfronts in the deal (in US\$);
- Level of milestones in the deal (in US\$) – note, for CelGro®, we assume no milestones given that US approval is pending, however we assume large upfronts and royalties.

Commercial life of future products. We assume that a product enjoys 14 years of commercial exclusivity, after which sales erode due to generic competition. While patent protection for a drug is notionally 20 years, patent

¹⁰⁶ Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.

¹⁰⁷ We assume that 'low risk' in the Life Sciences industry in Australia and New Zealand does not yet exist for most companies given the formative nature of the industry today.



term extension in the US only covers that part of clinical programme after the filing of an IND. This reduces the exclusivity window by around five or six years.

Elements of the commercial payoff for the major programmes – post-launch. We estimated, for each product that ultimately could be launched from the programmes, a base case and an optimistic case for the following elements:

- Date of product launch in the US;
- Date of product launch for the Rest of the World (RoW);
- Level of royalties, as a percentage of net sales;
- The level of sales (in US\$) to be achieved in the US at year five post launch;
- The level of sales (in US\$) to be achieved in the RoW at year five post launch;
- The growth rate of sales in both the US and the RoW between years 6 and 14;
- The percentage of the US and RoW markets still held by the product when it goes generic;
- The terminal growth rate of the product franchise.

We summarise our assumptions on commercial outcomes in the three tables below:

Ortho-ATI® Project

	Base case	Optimistic case
OCC investment required (AUDm)	4	2
License date	2020	2019
License upfront (USDm)	15	25
License milestones (USDm)	50	80
Royalty rate	7.0%	11.0%
Earliest approval	2021	2020
Peak sales (USDm)	200	300

Ortho-ACI® Project

	Base case	Optimistic case
OCC investment required (AUDm)	4	2
License date	2022	2021
License upfront (USDm)	5	10
License milestones (USDm)	20	40
Royalty rate	4.0%	7.0%
Earliest approval	2023	2022
Peak sales (USDm)	80	150



CelGro® Project

	Base case	Optimistic case
OCC investment required (AUDm)	4	2
License date	2021	2020
License upfront (USDm)	30	60
License milestones (USDm)	0	0
Royalty rate	10.0%	15.0%
Earliest approval	2020	2019
Peak sales (USDm)	400	650

Currency: We converted the US dollar cash flow streams into Australian dollars at the forecast exchange rates listed below:

<i>Our AUDUSD exchange rate forecasts</i>	
Half	AUDUSD
30/06/2018	0.790
31/12/2018	0.774
30/06/2019	0.759
31/12/2019	0.743
30/06/2020	0.729
31/12/2020	0.714
Later periods	0.700

Tax: We used the Australian corporate tax rate of 30%.

Further capital. We assume, for modelling purposes, a \$10m capital raising at 40 cents per share that would help seed early commercial sales of CelGro® as well as the completion of clinical work for both CelGro® and Ortho-ATI®.

Assumptions on peak sales. We argue that we have been conservative on sales assumptions given the versatility of Orthocell's products

Ortho-ATI®:

- We assumed usage mainly in tennis elbow and rotator cuff, with lower levels of usage in the repair of patellar tendons, Achilles tendons and so on;
- We assumed sales main in Europe and the US;
- We assumed pricing in the order of US\$4,500 - \$8,500 per procedure.
- We assumed that usage is around 2-4% of the market opportunity of ~US\$8bn



Ortho-ACI®:

- We assumed sales only in cartilage defects in the knee – there is reasonable prospects for widening indications over time;
- We assumed sales only in Europe and the US
- We assumed pricing in the order of US\$10,000 per procedure.

CelGro®:

- We assumed sales across only three main indications – dental, rotator cuff, and nerve regeneration;
- We assumed sales mostly in the US, with lesser market presences in Europe and the key Asian and other emerging markets
- We assumed pricing in the order of US\$1,000 per unit on average (ie US\$1,500 for nerve, US\$400 for dental membrane).

Re-rating Orthocell

We see a number of events helping to re-rate Orthocell to our target price over the next 12-18 months:

- FDA and CE Mark approval for CelGro® dental, nerve, tendon and cartilage applications;
- Further clinical data for Ortho-ATI® and CelGro®;
- Early sales for CelGro® in European and US markets;
- Strategic partnerships and distribution agreements for Ortho-ATI® and CelGro®;
- Publication of the Workers Compensation retrospective study data for Ortho-ATI®;
- Progress of the Cell Factories technology into clinical studies;
- Pre-clinical progress with the Lab-Grown Tendon product.

Orthocell's leadership

We think Orthocell has the leadership smarts to grow into a significant company in the tissue engineering space:

Founder and CEO **Paul Anderson** has a solid background in tissue engineering, having, as we noted above, brought the first generation Autologous Chondrocyte Implantation approach to Australia in 1999 for a German company called Verigen. Anderson started Orthocell in 2006 around a year after Genzyme had acquired Verigen. His Verigen colleague and Orthocell co-founder, CSO **Professor Ming-Hao Zheng**, brings the scientific insights that have enabled Orthocell to create Ortho-ATI® and CelGro® and to deepen its pipeline with other, more allogeneic projects. The development of this pipeline has shown that Anderson and Zheng can adapt their company to the fast pace of change in the regenerative medicine field. It's heartening to see that the two men have sizeable 'skin in the game', with Zheng holding 6.7% of the company and Anderson 6.3%.

**ORTHOCELL'S
LEADERSHIP
CAN ADAPT TO
THE FAST PACE
OF CHANGE IN
REGENERATIVE
MEDICINE**



The Orthocell board has the skills required to build a serious regenerative medicine company. **Dr Stewart Washer** has a track record as a bio-entrepreneur involving many companies, including the peptide drug discovery company Phylogica¹⁰⁸. **Matt Callahan** enjoyed a successful run with the drug reformulation company iCeutica¹⁰⁹ and now leads the dermatology drug developer Botanix Pharmaceuticals¹¹⁰. **Professor Lars Lidgren** of Lund University brings considerable knowledge of the orthopaedics space.

Appendix I – An Orthocell glossary

510(k) – Regulatory approval for a medical device in the US where the device has been found to be functionally equivalent to a device (called the 'predicate device') that was on the market before 1976.

Achilles tendon – The tendon which connects the heel bone to the muscles at the back of the calf.

ACI – Short for Autologous Chondrocyte Implantation – see Ortho-ACI®.

ACL – The Anterior Cruciate Ligament, one of the four main ligaments in the knee, binding the back of the thigh bone (femur) to the front of the shinbone (tibia).

ARTG – The Australian Register of Therapeutic Goods, the official list of the country's approved medical products.

ATI – Short for Autologous Tenocyte Implantation – see Ortho-ATI®.

Autologous – A type of stem cell or tissue transplant in which the recipient receives their own cells or tissue.

Allogeneic – A type of stem cell or tissue transplant in which the recipient receives their cells or tissue from an unrelated donor.

Barrier membrane – A membrane used in guided bone regeneration to prevent unwanted tissue invading the proposed site of bone regrowth.

Betamethasone – See corticosteroid.

Biopsy – Removal of a sample of tissue from the body in order to culture it for re-implantation in cellular therapy.

Bioreactor – A device to synthesise biological substances.

Bioscaffold – A structure designed to help tissue to be regrown inside a patient's body.

Cartilage – The connective tissue that covers the ends of bones in a joint.

CelGro® – Orthocell's tissue repair scaffold.

¹⁰⁸ Perth, ASX: PYC, www.phylogica.com.au. This company was built on a suite of 'Phylomer' libraries that allow new, versatile therapeutic peptides to be identified.

¹⁰⁹ iCeutica, founded in 2005 was built around drug reformulation technology called SoluMatrix. With this dry milling process, submicron particles of commercially available drugs can be engineered, enabling those drugs to be delivered at lower doses. iCeutica was acquired by the US drug developer Iroko Pharmaceuticals in April 2011, and that company has since secured multiple FDA approvals for drugs formulated using the SoluMatrix platform.

¹¹⁰ Radnor, Pa., ASX: BOT, www.botanixpharma.com. Botanix is a developer of cannabinoid-based therapeutics for diseases such as acne, psoriasis and atopic dermatitis.



CE marking – The process of gaining European approval for a medical device. CE stands for Conformaté Européenne.

cGMP – See Good Manufacturing Practice.

Chondrocyte – A cartilage cell.

Collagen – The fibrous protein that makes up connective tissue.

Corticosteroid – Steroid hormones used in the treatment of inflammatory disorders. Betamethasone is a corticosteroid that first gained FDA approval in 1961.

Cross-links – Bonds that link one polymer chain to another.

DASH – Short for Disabilities of the Arm, Shoulder and Hand, a questionnaire to measure self-rated upper-extremity disability and symptoms.

Extensor carpi radialis brevis – The short muscle on the radial bone in the forearm whose role is to straighten the wrist.

Extracellular matrix (ECM) – The proteins that surround cells and provide structural support for them.

Fibrin – A blood clot protein often used as a glue in surgical procedures.

Gluteal tendon – The tendon associated with the gluteal muscles in the buttocks. These tendons are important because the gluteus muscles are responsible for movement of the hip and thigh.

Good Manufacturing Practice (GMP) – The set of standards that have been laid down by regulators such as the FDA for the production of clinical-grade pharmaceuticals. cGMP refers to 'current' Good Manufacturing Practice, since GMP standards tend to change over time.

Guided bone regeneration – A procedure in which a bone graft is placed at a site where bone regeneration is needed, and the site is protected from unwanted tissue in-growth by a barrier membrane.

In vitro – Latin for 'in glass', referring to data obtained through testing in a test tube.

In vivo – Latin for 'in life', referring to data obtained through testing in live organisms including animal models and humans.

Lateral epicondylitis – Damage to the lateral epicondyle of the humerus. The humerus is the long bone in the arm that runs from the shoulder to the elbow. The lateral epicondyle of the humerus is the collection of tendons and muscles that help connect the humerus to the bones in the lower arm. Lateral epicondylitis is commonly known as tennis elbow.

Ligaments – Collagen-based tissues that connect bone to bone.

MRI – Short for Magnetic Resonance Imaging, a diagnostic imaging technique in which the variable resonance of hydrogen atom to magnetic fields is used to create contrast in an image.

Open label – A clinical trial in which both patients and doctors know what treatment is being administered.

Ortho-ACI® – Orthocell's cartilage repair product.



Ortho-ATI® – Orthocell’s tendon repair product.

Oxford Hip Score – A questionnaire that is designed to assess functional ability and pain from the patient's perspective as a result of hip problems¹¹¹.

Patellar tendon – The tendon which attaches the bottom of the kneecap (the patella) to the top of the shinbone (the tibia).

Predicate device – See 510(k).

p-value – A measure of statistical significance. Generally a p-value below 0.05 is considered ‘statistically significant’.

QuickDASH – Short for Quick Disabilities of the Arm, Shoulder and Hand¹¹², a patient-reported outcome measure used to assess disabilities and symptoms of the upper extremity.

Rotator cuff – Tendons and muscles in the shoulder which connect the upper arm to the shoulder blade. Patients with rotator cuff injury can’t properly rotate their shoulders.

SF36 – A measurement of health-related quality of life. The PCS component of SF36 are its physical components rather than its mental components.

Soft tissue – Tissues of the body that are not bone.

Statistical significance – The probability, measured by the ‘p-value’, that an observed outcome of an experiment or trial is due to chance alone. Generally, p-values below 0.05 are taken as markers of statistical significance.

Tendinopathy – Damage to a tendon.

Tendon – The collagenous tissue which attaches a muscle to a bone.

Tenocyte – A tendon cell.

UEFS – Short for Upper Extremity Functional Scale, a ratings system for rating upper limb problems.

Visual Analogue Score (VAS) – A method of evaluating self-reported pain in which patients specify their level of pain by indicating a position along a continuous line between two end-points representing extreme pain and no pain respectively.

¹¹¹ J Bone Joint Surg Br. 1996 Mar;78(2):185-90.

¹¹² J Bone Joint Surg Am. 2005 May;87(5):1038-46.



Appendix II – Orthocell’s intellectual property

Tenocyte cell culturing method, WO/2007/106949, priority date 23 March 2006, Invented by Ming-Hao Zheng¹¹³.

- This patent application covers the ways in which Ortho-ATI® can expand the tenocytes from the patient biopsy.

A method of producing native components, such as growth factors or extracellular matrix proteins, through cell culturing of tissue samples for tissue repair, WO/2008/041909, priority date 2 October 2006, invented by Lars Lidgren¹¹⁴.

- This patent application covers Orthocell’s ‘cell factory’, in which growth factors and extracellular matrix proteins are produced from cultured cells and extracted for use as an allogeneic stem cell therapy.

Tenocyte-containing bioscaffolds, WO/2008/128304, priority date 24 April 2007, Invented by Ming-Hao Zheng¹¹⁵.

- This patent application covers the combination of Ortho-ATI® and CelGro®.

A collagen scaffold for cell growth, WO/2010/009511, priority date 24 July 2008, Invented by Ming-Hao Zheng.

- This patent application covers Orthocell’s CelGro® product.

Method of tissue repair, WO/2010/108237, priority date 27 March 2009, Invented by Ming-Hao Zheng.

- This patent application covers the use of CelGro® as an implantation system rather than just a cell-culturing system.

Method for producing a collagen membrane, WO/2013/185173, priority date 12 June 2012, Invented by Ming-Hao Zheng¹¹⁶.

- This patent application covers the CelGro® manufacturing process.

Collagen construct and method for producing the collagen construct, WO/2016/054686, priority date 10 October 2014, Invented by Ming-Hao Zheng.

- This patent application covers the adaptation of CelGro® to tissue-specific implantable scaffolds.

Sutureless repair of soft tissue, WO/2016/054687, priority date 10 October 2014, Invented by Ming-Hao Zheng.

- This patent application covers the use of CelGro® in treating soft tissue injuries such as ACL injuries.

¹¹³ This application was granted at US Patent 7,985,408 in July 2011.

¹¹⁴ This application was granted in Europe as EP2076589 in February 2017; and in the US as Patent 9,220,803 in December 2015 and Patent 9,889,233 in February 2018.

¹¹⁵ This application was granted at US Patent 9,463,263 in October 2016.

¹¹⁶ This application was granted at US Patent 9,096,688 in August 2015.



Appendix III – Capital structure summary

		% of fully diluted	Note
Ordinary shares, ASX Code OCC (million)	110.0	87.7%	
Unlisted options (million)	15.5	12.3%	Average exercise price 58 cents, average expiry date 12-Aug-2020
Fully diluted shares	125.4		

Current market cap:	A\$31.9 million (US\$24.7million)
Current share price	\$0.290
Twelve month range	\$0.275 - \$0.495
Average turnover per day (last three months)	0.1 million

Appendix IV – Orthocell’s major shareholders

Orthocell currently has four substantial shareholders:

- **Stone Ridge Ventures** (9.3%), the Perth-based venture capital firm that seeded Orthocell, represented on the board by Matt Callahan.
- **Professor Ming-Hao Zheng** (6.7%), Orthocell’s Chief Scientific Officer, who invented the ATI and CelGro® technologies.
- **Paul Anderson** (6.3%), the founder and current CEO of Orthocell.
- **Qi Xiao Zhou** (5.8%), a Chinese businessman.



Appendix V – Papers relevant to Orthocell

Chen et. al. (2007), *Autologous tenocyte therapy using porcine-derived bioscaffolds for massive rotator cuff defect in rabbits*. Tissue Eng. 2007 Jul;13(7):1479-91.

- This paper showed that ACI could generate tendon healing and remodelling in animal models.

Chen et. al. (2010), *In chronic lateral epicondylitis, apoptosis and autophagic cell death occur in the extensor carpi radialis brevis tendon*. J Shoulder Elbow Surg. 2010 Apr;19(3):355-62.

- This paper sheds some insight on the 'natural history' of tennis elbow as involving the death of cells in an area apart from the actual lateral epicondyle.

Chen et. al. (2011), *Autologous tenocyte therapy for experimental Achilles tendinopathy in a rabbit model*. Tissue Eng Part A. 2011 Aug;17(15-16):2037-48. Epub 2011 Jun 10.

- This paper shows the effectiveness of ATI in animal model of Achilles tendinopathy.

Wang et. al. (2013a), *Autologous tenocyte implantation, a novel treatment for partial-thickness rotator cuff tear and tendinopathy in an elite athlete*. BMJ Case Rep. 2013 Jan 11;2013 (full text available for free online).

- This paper reports the first clinical case of Ortho-ATI® in a 20-year-old elite gymnast with a rotator cuff tendon injury.

Wang et. al. (2013b), *Autologous tenocyte injection for the treatment of severe, chronic resistant lateral epicondylitis: a pilot study*. Am J Sports Med. 2013 Dec;41(12):2925-32. Epub 2013 Sep 25.

- This paper covers the 20-patient pilot study of Ortho-ATI® in tennis elbow.

Wang et. al. (2015), *Evidence for the durability of autologous tenocyte injection for treatment of chronic resistant lateral epicondylitis: mean 4.5-year clinical follow-up*. Am J Sports Med. 2015 Jul;43(7):1775-83. Epub 2015 Apr 23.

- This paper reports continued improved function for the tennis elbow pilot study out to five years for the early patients.

Gupta et. al. (2015), *Cell factory-derived bioactive molecules with polymeric cryogel scaffold enhance the repair of subchondral cartilage defect in rabbits*. J Tissue Eng Regen Med. 2015 Jul 14. [Epub ahead of print].

- This paper demonstrates that the growth factors and extracellular matrix proteins from 'cell factories' can be synergistic with CelGro® scaffolds in cartilage repair.

Teotia et. al. (2016), *Gelatin-modified bone substitute with bioactive molecules enhance cellular interactions and bone regeneration*, ACS Appl Mater Interfaces. 2016 May 4;8(17):10775-87. Epub 2016 Apr 25.

- This paper shows that growth factors from 'cell factories' can enhance bone regeneration with the help of a scaffold – in this case a gelatin-based scaffold.



Raine et. al. (2016), *Muscle as an osteoinductive niche for local bone formation with the use of a biphasic calcium sulphate/hydroxyapatite biomaterial*. Bone Joint Res. 2016 Oct;5(10):500-511 (full text available for free online).

- This paper shows, *in vivo*, that growth factors from 'cell factories' can induce new bone growth, with muscle being used as the scaffold in this case.

Bucher et. al. (2017), *Autologous Tenocyte Injection for the treatment of chronic recalcitrant gluteal tendinopathy: a prospective pilot study*. Orthop J Sports Med. 2017 Feb 21;5(2):2325967116688866. eCollection 2017 (full text available for free online).

- This paper reports the results of Orthocell's 12-patient study of Ortho-ATI® in gluteal tendinopathy.

Appendix VI – Companies to watch

Anika Therapeutics. This company has been built on proprietary technologies for the manufacture of medical-grade hyaluronic acid (HA), often used in the treatment of osteoarthritis. Revenue in calendar 2017 from HA and related products was US\$113m.

Histogenics. This company's platform allows for autologous rebuilding of bone and cartilage using scaffolds and tissue processing systems. The company's first product, NeoCart, is in Phase 3 under a Special Process Assessment for articular cartilage injuries in the knee.

InVivo Therapeutics. This company is commercialising the Neuro-Spinal Scaffold, a bioresorbable polymer scaffold that is implanted into the epicentre of a spinal cord injury to support endogenous neuroregeneration. The Neuro-Spinal Scaffold is in a pivotal study in complete thoracic spinal cord injury.

Organovo. This company, based on scaffold-free 'bioprinting' technology originally developed at the University of Missouri–Columbia, is working on functional, three-dimensional tissues that can potentially be implanted or delivered into the human body. At present the target market is researchers needing functional human tissue to experiment with. Kidney and liver tissue have been the first Organovo products.

Osiris Therapeutics. This company, known historically for Remestemcel-L, the first cellular therapy product for the treatment of Graft-versus Host Disease¹²⁷, is now growing with various scaffold and tissue repair products such as Grafix, a placental derived membrane for wound healing; Cartiform, an osteochondral mesh for cartilage repair; and BIO4, a bone matrix for bone repair.

PolarityTE. This company's platform allows for tissue to be engineered that is 'functionally polarised', meaning that the cells in the tissue have the asymmetric organization that the cell is meant to exhibit¹²⁸. The lead product is SkinTE, for skin regeneration.

¹²⁷ A product now being taken to market by the world's leading stem cell company, Mesoblast.

¹²⁸ It can do this in part through the use of stromal vascular fractions – see Plast Reconstr Surg. 2016 Feb;137(2):495-507.



RTI Surgical. This company, which has its origins as the allograft processing operation of the University of Florida's Tissue Bank, has grown into a leading supplier of various tissue-based implants as well as metal and synthetic medical implants.

Tissue Regenix. This company's dCELL decellularisation technology allows DNA and other cellular material from tissue to be removed from scaffolding material. The company develops decellularised scaffolds for use in wound care, orthopaedics, and cardiovascular tissue repair.

Vericel. This company, which in 2014 acquired Sanofi's cell therapy and regenerative medicine business, is a developer of autologous cell therapies. The company gained FDA approval in December 2016 for MACI (autologous cultured chondrocytes on porcine collagen membrane), an autologous cellularised scaffold for repairing cartilage defects in the knee. Epicel (2017 revenue US\$15.5m), a cultured epidermal autograft, is a skin replacement product for burns patients while Carticel (2017 revenue US\$38.9m) is a first-generation ACI product for repair of articular cartilage defects in the knee. Vericel is also continuing to develop ixmyelocel-T, an autologous multicellular therapy intended for advanced heart failure due to ischemic dilated cardiomyopathy¹¹⁹.

Comparable companies to Orthocell

Company	Location	Code	Market cap (USDm)	Web
Anika Therapeutics	Bedford, Ma.	Nasdaq: ANIK	756	www.anikatherapeutics.com
Vericel	Cambridge, Ma.	Nasdaq: VCEL	405	www.vcel.com
Osiris Therapeutics	Columbia, Md	Nasdaq: OSIR	298	www.osiris.com
RTI Surgical	Alachua, Fl.	Nasdaq: RTIX	304	www.rtix.com
Tissue Regenix	Leeds, UK	LSE: TRX	139	www.tissueregenix.com
PolarityTE	Salt Lake City, Ut.	Nasdaq: COOL	129	www.polarityte.com
Organovo	San Diego, Ca.	Nasdaq: ONVO	122	www.organovo.com
Histogenics	Waltham, Ma.	Nasdaq: HSGX	72	www.histogenics.com
InVivo Therapeutics	Cambridge, Ma.	OTCBB: NVIV	22	www.invivotherapeutics.com
Orthocell	Perth, Australia	ASX: OCC	25	www.orthocell.com.au

¹¹⁹ As we noted in a footnote above, Vericel was formerly Aastrom Biosciences of Ann Arbor, Mi. Ixmyelocel-T was Aastrom's lead product prior to the Sanofi transaction.



Risks related to Orthocell

Risks specific to Orthocell. We see five major risks for Orthocell as a company and as a listed stock:

- **Clinical risk.** There is the risk that Orthocell's products may fail to meet their primary or secondary endpoints in the clinical trials into which they are taken.
- **Funding risk.** More capital will likely be needed to continue clinical development of Orthocell's.
- **Class risk.** There is the risk that the regulatory environment for regenerative medicine products may become less liberal than is currently the case
- **Timing risk.** There is the risk that the clinical studies we discuss in this note may take longer than we expect to complete.
- **Regulatory risk.** There is the risk that regulatory decisions may slow or stop the progress of Orthocell's various products.

Risks related to pre-revenue Life Science companies in general.

- The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.
- Since most biotechnology and medical device companies listed on the Australian Securities Exchange fit this description, the term 'speculative' can reasonably be applied to the entire sector.
- The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including Orthocell.



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