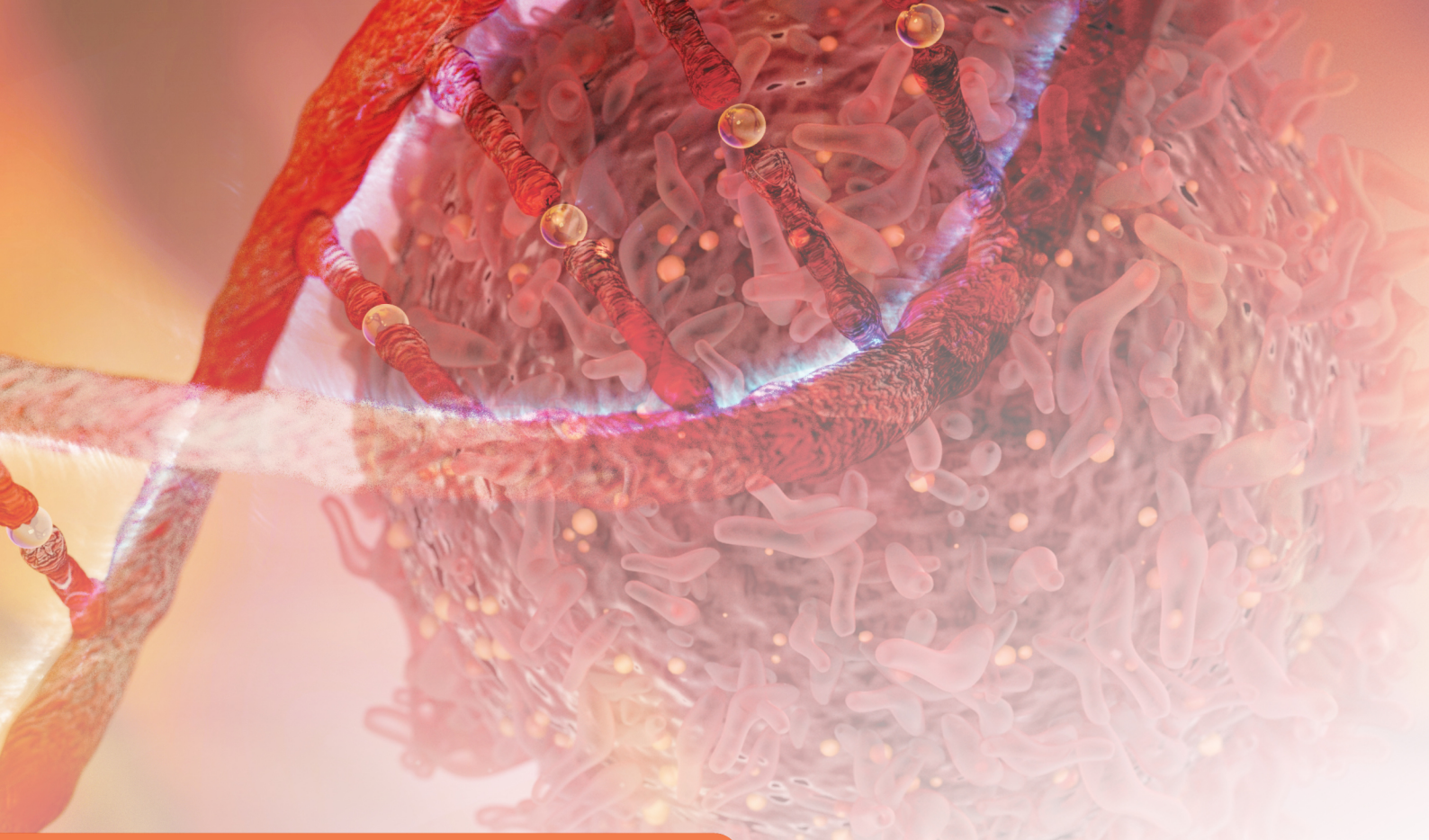

Australia's Regenerative Medicine Therapies

Case Studies of Cell, Gene, Gene Modified Cell and Tissue Engineered Products

AusBiotech

Biointelect

cell therapies

Medicines Australia

Supported by MTPConnect MedTech and Pharma Growth Centre

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Acknowledgements

The authors would like to thank all of the contributors to the Australian Regenerative Medicine Therapies report including:

- Mesoblast Ltd
- Pfizer Pty Ltd
- Novartis Pharmaceuticals Australia Pty Ltd
- Orthocell Ltd

This Australian Regenerative Medicine Therapies project was conducted between September 2020 and September 2021 as a key part of the Regenerative Medicine Catalyst Project. The project has been supported by a consortium of seven members that hold extensive insight and experience in the life sciences and regenerative medicines landscape in Australia: AusBiotech, Medicines Australia, Cell Therapies Pty Ltd, Novartis Pharmaceuticals Australia Pty Ltd, Biointelect Pty Ltd, Research Strategies Australia and Australia's Industry Growth Centre, MTPConnect.

The Regenerative Medicine Catalyst Project is funded through MTPConnect's Growth Centre Project Fund Program, an Australian Government initiative supported by the Department of Industry, Science, Energy and Resources. It is a competitive matched funding program that aims to invest in ideas to boost the innovation, productivity and competitiveness of Australia's MTP sector. Six consortium members are providing matched funding.

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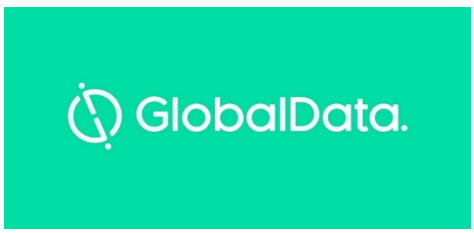
Regenerative Medicine Catalyst Project also thanks GlobalData for its assistance in preparing this report, www.globaldata.com, info@globaldata.com.



Contents

List of Figures

Foreword

The Regenerative Medicine Catalyst Project (the Project) has brought together seven partners in a consortium to build the foundations for a national regenerative medicines (RM) sector 'catalyst' collaboration body. The Regenerative Medicine Catalyst Project will address priority action areas including: workforce capabilities, collaboration, funding, regulation and policy infrastructure, and Australian manufacturing capability. The Consortium and the subsequent Catalyst Body aim to support the Australian RM industry to see it thrive and drive benefits to the health of its people and Australia's economy. This Australian Regenerative Medicine Therapies forms a key part of the Project.

The significance and need for the Project was highlighted in a national, sector-wide report that assessed the current state of the Australian RM sector and made recommendations on the priorities and goals, see Regenerative Medicine: Opportunities for Australia (MTPConnect, LEK, 2018).

Major outcomes of the Project include other reports and data that each add further to the body of evidence and understanding of the sector. The reports include:

- A researched, strategic roadmap for the RM sector's development in Australia;
- Sub-report on skills and talent specific to the sector, determining a plan to attract long-term (or patient) venture capital investment and the role of Australian biotech companies partnering with global companies, and case studies;
- Determining a sustainable funding and model structure for an RM sector 'catalyst' collaboration body;
- A regulatory white paper;
- Establishing annual data points and information resources to: map/benchmark GMP manufacturing capability and capacity; establish a model for an annual clinical trial database; and capture investments in Australian RM;
- Mapping the pathway for a typical product from early research to market, and patients receiving a therapy; and
- Mapping the global pipeline of gene and cell therapy products on the horizon;
- Case studies of different gene and cell therapy types, identifying their unique characteristics (this report).

Context

Australia has an opportunity to harness and leverage a growing and active global RM industry. If we get this right, success could be worth at least $6 billion (B) in annual revenue, 6,000 new jobs for Australia by 2035 and earlier access to ground-breaking therapies for Australian patients[1].

RM is a multidisciplinary field that seeks to develop the science and tools that can help repair, augment, replace, or regenerate damaged or diseased human cells, tissues, genes, organs, or metabolic processes, to restore normal function. It may involve the transplantation of stem cells, progenitor cells, or tissue, stimulation of the body's own repair mechanisms, or the use of cells as delivery vehicles for therapeutic agents such as genes and cytokines.

RM includes gene therapies, cell therapies, and tissue-engineered products intended to regenerate or replace injured, diseased, or defective cells, tissues, or organs to restore or establish function and structure.

Globally, the growing sector has more than 1,200 clinical trials in progress, and attracted about AU$26.3B (or US$19.9B) in financing in 2020[2]. With 97 ongoing RM Phase III clinical trials or products awaiting regulatory decisions in the coming months, therapeutics companies are turning their attention to the RM sector[3]. There are also increasing numbers of gene and cell therapies being developed in and brought to Australia for patient access.

Australia has a strong and active RM industry eco-system with basic and translational research capabilities, a clinical trials framework and clinical centres that are all internationally-recognised. More than 60 companies in Australia are developing RM products and more than 130 clinical trials in progress[4].

[1] *MTPConnect, LEK Consulting. (2018). Regenerative Medicine - Opportunities for Australia*
[2] 2020: Growth & Resilience in Regenerative Medicine, Annual Report Cell & Gene State of the Industry Briefing, Alliance for Regenerative Medicine, 2021
[3] 2020: Growth & Resilience in Regenerative Medicine, Annual Report Cell & Gene State of the Industry Briefing, Alliance for Regenerative Medicine, 2021
[4] Regenerative Medicine Catalyst Project. (2021). Australia's Regenerative Medicine Clinical Trials Database.

Cell Therapy (Remestemcel-L)

Cell therapies are perhaps the most widely known Regenerative Medicine (RM), accounting for more than half of all late-stage, phase three RM products in development. Cell therapy aims to introduce new, healthy cells into a patient's body to replace the diseased or missing ones.[5] The concept is simple: live cells are transferred into a patient and as the cells develop they replace cells that are missing or unhealthy, or provide cells that have improved function.[6] The description is straightforward and intuitive, but the realities of the procedure are substantially more complex. Following is an explanation of what stem cell therapies entail, using the cell therapy product remestemcel-L as a case study.

Cell Therapy Explored

The human body is composed of approximately 30-40 trillion cells, of which there are about 200 varieties. Stem cells are the undifferentiated cells that have not yet developed into specialised cell types (like a skin or muscle cell). They are the predecessor of all specialised cells, akin to a new, untrained employee waiting to be assigned to whichever role is required. This is the crux of their therapeutic potential, a versatility that permits the cells to fulfill the cellular function the local area needs. However, not all stem cells are the same and not all varieties of stem cells can develop to perform any function. The two cell types considered here are hematopoietic stem cells (HSC), capable of giving rise to certain blood cells, and mesenchymal stromal cells (MSC) which can develop into bone, cartilage, muscle, or fat cells. Here we will discuss cell therapies, specifically stem cell transplants to treat blood, bone and immune disorders.

HSCs have been used for decades for transplantation treatment of many blood, bone and immune disorders, namely leukaemia, myeloma, and lymphoma. The cells themselves are either mobilised from the bone marrow and collected from the blood or, less commonly, obtained directly from the marrow. Alternatively, HSCs can be isolated from a newborn's umbilical cord shortly after birth (upon parental consent, of course).

MSCs are a slightly more recently discovered cell type with a wider variety of cell specialisation capabilities. MSCs can produce a range of cell types, but not all cell types. This cell type can also be harvested from bone marrow and umbilical cord blood, as well as adipose (fat) tissue. As will be explored, the adaptability of MSCs has inspired research for treatment in orthopaedic and cardiovascular conditions and autoimmune disorders, leading to a surge in optimism and clinical trials using MSCs[7]

Stem cell transplantations can be split into two distinct categories based on the origin of the cells. An autologous procedure is one wherein the donor and the recipient are one and the same, they will have their own cells harvested and readministered (after some interim conditioning treatment such as chemotherapy). This procedure differs from allogeneic transplantation, where a separate donor will provide the cells to be administered to the patient. The set of conditions both autologous and allogeneic procedures are utilised as treatment for are largely overlapping, though the allogeneic variety is more commonly used.

Stem Cell Transplants and Graft-versus-Host Disease

Allogeneic HSC transplantation is one of the first RM procedures to be developed, having been used for decades to treat various diseases. Internationally there are approximately 30,000 allogeneic bone marrow transplants (BMTs) per year, principally conducted on disorders of the bone, blood and immune system. The first step in an allogeneic BMT, is identification of an adequate donor who is matched for various biological compatibilities. Once this has been completed and the stem cells have been harvested, the patient undergoes a conditioning regimen of chemotherapy and radiation therapy intended kill the malignant bone marrow tissue

[5] British Society for Gene & Cell Therapy. What is Cell Therapy? (https://www.bsgct.org/education/what-is-cell-therapy.aspx)
[6] AusBiotech. (2021). Regenerative Medicine Value Chain, Pathway from Discovery to Patient Delivery Report. ausbiotech.org
[7] The National Stem Cell Foundation of Australia, Stem Cells Australia. (2015). The Australian Stem Cell Handbook.

specific to the disease, often cancer cells. This primes the patient for reception of the transplant which usually takes place two days after the radiation therapy. The donor (allogenic) stem cells are then administered intravenously and migrate to the bone marrow to resupply bone marrow stem cells stores and resume healthy function.

Unfortunately, despite extensive histocompatibility matching of donor and recipient intended to locate donors with tissues unlikely to reject those of the host, occasionally even predicted matches can lead to a complication called acute graft-versus-host-disease (aGVHD) in the recipient. In fact, estimated incidence of the aGVHD is between 40% and 60% of all allogeneic HSC transplant patients.[8]

Treatment of GVHD is a delicate balance. While immunosuppression of donor T cells is critical to limit GVHD progression, too strong a treatment will weaken the effects of the same cells on the tumor. Keep in mind that the HSC transplantation procedure itself is often performed as an attempt at treating advanced and dangerous tumors. This dynamic is referred to as "balancing the GVHD and GVT (graft-versus-tumor) effect."

As with any disease, the optimal treatment strategy of GVHD should account for the properties and severity of the disease state, as well as the environmental conditions of the patient. In most cases, the first line of therapy for a GVHD patient will be systemic glucocorticoids, with ancillary treatments (topical steroids, antihistamines) employed to address any outstanding symptoms.

In the case of GVHD patients with disease unresponsive to cortico-steroids and continued progression, there is no clinical consensus for second line treatment. In such circumstances, clinical trials are an option, granting the opportunity to receive a cutting-edge therapy in the final stages of development. One such therapy is, interestingly, the stem cell therapy remestemcel-L originally developed by Osiris Therapeutics, and now owned by the Australian-based Mesoblast.

Therapeutic Potential of Mesenchymal Stromal Cells

Remestemcel-L is an allogeneic cell therapy product consisting mainly of adult MSCs and is thought to have immunomodulatory properties to counteract the cytokine storms that are implicated in various inflammatory conditions by downregulating the production of pro-inflammatory cytokines, increasing production of anti-inflammatory cytokines, and enabling recruitment of naturally occurring anti-inflammatory cells to involved tissues. Among many other therapeutic uses, Mesoblast has completed several clinical studies of remestemcel-L for use in treating SR-aGVHD (steroid-refractory aGVHD), the cohort of GVHD patients that prove unresponsive to corticosteroids. Currently MSCs are only approved for SR-aGVHD Japan, where it is marketed as TEMCELL® HS Inj.[9] By Mesoblast's licensee, JCR Pharmaceuticals. Mesoblast continues to be in discussion with the US Food and Drug Administration (FDA) through a well-established regulatory process that may include a Biologics License Application (BLA) resubmission with the aim of achieving approval in the United States for remestemcel-L in children with SR-aGVHD. Additionally, the company has undertaken multiple clinical trials globally in a number of other inflammatory diseases using its second generation platform technology, rexlemestroccel-L a immunoselected homogeneous mesenchymal stromal cell product. Among the indications for which rexlemestrocel-L is being developed and where there remains a high clinical unmet need, including Chronic Lower Back Pain and Congestive Heart Failure, and the company is in active engagement with the FDA to establish the regulatory pathways forward for these indications.

Remestemcel-L potential as a treatment for aGVHD is driven by three characteristics of the MSCs. The first quality of MSCs that make them attractive as a potential therapy is their ability to alleviate many of the underlying causes of aGVHD, namely the immune activation of the donor T cells. Remestemcel-L is activated by proinflammatory molecules like TNFa (Tumour Necrosis Factor alpha), a cytokine produced during inflammation that proliferates and compounds that damaging response. The MSCs act as an inhibitor of this

[8] Gooptu M, Koreth J. Better acute graft-versus-host disease outcomes for allogeneic transplant recipients in the modern era: a tacrolimus effect?. Haematologica. 2017;102(5):806-808. doi:10.3324/haematol.2017.165266
[9] TEMCELL® HS Inj. is a registered trademark of JCR Pharmaceuticals Co. Ltd.

process, in essence easing the cascade of immune reaction by "suppress(ing) T cell activation and proliferation,"[10] giving MSCs tremendous appeal for aGVHD therapy.

The second quality of MSCs is their "hypo-immunogeneic phenotype." GVHD itself is a consequence of incompatibility of the donor cells with the recipient during an allogeneic HSC transplantation. MSCs, on the other hand, have low or minimal levels of many of the traits responsible for immune recognition contained in HSCs.[11] In other words, the mesenchymal cells don't have the biological properties of their hematopoietic counterparts that trigger an immune response. As such, treatment with remestemcel-L means the donor-recipient matching procedure is not required unlike other stem cell therapies and requires no immunosuppression of the recipient.

Finally, sophisticated manufacturing techniques have been developed, allowing MSCs to be multiplied (by a process called "culture expansion") to numbers that provide sufficient efficacy for treatment. Though MSCs were found to have enormous therapeutic potential, they make up only 0.001-0.01% of bone marrow cells.[12] This receptivity of MSCs to biological manufacturing technologies positions remestemcel-L as a prime candidate for aGVHD therapy.

Bone to Vein: How Bone Marrow is Transformed into Remestemcel-L

Remestemcel-L is a complex therapeutic product requiring complex and highly technical manufacturing. As mentioned previously, part of the benefit of remestemcel-L is the versatility of the MSCs it leverages. As such, though the donors are pre-screened and are young and healthy, they do not need to be matched for blood type or human leukocyte antigen (HLA).[13] [14]

To produce remsetemcel-L a bone marrow sample from a donor, referred to as bone marrow aspirate (BMA), is collected and processed. Processing of the sample includes washing and isolation of the target cell type, culture expansion, and harvesting and cryopreservation of the final product, called the donor cell bank (DCB). Culture expansion allows each DCB lot to be grown to a size capable of generating multiple DCB units, and cryopreservation, a cooling technique that prevents decay of biological samples, permits sample integrity throughout shipping. Thanks to these two steps, a single donation of bone marrow can be expanded to treat many hundreds to thousands of patients. This manufacturing chain is undertaken across sites in the US and Singapore.

Remestemcel-L, like all current stem cell therapies, requires scrupulous control and identification of each sample from end to end of the manufacturing process. Autologous products are more logistically demanding than allogeneic, as the identity of the donor, and therefore tracking of the sample, is paramount. Allogeneic products, on the other hand, are administered to a different individual than they were harvested from, and the recipient will not even have been identified at the time the sample is provided. Nonetheless, the delicate nature of all stem cells warrant chains of identity and custody to guarantee identification of the original donor and sample traceability ubiquitously throughout the manufacturing process until administration. The cells are monitored constantly during development, and comprehensive release tests are performed prior to shipping the sample at each stage to ensure freedom from byproducts or contaminants. According to the US FDA, "the

[10] Idriss HT, Naismith JH. TNF alpha and the TNF receptor superfamily: structure-function relationship(s). Microsc Res Tech. 2000 Aug 1;50(3):184-95. doi: 10.1002/1097-0029(20000801)50:3<184::AID-JEMT2>3.0.CO;2-H. PMID: 10891884.
[11] Klyushnenkova E, Mosca JD, Zernetkina V, Majumdar MK, Beggs KJ, Simonetti DW, Deans RJ, McIntosh KR. T cell responses to allogeneic human mesenchymal stem cells: immunogenicity, tolerance, and suppression. J Biomed Sci. 2005;12(1):47-57. doi: 10.1007/s11373-004-8183-7. PMID: 15864738.
[12] Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999; 284: 143–147.
[13]Therapeutic Goods Administration. (2021). Australian Regulatory Guidelines for Biologicals (ARGB).
[14]Therapeutic Goods Administration. (2015). Australian Public Assessment Report for Remstemcel-L, *ex vivo* adult human mesenchymal stem cells.

characteristics and attributes of MSC are well understood, and robust quality assurance processes ensure final product with batch-to-batch consistency and reproducibility."[15]

The Place of Stem Cell Therapies in the Australian Regulatory Framework

The Therapeutic Goods Administration (TGA) is responsible for regulation of the Australian therapeutic market, including prescription medicines, biological products, and medical devices. Stem cell therapies occupy an unusual position in the regulatory framework. Whereas the cells themselves may technically be considered biologicals (and therefore under the jurisdiction of the TGA), given an autologous procedure performed by a medical professional, the therapy is excluded under the Therapeutic Goods (Excluded Goods) Determination 2018. This particular provision releases autologous stem cell therapies, considering them "medical practice."

Biologicals, (the therapeutic category most cell and tissue therapy products), are stratified into risk classes by the Australian Register of Therapeutic Goods (ARTG). The classification is dependent upon the separation of the product from its naturally occurring state and function. As an example, isolation of a cell type by centrifuge is a low manipulation technique, while genetic modification is considered highly biologically manipulative and therefore riskier. Remestemcel-L falls into class 3.[16]

Stem cell therapy trials in Australia, like all clinical trials, must be reviewed by a Human Research Ethics Committee (HREC), composed of experts in relevant fields such as law, research, and ethics, in addition to members of the public. The group is responsible for ensuring human research trials uphold ethical standards, particularly necessary when dealing with sophisticated RM approaches utilising live tissues (like the cells used in remestemcel-L) or novel genetic technologies (used in some other RM products).

In addition to SR-aGVHD, remestemcel-L is also being investigated as a treatment for acute respiratory distress syndrome (ARDS) due to COVID-19. Patients with COVID-19 who develop moderate or severe ARDS generally require invasive mechanical ventilation in a hospital intensive care setting. Mortality rates are high, ranging from almost 50% in younger patients (< 40 years old) to over 80% in the elderly.[17] In 2020, Mesoblast commenced a 300 patient randomized controlled trial in patients mechanical ventilation with moderate or severe ARDS due COVID-19. Mesoblast sort to include Australian sites in the study alongside US hospitals and was granted approval by the Human Research Ethics Committee of Monash Health. In the patient group younger than 65 years of age, 60-day mortality was reduced by 46% when treating with remestemcel-L alone, and 75% when remestemcel-L was combined with dexamethasone. Following discussions with the FDA Mesoblast has reported that a single confirmatory study in this younger patient population, if positive, will be sufficient to obtain emergency use authorization in the US. Other indications for remestemcel-L being pursued globally include Crohn's disease, ulcerative colitis and chronic GVHD. Remestemcel-L is also available in the US under an Expanded Access Program (EAP) for multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, and several children have already been treated under this program.

Looking Forward

In 2020, the FDA's Oncologic Drugs Advisory Committee (ODAC) panel voted overwhelmingly in favor that the available data support the efficacy of remestemcel-L in pediatric patients with SR-aGVHD. Remestemcel-L, however, has not yet been approved by the FDA. Mesoblast continues to be in discussion with the FDA through a well-established regulatory process that may include a Biologics License Application (BLA) resubmission with the aim of achieving approval. Three separate earlier clinical trials have shown that

[15] Oncologic Drugs Advisory Committee. (2020). Remestemcel-L for Treatment of Steroid Refractory Acute Graft Versus Host Disease in Pediatric Patients.
[16] Therapeutic Goods Administration. (2017). Regulation of cell and tissue therapies and clinical research in Australia.
[17] Am J Respir Crit Care Med Vol 203, Issue 1, pp 54–66, Jan 1, 2021. Sixty-nine studies were included, describing 57,420 adult patients with COVID-19 who received IMV. Fifty-four of 69 studies stated whether hospital outcomes were available but provided a definitive hospital outcome on only 13,120 (22.8%) of the total IMV patient population.

treatment with remestemcel-L resulted in consistent treatment responses and survival outcomes in children with steroid-refractory aGVHD[18].

Potential pricing for remestemcel-L is unclear at this stage. Of course, treatment received during participation in clinical trial comes at to no cost to the patient, however the future pricing of remestemcel-L for GVHD in Australia is yet to be explored. In Japan, where the product has been approved for aGVHD since 2015, the reimbursement price averaging around $165,000 USD per treatment. This price point is in accordance with healthcare savings that may be seen with remestemcel-L in this very high risk and predominantly hospitalized patient population where treatment for SR-aGVHD can reach over one million USD for the current most efficacious treatment, and sums of hundreds of thousands of dollars are not uncommon for alternative treatments.[19]

Moreover, the Australian government has expressed enthusiasm for supporting homegrown RM efforts. In October of 2019 the Australian Research Council announced the Stem Cell Therapies Mission, a program designed to distribute $150 million to research, innovation, and commercialisation of safe and efficacious stem cell therapies. Minister for Health Greg Hunt added, "our $150 million, 10-year Australian Stem Cell Therapies Mission, funded through the landmark Medical Research Future Fund, recognises the huge potential of stem cell science to solve currently incurable health issues."[20]

Ultimately, the future of remestemcel-L and its place in the treatment algorithm for aGVHD remains to be determined. However, this disease is a dangerous one, particularly when the patient fails to respond (or responds adversely) to the first line of therapy, which is oftentimes some form of steroid, and remestemcel-L is showing promising clinical trial results.

Other indications under investigation for stem cell therapy utilisation include neurodegenerative diseases like Parkinson's disease or autoimmune diseases such as systemic sclerosis. As a matter of fact, in 2017 results from a study comparing stem cell therapy to conventional therapy concluded that SCT is "effective in prolonging survival, as well as in inducing a rapid reduction of skin involvement and disease activity, and preserving lung function in patients" with the latter condition.[21]

Remestemcel-L has demonstrated that cell therapies can be developed as safe medicinal products with great potential for treatment of a broad range of diseases.

Note: See following page for possible infographics.

[18] Kurtzberg J, Abdel-Azim H, Carpenter P, et al. A Phase 3, Single-Arm, Prospective Study of Remestemcel-L, Ex Vivo Culture-Expanded Adult Human Mesenchymal Stromal Cells for the Treatment of Pediatric Patients Who Failed to Respond to Steroid Treatment for Acute Graft-versus-Host Disease. Biol Blood Marrow Transplant. 2020 May;26(5):845-854. doi: 10.1016/j.bbmt.2020.01.018. Epub 2020 Feb 1. PMID: 32018062

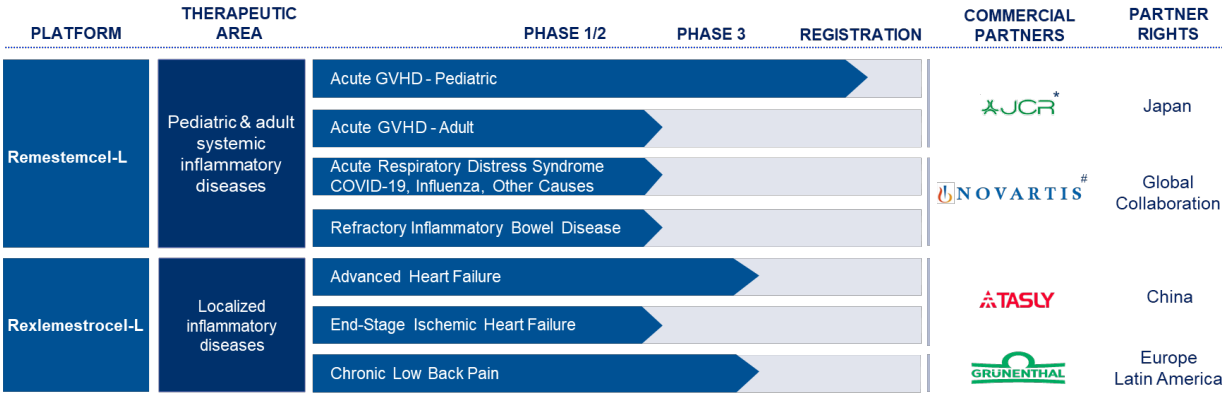
[19] Yalniz FF, Hurad MH, Lee SJ, et al. Steroid Refractory Chronic Graft-Versus-Host Disease: Cost-Effectiveness Analysis. Biology of Bone and Marrow Transplantation. 2018; 24.9: 1920-1927.

[20] Australian Research Council. (2019). Research to improve medical treatment for Australians

[21] Del Papa, N., Onida, F., Zaccara, E. et al. Autologous hematopoietic stem cell transplantation has better outcomes than conventional therapies in patients with rapidly progressive systemic sclerosis. Bone Marrow Transplant 52, 53–58 (2017).

Additional graphics/information

Figure 1: Graphic showing remestemcel-L clinical trial progress, obtained from Mesoblast Q1 report.

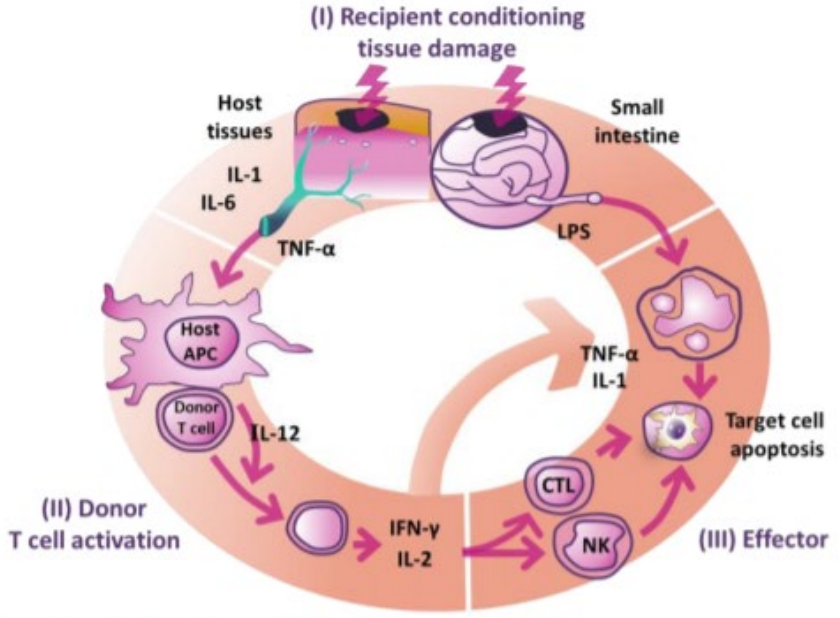


This chart is figurative and does not purport to show individual trial progress within a clinical program

* Mesoblast has the right to use data generated by JCR Pharmaceuticals Co Ltd in Japan to support its development and commercialization plans for remestemcel-L in the US and other major healthcare markets, including for GVHD and Hypoxic Ischemic Encephalopathy

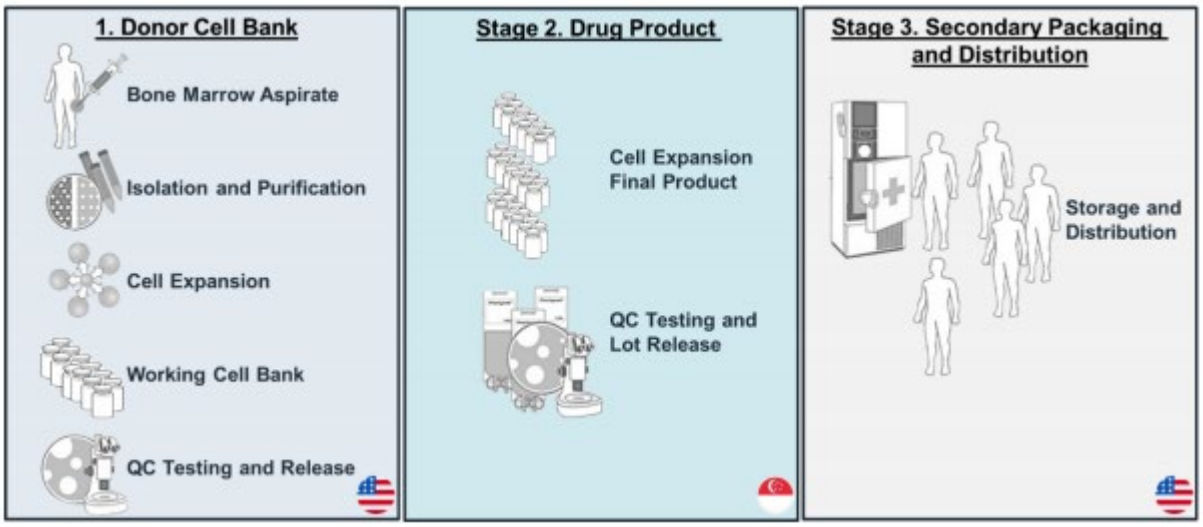
\# The agreement remains subject to certain closing conditions, including time to analyze the results from the COVID-19 ARDS trial

Figure 2: GlobalData graphic depicting GVHD pathology, from 2020 GVHD opportunity analysis and forecast.



Source: GlobalData; adapted from Reddy and Ferrara, 2008
LPS = Lipopolysaccharides

Figure 3: Remestemcel-L manufacturing process, from FDA briefing document.



Gene Therapy (Gene transfer therapy for Duchenne muscular dystrophy)

The Potential of Gene Therapy for the Management of Rare Genetic Diseases

In Australia, a disease is considered rare if it affects less than 5 in 10,000 people. While Rare Diseases may be individually rare, they are collectively common, with around 8% of Australians (2 million people) living with a rare disease.[22] Of the known 7,000 rare diseases currently identified, about 80% (4 out of 5) are genetic in origin[22], and an estimated 95% of all rare diseases have no approved medicines as treatment options.[23]

Gene therapy holds promise for many of the millions of people worldwide living with rare, genetic diseases.[23] Unlike traditional medicines or therapies that typically require frequent administration and focus on managing symptoms and disease progression, gene therapy may offer long-term transformative benefits for people with rare genetic diseases, either potentially eliminating the need for ongoing therapies, or reducing the burden of daily disease management.[24,25]

The critical unmet need

For Michael Atkinson, his journey with one such rare disease, Duchenne muscular dystrophy (DMD) started with the very late diagnosis of his son Bailey at age 10.

DMD is a rapidly progressive form of muscular dystrophy that occurs primarily in boys. It is caused by an alteration (mutation) in a gene, located on the X-chromosome, that can be inherited in families, but also occurs in people without a known family history of the condition. The DMD gene is the second largest gene to date. It encodes the muscle protein, dystrophin, which is important for muscle strength, support and repair. Boys with DMD do not make the dystrophin protein in their muscles and experience progressive loss of muscle function and weakness, which begins in the lower limbs.[26,27]

DMD affects approximately 1 in 3500 male births worldwide[26] and up to an estimated 45 boys are born with this condition each year in Australia.[28] Girls can also be affected, although this is extremely rare. Females can be carriers of the altered gene without been affected by the disease and have a 50% chance of passing the gene to each of their children.[26]

The search for a diagnosis typically begins when parents start noticing that their children are not reaching their milestones. A pre-schooler with DMD may seem clumsy and fall often. Parents also may note that children have trouble climbing stairs, getting up from the floor, or running. When arising from the floor, affected boys may use hand support to push themselves to an upright position. By school age, children with DMD may walk on their toes or the balls of their feet with a slightly waddling gait and fall frequently. To try to keep their

[22] Australian Government Department of Health. What we're doing about rare diseases. Available at: https://www.health.gov.au/health-topics/chronic-conditions/what-were-doing-about-chronic-conditions/what-were-doing-about-rare-diseases#:~:text=In%20Australia%2C%20a%20disease%20is,of%20rare%20diseases%20are%20genetic (Accessed 11 October 2021).
[23] Global Genes: Rare Disease Facts. Available at: https://globalgenes.org/rare-disease-facts/ (Accessed 11 October 2021).
[24] Kumar SR, et al. *Mol Ther Methods Clin Dev* 2016;3:16034.
[25] Murphy SL, High KA. *Br J Haematol* 2008;140:479-87.
[26] NIH National Human Genome Research Institute. About Duchenne muscular dystrophy. Available at: https://www.genome.gov/Genetic-Disorders/Duchenne-Muscular-Dystrophy (Accessed 11 October 2021).
[27] Healthdirect. Duchenne muscular dystrophy. Available at: https://www.healthdirect.gov.au/duchenne-muscular-dystrophy (Accessed 11 October 2021).
[28] Australian Bureau of Statistics. Births, Australia. Available at: https://www.abs.gov.au/statistics/people/population/births-australia/latest-release (Accessed 20 July 2021).

balance, they may stick out their bellies and pull back their shoulders. Children with DMD also have difficulty raising their arms. [29]

Michael and his family had been fighting for years for an explanation for what Bailey was going through, as he struggled physically. Numerous health professionals assured him that all was okay and Bailey was just a bit behind. When Bailey was finally diagnosed with DMD it explained a lot.

Being a genetic condition, Michael was informed there could be a potential risk his other sons. He went ahead and had his three boys tested for the condition and heartbreakingly learned his youngest son Oakley, who was 3 at the time, also had the condition.

The symptoms of DMD can appear as early as 2-3 years of age, but DMD is usually diagnosed around the age of 4 or 5 years. Early diagnosis can lead to better outcomes and an improved quality of life however, the progression of DMD symptoms is aggressive. Boys with DMD typically lose the ability to walk when they reach 8 to 12 years of age. Gradually, as muscle degeneration continues, they suffer from cardiac (heart) and respiratory (lung and breathing) involvement, which can eventually prove fatal.[26,29]

Both diagnoses were devastating for Michael's large family of seven. DMD now impacts every aspect of their day-to-day lives. Bailey requires an incredible amount of support to complete normal, everyday tasks including getting dressed, showering, and manual transfers. It is extremely difficult for him and highly physically demanding on Michael and other family members.

Now aged 15, Bailey has almost lost his ability to walk and instead of gaining independence like his peers, he is becoming more dependent, which is heartbreaking to watch as a parent. "Our son Oakley is 8 and struggles daily with falls, resulting in constant bruises, scrapes, and tears. He has never been able to run and is unable to keep up with his friends in the playground without the support of a mobility device," Michael said.

Management of DMD today

There are currently no approved treatments available in Australia that can stop or reverse the disease process of DMD.[27] The only widely available medications that have been shown to slow the course of the disease are corticosteroids, which are also associated with additional health consequences when used long-term. Other therapies aim to ease the symptoms of the disease and improve the person's quality of life. There have been advances in heart and lung care and physical therapy regimens that can improve the function of the heart and lungs while also slowing the damage to muscle. These treatments can help some people with DMD to continue to walk for longer as well as maintain their independence.[26,29]

Physical therapy is used to promote mobility. Assisted breathing devices are also often used, especially at night. Surgery is sometimes helpful in cases where the person with DMD has scoliosis (curvature of the spine) and experiences muscle pain. Medicines can also be given to improve heart function.[26,29]

Caring for a person with DMD can be very demanding and affect the lives of all individuals in the family. Carers are often left to bear the responsibility for the person they care for without sufficient support. Carers' health and wellbeing can suffer as a result. They can also feel socially isolated and financially disadvantaged.

As the parent of two boys with DMD, as well as three other healthy children, Michael is constantly attending specialist appointments, making meeting work commitments incredibly difficult. This has required he and his family to make significant sacrifices to ensure they can meet their boys' needs. It also takes precious time away from their other children: siblings who also have to endure watching their brothers' physical deterioration.

[29] Muscular Dystrophy Association. Duchenne Muscular Dystrophy. Available at https://www.mda.org/disease/duchenne-muscular-dystrophy Accessed 11 October 2021).

Looking ahead - approaches to genetic medicine

There has been considerable investment in genetic medicine, which has the potential to correct the underlying genetic defect in some rare diseases, and modify the course of the disease, rather than simply managing symptoms.[24,25]

Pfizer is working to pioneer breakthroughs that change patients' lives. We hope to unlock the promise of gene therapy for patients worldwide living with rare genetic diseases, including DMD, for whom the current standard of care falls short. Every step forward helps us to better understand the potential of the technology for the treatment of DMD as well as other diseases.

Gene therapy is the introduction, removal or change in genetic material—specifically DNA or RNA—into the cells of a person to treat a specific disease. [30]

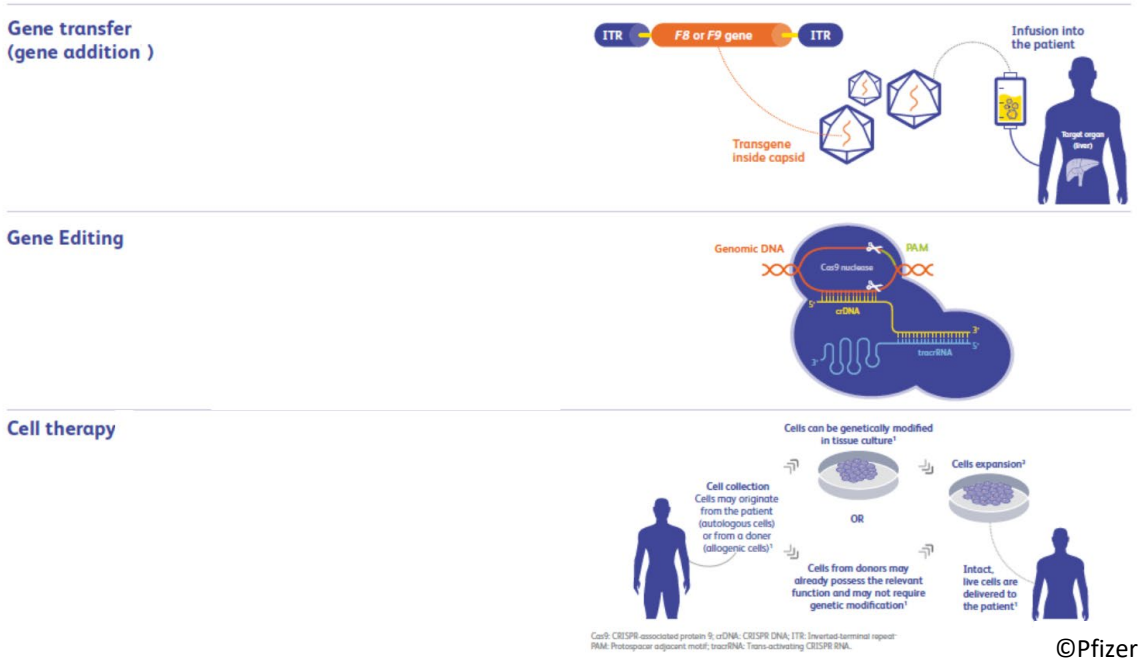
In its broadest interpretation, the term "gene therapy" may refer to[30]:

Gene Editing aiming to achieve gene correction by modifying part of a gene using recently-developed technology e.g. clustered regularly interspaced short palindromic repeats associated protein 9 (CRISPR/cas9), transcription activator-like effector nuclease (TALEN) or Zinc Finger (ZFN) to remove repeated or faulty elements of a gene, or to replace a damaged or dysfunctional region of DNA. The goal of gene correction is to produce a protein that functions in a normal manner instead of in a way that contributes to disease. [31]

Cell Therapy involving the transfer of intact, live cells into a person with a specific genetic disease.

Gene Transfer (Gene Addition) involving an addition of a functional copy of a missing gene or augmentation of a gene that is non-functional into target cells to produce more of a protein. Gene transfer therapy is currently being investigated at a therapeutic approach for the management of DMD.

Figure 4: Approaches to Gene Therapy[30]



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[30] American Society of Gene and Cell Therapy: Gene and Cell Therapy FAQs. Available at: www.asgct.org/education/more-resources/gene-and-cell-therapy-faqs (Accessed 12 October 2021).
[31] Cox DBT, et al. *Nat Med* 2015;21(2):121–31.

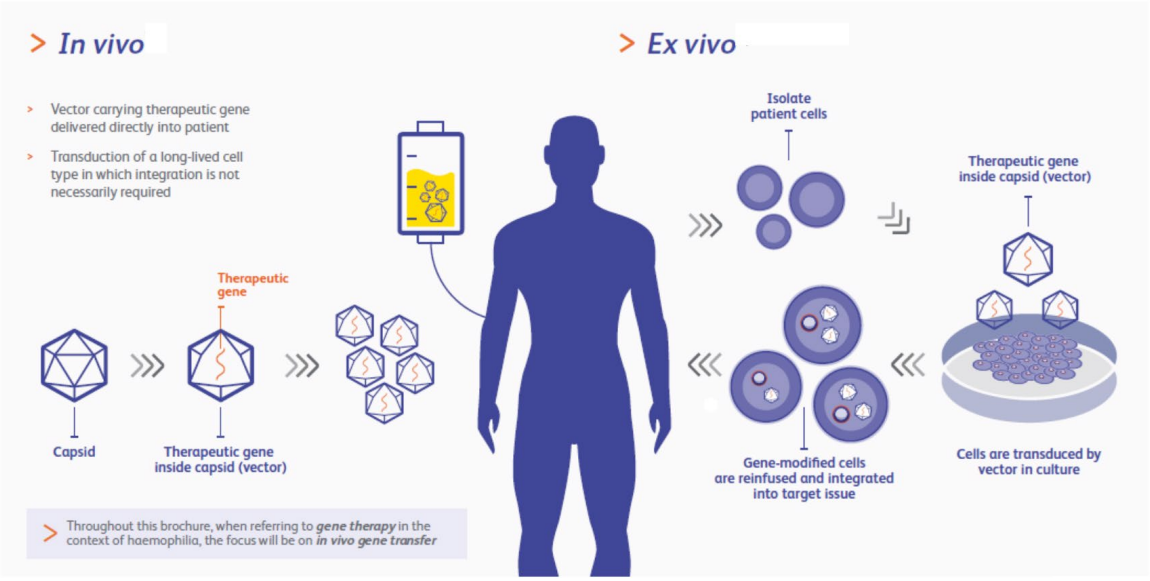
Gene transfer therapy aims to deliver a functional copy of the dystrophin gene to the muscle cells in suitable people with DMD. As these DNA molecules are rapidly degraded in biological fluids (and therefore unable to reach the target cells), delivery vectors are utilised to protect the genetic material.[32] The functional gene (referred to as a transgene) is packaged into a capsid (protein shell), resulting in a vector that can deliver the transgene to the nucleus of the target cell, where the cell can then express the therapeutic protein of interest.[24, 33] The success of gene transfer therapy is therefore dependent on the development of effective vectors that act as vehicles for gene transfer, that are based on recombinant viral sequences, but are not viruses themselves.[34]

Gene transfer therapy can be administered in two ways.[24,33]

In vivo – the vector is administered intravenously, and reaches the target cell of interest via the systemic circulation, or the vector is administered locally, directly to the target organ

Ex vivo – cells are taken from the patient. The vector is introduced to the patient's cells in the laboratory and the cells are then reintroduced into the body

Figure 5: Gene Transfer Therapy Administration[24,33]



With gene transfer therapy, both capsid components and the transgene may be seen as 'foreign' by the immune system, potentially triggering an immune response. Therefore, both pre-existing immunity to the capsid or an immune response to the gene transfer therapy vector (capsid or transgene) can be important considerations for gene transfer therapy.[35]

Considerations in determining eligibility for gene therapy

Eligibility for gene therapy will be determined by a number of criteria, including a blood test to check for the presence of antibodies to the viral vector used to deliver a specific gene transfer therapy. Other medical conditions, age and stage of the disease may also impact eligibility of individuals for gene therapy. While gene therapy holds potential for people with genetic diseases, it will not be an appropriate solution for every person with a given genetic condition.

[32] Nobrega C, et al. A Handbook of Gene and Cell Therapy. Springer International Publishing; 2020.
[33] Sidonio R, Jr. *Blood Rev* 2020;100759. doi: 10.1016/j.blre.2020.100759 (Online ahead of print).
[34] Lheriteau E, et al. *Blood Rev* 2015;29(5):321–8
[35] Mingozzi F, et al. *Blood* 2013;122(1):23–36.

The potential of gene therapy for DMD

Promising new treatments for various muscle and nerve conditions have been developed in recent years, many of which are progressing to the clinical trial stage. As DMD is caused by an alteration (mutation) in a gene, located on the X-chromosome responsible for the expression of dystrophin, the condition is a suitable candidate for gene therapy.

Along with possible savings on direct health care costs, such as reduced medical and/or hospital visits, gene therapy could offer the opportunity to improve quality of life, including the potential to return to school or work and reduce the burden of care for family members and other caregivers.[36,37] Gene therapy has the potential to increase or restore function in affected tissues or cells over a long period of time and may enable a person living with a genetic condition to manage his or her disease without the need for ongoing treatments.[24,25]

For patients and caregivers, this represents the potential to avoid years—and potentially a lifetime—of burden associated with chronic disease management - a welcome relief for people living with a condition such as DMD.

Pfizer's gene therapy clinical development program for DMD

Clinical trials of gene therapy in patients with DMD are currently underway. The efficacy and safety of Pfizer's gene transfer therapy candidate, fordadistrogene movaparvovec (PF-06939926), is currently being evaluated in a Phase 3 study involving a number of countries across the globe.[38]

Pfizer is starting its Phase 3 studies with patients aged 4 to 7 years as boys with DMD are still functionally improving from ages 4 to 5, and then begin to decline between 6 to 7 years of age.[26,29] As of July 2021, patients have been dosed as part of the Phase 3 CIFFREO study in Spain, the UK and Italy.[39]

The DMD clinical program aims to address the full spectrum of the disease, with plans to conduct additional studies enrolling non-ambulatory boys with DMD with eligible genetic mutations and those under 4 years of age.

Pfizer is committed to better understanding the impact of neutralising antibodies to the recombinant adeno-associated virus (AAV) vectors used to deliver gene therapy. We also are conducting a study to evaluate the risks of seroconversion in families following the administration of gene therapy, which is of particular concern to families with multiple children who may be eligible for treatment.

Establishing sustainable commercial manufacturing for gene therapies

Manufacturing gene therapies is very specific, delicate and intentional. One of the most significant challenges facing the availability of gene therapies delivered by viral vectors is the ability for end to end production. This process follows four main steps to produce each dose of a gene therapy: preparing raw materials, encapsulating the desired gene during the upstream process, purifying the viral vector during the downstream process and then packaging the treatment for clinical or commercial use.[40]

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[36] Murphy SL, High KA. *Br J Haematol* 2008;140:479–87.
[37] Salzman R, et al. *Mol Ther* 2018;26(12):2717–26
[38] NIH US National Library of Medicine ClinicalTrials.gov. A Phase 3 Study to Evaluate the Safety and Efficacy of PF-06939926 for the Treatment of Duchenne Muscular Dystrophy. Available at: https://clinicaltrials.gov/ct2/show/NCT04281485?term=06939926&draw=2&rank=2 (Accessed 14 October 2021).
[39] Pfizer Inc. Pfizer Doses First Participant in Phase 3 Study for Duchenne Muscular Dystrophy Investigational Gene Therapy. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-doses-first-participant-phase-3-study-duchenne (Accessed 14 October 2021).
[40] Pfizer Inc. Gene Therapy Videos. Available at: https://www.pfizer.com/science/research-development/gene-therapy/gene-therapy-videos (Accessed 14 October 2021).

There are currently very few companies that have the facilities, hardware, experienced staff, in-house platform, or licensed technologies to produce such vectors. Companies that do not have such capacity must rely on contract manufacturing organisations (CMOs) for production. However, there is presently a significant industry backlog with an average wait time of 16 months for CMOs to start new viral vector projects, even on a smaller clinical scale.

Scaling up production capacity of gene therapies is both difficult and costly. It is important to educate payers and policymakers around gene therapy including that the complexity and regulation of gene therapy materials and manufacturing can make it difficult to achieve commercial production on a larger scale. Therefore, it will be vital that policymakers are open to changes required to support innovative therapies and actively encourage growth in the gene therapy manufacturing landscape.

There is also a need for quality assurance standards. Given the highly complex production and material requirements surrounding gene therapy, there are currently few standards in place to assure their quality. As companies accelerate their efforts and CMOs strive to rapidly build capacity, regulators must provide guidelines that work alongside existing traditional Good Manufacturing Process (GMP) standards, to ensure that gene therapy production and materials are safe and quality is assured.

How does the healthcare system attribute value to gene therapy and potentially transformative treatments?

Gene therapies have the potential to offer long-term, transformative benefits through just one dose, and are expected to provide greater value and benefit to patients with rare genetic diseases than existing treatment options.[24,25,36,37]

This raises the need for new ways to define value, solve for affordability, and provide access. This new treatment paradigm requires payers to shift away from the traditional pricing model of conventional chronic therapy to which they are accustomed.

As medical innovation evolves, so too must payer models and systems. Approaches could include horizon scanning, longer-term budget planning, and creating more fluid budgetary structures, whereby value gains in one part of the health system can be used to fund high-value therapies, while working with manufacturers to develop alternative payment models that allow the cost of therapy to be spread over time.

If standard value assessment methods overlook and undervalue these benefits, there will be a real risk of delayed or denied patient access. There is an acute need to work together to find innovative solutions that provide timely patient access to gene therapy, while simultaneously addressing any additional evidence needs through the following principles: acceptance of new evidence, recognition of the extent of the unmet need and consideration of broader economic benefits.

Patients are anxiously awaiting these treatments, so it's imperative all stakeholders work together to ensure health systems are ready to deliver these therapies as soon as possible.

The outlook for Michael and his family

Michael and his family are extremely fortunate to have a very supportive Duchenne community who also share similar experiences. This community is a wonderful group of parents who support one another on the Duchenne journey. They are a very close-knit community and often collaborate to campaign for change and fight for the opportunity to gain access to critical clinical trials for emerging DMD therapies.

"The ability to walk for longer or stand up so we can hug them would mean the absolute world to us. Even prolonging the effects of the condition would buy them valuable life saving time while a cure can be found. This condition typically takes our sons from us from as young as their 20s or younger. To be able to live a longer fuller life would have an incredible impact on the entire Duchenne community."

Gene therapy may offer this possibility.

Gene therapy for DMD is currently still in development and under investigation. It is not currently available nor provide safe or effective.

Judy's Journey

Judy, a 57-year-old self-employed hairdresser, was two years into the standard treatment for her follicular lymphoma (FL), in a period of watchful waiting, with testing to see if the treatment was working. The relatively mild nature of the early stage of the disease allows patients of follicular lymphoma to forego some of the more intense treatment options of other lymphomas, and cancers in general. But as is often the case with those engaging in a watch and wait strategy, Judy's lymphoma eventually progressed, prompting a need for a more proactive treatment approach.

Following a deteriorating condition, Judy was taken in for a PET scan and bone marrow biopsy, which revealed transformation to diffuse large B-cell lymphoma (DLBCL), a much more aggressive cancer that can be fatal within months if left untreated. As per National Comprehensive Cancer Network (NCCN) guidelines, Judy was treated with three different regimens of chemotherapy over the ensuing year and a half.[41] Although mixed response was achieved occasionally, Judy was ultimately met with disease progression.

For a patient with DLBCL, an autologous stem cell transplant (SCT) is an accepted next line of therapy, however such an option was off the table for Judy given the refractory nature of her disease to chemotherapy treatment. Instead, Judy was initiated on lenalidomide and rituximab treatment.

At this point, many haematologists and oncologists will recommend a more aggressive intervention, based upon the response of the patient to previous therapies. Judy, having been disqualified from autologous stem cell transplantation, was presented with the option of an allogeneic stem cell transplant. Though there is no patient characteristic that would necessarily exclude Judy from being a candidate for such a procedure, the allogeneic sourcing of cells is markedly riskier than its autologous counterpart, manifesting in higher rates of transplant-related morbidity and mortality. Beyond the daunting reality of facing a procedure with such well-documented risks, Judy also had to consider a year out of work, a necessary recovery window following the surgery.

Despite the best efforts of her medical professionals, Judy had no further treatment options available to her. It was at this point in Judy's journey that her haematologist heard about a vacancy in a clinical trial for CAR T-cell therapy. Judy was enrolled in the clinical trial and treated with CAR-T.

What is DLBCL and how is it treated?

DLBCL is the most common form of non-Hodgkin Lymphoma (NHL), making up between 33% and 51% of all B-cell NHL. The National Cancer Control Indicators (NCCI) of Australia estimated the incidence of NHL to be 5,720 patients in 2019,[42] and given a conservative estimate of 35%, the subgroup of Australian NHL patients with DLBCL can be calculated at approximately 2,000 per year. In 2017, there were over 50,000 diagnosed adult patients with DLBCL in the United States, and that number is expected to swell to over 56,000 by 2027.[43]

The standard, preferred treatment for relapsed or refractory DLBCL is based on the patient's eligibility or intention to undergo SCT and is determined by a number of factors, including medical fitness (represented by an International Prognostic Index score) and comorbidities.[44] For those patients who are willing and able, potential therapeutic procedures include autologous SCT, allogeneic SCT, clinical trials for unapproved

[41] National Comprehensive Cancer Network. (2021). B-Cell Lymphomas (version 4.2021).
[42] National Cancer Control Indicators. (2019). Cancer incidence (https://ncci.canceraustralia.gov.au/diagnosis/cancer-incidence/cancer-incidence).
[43] GlobalData. (2019). B-Cell Non-Hodgkin's Lymphoma (NHL): Opportunity Analysis and Forecasts to 2027.
[44] Liu Y, Barta SK. Diffuse large B-cell lymphoma: 2019 update on diagnosis, risk stratification, and treatment. *Am J Hematol*. 2019;94(5):604-616. doi:10.1002/ajh.25460

therapies currently under investigation or CAR T-cell therapy (though at the time of Judy's disease CAR T-cell therapy was still itself in the clinical trial phase).

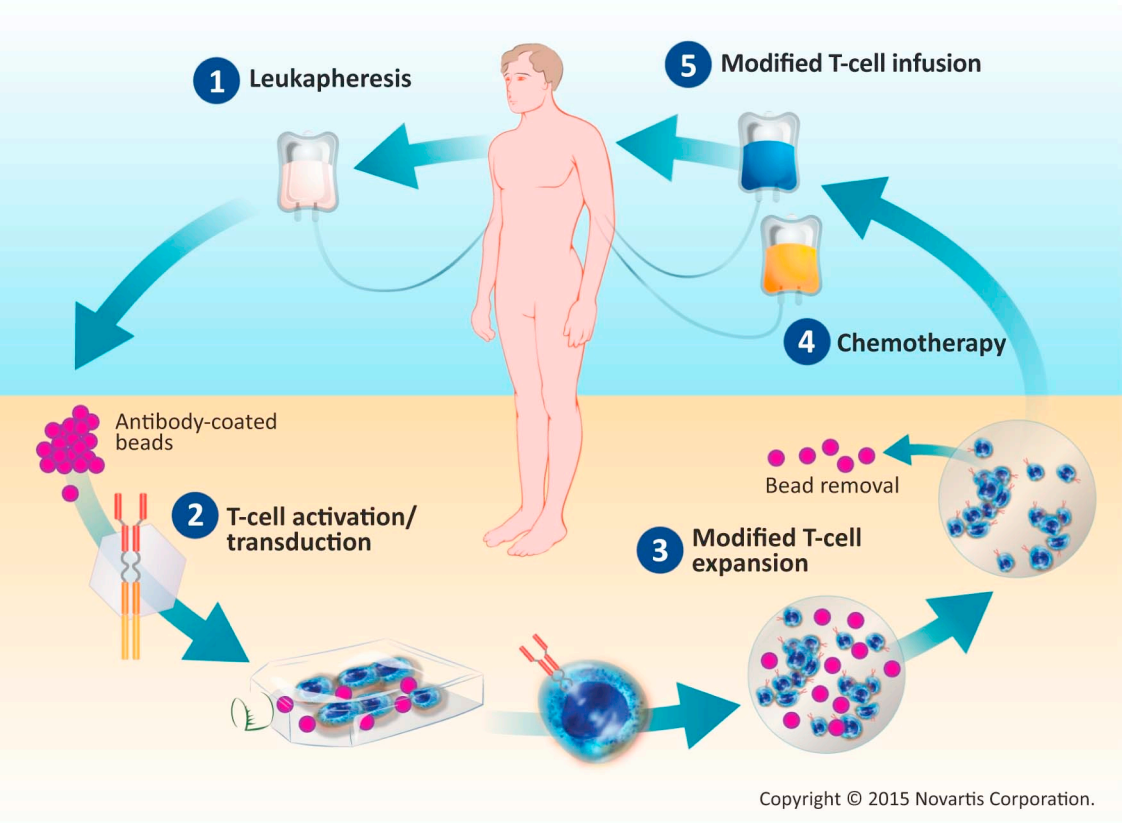
As mentioned earlier, the stage of Judy's disease rendered her ineligible to undergo the autologous procedure. For such a patient, salvage therapy alone or salvage therapy and allogeneic transplantation are the next best option. Nonetheless, she found the toxicities of the allogeneic transplant troubling, leaving her options limited.

What is CAR T-cell therapy?

In terms of cancer treatments, CAR T is a relatively new one. The first CAR T-cell therapy to be approved in Australia, Kymriah®, was authorised by the TGA (Therapeutic Goods Administration) in 2018 for the treatment of relapsed or refractory DLBCL after two or more lines of systemic therapy, and paediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse. Put simply, in the case of autologous CAR T-cell therapy, a patient's own T-cells are collected by apheresis, genetically modified to target and attack cancer cells, and then infused back into the patient.

Of course, the actual development of such a complex treatment is much more intricate, see Figure 1. The first step in the manufacturing process of Kymriah® is the harvesting of non-mobilised peripheral blood mononuclear cells by apheresis. Within 24 hours the cells are cryopreserved and stored. Shortly thereafter the material is shipped to the Novartis-accredited Kymriah® manufacturing facility, which will be explained later, and stored once again.

Figure 6. Kymriah® treatment and processing cycle (Image provided by Novartis Pharmaceuticals)



Once manufacturing capacity is available to process this sample, the apheresis material is thawed and washed. At this point the T-cells are transduced and genetically modified. Afterward, the cells are grown or "expanded"

until the target cell volume is reached. The modified T-cells are then separated from the rest of the growth-stimulating culture, collected in infusible media in infusion bags and cryopreserved. This bag of modified patient cells is the personalised cell therapy Kymriah® (tisagenlecleucel). Following quality testing, the cryopreserved tisagenlecleucel is transported back to the treatment site to be stored until thawing and patient administration.[45]

A logistics network as complex as that required for Kymriah® necessitates many moving parts. There are demanding logistics in the cold chain necessary to transport the cryopreserved material. The manufacturing of Kymriah® is a highly centralised process, the patient's cells are shipped to the manufacturing facility to be processed before being shipped back to the site of treatment of the patient. The management of lead times in these processes is critical to limit the chance of disease progression. These lead times have now been optimised in Australia. The operation of shipping such sensitive cargo has incentivised manufacturers to contract large and specialised couriers to guarantee standards of quality and sample authentication.[46]

Though Kymriah® has been approved by the TGA since 2018, until recently there were no on-shore manufacturing facilities for commercial supply. Peter McCallum Cancer Centre in Melbourne hosts Cell Therapies Pty Ltd, a contract development and manufacturing organisation (CDMO) that specialises in the complex manufacturing of cell and gene therapies. Cell Therapies Pty Ltd was recently granted approval by the TGA to commercially manufacture Kymriah® for patients in Australia, making it the first of its kind in Australia, and one of only 6 locations in the world manufacturing Kymriah®. Beginning production early in 2021, the facility has been able to supply Kymriah® to other CAR T-cell cancer centres in Melbourne, Sydney, Brisbane and Perth that were previously relying on a manufacturing network stretching all the way to New Jersey, USA for processing. For Judy, this means her potentially lifesaving cells no longer need to be shipped around the world as she was battling her disease, significantly decreasing the risk of loss of the product during transport and reducing the time for the return of the manufactured dose.

Navigating the regulatory environment

In order for Kymriah® to be approved in Australia to treat patients like Judy it had to go through clinical trials and be approved by the TGA, the government agency that regulates the use of medicinal products.

The Australian clinical trial protocol is broken down into the CTN (clinical trial notification) scheme and the CTA (clinical trial approval) scheme (formally CTX). Kymriah® went through the CTN scheme because there was evidence from previous clinical use supporting the use of the biological. The prior clinical studies were reviewed by international regulatory authorities and the Australian ethics committee had sufficient expertise to review these prior studies. In general CAR T-cell therapy, as a gene-modified cell therapy, is classified as a Class 4 biological by the TGA which must be submitted under the CTA scheme.

The CTA scheme is differentiated from the CTN scheme by the level of involvement of the TGA. Whereas with the CTN scheme the human research ethics committee (HREC) reports to the TGA as an intermediary, CTA trials have both an HREC and direct involvement from the TGA. With this distinction in mind, the CTA scheme application procedure is currently undergoing review by the TGA.[47]

The TGA provides accelerated application and approval timelines in hopes of incentivising cell therapy manufacturers and encouraging research activity. Though the CTN scheme timeline for document preparation is approximated at a brief two week period from notification to acknowledgment, the CTA scheme used for CAR T-cell therapies is in line with that of the US and EU at two to three months.

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[45] Tyagarajan S, Spencer T, Smith J. Optimizing CAR-T Cell Manufacturing Processes during Pivotal Clinical Trials. *Mol Ther Methods Clin Dev*. 2019 Nov 29;16:136-144. doi: 10.1016/j.omtm.2019.11.018. PMID: 31988978; PMCID: PMC6970133.
[46] GlobalNewswire. (2019). Vineti announces strategic partnership with Autolus Therapeutics to support delivery of novel T cell therapies.
[47] Australian Clinical Trials. (https://www.australianclinicaltrials.gov.au/researchers/regulatory-environment)

For CAR-T therapies in Australia, approval by the HREC may be shorter than in the US but longer than in the EU at twelve to eighteen weeks, with no predetermined time constraints. Environmental risk is typically addressed by the Office of the Gene Technology Regulator (OTGR), but CAR T-cell therapy is exempted, and will take approximately 30 to 50 days for approval.[48]

Additionally, and as with all ex vivo gene therapies, CAR T-cell therapies must comply with the Australian regulatory guidelines for biologicals (ARGB).[49]

Kymriah® is obviously not alone in being the subject of much enthusiasm in the medical community, as evidenced by the 1,100 reported CAR T-cell technology-based clinical trials underway globally in September 2020. Australian clinical trials operate by a different but similar mechanism to those in the United States. Kymriah® was approved for DLBCL by the FDA in 2018 with orphan drug and Breakthrough Therapy designations. Both qualifications are mechanisms to expedite treatments for diseases that are sufficiently rare (less than 200,000 patients in the US) or particularly serious, respectively.

The TGA classifies CAR T-cell therapy as a GMO therapeutic, or a "biological medicine derived from living genetically modified organisms." Prior to initiating clinical trials involving GMOs, an authorisation under the Gene Technology Act and the Therapeutic Goods Act of 1989 must be acquired. Clinical trials with CAR T-cell therapy, however, are considered "Exempt Dealings" as they are autologous and do not require licensing under the Gene Technology Act.[50]

The Federal Government also plays a role in the delivery and administration of CAR T-cell therapy, announcing in 2020 an intent to expand subsidised access to CAR T-cell therapy for indicated patients. Government sponsored access and funding of Kymriah® by way of the National Health Reform Agreement (NHRA) is expected to benefit ~200-250 DLBCL patients like Judy each year. Australians looking to treat with Kymriah® would be charged up to $500,000 without government funding but following a recommendation from the Medical Services Advisory Committee (MSAC) early 2019 and early 2020, Kymriah® therapy became free for eligible patients under 26 years of age with ALL, and eligible adult DLBCL patients respectively. This comes following the 2019 $80 million Federal Government funding of Cell Therapies Pty Ltd, the company licensed by Novartis to manufacture Kymriah® locally.[51]

With such a substantial price tag, Novartis has garnered much global public scrutiny. In response, in 2018 the Institute for Clinical and Economic Review (ICER) released a report evaluating CAR T-cell therapy in comparison to traditional chemoimmunotherapy in B-ALL and NHL patients. They concluded that both Kymriah® and its competitor CAR T-cell product Yescarta® "provide a net health benefit compared to standard chemoimmunotherapy regimens and found both therapies to be cost-effective in the long-term,"[52] thereby verifying the product's legitimacy regardless of its steep cost. It is also possible that in the future CAR T therapies will become available as earlier stage treatments and the costs currently associated with multiple alternative treatments prior to CAR T therapies will be saved, this too will decrease the cost outlay for treatment.

Put another way, though the product price is much higher than traditional alternatives, the cumulative cost of these alternatives accrues over time, whereas the full cost of Kymriah® is singly incurred at the point of administration.

[48] TGA. (https://www.tga.gov.au/accessing-unapproved-products)
[49] TGA. (https://www.tga.gov.au/publication/australian-regulatory-guidelines-biologicals-argb)
[50] Australian Government: Department of Health. (2020). Approval processes for new drugs and novel medical technologies.
[51] Novartis. (2021). TGA approves first Australian commercial CAR-T manufacturing site – bringing faster access to eligible Australians with life-threatening blood cancers.
[52] Institute for Clinical and Economic Review. (2018). A look at CAR-T therapies.

Kymriah® as a Regenerative Medicine

Single administration Regenerative Medicines (RM) like Kymriah® offer governments an opportunity to explore new healthcare coverage strategies, as opposed to the traditional "pay as you go" system. Countries within the EU5 are employing various such strategies better aligned with outcome-based reimbursement, including individual patient outcome-based instalment payments, or scaling reimbursement with efficacy data. [53] [54]

One of the ways by which RM differentiates itself from more traditional therapeutic options is the fewer number of doses required, and CAR T-cell therapy is no different. First line therapies for DLBCL usually consist of many rounds of chemotherapy or chemoimmunotherapy, administered over long periods of time with commensurately long hospital stays. For all parties involved, the costs are burdensome.

On the other hand, though coming at a larger upfront cost, a RM therapy like Kymriah® offers the possibility of efficacy after a single infusion, requiring modest inpatient stays, if any stay at all.

Judy's recovery

Four weeks following her CAR T procedure, a PET scan revealed Judy had achieved a complete response and was able to return to work just two weeks later. One year following the infusion she is showing ongoing remission in her scans.

In terms of her adverse effects from the Kymriah® treatment the worst of Judy's symptoms was a few days of fever, reported to her treating clinic and managed and reported through the adverse events system. All adverse effects related to Kymriah® or any regulated medical products in Australia are reported through the adverse effects systems of the relevant company (usually via the website, email or telephone) to ensure the safety of products and patients.

Results like Judy's are not uncommon. As a matter of fact, interim analysis of Kymriah® in a trial for relapsed or refractory DLBCL showed that 52% of patients responded to treatment with 40% achieving complete remission and 12% partial remission. [55]

Many such anecdotes related to Kymriah® are widely available, with subjects of clinical trials experiencing near-miraculous improvement in their condition at a point in their treatment course they previously thought unsalvageable, not to mention the countless equivalent experiences of patients receiving the therapy post-approval. Among these stories, one unifying sentiment emerges; an optimistic relief that the lifesaving intervention they received was approved and will soon be available to other patients like themselves who so desperately need it.

[53] Schmidt C. What Drives Diffusion of New Cancer Therapies. *Cancer Epedemiol Biomarkers Prev*. 2015; 107(6):2-3. doi:10.1093/jnci/djv162

[54] Jorgensen J, Hanna E, Kefalas P. Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. *J Mark Access Heal Policy*. 2020;8(1):1715536. doi:10.1080/200116689.2020.1715536

[55] Schuster S, Bishop M, Tam C et al. Tisagenlecleucel in Diffuse Large B-Cell Lymphoma. N Engl J Med 2019; 380(16): 1585-1586. Doi:10.1056/NEJMc1901464

Tissue Engineered Products (CelGro™)

Regenerative Medicine: Adrians's Best Hope for Restoring Independence

Adrian Walsh was a fit, active 43-year-old father of three, who loved nothing more than getting out to the Perth hills on the weekend with his mates and his mountain bike. That all changed in June 2017, when Adrian went over the handlebars of his bike on a downhill run, headbutting a tree before hitting the ground. He knew straight away something wasn't right. He couldn't feel his legs. After a week in ICU, and three weeks in the trauma ward, Adrian spent the next four months in hospital undergoing extensive rehabilitation. Adrian was diagnosed with C6 quadriplegia. He couldn't straighten his elbow and had no movement in his wrists, hands, trunk and legs. Doctors told Adrian that he would need a wheelchair to get around and help with daily living for the rest of his life. With the help of his surgeon and occupational therapist, and thanks to advances in the regenerative medicine (RM) technology of bioscaffolding, Adrian underwent complex reconstructive surgery to restore movement to his paralysed arms. The 12-month and two-year outcomes have astounded everyone.

What is a Bioscaffold?

Bioscaffolds are natural or artificial structures used alone or in conjunction with cells, and often stimulatory compounds, to help repair damaged body tissues. Bioscaffolds are a component of what is referred to as "tissue engineering", an area of RM. The scaffold itself acts as a structure around and on which cells can form tissue, while stimulatory compounds encourage new tissue growth, like the fertiliser for a newly-potted plant. Referred to as the "tissue engineering triad," these techniques can be leveraged to regenerate various types of tissues around the body, like nerves in Adrian's case, giving the procedure incredible therapeutic potential.[56]

CelGro™ is a collagen (the most common protein found in the body) membrane product developed by Orthocell, an Australian biotechnology company based in Perth. The manufacturing process is designed to make it biologically unreactive, unlike some other scaffold alternatives. CelGro™ can be used on its own to facilitate host tissue growth, or in tandem with a cell therapy to support tissue regeneration. In Adrian's case, the CelGro™ scaffold was used on its own, wrapped around the repaired nerves, to support the nerve regeneration and re-connect signals from Adrian's brain to activate his paralysed muscles.

[56] Fergal J. O'Brien. (2011). Biomaterials & scaffolds for tissue engineering. Materials Today, Volume 14, Issue 3, Pages 88-95. ISSN 1369-7021. https://doi.org/10.1016/S1369-7021(11)70058-X.

Nerve Regeneration

Adrian's paralysis was caused by damage to his spinal cord, disrupting the signals from the brain that control muscle movement. It's a very serious diagnosis, as damage to the spinal cord is irreversible. The majority of people living with quadriplegia are young men, in the prime of their lives, which has devastating emotional and financial consequences for those affected and their families. Luckily, however, peripheral nerves – those outside the spinal cord – do have the ability to regenerate, like a lizard regrowing it tail. Doctors have been able to use this ability to "re-wire" active peripheral nerves above the spinal cord injury to peripheral nerves made inactive below the spinal cord injury. The process is called nerve transfer surgery. The surgeon identifies a healthy, expendable nerve and joins it using microsutures to an inactive nerve serving the muscle group that is paralysed. Regenerating nerve fibres grow from the healthy nerve into the inactive nerve to reconnect it with the target muscle group. The CelGro™ scaffold is wrapped around the join to create a healing environment and support nerve regeneration.

Without nerve transfer surgery, Adrian's only other treatment option was rehabilitation with intense, ongoing physical and occupational therapy. Rehabilitation can only preserve and strengthen whatever function was left after his injury, and Adrian would be left needing help with almost all facets of his daily life – showering, eating, dressing getting in and out of bed. Before his nerve transfer surgery, Adrian couldn't even push his wheelchair independently.

Circumstances like Adrian's, where traditional treatment does not lead to any improvement, are ideal for an RM approach. Adrian's condition positioned him as a prime candidate for a collagen scaffold-assisted reconstructive surgical procedure. Luckily, there was a local hospital conducting clinical trials of Orthocell's tissue engineered product, CelGro™ collagen scaffold, for nerve repair and Adrian was able to enroll in the clinical trial.

RM and Bioscaffolds in Australia

Collagen scaffolds like CelGro™ are subject to the Australian Regulatory Guidelines for Medical Devices (ARGMD), which regulate standards of import, export, manufacture, and supply of medical devices. As of June 2021, the guidelines are being reviewed and updated by the Department of Health, though the requirements for clinical trials will likely remain largely unchanged[57].

CelGro™ has already received regulatory approval for bone and soft tissue regeneration in dental surgeries in Australia, the EU, and the US. Orthocell also has a number of products in the clinical trial process using CelGro™, as well a unique cell therapy using the patient's own tenocytes, Ortho-ATITM, to repair damaged tendon. Adrian, like many other patients in need of peripheral nerve or tendon repair, received his treatment via one of these clinical trials. These products must demonstrate efficacy and safety in order to be approved by the Therapeutic Goods Administration (TGA). In the regulatory framework, CelGro™ falls under the approval area of medical devices while Ortho-ATITM is classified as a biological. Approval of therapies allows them to be included on the Australian Register of Therapeutic Goods (ARTG), a critical achievement on the journey to get a product reimbursed.[58]

Early in 2021, CelGro™ Dental (the application of the scaffold in dental procedures) was added to the Australian Prostheses List. The inclusion increases the accessibility of the product to patients for approved dental and soft tissue procedures by enabling dental practitioners to receive reimbursement from private insurers. This is just one example of the ways that the Australian government is enhancing the availability of promising, cutting edge RM therapies for the Australian public.

[57] https://www.tga.gov.au/publication/australian-regulatory-guidelines-medical-devices-argmd
[58] Orthocell. (2021). CelGro recommended for reimbursement.

The TGA also serves as a regulatory body to oversee manufacturing of the therapeutic products under their jurisdiction. All such products must be manufactured in a facility that is licensed by the TGA as complying with Good Manufacturing Practice (GMP). Orthocell's GMP-certified laboratory was constructed in 2007, followed by a license from the TGA to manufacture Human Tissue in 2009. A few months later, Orthocell began manufacturing their cell therapy products and launching them into the Australian market.

The CelGro™ manufacturing chain developed by Orthocell utilises their proprietary SMRTTM tissue engineering system, which ensures the scaffolds do not contain any impurities. This improves the biocompatibility of the product, eliminating the rejection response of the body that would accompany the presence of contaminants. Moreover, raw materials for CelGro™ are sourced from Australia, which has a dual advantage of shortening the length of the manufacturing chain (and therefore logistic complexity, a cost saving that can be passed on to the patient) and elimination of many disease-transmission concerns.[59]

A RM Team Effort

Adrian underwent surgery in 2018, where his surgeon joined a healthy nerve controlling his shoulder muscles and to the nerves controlling arm extension (tricep muscles) to allow Adrian to straighten his arm. The surgeon also reconnected the nerves controlling muscles in his hands, allowing Adrian to open and close his fingers. CelGro™ scaffold was wrapped around each join. The scaffold has three functions. It acts as a barrier to protect the nerve from other types of cells invading the repair site, it helps retain the supportive cells and growth factors needed by the regenerating nerve fibres and it directs the growth of nerve fibres into the inactive nerve, preventing neuroma formation and ensuring that the regenerating fibres reach their target muscle. Another advantage of using CelGro™ is that fewer sutures are needed to join the nerve ends together. Sutures are generally used to keep the two ends of the nerves together, but sutures cause damage to the delicate nerve tissue that can have a negative effect on nerve regeneration. CelGro™ adheres to the nerve tissue due to its unique surface properties, so that far fewer sutures are needed to keep the nerves in place. Over time, the CelGro™ scaffold is naturally resorbed, replaced by normal, healed nerve tissue.

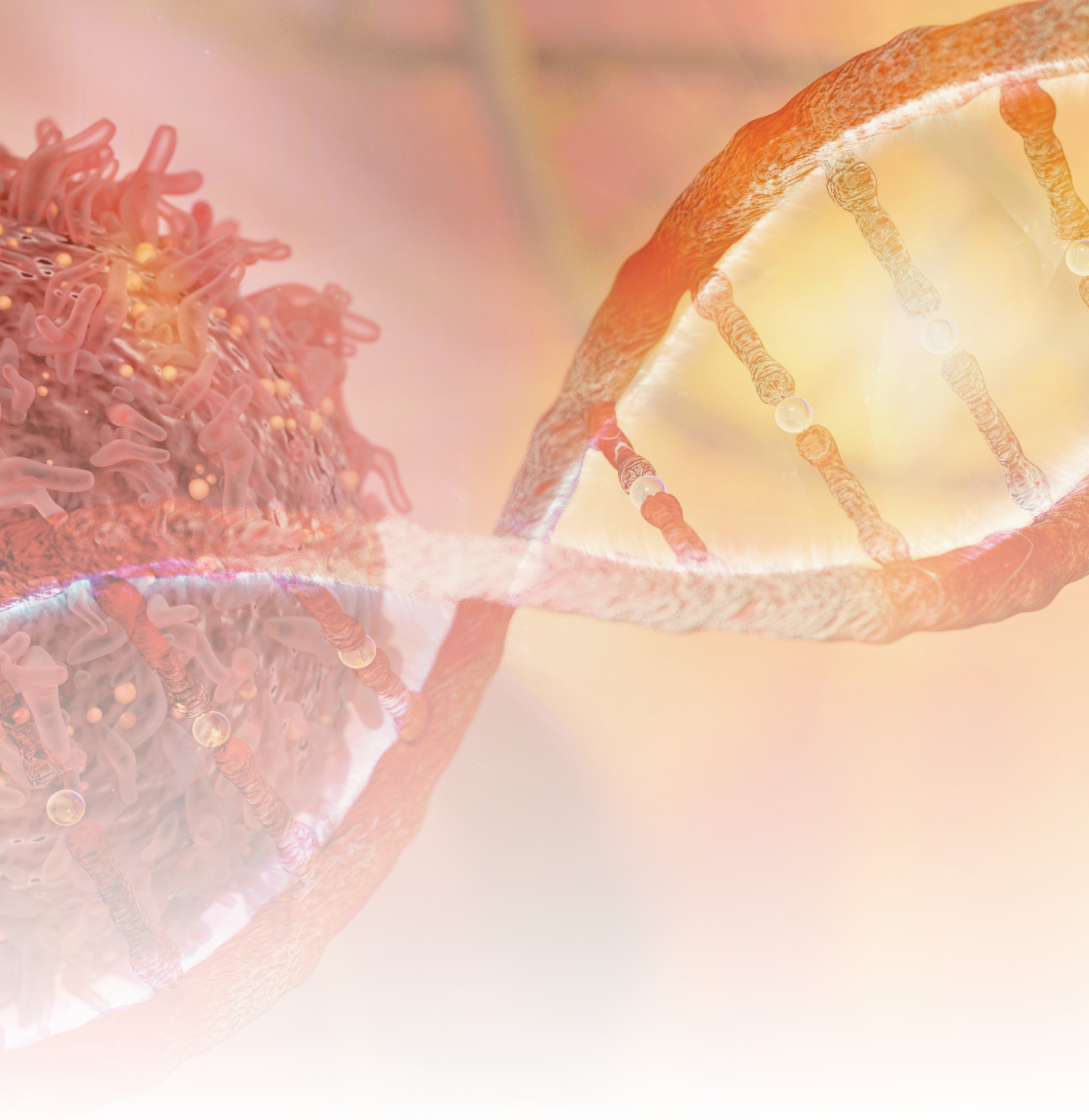
[59] Orthocell. CelGro. (https://www.Orthocell.com.au/CelGro)

Adrian's Outcome and the Future of Australian RM

Within 12 months post-surgery, Adrian's hard work with the occupational therapist is really paying off. Adrian is now playing wheelchair rugby, thanks to the improved strength in his triceps, and although the former electrician can't return to his previous line of work, he's forging a new career path with a Diploma in Project Management and Building Construction Management. He has a driver's license and with a modified car, has regained a level of independence he thought impossible before his surgery. Being able to help around home, helping with the school runs and being more involved with his family has meant the world to Adrian. Even his surgeon is impressed, noting that the level of function Adrian experienced at 12 months would not normally be achieved until two years after surgery. The other participants in the clinical trial also experienced similar results, with over 75 percent of nerve transfers resulting in restored movement to previously paralysed limbs, allowing them to regain the ability to do simple, everyday tasks that are normally taken for granted, like brushing your teeth or drinking from a cup.[60]

Impressive recoveries like Adrian's have attracted the attention of researchers, medical professionals, and institutions around the world, inspiring surges of resource allocation to the RM sector including from the Australian Government. In 2019, Minister for Education Dan Tehan announced that $5 million would be directed toward the Australian Research Council Training Centre for Cell and Tissue Engineering Technologies at Monash University.[61] Australia has been ahead of the curve in the RM sector opening one of the world's largest RM hubs, the Australian Regenerative Medicine Institute, in 2009 through a $153 million joint venture of between Monash and the Victorian Government. Orthocell was founded on medical research from the University of Western Australia and the Perron Institute in Western Australia. The wide range of institutions involved in RM and the increasing funding for RM are part of ensuring that Australia is well placed to continue to see successes in the development of RM that lead to improved treatments for patients like Adrian, and an increasingly wide range of other illnesses.

[60] Orthocell. (2021). Positive CelGro nerve regeneration results in quadriplegic patients
[61] Ministers' Media Centre. (2019). Research to improve medical treatment for Australians.



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