NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

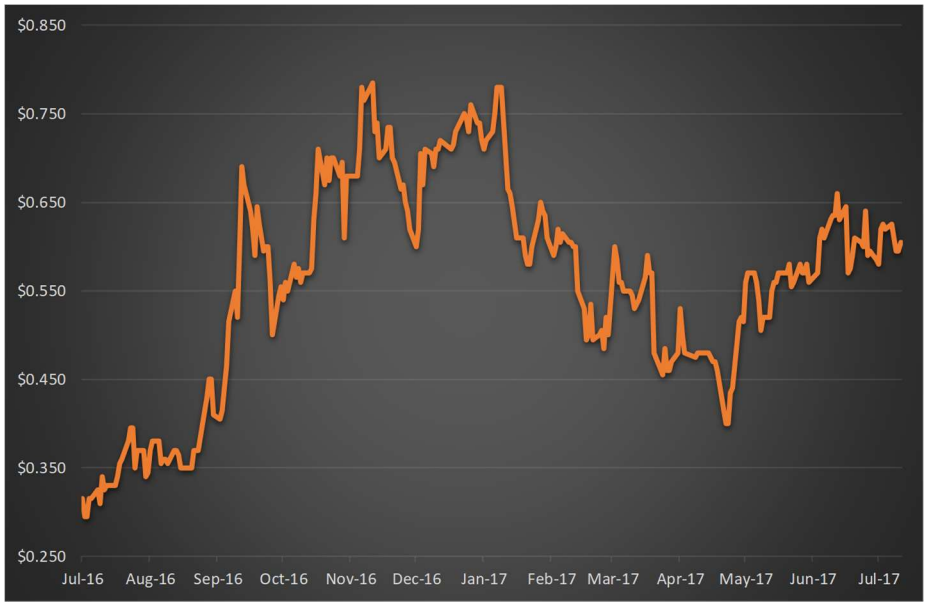
Cynata (ASX: CYP)

Initiation of Coverage – Monday 24 July 2017

The Swiss Army Knife of cellular remedies

Regenerative medicine is the future – and will create some billion-dollar companies. Cynata is well placed for this race. Its Cymerus technology uniquely produces vast quantities of Mesenchymal Stem Cells (MSCs) from a single blood donation. This science, originated by Prof. Igor Slukvin at the world-leading stem-cell labs of the University of Wisconsin-Madison, is exclusively licensed to Cynata. MSCs have wide application: heart repair, rebuilding bones and cartilage, reducing inflammation and much more. For example, in early 2017 (with backing from Britain's NHS), Cynata initiated a UK-based Phase 1 trial in steroid-refractory acute Graft vs Host Disease (GvHD). Happily, international majors are noticing Cynata's ground-breaking progress. In January of this year, Fujifilm (now a global leader in cellular medicine) initiated a strategic partnership with Cynata and optioned the GvHD indication in a deal with upfront, milestone and royalty payments. The company also made a $4m equity investment in Cynata. The future is on the way. Our target of $2.00 per share sits at around the mid-point of our probability-weighted valuation range of $1.03 per share base case and $2.77 per share optimistic case.

Rating	Risk	Current price	Target price
Buy	Medium	$0.605	$2.00



Stock details

Daily Turnover: ~A$131,000
Market Cap: A$54.5m
Shares Issued: 90.1m
52-Week High: $0.805
52-Week Low: $0.029

Analyst: Stuart Roberts
stuart@ndfresearch.com
+61 447 247 909

Please note: This report has been commissioned by Cynata and NDF Research will receive payment for its preparation. Please refer below for risks related to Cynata 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

In this report

Eleven reasons to consider Cynata 5
Mesenchymal Stem Cells are hot, right now 8
Traditionally-sourced 'Gen 1' MSCs have limitations 9
Cynata is scaling up its Cymerus MSC production 10
Regenerative medicine is big news in Japan 12
Fujifilm is a great partner to have 13
A first clinical evaluation in GvHD 14
In vivo data on other indications is building up 15
Valuing Cynata – A probability-weighted approach 16
Valuation – Discounted cash flows 17
Re-Rating Cynata 21
Cynata's leadership team 21
Appendix I – A tale of antibodies and stem cells 22
Appendix II – A Cynata glossary 30
Appendix III – Cynata's IP position 32
Appendix IV - Major shareholders 32
Appendix V – Key relevant papers 33
Appendix VI – Cynata's capital structure 34
Appendix VII – Comparable companies 35
General Advice Warning, Disclaimer & Disclosures 38

Introducing Cynata (ASX: CYP)

CYNATA IS PART OF A REVOLUTION IN MODERN MEDICINE

Cynata is part of the next Revolution in modern medicine. Over the three decades or so medicine has passed through a series of what can reasonably be called Revolutions, where new technologies enable treatments for disease previously not considered possible. In the 1980s, we had the Biotech Revolution, where the tools of genetic engineering were harnessed to create powerful protein-based drugs. Then came the Antibody Revolution from the late 1990s with its succession of exquisite targeted monoclonal antibodies drugs. We argue that the next Revolution, into which we are now headed, is the Stem Cell Revolution, where the healing power of stem cells is harnessed to help re-create and repair damaged tissue. It is not unreasonable to see many stem cell and regenerative medicine[1] companies emerge from this Revolution with market capitalisations of over a billion US dollars. Today, most of them are publicly traded at under US$200m. Cynata is available for only ~US$43m. We suggest that stem cell companies like Cynata today are where the monoclonal antibody companies were in the mid-to-late 1990s.

Cynata uses induced Pluripotent Stem Cells (iPSCs) to make large amounts of Mesenchymal Stem Cells (MSCs). This makes Cynata, in effect, a play on the two most powerful stem cell technologies that have emerged in the last decade. iPSCs represent a more-or-less unlimited source of starting material to make stem cells, while MSCs represent a class of adult stem cells that the clinical evidence suggests is safe and effective in treating a range of disease conditions. Cynata uses these two types of stem cells together to overcome the key problem for the regenerative medicine field: consistent and sufficient production of potent stem cells on an industrial scale.

Cynata's stem cell production method sets it apart. Cynata's stem cell platform technology, which it calls Cymerus, represents a process to create MSCs using iPSCs from a single donor, rather than from multiple bone marrow or adipose tissue donations, which is the current practice for a number of incumbent stem cell players. Cymerus originates from the identification by Slukvin et. al. at the University of Wisconsin-Madison of a powerful MSC precursor called a mesenchymoangioblast (MCA), the derivation of which was patented and then reported in a key 2010 paper in the respected journal *Cell Stem Cell*[2]. Slukvin et. al. showed[3] that these MCAs could be markedly expanded without losing their therapeutic potency as members of the Mesenchymal Stem Cell family, and this technology became the basis for Cynata, which was backdoor-listed in late 2013[4]. Cynata since proceeded to develop iPS methods of making these mesenchymoangioblasts at scale, becoming in February 2015 the first company in the world to show that iPS-based production of MSCs at scale was possible[5]. At that time, there wasn't any *in vivo* data on the effectiveness of iPSC-derived MSCs in treating patients. The achievement, however, was notable because now virtually unlimited quantities of MSCs of consistent quality can be manufactured at very low cost.

[1] The term 'regenerative medicine' is believed to have been coined in the late 1990s by the US bio-entrepreneur William Haseltine, founder of Human Genome Sciences - see Sampogna et. al., *Regenerative medicine: Historical roots and potential strategies in modern medicine,* Journal of Microscopy and Ultrastructure, Volume 3, Issue 3, September 2015, Pages 101-107.
[2] A 'sub-journal' of the journal *Cell* focused on stem cells.
[3] The paper was entitled *A mesoderm-derived precursor for mesenchymal stem and endothelial cells* – see Cell Stem Cell. 2010 Dec 3;7(6):718-29.
[4] The shell was Ecoquest, ASX Code ECQ.
[5] Specifically, the company creates iPS cells which are then expanded, and then induced to express two proteins called APLNR and PDGFRa, indicative of MCAs. Both are considered a good marker for isolation of early mesoderm-committed cells from hESCs.

Using iPSCs allows Cynata to make MSCs in very, very large amounts. This point is worth re-iterating. iPSCs are normal adult cells - blood cells for example - reprogrammed so that they once again exhibit the potential to differentiate into nearly all different cell types ('pluripotency'). They're created using various transcription factors[6], and once a cell has been reprogrammed to the pluripotent state, it can expand in exceedingly large numbers just like embryonic stem cells, but without the ethical hassles traditionally associated with that class of cell.

Cynata has important *in vivo* evidence of the effectiveness of Cymerus MSCs that, it believes, shows iPSC-derived MSCs working like other MSCs. One early example was in Critical Limb Ischemia (CLI), which is a severe blockage in the arteries of the lower extremities[7]. MSCs have been shown to treat CLI by rebuilding blood vessels, and in the standard mouse model of CLI, Cynata's MSCs have been able to restore blood flow in the ischemic limbs. The mice treated with saline ended up losing those limbs[8]. The company has also announced compelling data in models of asthma, Graft-versus-Host Disease and heart attack.

Cynata has scaled up its manufacturing processes. In February 2014, the company retained a firm in Madison, Wi. called Waisman Biomanufacturing[9] to work on increasing the amount of MSCs it can produce with Cymerus, and validating, documenting and improving the production process. This step-up to industrial production has allowed Cynata to achieve two things:

1. Initiate a proof-of-concept clinical study to show that iPSC-derived Cymerus MSCs work like traditionally sourced MSCs. There is already substantial clinical knowledge of the effectiveness MSCs, so this study has the potential to unlock considerable shareholder value.
2. Allow Cynata's cells to be used, under commercial agreements, in studies throughout the academic community, potentially generating many new indications for the cells.

Cynata has dosed its first patient in a human clinical trial. Cynata chose steroid-refractory Graft-versus-Host-Disease as its proof-of-concept indication, and in May 2017 dosed its first patient. The fact that approval was granted for this trial is a good sign, because it means that the UK's MHRA saw potential in Cynata's pre-clinical proof-of-concept animal studies with the same cells and was comfortable with their safety profile. And, we argue, it's a big deal. This is the first patient anywhere in the world to be treated with an allogeneic, iPSC-derived MSC therapy.

CYNATA DOSED ITS FIRST GvHD PATIENT IN MAY 2017

Eleven reasons to consider Cynata

1. **The time is now for regenerative medicine**. Over the last two decades, the scientific knowledge around stem cells and regenerative medicine has progressed in leaps and bounds. Early products are now in late stage trials or have gained regulatory approval and commercial launch. In this environment, the field is

[6] Once again, Cynata's founder Sluvkin was involved - See: Yu et. al., *Induced pluripotent stem cell lines derived from human somatic cells*. Science. 2007;318:1917–1920. This is another interesting paper for the aspiring investor, particularly as *Science* articles are generally easier for the lay reader to digest than other journals.
[7] And often arises in diabetics as a complication of their underlying diabetes.
[8] See the slides in the company's 26 November 2013 presentation headed '*Tissue salvage in mouse ischemic hind limb with Cynata's MCA-Derived MSCs'*.
[9] See www.gmpbio.org.

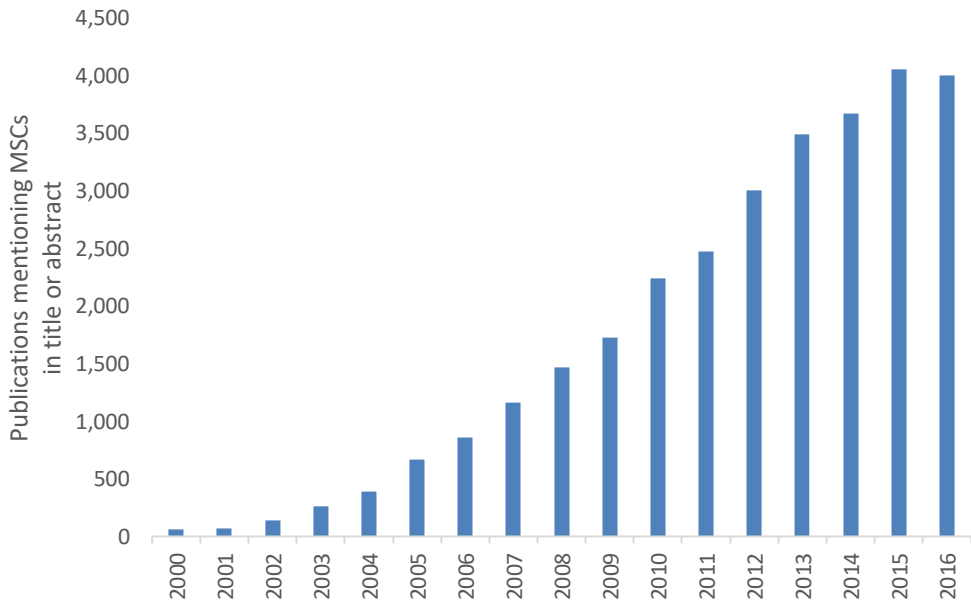
becoming increasingly important in modern medicine and we see strong upside for stem cell companies as investors realise the importance of having exposure to this novel form of therapy.

2. **Diverse treatment opportunities**. Mesenchymal Stem Cells (MSCs) have many potential indications. The cells can enable the repair of cardiac tissue, they can rebuild bone and cartilage, and, most importantly, they have been shown to have immunomodulatory properties. In addition to these applications, the apparent lack of immune reactions to MSCs derived from unrelated donors points to their potential to be used as 'off the shelf' products. This last property suggests drastically lower costs, as a one-size-fits-all product is far cheaper in many cases than one that is personalised for each patient. It also dramatically increases the potential commercial opportunity.
3. **Availability and cost**. Cynata solves one of the original problems with stem cells - quantity. The company's IP centres on a precursor cell called a mesenchymoangioblast (MCA), where a single colony can create up to 10^{22} MSCs. Cynata, in fact, begins with an earlier cell, called an induced Pluripotent Stem cell or iPS cell. This cell can be caused to differentiate into the precursor mesenchymoangioblasts and thence to MSCs. These iPS cells can be expanded indefinitely, which means that Cynata can potentially create an unlimited number of MSCs from the same starting material. Abundance leads the way to low-cost therapy.
4. **A thought-leader in stem cell technology is working with Cynata**. The inventor of the Cymerus technology, Professor Igor Slukvin, continues to work with Cynata, and is its third largest shareholder. Slukvin has done pioneering work on systems for making blood and blood-making cells from human pluripotent cells, and his institution, the University of Wisconsin-Madison, was the place where in 1998 the first human embryonic stem cell line was derived by Slukvin's colleague and co-inventor, Professor James Thomson. Slukvin was also a founder of another University of Wisconsin spinout, Cellular Dynamics International, which was acquired by Fujifilm in 2015 for US$307m (over 7 times Cynata's market cap).
5. **Cynata has an early-mover advantage**. Cynata is one of the first publicly traded companies in the world to make use of iPSC technology, the science of which delivered part of the 2012 Nobel Prize in Physiology or Medicine to Japan's Shinya Yamanaka. This makes Cynata a great concept stock for investors in the regenerative medicine field.
6. **Moving into practice**. Cynata is working with product development specialists Waisman Biomanufacturing in Madison on manufacturing process validation and documentation, as well as the actual manufacture of their product. To be made at commercial scale, there will need to be further work from a major contract manufacturer and we see the completion of scale-up to pilot plant as providing evidence that the technology works as expected.
7. **Cynata is now working closely with Fujifilm**. Fujifilm became a major global player in stem cells after it bought Cellular Dynamics in 2015 (as noted above). The Japanese conglomerate recently optioned the global rights to the use of Cynata's cells in Graft-versus-Host-Disease (GvHD). Should Fuji choose to exercise its option, it will pay US$3m upfront and up to US$60m in milestones, together with royalties, for a global license. We think this deal has helped further de-risk Cynata.

CYNATA IS A REGENERATIVE MEDICINE CONCEPT STOCK

8. **Favourable data**. The research data to date looks good, with evidence that Cymerus MSCs can make a serious difference in Critical Limb Ischemia (CLI) and in GvHD. GvHD provides a good 'proof of concept' test for Cynata as it represents an Orphan disease condition with great unmet medical need. The company has further proof-of-concept data in asthma and Acute Myocardial Infarction and is making progress in a cancer model.
9. **A Phase 1 trial in GvHD is now treating patients** Cynata dosed the first patient in a clinical trial in steroid-refractory GvHD in May 2017. A total of 16 patients are expected to be enrolled. Given evidence from many earlier studies that MSCs can be effective in this setting, we expect good results from this maiden clinical effort.
10. **Cynata's leaders have proven experience**. Dr Ross Macdonald, Cynata's CEO, gained important drug development knowledge at F.H. Faulding, Connetics and Stiefel. Dr Paul Wotton, Cynata's Chairman, brings valuable experience of the regenerative medicine field gained at Nasdaq-listed stem cell company Ocata Therapeutics before it was sold last year to Astellas for US$379m.
11. **Cynata is currently good value, in our opinion**. We value Cynata at $1.03 per share base case and $2.77 per share optimistic case, using a probability-weighted DCF method. This puts our target price at $2.00 per share, around the mid-point of our valuation range. Should the GvHD study show the clinical utility of the Cymerus technology, we see Cynata being re-rated.

Figure 1: Publications related to MSCs



Mesenchymal Stem Cells are hot, right now

Academic and commercial interest in MSCs has been increasing exponentially. Biotech companies and academic groups have been working on stem cell therapies ever since the first isolation of embryonic stem cells in 1998. We cover the recent history of stem cell and regenerative medicine research in Appendix I of this note. As more academic interest came to be focused on the regenerative medicine space from the early 2000s, Mesenchymal Stem Cells became an area of particular research focus, with the number of publications rising an average 33% p.a. between 2000 and 2015 (see Figure 1)[10]. That research interest has translated into a considerable number of clinical trials - there are currently around 750 studies underway around the world investigating the medical utility of MSCs – and an increasing number of commercial biotech companies with MSC-based therapies in their pipelines. Three important considerations have driven much of this research:

THE KNOWLEDGE BASE ON MSCs IS GROWING RAPIDLY

- **MSCs can be sourced relatively easily**. Researchers working on MSCs are zeroing in on the specific markers on the cell surface that denotes a stem cell of mesenchymal lineage. Understanding what these markers are makes it possible to extract the correct cells from a cell culture. That said, such cells are difficult to source efficiently, at least in the context of mass production.
- **There are no ethical issues.** Unlike embryonic stem cells, which will forever be associated with controversy, MSCs are adult stem cells which come from consenting donors and have never involved embryo destruction.
- **There is clinical evidence that they work, in important areas of medicine.** These areas, such as Graft-versus- Host-Disease, are in sore need of new treatments. Most of the clinical evidence has appeared in the last few of years, and a good deal of it relates to the immunomodulatory properties of MSCs.

And it's not just GvHD - MSCs have the potential to treat a broad range of diseases. Some examples are Acute Myocardial Infarction[11]; osteogenesis imperfecta[12]; Graft-versus-Host Disease[13], Spinal Cord Injury[14], Multiple Sclerosis[15], Crohn's disease (fistula)[16] and diabetes[17]. This broad potential medical application is a reason that the Australian company Mesoblast[18], which is the world leader in MSCs, has previously enjoyed a market capitalisation of more than US$2bn[19].

Cynata represents a play on the future popularity of MSCs in regenerative medicine. As we'll see below, it's reasonably likely that in the next few years MSCs will be involved in approved therapies in a wide range of disease conditions. Obtaining those cells at scale may then become a challenge for the makers of those therapies. Cynata has a solution to that forthcoming issue.

CYNATA IS A PLAY ON THE FUTURE POPULARITY OF MSCs

[10] Source: PubMed search for 'Mesenchymal Stem Cells' in title or abstract. Around 4,000 papers are year now publish on MSCs.
[11] See, for example, Circ Res. 2013 Jul 5;113(2):153-66. Epub 2013 May 8.
[12] See, for example, Transplantation. 2005 Jun 15;79(11):1607-14.
[13] See, for example, Immunol Invest. 2008;37(1):29-42.
[14] See J Vet Sci. 2007 Sep;8(3):275-82.
[15] See Cell Adh Migr. 2013 Sep-Oct;7(5):404-7. Epub 2013 Oct 30.
[16] Something Tigenix (Leuven, Belgium, Euronext Brussels: TIG, www.tigenix.com) is working on – see below
[17] See Clin Invest Med. 2008 Dec 1;31(6):E328-37.
[18] Melbourne, Australia, ASX: MSB, www.mesoblast.com.au.
[19] At its all-time closing high of A$9.99 in October 2011 it was capitalised at ~US$2.7bn.

Traditionally-sourced 'Gen 1' MSCs have limitations

Mesenchymal Stem Cells are rare in the human body. One of the ways that the incumbent companies can source MSCs is by 'fishing' them out of donated human bone marrow, however there is only around one MSC per hundred thousand bone marrow cells with a typical bone marrow aspirate yielding less than 20,000 MSCs[20]. Once those cells are obtained and purified, they then need to be expanded in culture. This is because a typical therapeutic dose requires around millions of MSCs for every kilogram of patient body weight[21]. Adipose tissue can yield much greater number of MSCs than bone marrow[22], but beyond sourcing there are other issues to deal with.

MSCs have a limited potential to expand. The way MSCs are expanded is by culturing them in a growth media so that the cells double and continue to double until there is a large number of cells. There is, however, a limitation to the number of potential doublings because after a point, the MSCs undergo 'replicative senescence', a term which means that the cells have lost potency and ultimately the ability to continue dividing and creating more cells. So, a single MSC batch can only create so many stem cells[23]. In addition, there is evidence that after many cycles of expansion, the immunomodulatory properties of MSCs and their ability to release of cytokines etc, are impaired by excessive expansion[24]. Thus, MSCs created using first generation techniques may have uses that are restricted to diseases with only very small patient numbers, somewhat limiting their commercial potential.

It has been suggested that the only truly potent MSCs are from the early passages[25]. A 2008 study published in the journal PLOS One[26] demonstrated that noticeable replicative senescence for MSCs could show up after only about seven passages, achieving no more than 13 and 25 population doublings. This would *at most* create about 7,000 MSC doses from a typical bone marrow donation; not a large number if we consider diseases with patient numbers in the many millions. It also showed that the genetic changes which contribute to senescence show up from the very first passage. So, the mass of product required can only be generated by either massively expanding the cells, which has the noted problems, or by repeatedly extracting tissue donations from multiple donors, which also has problems (see below). These studies indicate a potential issue with the old way of obtaining MSCs.

DIFFERENT DONORS PRODUCE SLIGHTLY DIFFERENT MSCs

Different donors produce slightly different MSCs. The quality of a starting batch of MSCs will vary widely depending on where it was sourced. Invariably, one needs younger donors because they yield more MSCs[27], and more effective MSCs[28]. The problem with having differences in MSCs from different donors and from batch to batch means that it is difficult to do the appropriate clinical trials, or even to just have a consistent therapy: every individual donor is different, meaning MSCs derived from them are also different. Every single batch of drug

[20] See Biomed Res Int. 2014;2014:951512. Epub 2014 Jan 6 and and Annu Rev Pathol. 2011;6:457-78.
[21] See, for example, Biol Blood Marrow Transplant. 2009 Jul;15(7):804-11.
[22] J Nippon Med Sch. 2009 Apr;76(2):56-66.
[23] The result can be fewer cells than would be ideal for large patient populations. Consider Osiris' estimate of the expansion potential of its cells – '*The MSCs are selected from the bone marrow and grown in culture so that up to 10,000 doses of Prochymal can be produced from a single donor*' (source: Osiris press release dated 28/9/2012 and headlined '*Swissmedic invokes rapid authorization procedures for Prochymal review*'). 10,000 doses from one donor may seem like a lot, but not if you're going after a market like, say, osteoarthritis, where 27 million US adults were affected in 2005 (source: CDC). This would take 2,700 donors assuming one dose was good for one patient per year in this population.
[24] See, for example, Cytotherapy, 2017; 19: 798–807; and Biol Blood Marrow Transplant 18: 557-564 (2012).
[25] See, for example, Shock. 2006 Dec;26(6):575-80; Neurosci Lett. 2010 Mar 19;472(2):94-8. Epub 2010 Feb 1; and J Tissue Eng Regen Med. 2014 May;8(5):407-13. Epub 2012 Jun 4.
[26] PLoS One. 2008; 3(5): 32213.
[27] One study found a 10-fold decrease from birth to the teenage years in terms of MSCs per nucleated bone marrow cell, and another 10-fold decrease from the teenage years to old age. See J Pathol. 2009 Jan;217(2):318-24.
[28] One 2013 animal study found that adipose-derived Mesenchymal Stem Cells from younger donors were much more effective in treating MS than were cells from older donors. See Stem Cells Transl Med. 2013 Oct;2(10):797-807. Epub 2013 Sep 9.

sourced from a different donor effectively becomes a different product, and needs a new 'potency assay' to show that it works as demonstrated when production is scaled up[29].

Purity is difficult, since there isn't a marker, or markers, that everyone agrees identifies a therapeutic MSC. As a result, cells that express the markers chosen may or may not carry other markers that are relevant for the efficacy of the therapy. In other words, we don't yet know exactly what markers or characteristics specify desirable functional attributes in stem cells, so we can't yet reproducibly generate functionally equivalent MSC populations unless you start from a single cell bank[30].

Cynata has the answer to all these production problems, with Cymerus because, as we noted above, iPS cells can produce as many MSCs as are needed. And the product it makes, originating from the same source cells, is consistent from batch to batch. This is a key reason why we think Cynata has such potential.

Cynata is scaling up its Cymerus MSC production

At the scale required for drugs used in clinical trials, Good Manufacturing Practice (GMP) is vital. GMP is a system of manufacturing used in food and drug production that ensures consistency and quality in products that will be consumed by humans (in some way or another). An important hurdle for stem cell manufacturers is making stem cells under GMP. Not only does the starting material need to be properly defined, but also the cell density in culture must be known, and the medium used optimised. In addition, best practice involves a serum-free medium which is more difficult to use in culture compared to the standard foetal bovine serum[31]. After all this is set up, further analysis and validation is required to ensure consistency of functional potential, phenotype, and microbiological safety. It is also important that the cells have remained untransformed throughout. Reaching GMP is, evidently, not easy.

Cynata has had its manufacturing process for Cymerus validated, meaning that its cells can be made under GMP. Cynata made this announcement back in February 2015[32], stating that the company would have both sufficient MSCs for future clinical trials, and the increased attraction to potential commercial partners as a result of the validation process. For its scale-up, Cynata chose the biomanufacturing facility Waisman Biomanufacturing, in Madison, Wi. This was a sound decision, in our opinion, because of all the expertise emanating from this geographic area. The company is now influenced directly and indirectly by a vast stem cell knowledge, particularly that coming out of the University of Wisconsin's Department of Medicine and Public Health, and the team at Cellular Dynamics (acquired by Fujifilm in 2015 for US$307m). Notably, the founding scientists behind Cellular Dynamics include members of the same team behind Cynata's Cymerus technology.

CYMERUS MSCs CAN NOW BE MADE UNDER GMP

[29] A potential issue for any biotech product is what happens to that product in scale-up. Should the product itself change because of a new manufacturing process, the FDA may require new clinical trials before it will approve products that are made in the scaled-up facility. Ordinarily producers of biotech products manage this issue through 'potency assays', allowing pre-scale-up and post-scale-up products to be compared.
[30] See J Cell Biochem. 2012 Sep;113(9):2806-12.
[31] Avoidance of fetal bovine serum in manufacturing of biological drugs became important in 1996 when British government admitted for the first time that bovine spongiform encephalopathy (BSE) could be transmitted to humans in the new form of Creutzfeldt-Jakob disease (vCJD). See PLoS One. 2015 Apr 13;10(4):e0122300. eCollection 2015.
[32] See Cynata's market release dated 19 February 2015 and headlined '*Cynata achieves major stem cell manufacturing milestone*'.

Next step: 3D manufacturing. Cynata's announcement in February 2015 related to '2D' manufacturing, meaning that their stem cells could be cultured in planar plastic flasks with a thin layer of media for nourishment. Large-scale cell production generally happens in 3D bioreactors and can greatly reduce costs and increase efficiency. There are various tricks that the Waisman people may have to get maximum yield from iPS cells, such as choice of media (both basal and supplementary), cell seeding density, the bioreactors used and the physiochemical environment within the bioreactor (which involves such variables as dissolved oxygen and carbon dioxide concentrations, temperature, pH, osmolality, and the buffer system). Given this array of tools, scale-up to 3D manufacturing is an engineering process rather than a scientific breakthrough in the making. It is notable that Cynata's partner, Fujifilm, has extensive cell product manufacturing expertise.

iPS-BASED THERAPIES ARE NOW IN THE CLINIC

The first clinical trial of an iPS-derived cell product only started in September 2014, so it is early days for this key regenerative medicine technology. The inaugural study, conducted by scientists at the Riken institute's Center for Developmental Biology in Kobe[33] led by Masayo Takahashi[34] involved the treatment of a 77-year-old Japanese woman with Age-related Macular Degeneration[35]. Takahashi et. al. treated their first patient and could report, in March 2017, that their therapy was safe and seemed to halt disease progression[36]. However, when a second patient came to be treated, issues arose with both the Japanese regulatory guidelines and the identification of potentially harmful mutations in the iPSCs as the Riken team attempted to reprogram the cells of that patient. This led to a temporary pausing of clinical work[37]. The latter problem highlights a key issue with using autologous cells (the patient's own cells) where producing a new cell line for every patient increases the risk that something will go wrong. Takahashi's trial has since been re-initiated, using allogenic cells (like Cynata's) to provide the trial with consistency. We argue that the Riken team's work since 2014 has helped move the iPS field forward, which is good for Cynata as an early user of iPS technology.

apceth Biopharma has given its tick of approval to Cynata. As well as having its own therapeutic MSC development program involving genetically engineered MSCs, this Munich-based company[38] helps manufacture and develop other biopharma companies' cell-based products. Cynata announced a license option agreement with apceth in May 2016 and as part of that relationship apceth undertook an evaluation of Cynata's Cymerus MSC's. During the evaluation in apceth's in-house cell culture and genetic modification systems, Cynata's cells demonstrated the necessary characteristics required for use with apceth's technology. apceth would see many different therapies day to day, so its validation is a good sign for Cynata. The original intention, which was to partner with Cynata to genetically modify Cynata's MSCs, did not proceed because of a early 2017 change in apceth's strategy, which de-emphasised oncology[39]. There is, however, the potential for continued collaboration, in other diseases. We see this as an opportunity for Cynata, as the company moved on to partner with Dr Khalid Shah of Massachusetts General Hospital (see below) for this area of great possibility.

[33] www.cdb.riken.jp/en/
[34] For some background on this stem cell pioneer see *Bringing sight to the blind* by Rebeca Tan, Asian Scientist, 11 February 2016.
[35] See N Engl J Med March 2017; 376:1038-1046. The inventor of the iPS cell, Shinya Yamanaka, supplied the cells.
[36] N Engl J Med. 2017 Mar 16;376(11):1038-1046.
[37] See *Mutation alert halts stem-cell trial to cure blindness* by Andy Coghlan, New Scientist, 31 July 2015.
[38] Ottobrunn, Germany, privately held, www.apceth.com.
[39] See Cynata's market release dated 31 March 2017 and headlined '*Cynata partner apceth GmbH & Co completes Cymerus evaluation*'.

Regenerative medicine is big news in Japan

JAPAN NOW APPROVES STEM CELL MEDICINES AFTER PHASE 2

Japan now approves stem cell products after Phase 2. 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'[40]. This will allow the Japanese Ministry of Health to give conditional approval to such products if their safety is confirmed after Phase 2, dramatically fast tracking commercial returns. This is significant because Japan is the world's second largest drug market after the US, worth ~US$100bn, and ten Japanese companies are in the list of the world's 50 largest pharma companies[41].

In early 2016, JCR Pharmaceuticals was given the green light from the Japanese Government to sell its product, called Temcell[42]. Temcell, licensed from Australia's Mesoblast (who, as we'll see below, acquired it from a US biotech company called Osiris Therapeutics in 2013), is an MSC product made from a donor's bone marrow cells. It's like Cynata's product, as it's an allogenic MSC product, however Temcell comes from human bone marrow cells so is not nearly as sustainable or scalable.

A second example, Holoclar, is a product developed by Holostem and Chiesi Pharmaceuticals. Registered in Europe in 2015, it's based on a treatment that involves the patient's own stem cells (read: autologous). It is currently for burns patients that have had their eyes damaged, and thus most limbus stem cells destroyed. The team extracts the remaining cells, grows them up on a fibrin scaffold, and then re-introduces them back into the patient's eye[43]. It appears to be a fairly successful use of stem cell therapy with 'permanent restoration of a transparent, renewing corneal epithelium attained in 76.6% of eyes' – time will tell.

Heartsheet is another Japan-approved regenerative medicine product. The product, made by Terumo[44], is sourced from a patient's own thigh muscle (again, read: autologous), grown up in the lab[45]. The stem cells in this case are called myoblasts, and are grown into a sheet which is transplanted 'onto a large area extending from the anterior wall to the lateral wall of the left ventricle'. This product is safe, indicated by the above clinical trial, however Terumo has five years to submit data to show that it is effective, to renew its license.

[40] These amendments were embodied in the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act.
[41] Astellas, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Kyowa Hakko Kirin, Mitsubishi Tanabe, Ono Pharmaceutical, Otsuka, Sumitomo Dainippon and Takeda.
[42] See the Mesoblast press release dated 27 November 2015 and headlined *'Mesoblast's Japan licensee receives pricing for TEMCELL HS Inj. for treatment of acute Graft Versus Host Disease'.*
[43] See N Engl J Med 2010; 363:147-155.
[44] Terumo (Tokyo, Japan, TSE: 4543, www.terumo.com) is a major medical device company with significant businesses in apheresis equipment, stent grafts, sterilisation trays and so on.
[45] See Circ. J. 79, 991–999; 2015.

Fujifilm is a great partner to have

Fujifilm optioned the global rights to the use of Cynata's cell product for GvHD, CYP-001, in January 2017. Under this deal Fujifilm can execute a licensing deal at any time within 90 days of Cynata getting clinical data in GvHD from the Phase 1 which is now underway. If it happens, Fujifilm will pay US$3m cash upfront and up to US$60m in milestones, together with double-digit royalties on product sales. Fujifilm will fund all further development and commercialisation costs associated with bringing CYP-001 to market, a huge advantage to Cynata. Fujifilm also took an equity stake in Cynata – investing $4m at ~$0.49 per share – and are its only substantial shareholder, with 9% of the company. It is notable that Fujifilm have publicly announced that they expect peak sales of a Cymerus GvHD product to reach US$300m pa[46]. Based on Cynata earning a double-digit royalty on such sales, this amounts to an EBIT revenue to Cynata of at least US$30m per year, worth US$150m on a 5x p.e. multiple. In view of the fast-track pathway for stem cell products in Japan, Fujifilm could conceivably be making sales and so paying royalty revenue to Cynata by as soon as 2019.

Fujifilm are a major player in stem cells. Fujifilm aren't just cameras and film anymore. The company has in fact been gradually deepening its involvement in healthcare for decades, beginning with its first move into X-Ray film in the 1930s. More recently, its 2015 acquisition of Cellular Dynamics for US$307m positioned it at the forefront of the Stem Cell Revolution. Cellular Dynamics (now owned by Fujifilm) is basically an industrial-scale manufacturer of iPS cells based in Madison, WI. It was primarily founded by Slukvin's Madison-Wisconsin colleague Professor James Thomson, with Slukvin himself as a co-founder. Thomson is famous as the man who isolated the first human embryonic stem cell line in 1998 as well as the man who almost beat Yamanaka to the first iPS cell. Thomson was featured on the front cover of *Time* magazine in 2001 as '*The man who brought you stem cells*'[47]. By 2009 Thomson and colleagues had invented a 'footprint free' technique for reprogramming adult cells into iPS cells that involve the use of episomes to deliver six reprogramming genes[48]. This provided a way to make clean iPS cells from any individual's blood, and then use them to manufacture differentiated tissue cells in industrial quality, quantity and purity.

FUJIFILM BOUGHT CELLULAR DYNAMICS FOR US$307M

The Fujifilm relationship has the potential to lead to other commercial opportunities. For one thing, Fujifilm's investment has the potential to de-risk the Cymerus technology given its control of Cellular Dynamics. Secondly, it may lead other partnership opportunities in Japan and elsewhere in the world.

[46] Source: Fujifilm Corporate Presentation, December 2016.
[47] This was the cover of the 20 August 2011 issue of the magazine.
[48] See Science. 2009 May 8;324(5928):797-801.

A first clinical evaluation in GvHD

In 2013 Cynata set itself the goal of a single proof-of-concept study in GvHD, to show that its cells worked at least as well as conventional MSCs. While steroid-refractory GvHD incidence is small, we believe it is growing rapidly: some estimates put the occurrence at 35-50% of BMT patients[49]. Bone Marrow Transplant becoming more common - marrow donations through the 'C.W. Bill Young Cell Transplantation Program', a US Government initiative, tripled between 2003 and 2013[50]. That probably means GvHD incidence is increasing as well. Patient outcomes are, however, still poor. For steroid-refractory patients, where powerful drugs like prednisone can't blunt the severe inflammation, only around 40-50% of patients will respond to this second-line therapy and only around 30% of patients will be alive after two years[51].

SURVIVAL RATES FOR STEROID-REFRACTORY GvHD ARE LOW

Others have validated the use of MSCs in GvHD. Osiris Therapeutics is a notable example with its Prochymal product, now approved in Japan for steroid refractory GvHD and in a Phase 3 study ahead of a filing for US approval. In effect, Osiris and Prochymal's acquirer, Mesoblast, did a lot of the 'heavy lifting' for Cynata, with a Fast-Track status[52] being assigned to their MSC treatment for children's GvHD by the FDA in March this year. This was off the back of positive interim results for a 60-patient Phase 3 trial they are conducting, and a 241 patient Expanded Access Protocol. On top of this, as we've already seen, Mesoblast has licensed its stem cell therapy for steroid-refractory GvHD in Japan through JCR Pharmaceuticals, who market it as Temcell. We think this product helps significantly de-risk Cynata from a clinical and commercial perspective.

The pre-clinical data looked good. Cynata announced in April 2016 that, in an animal model of severe acute GvHD, animals pre-treated with Cynata's cells lived for a median 54 days versus only 25.5 days for untreated controls. This outcome had a high level of statistical significance (p=0.0011). This study was conducted at the University of Massachusetts Amherst[53]. Animal studies with larger numbers of animals confirmed this interim data in February 2017[54].

IN VIVO, CYMERUS MSCs WORK IN GvHD

Cynata's GvHD study is now underway, expected to complete late 2017. Cynata sought approval to run a Phase 1/2 study in GvHD from the UK's Medicines and Healthcare products Regulatory Agency (MHRA) in August 2016, which was granted the following month. Four months later, the NHS's Health Research Authority approved the study for NHS hospitals. Cynata dosed its first patient in May 2017. The study will recruit up to 16 patients with steroid-resistant acute GvHD and will track complete and partial responses on Cymerus therapy, as well as survival at Days 28 and 100[55]. The company expects to complete patient dosing in 2017, based on historic diagnosis rates at the relevant hospitals. A DSMB analysis will be conducted after 8 patients have been treated, providing an indicative look-see at the results.

After the Phase 1/2 study comes a full US Phase 2. Cynata announced in June 2017 that it had had a pre-IND meeting with the FDA. Significantly, the Agency confirmed that it was comfortable with Cynata's CMC package

[49] See Blood. 2013 Nov 7;122(19):3365-75. Epub 2013 Sep 16.
[50] See http://bloodcell.transplant.hrsa.gov.
[51] See Biol Blood Marrow Transplant. 2012 Mar;18(3):406-13. Epub 2011 Jul 4.
[52] A shortening of the FDA review process from ten months to six.
[53] See the company's market release dated 7 April 2016 and headlined '*Compelling results from pre-clinical stem cell study in GvHD*'.
[54] See Cynata's market release dated 6 February 2017 and headlined '*Treatment benefit confirmed in final report of GvHD preclinical study using Cynata's MSCs*'.
[55] See NCT02923375 at www.clinicaltrials.gov.

related to Cymerus MSCs, and clarified that Cynata could file to for Regenerative Medicine Advanced Therapy status for these cells[56].

In vivo data on other indications is building up

Since 2013 Cynata's strategy for building a pipeline of Cymerus MSC therapies has been to make its cells available to various academic researchers to try them out *in vivo*. We see potential for these projects to grow into new programmes for Cynata, as well as attract further research interest as its academic collaborators publish their work. So far three groups have generated interesting results:

- **Critical Limb Ischemia, University of Wisconsin-Madison, December 2015**. The laboratory of Dr Timothy Hacker at the University of Wisconsin-Madison showed that Cynata's cells would work in this indication[57].
- **Asthma, Monash University, October 2016**. A group at Monash University in Melbourne led by Drs Chishan Samuel and Simon Royce had evaluated Cymerus MSC in an animal model of chronic allergic airways disease, finding that the cells could reduce airway hyper-responsiveness by 60-70% in the standard ovalbumin challenge test[58]. This decrease was statistically significant ($p<0.01$)[59]. Samuel and Royce published this study in The FASEB Journal in June 2017[60]. The Monash team is now looking *in vivo* at how Cynata's cells can work with steroids[61].
- **Acute Myocardial Infarction (AMI), Westmead Hospital, February 2017**. Cynata announced a collaboration in July 2015 with Dr James Chong of Westmead Hospital in Sydney to evaluate Cynata's cells in AMI. The Chong lab generated interesting data in February 2017 showing, in rat models of AMI, that Cynata's cells could improve cardiac function and scar size at 28 days[62].

CYMERUS MSCs MAY IMPROVE CARDIAC FUNCTION AFTER A HEART ATTACK

We believe more interesting data is coming:

- **Glioblastoma, Massachusetts General Hospital**. Cynata announced in October 2015 that it was collaborating with Dr Khalid Shah of Massachusetts General Hospital on the re-engineering of Cymerus MSCs to secrete cancer-killing toxins. A potential gliobastoma indication is being explored. Shah believes that, since MSCs tend to migrate to the site of tumours in response to signals sent out by the cancer, that MSCs could become targeted delivery vehicles for cancer drugs[63]
- **Acute Respiratory Distress Syndrome, Critical Care Research Group, Brisbane**. Cynata announced in April 2017 that a group in Brisbane was evaluating the use of Cymerus MSCs in the treatment of ARDS,

[56] See the Cynata market release dated 5 July 2017 and headlined '*FDA meeting provides clear path for Cynata US development plans*'.
[57] Cytotherapy. 2016 Feb;18(2):219-28. Epub 2015 Dec 28.
[58] Ovalbumin, a protein to be found in egg white, has long been used in the study of immune function because it provokes a strong immune reaction in test mice.
[59] See the company's market release dated 17 October 2016 and headlined '*Cynata's MSC technology demonstrates significant efficacy in preclinical asthma study*'.
[60] FASEB J. 2017 Jun 16. [Epub ahead of print].
[61] See the Cynata market release dated 2 March 2017 and headlined '*Cynata advances development of Cymerus MSCs for the treatment of asthma*'.
[62] See the Cynata market release dated 2 February 2017 and headlined '*Positive preliminary data from preclinical heart attack study with Cynata's MSCs*'.
[63] See Adv Drug Deliv Rev. 2012 Jun 1;64(8):739-48. Epub 2011 Jun 29.

in conjunction with the standard extracorporeal membrane oxygenation, where the blood is circulated through an artificial lung and back into the bloodstream of the patient[64].

Valuing Cynata – A probability-weighted approach

The chances of a new drug candidate just starting out in the clinic are about one in five. Drug development is risky, and many drug candidates fail either at pre-clinical, in the various clinical stages of development (Phase 1, 2 and 3), or at the regulatory stage when agencies have to make the decision to approve or not approve a drug. For clinical stage drug candidates, there are databases available[65] stretching back to the 1960s that have allowed researchers to estimate the probability of success at various stages of development. One recent estimate is shown in Figure 2:

Figure 2: Historical probabilities of success in drug developments[66]

	SMALL MOLECULES	LARGE MOLECULES
Phase 1	63%	84%
Phase 2	38%	53%
Phase 3	61%	74%
Filing for approval	91%	96%
Phase 1 to approval	13%	32%

Looking at Figure 2, we see most drug candidates make it through Phase 1 (the safety stage of development) – 63% in the case of small molecules and 84% in the case of large molecules. For those that survive Phase 1 and enter Phase 2, only 38% of small molecules and 53% of large molecules are successful. And so on. Some drugs are successful in the clinical stage but then rejected by regulators - 8% (ie 100% minus 91%) for which approval is sought in the case of small molecules, and 4% in the case of large molecules. Multiplying the probabilities in each case suggests that the probability that a drug entering Phase 1 will ultimately gained regulatory approval is around 13% for small molecules and 32% for large molecules.

We argue that the reason large molecules have a historically higher success rate than small molecules are threefold

1) Historically the biotechnology industry from the 1980s worked on 'low-hanging fruit' proteins that were easier to develop;

[64] See the Cynata market release dated 11 April 2017 and headlined '*Cynata collaborates with world leading team on Acute Respiratory Distress Syndrome project*'.
[65] Most notably from the Center for the Study of Drug Development at Tufts University in Medford, Ma. (see csdd.tufts.edu).
[66] Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.

2) Large molecules (eg monoclonal antibodies) have tended to be better targeted and therefore safer and more effective.

3) Large molecules have often been used in Orphan indications where the hurdles to gain approval are lower.

We argue that stem cell therapies have the potential for the success rates of large molecules, because of the multiple mechanisms of action, the apparently high safety profile from the early studies, and what we know about clinical efficacy from various stem cell programmes. However, for conservatism's sake in this valuation we have generally used a rough midpoint between the small molecule and the large molecule probabilities of ~21%.

Valuation – Discounted cash flows

We develop Discounted Cash Flow (DCF) models for four major programmes. As we have shown, Cymerus MSCs have multiple potential applications. For our valuation approach, we assumed payoffs from the Fujifilm relationship in GvHD, and from later partnerships in asthma and Acute Myocardial Infarction. We calculated DCFs of these programmes and weighted them by the historic probability of success of early-stage clinical programmes, as per the section above, ie 21%.

Cost of capital. 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 2.7%;

  Market Risk Premia. 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, or have optioned their products to larger partners, but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'. We regard Cynata as 'High Risk'.

  Ungeared beta. We use an ungeared beta of 1.1.

This approach suggests a discount rate for Cynata of 13.1% at the present time.

Elements of the commercial payoff for each programme – pre-launch. We estimated, for each notional Cynata programme, 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$);
- Level of milestones in the deal (in US$) – we assume that the probability of receiving those milestones declined evenly over time. We weighted the dollar value of milestones towards completion of Phase 2 and 3 as well as including some sales milestones.

For the current collaborations, there were in several cases milestone figures disclosed, but we had to estimate royalty rates.

Commercial life of future products. We assume that a product enjoys 15 years of commercial exclusivity, after which sales erode due to generic competition. While patent protection for a drug is notionally 20 years, patent term extension in the US only covers that part of clinical programme after the filing of an IND. This reduces the exclusivity window by a few years. For large companies marketing blockbuster drugs, the window is around 15-16 years[67].

Elements of the commercial payoff for each programme, 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.

Currency: We converted the US dollar cash flow streams into Australian dollars at the forecast exchange rates listed in Figure 3:

Figure 3: Our AUDUSD exchange rate forecasts

Half	AUDUSD
31/12/2017	0.773
30/06/2018	0.760
31/12/2018	0.748
30/06/2019	0.736
31/12/2019	0.723
30/06/2020	0.712
31/12/2020	0.700
Later periods	0.700

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

[67] Consider the Roche/Genentech cancer drug Herceptin. It gained FDA approval in September 1998 and enjoyed peak sales in 2014, for a 16-year window. Going further back in time, Amgen gained FDA approval for Epogen in June 1989. Its peak sales year was 2004, another 16-year window.

Further capital. We assume that after the January 2017 raisings to Fujifilm and other investors no further capital needs to be raised.

Potential for further valuation increments. We see potential for increases to our valuation as Cynata undertakes more *in vivo* work on new indications such as Crohn's disease, particularly where the disease in question has potential billion-dollar payoffs for new products and where the animal models used are considered 'gold standard'.

WE SEE POTENTIAL FOR FUTURE VALUATION INCREMENTS

Valuation – Project parameters

Figure 4: GvHD project parameters

	Base case	Optimistic case
PYC investment required (AUDm)	10	5
License date	2017	2017
License upfront (USDm)	3	3
License milestones (USDm)	60	60
Royalty rate	10.0%	12.0%
Earliest approval	2024	2023
Peak sales (USDm)[68]	400	600

Figure 5: AMI project parameters

	Base case	Optimistic case
PYC investment required (AUDm)	10	5
License date	2020	2019
License upfront (USDm)	25	50
License milestones (USDm)	100	200
Royalty rate	12.0%	15.0%
Earliest approval	2027	2026
Peak sales (USDm)[69]	700	1,200

[68] This kind of sales outcome wold involve 12,000 patients at US$50,000 p.a. For evidence that this is conservative consider Bone Marrow Transplant. 1993 Jul;12(1):43-8.
[69] For background on the reasonable sales prospects for a new AMI drug see *Pharma sector hails 'sea change' in heart disease treatment* by David Crow and Andrew Ward, Financial Times, 16 March 2015.

Figure 6: Asthma project parameters

	Base case	Optimistic case
PYC investment required (AUDm)	10	5
License date	2022	2021
License upfront (USDm)	25	50
License milestones (USDm)	100	200
Royalty rate	12.0%	15.0%
Earliest approval	2029	2028
Peak sales (USDm)[70]	1,400	2,400

Figure 7: Our valuation of Cynata.

	Base	Optim.
GvHD (A$m)	30.9	56.2
AMI (A$m)	40.2	115.8
Asthma (A$m)	38.0	113.0
Total programme value	109.2	285.0
Value of tax losses	7.5	7.5
Corporate overhead	-32.0	-32.0
Cash now (A$m)	11.6	11.6
Cash to be raised (A$m)	0.0	0.0
Option exercises (A$m)	7.2	7.2
Total value (A$m)	103.4	279.2
Total diluted shares (million)	100.9	100.9
Value per share	$1.025	$2.768
Valuation midpoint	$1.897	
Share price now (A$ per share)	$0.605	
Upside to midpoint	213.5%	

Valuation – Putting it all together

We completed our valuation of Cynata by adding.

1) The individual programme DCFs;

2) The notional value of the tax losses (ie the A$25m in retained losses as at December 2016 multiplied by the 30% Australian corporate tax rate);

3) The current cash on hand (A$11.6m as at March 2017);

[70] For background on the reasonable sales prospects for a new asthma drug see *AstraZeneca climbs after positive asthma treatment results* by Nick Fletcher, The Guardian, 17 May 2016.

4) The notional value of A$6m p.a. in corporate overhead, discounted in perpetuity at the discount rate calculated above, and adjusted for tax.

5) The $7.2m that can be received from option exercises by December 2020.

Valuation range $1.03 / $2.77. As per Figure 7 we value Cynata at $1.03 per share base case and $2.77 per share optimistic case. We regard $2.00 per share as a reasonable mid-range value of the company.

Re-Rating Cynata

We see the following factors helping to re-rate Cynata stock:

- DSMB analysis of the GvHD trial after the first eight patients;
- Completion of the GvHD study (with successful outcomes);
- Filing of an IND with the FDA;
- Potential transition to a formal licensee agreement with Fujifilm;
- Further commercial partnerships beyond Fujifilm and apceth;
- *In vivo* data on other Cymerus MSC indications.

Cynata's leadership team

Dr Ross Macdonald (CEO) has worked in large and small drug development companies including Amrad[71], F.H. Faulding[72], Connetics[73] and Stiefel[74] as well as Living Cell Technologies[75], another cellular therapy company, and Hatchtech[76]. Macdonald's varied managerial experience has enabled Cynata to move rapidly since he joined as CEO in July 2013.

Dr Paul Wotton (Chairman), who joined Cynata's board in June 2016 and became Chairman in February 2017, has an enviable resume for a stem cell company, having been CEO of Ocata Therapeutics prior to that company's acquisition to Astellas[77] for US$379m in November 2015. Wotton brings a background working for both Big Pharma and emerging Life Science companies such as the drug delivery company SkyePharma[78], where he was Global Head of Business Development.

[71] Amrad was bought by CSL in 2006 for A$108m mainly for its antibody projects. Macdonald assembled many of its early projects as VP, Business Development.
[72] This company was acquired in 2001 for US$2.4bn by Mayne Group, then mainly a private hospital group. Elements of the old Faulding have since shown up in two companies called Mayne Pharma, one of which was bought in 2007 by Hospira for its injectable cancer generic drug business, and another which is currently publicly traded on the ASX, code MYX. Ross Macdonald worked at Soltec, Faulding's drug delivery business.
[73] This company bought Soltec in 2001
[74] Bought by GSK in 2009 for US$2.9bn.
[75] This company (Auckland, New Zealand, ASX: LCT, www.lctglobal.com) works on transplantation of porcine islet cells for the treatment of diabetes in humans.
[76] Developer of a new lice control product (Melbourne, Australia, privately held, www.hatchtech.com.au).
[77] Astellas is the world's 21 largest pharma company with US$11.1bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[78] London, UK, LSE: SKP, www.skyepharma.com.

Dr Kilian Kelly (VP, Product Development) has worked at Amgen and AstraZeneca in Regulatory Affairs, and spent four years at Mesoblast in Regulatory and Clinical (2009-2013) before joining Cynata in 2014. Kelly was instrumental in helping Cynata achieve scale-up for its cells in early 2015.

Professor Igor Slukvin (Cynata co-founder and a member of Scientific Advisory Board) of the University of Wisconsin-Madison brings scientific credibility and deep knowledge of stem cells, as well as connections at what is a leading research centre for stem cells. Slukvin was a co-founder with James Thomson of Cellular Dynamics.

IGOR SLUKVIN CO-FOUNDED CELLULAR DYNAMICS WITH JAMES THOMSON

The Cynata board chaired by Wotton, which includes Macdonald, has enough expertise to keep the company moving forward. **Dr Stewart Washer**, who was Executive Chairman of Cynata from August 2013 to February 2017, and remains a non-executive director, has broad experience in drug and medical device start-ups[79]. **Dr John Chiplin**, a San Diego-based director best known for his time at the antibody company Arana Therapeutics from 2006 until its sale to Cephalon in 2009, is well connected in both US and European biotech circles. **Peter Webse**, a Perth-based director, brings corporate skills.

Appendix I – A tale of antibodies and stem cells

What is regenerative medicine and what are stem cells? Regenerative medicine is the emerging field of disease therapy focused on repairing or even replacing tissues damaged due to age or disease. The most widely visible form is stem cell therapy. Stem cells are undifferentiated cells that have the potential to become specialised cell types. Think back to high school biology. When an egg is fertilised it creates a zygote, which will go on to create every cell in your adult body. That is absolute potential, also called pluripotency[80]. The zygote divides, and, fast forward a few weeks, the three distinct environments have come into being: the endoderm, mesoderm, and ectoderm. By now, cells within these layers can only form restricted cell types in their cell-futures. For example, cells in the mesoderm ('meso' being Greek for 'middle') become everything in the middle of us – the blood, bones and connective tissues, to name a few. The once almost identical cells have begun to be restricted in what they will become. Kind of like a child growing up and choosing a career. There are three kinds of stem cell:

- **human Embryonic Stem Cells (hESCs)** – These are the most potent stem cells. They have the potential to form every cell of the human body. Discovered in 1998, hESCs are like the above example about zygotes because they are extracted soon after the egg has been fertilised *in vitro*[81].
- **Adult stem cells** – not as potent as hESCs, these cells are nonetheless capable of becoming a wide variety of cell types. One important example is Mesenchymal Stem Cells or MSCs, on which more below.
- **Induced Pluripotent Stem Cells (iPSCs)** – these cells are run-of-the-mill somatic cells[82] that have been reprogrammed back to a pluripotent state. They function like hESCs. This was a ground-breaking

[79] Gained at companies such as Calzada (polymer biomaterials), Phylogica (peptide drugs and vaccines) and iSonea (airway patency diagnostics).
[80] pluri = many, and potency = potential of the cell to differentiate. The 'potency' part of the word has nothing to do with the pharmacological meaning. For example, 'the most potent stem cell type' means that the stem cell type can differentiate into the most number of cell types.
[81] These cells are commonly obtained from IVF clinics, which often have surplus fertilised cells.
[82] For example, a skin cell is a somatic cell. So is a muscle cell. They are the standard, fully differentiated cell type. To continue the child metaphor, somatic cells are the working parent.

discovery in 2007 and won its discoverer, Japan's Shinya Yamanaka, a Nobel Prize in 2012. The applications of iPSCs in medicine are huge.

What are Mesenchymal Stem Cells and why is there so much regenerative medicine efforts focused on this family of cells? MSCs are stem cells that originate primarily in the bone marrow but also existing in many other organs and tissues. They were first identified in the 1980s by Dr Arnold Caplan at Case Western Reserve University in Cleveland, Oh.[83] What Caplan identified at that time ran counter to the dogma of that day was that adult animals only had hematopoietic stem cells. As research on MSCs progressed in the 1990s and into the 2000s it became apparent that whereas embryonic stem cells are associated with tumorigenesis[84] and involve ethical and legal considerations[85], MSCs are not only less problematic with regard to these issues but are self-renewing and also exhibit multilineage differentiation[86] – they have the potential to form bone, cartilage, and adipose tissue[87]. More recently, MSCs were discovered to be potent immune system modulators[88], which is where a considerable amount of research interest is being directed to at the moment, and one reason why Cynata's first clinical trial is in GvHD;

MESENCHYMAL STEM CELLS ARE POTENT IMMUNO-MODULATORS

What is the role of stem cells in medicine? Stem cells work with the human body, rather than against it, which is how most therapies work. They could potentially stimulate the body's endogenous systems to encourage new cell growth, and to modulate the immune system to reduce inflammation in certain cases. As a result, stem cells may be able to treat the actual underlying biology of many diseases. A good example is in cardiovascular medicine where a treatment of stem cells for heart failure could repair the heart tissue whereas current therapies such as drugs, defibrillators and pacemakers can only offer a reduced rate of tissue damage. It is therefore reasonable to expect that good data for a stem cell therapy could lead to a product with annual sales more than a billion dollars.

How close is the Revolution? Given the pace of new discoveries in the stem cell field, combined with the full amount of time since the initial discovery of hESCs, it is reasonable to see the Revolution kicking off before the next decade. Our reasoning is based on the following facts:

- Ethical issues have been overcome with the discovery of iPSCs;
- Clinical evidence is building up, demonstrating that stem cells work in areas of unmet medical need, particularly in chronic diseases of ageing. Much of it has emerged in the last five years;
- Governments have shown a willingness to fast-track stem cell medicines and to pour large sums of money into developing stem cell products;
- The move from autologous to allogeneic, meaning that the patient receives stem cells sourced from someone else's body, has created a commercially viable product. As a rule, allogeneic therapies are cheap because they can be 'off-the-shelf' whereas autologous therapies (using the patient's own cells) are expensive; and

[83] J Orthop Res. 1991 Sep;9(5):641-50.
[84] Adv Cancer Res. 2008;100:133-58..
[85] Nat Rev Genet. 2001 Jan;2(1):74-8.
[86] Cell Transplant. 2011;20(1):5-14.
[87] Bull Exp Biol Med. 2007 Jan;143(1):114-21.
[88] For a good review article see Immunol Cell Biol. 2013 Jan;91(1):19-26. Epub 2012 Oct 23.6.

- Industrial scale production using GMP, which regulators require, has been achieved.

What is the upside of Cynata? Availability of stem cells. Cynata has clear IP on the generation of MSCs from iPSCs. Since iPSCs are effectively an infinite source of starting material, and the intermediate cell in Cynata's process, called a mesenchymoangioblast (MCA), can create up to 10^{22} Mesenchymal Stem Cells, Cynata offers very high production volumes. This ability to make stem cells in bulk will be valuable as the Revolution draws near.

THE ABILITY TO MAKE STEM CELLS IN BULK WILL BE VALUABLE AS THE STEM CELL REVOLUTION DRAWS NEAR

Antibodies have been a great success, but stem cells offer more. Antibodies are great drugs because they have an exceptional ability to hit their target, and only their target. As a result, they have far fewer side effects than conventional small molecule drugs. Antibodies are, in effect, Paul Ehrlich's famous 'magic bullet' against disease[89].This specificity is why, a decade after the FDA approved the first monoclonal antibody, global sales hit US$31bn and then a mind-numbing US$84bn in 2016. Antibodies today are ~8% of the entire world pharmaceutical market, 21 are blockbusters[90], and six are among the top 20 highest grossing drugs worldwide[91]. It didn't happen overnight, however. It needed 22 years, a lot of capital and a few true believers to get that Revolution started.

Monoclonal antibodies were long considered far-fetched science. The technology, invented back in 1975[92], won its inventors, in 1984[93], the Nobel Prize in Physiology or Medicine. In the 1980s and 1990s, however, there were multiple clinical set-backs that threatened to resign the potential new therapy to a dusty shelf[94]. The main problem was the early antibodies were mice antibodies and the two species just had too many genetic differences. Moreover, as is the present case with MSCs, they were exceedingly difficult to manufacture consistently and economically. Once the technology was developed to 'humanise' the mouse antibodies, around 1988[95], and the manufacturing bugs were eliminated, the field hardly ever looked back again.

The Antibody Revolution almost never happened. The drug that kicked off the Antibody Revolution almost didn't get a shot at a Phase 3 trial. The San Diego-based antibody pioneer Idec Pharmaceuticals had good Phase 2 data but only US$22m in cash in March 1995 before Genentech gambled that the story had merit, and agreed to fund the Phase 3 work. That investment paid off in spades because, by 2001, Rituxan was a blockbuster. Idec went on in 2003 to become Biogen Idec, and now simply Biogen, in a deal which valued Idec at US$6.6bn[96]. Biogen today has a market cap of ~US$60bn.

[89] Paul Ehrlich (1854-1915) was awarded the 1908 Nobel Prize in Physiology or Medicine for discovering the syphilis drug Salvarsan. Ehrlich's magic bullet is a drug that selectively targets disease-causing bacteria.
[90] Actemra, Avastin, Cimzia, Cosentyx, Entyvio, Erbitux, Herceptin, Humira, Keytruda, Lucentis, Opdivo, Perjeta, Prolia, Remicade, Rituxan, Simponi, Soliris, Stelara, Tysabri, Xolair and Yervoy.
[91] Avastin, Herceptin, Humira, Remicade and Rituxan.
[92] See Nature. 1975 Aug 7;256(5517):495-7.
[93] Georges Köhler pf Germany (1946-1995) and César Milstein of the UK (1927-2002) won their Nobels for their hybridoma work. Also recognized with a Nobel that year was a Dane, Niels Jerne (1911-1994), who first proposes the theory of natural selection for antibody formation in the mid-1950s (see Proc Natl Acad Sci U S A. 1955 Nov 15; 41(11): 849–857).
[94] Consider, for example, the experience of Centocor. In January 1993 that antibody company suspended a trial of its Centoxin antibody in sepsis on an interim analysis showing a higher death rate in the treatment arm. The stock plunged 64% on the news.
[95] See US Patent 5,225,539, priority date 27/3/1986 (the so-called Winter I patent) and Nature. 1988 Mar 24;332(6162):323-7.
[96] Technically, Idec issued 1.15 of its shares per Biogen shares, with Biogen valued at US$6.5bn and Biogen shareholders owning 49.5% of the merged entity. Biogen is currently the world's 24th largest pharma company, with US$9.8bn in 2016 revenue (source Pharmaceutical Executive magazine).

Table 1: Key monoclonal antibody acquisitions

Company	Buyer	Therapy / Technology	Price (US$ bn)	Year
Centocor	J&J	Remicade	4.9	1999
BASF	Abbott	Humira	6.9	2000
Idec	Biogen		6.6	2003
Celltech	UCB	Cimzia	2.6	2004
Abgenix	Amgen	Vectibix[97]	2.2	2005
AstraZeneca	Cambridge Antibody	Phage Display	1.3	2006
GSK	Domantis	Domain Antibodies	0.5	2006
AstraZeneca	Medimmune	Synagis	15	2007
Genentech	Tanox	Xolair	0.9	2007
Eli Lilly	ImClone	Erbitux	6.5	2008
Bristol-Myers Squib	Medarex	Yervoy[98]	2.4	2009

There have been some solid acquisitions in the monoclonal antibody space since Genentech's 1995 gamble. A year later, new antibody therapies were approved at a rate of one or two a year, and sales of existing antibodies increased sharply. This lead to some big acquisitions of antibody companies by Big Pharma, as shown in in **Error! Reference source not found.**.

Today, antibody therapies are the key to Big Pharma's medium-term growth plans. In the 1990s the early developers of antibodies were mostly emerging companies such as Centocor, Medimmune and Idec. Big Pharma didn't play, except for Roche, which in 1990 bought 60% of Genentech[99]. As **Error! Reference source not found.** will have hinted, antibody development became routine for Big Pharma after 1997, so that by 2012, the 21 largest drug-makers had the majority of their biological drug pipelines in antibodies[100].

BIG PHARMA LOVES ANTIBODIES TODAY. IT DIDN'T IN THE 1990s

Stem cells today are where monoclonal antibodies were in the mid-to-late 1990s. Stem cells, just like antibodies, have had the early latency period before the 'right' kinds of products could enter clinical trials. The controversy surrounding embryonic stem cells, because they required embryo destruction, was an extra impediment. It wasn't until 2010 that the first hESC-derived cells made it into a trial[101], seven years after the relevant pre-clinical data had been published[102]. Around the same time, iPSC technology was invented[103], with the first clinical trial of iPSCs re-initiating this year[104]. These long lag times between discovery and clinical trials parallels the period before humanised antibodies succeeded murine monoclonal antibodies in the 1990s. The difference is that Mesenchymal Stem Cells could move forward much faster: The US biotech company Osiris

[97] Also, the 'Xeno-Mouse' which was a source of fully human antibodies.
[98] As well as a transgenic mouse called the 'HuMAb-Mouse'.
[99] For only US$2bn. The other 40%, acquired in 2009, cost US$46.8bn. That's what a few good antibodies could do for Genentech shareholders.
[100] See *Biotech meds are swelling those pharma pipelines* by Ed Silverman, Forbes, 18/11/2013.
[101] See Geron press release dated 11/10/2010 and headlined '*Geron initiates clinical trial of human Embryonic Stem Cell-based therapy*'. The trial was for GRNOPC1, a hESC-derived oligodendrocyte progenitor cell product considered useful in the treatment of spinal cord injury.
[102] See *Stem cells enable paralysed rats to walk* by Alexandra Goho, New Scientist, 3/7/2003. The work was later published in J Neurosci. 2005 May 11;25(19):4694-705.
[103] See Cell. 2007 Nov 30;131(5):861-72.
[104] As we noted above, a clinical hold was put in place in 2015 due to a gene abnormality found in the iPS cells being used.

Therapeutics[105] was in a Phase 1/2 trial of its Prochymal MSC product in paediatric bone marrow transplant patients in 2000, and the first clinical study by Mesoblast with its autologous MSCs was in 2006.

There are Nobel Laureates in the stem cell field, just like antibodies. The 2012 Medicine/Physiology Nobel was won jointly by Britain's Sir John Gurdon, for demonstrating that it was possible for cells to be reprogrammed[106], and Japan's Shinya Yamanaka, for creating the first iPSCs.

Clinical successes are building for stem cell therapies. There are currently over 1,600 active clinical trials of stem cells (out of 6,000 registered), mainly in the US[107], and a number of important Phase 3s are now recruiting, such as Mesoblast's DREAM HF-1 study in heart failure[108] and Pluristem Therapeutics' Phase 3 in CLI[109] . A few notable clinical successes of recent days have included:

THERE ARE OVER 1,600 ACTIVE STEM CELL CLINICAL TRIALS GLOBALLY

- **Tigenix, August 2015.** This company's adipose-derived MSCs hit the primary endpoint in a Phase 3 study. In Crohn's disease patients suffering 'complex perianal fistulas'[110] a single injection of Tigenix's Cx601 product was statistically superior to placebo in achieving remission at 24 weeks[111]. These results were published in *The Lancet* in July 2016[112] and the product is in registration in the EU
- **Athersys[113], February 2016**. This company's MultiStem 'multipotent adult progenitor cells' were able to bring about a significantly higher rate of 'Excellent Outcomes' in stroke recovery patients at the one year mark than placebo in a Phase 2 study (p=0.02)[114].
- **Vericel[115], April 2016.** This company's ixmyelocel-T, an autologous multicellular therapy intended for advanced heart failure due to ischemic dilated cardiomyopathy, was able to show, in Phase 2b, a 37% reduction in cardiac events compared with placebo (p=0·0344)[116].
- **BrainStorm Cell Therapeutics[117], July 2016**. This company, which uses MSCs in CNS disorders, announced topline results of a Phase 2 study in Amyotrophic Lateral Sclerosis (ALS) which showed a statistically significant slowing of progression for patients in the treatment group[118].
- **Pluristem Therapeutics[119], January 2017**. This company initiated Phase 3 of its placenta-derived, mesenchymal-like adherent stromal cells in Critical Limb Ischemia[120]. Two previous Phase 1 studies generated favourable data on amputation free survival one year post-treatment, improved tissue perfusion, and a reduction of ischemic pain at rest.

THE DATA FROM VARIOUS STEM CELL PROGRAMMES IS LOOKING GOOD

[105] Columbia, Md, Nasdaq: OSIR, www.osiris.com.
[106] See J Embryol Exp Morphol. 1962 Dec; 10:622-40. Gurdon placed the nucleus from a mature frog cell into a frog's egg cell and the egg promptly turned into a fully functional cloned tadpole.
[107] Trials that reference 'stem cells' in the clinicaltrials.gov database.
[108] See NCT02032004 at www.clinicaltrials.gov.
[109] See NCT03006770 at www.clinicaltrials.gov.
[110] A fistula is an abnormal channel connecting one internal organ to another, IN this case the channel is between the anus and the skin overlying the buttock.
[111] See the TiGenix press release dated 23 August 2015 and headlined '*Tigenix announces Cx601 meets primary endpoint in pivotal Phase III trial*'. Tienix is now initiating a second Phase 3 for US regularities purposes, with that study to be conducted under a Special Protocol Assessment.
[112] Lancet. 2016 Sep 24;388(10051):1281-90. Epub 2016 Jul 29.
[113] Cleveland, Oh., Nasdaq: ATHX, www.athersys.com.
[114] See the Athersys press release dated 17 February 2016 and headlined '*One-year results from Phase 2 stroke study of MultiStem cell therapy demonstrate a significantly higher rate of complete or nearly full recovery*'.
[115] Cambridge, Ma., Nasdaq: VCEL, www.vcel.com.
[116] Lancet. 2016 Jun 11;387(10036):2412-21. doi: 10.1016/S0140-6736(16)30137-4. Epub 2016 Apr 5.
[117] Petah Tikva, Israel, OTCBB: BCLI, www.brainstorm-cell.com.
[118] See the BrainStorm Cell press release dated 18 July 2016 and headlined '*BrainStorm announces positive top line results from the U.S. Phase 2 study of NurOwn in patients with Amyotrophic Lateral Sclerosis (ALS)*'.
[119] Haifa, Israel, Nasdaq: PSTI, www.pluristem.com.
[120] See the Pluristem press release dated 10 January 2017 and headlined '*Pluristem's Phase III study of PLX-PAD cells for the treatment of Critical Limb Ischemia cleared by U.S. FDA*'

- **Reneuron[121], December 2016**. This company's CTX cell therapy hit enough endpoints in a Phase 2 study in stroke recovery to warrant a move into Phase 3[122].
- **Mesoblast, February 2017**. Mesoblast reported favourable Phase 2 data from a trial of its MPCs in Rheumatoid Arthritis resistant to anti-TNF therapy. A single 2 million / kg dose of Mesoblast's MSCs saw early improvements at 12 weeks (median ACR-N[123] of 50%) sustained at week 39 (median ACR-N of 49%). This outcome had statistical significance[124]. Mesoblast has also recently had interim success with the DREAM HF-1 Phase 3, due to end in 2018[125].

Despite these successes, Big Pharma is yet to show full support for the regenerative medicine field. The first major partnering deal in the stem cell space was the Osiris/Genzyme deal of November 2008, in which the latter company, a pioneer of the Orphan Drug space bought by Sanofi in 2011[126], partnered with Osiris over Prochymal and another product. This deal was large[127] but was unwound in 2012 by Sanofi, after a clinical failure in a Type I diabetic study. A similar fate awaited the Mesoblast/Cepahlon partnership of December 2010, which was also significant[128] but was unwound by Cephalon's acquirer, Teva, in June 2016 after a change in strategic direction by that company[129]. We think these partnerships, while they ultimately didn't work out, show that Big Pharma is interested in playing in this space, and we think that if the monoclonal antibody experience is any guide the truly big transactions are yet to come. Celgene[130] and Mallinckrodt Pharmaceuticals[131] have both done deals with Mesoblast in recent days[132], and a 2014 deal between Johnson & Johnson's Janssen Biotech unit and a biotech company called Capricor Therapeutics[133] over a kind of a kind of stem cell called the cardiosphere-derived cell, lasted for around three years. This deal was worth $12.5m upfront and potentially US$325m in additional payments[134] however Janssen elected not to exercise its option in July 2017[135]. More recently, Bayer, together with a US VC fund, has invested US$225m to establish a toe-hold in stem cell medicine with the creation of the Boston-based BlueRock Therapeutics[136].

THERE HAVE BEEN SIGNIFICANT PARTNERING DEALS IN REGENERATIVE MEDICINE

[121] Guildford, UK, LSE: RENE, www.reneuron.com.
[122] See the ReNeuron press release dated 5 December 2016 and headlined '*Reports positive results in Phase II stroke trial*'.
[123] For a discussion of the ACR-N measure in Rheumatoid Arthritis and how it differs from the classic ACR20/50/70 see Arthritis Rheum. 2005 Jun;52(6):1637-41.
[124] See the Mesoblast market release dated 16 February 2017 and headlined '*Durable responses and sustained low disease activity over nine months after a single dose of Mesoblast cell therapy in Rheumatoid Arthritis patients resistant to anti-TNF agents*'.
[125] See the Mesoblast market release dated 10 April 2017 and headlined '*Successful interim analysis of efficacy endpoint in Mesoblast's Phase 3 trial for chronic heart failure*'.
[126] Sanofi paid US$20.1bn for Genzyme. Sanofi is today the world's 5 largest pharma company with US$34.2bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[127] US$130m upfront and potentially US$1.25bn more in milestones.
[128] US$130m upfront, a US$119m equity investment by Cephalon and US$1.7bn in milestones.
[129] Teva, chose to focus its efforts on being a successful generics company. The Israeli company did, however, design and fund Mesoblast's currently ongoing Phase 3 in heart failure, a study which was first unveiled in in October 2013.
[130] Celgene is the world's 20th largest pharma company with US$11.1bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[131] Mallinckrodt Pharmaceuticals is the world's 42nd largest pharma company with US$2.9bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[132] Celgene to take a US$45m equity stake in Mesoblast in April 2015, and Mallinckrodt to take a US$21m equity stake and option certain products and territories in December 2015.
[133] Beverly Hills, CA., Nasdaq: CAPR, www.capricor.com.
[134] See the Capricor press release dated 6 January 2014 and headlined '*Capricor Therapeutics and Janssen Biotech, Inc. enter into collaboration agreement and exclusive license*'.
[135] See the Capricor press release dated 6 July 2017 and headlined '*Capricor Therapeutics Retains Full Rights to CAP-1002 as Janssen Biotech, Inc. decides not to exercise option.*'
[136] http://bluerocktx.com.

Japan could the early corporate driver of value in regenerative medicine. Possibly the 'Genentech of Stem Cells', ie the established company that fosters the maturity of the sector the way Genentech did for monoclonal antibodies, will be a Japanese company.

ABENOMICS HAS BEEN GOOD FOR STEM CELLS

- Over the last few years, the Japanese government under Prime Minister Shinzo Abe, who took office in late 2012, has made regenerative medicine the 'third arrow' of the 'Abenomics' programme. Specifically, the Diet enacted the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act In late 2013 to established a framework for expedited approval in Japan of regenerative medical products. This law was designed to make Japan a world leader in the field[137] and Japan's leading companies are paying attention.
- It is worth remembering that Cynata's major partner, Fujifilm, is a leading Japanese healthcare company. The 2015 acquisition by Astellas of Ocata Therapeutics and the recent partnering deal between Takeda, the world's 19 largest pharma company[138] ,and Tigenix over non-US rights to Cx601 (€25m upfront, €355m in regulatory and sales milestones)[139] could therefore be a harbinger of truly significant partnering and M&A activity in this space.

CYNATA'S CHAIRMAN WAS FORMERLY CEO OF OCATA

- The Ocata deal is worth paying particular attention to. Cynata's current Chairman, Dr Paul Wotton, was the CEO who delivered the American company to Astellas, now the world's 21 largest pharma company[140]. As Advanced Cell Technologies, and Ocata Therapeutics from 2014, this US company had developed technology allowing stem cells to be sourced from embryos without embryo destruction[141]. Ocata's focus for its early clinical work was ophthalmic indications, with evidence that the cells could rebuild retinal pigment epithelium at the back of the eye. By the time of the Astellas deal the company was Phase 2 in Dry AMD and Phase 1 in a rare disorder called in Stargardt's Macular Dystrophy[142].

The value of listed stem cell companies has waxed and waned over the last ten years as the Revolution has neared. It's fair to say that stem cells have not been in favour with investors for most of the last decade. We constructed an equally-weighted index of 12 mostly American stem cell companies which we consider to be representative of the sector[143], and tracked this index back to July 2007. As Figure 8 illustrates, there was a single bull run for regenerative medicine that commenced around the time of Barack Obama's 2008 election as US President[144] and continued until shortly after Mesoblast's big November 2010 deal with Cephalon. Since then, the regenerative medicine stocks have mostly been trending down, despite the Nasdaq Biotechnology Index doing particularly well and only experiencing a bearish period in the first half of 2016.

[137] The act took effect in November 2014. Some recent commentary in the open access journal *Regenerative Medicine* is a very readable explanation of Japan's new laws, however keep in mind the corresponding author is from Japan's Office for Promotion of Regenerative Medicine. See Tobita et. al., *Japan's challenges of translational regenerative medicine: Act on the safety of regenerative medicine*, Regenerative Therapy, Volume 4, June 2016, Pages 78-81.
[138] 2016 revenue US$12.8bn (source: Pharmaceutical Executive magazine).
[139] See the Takeda press release dated 6 July 2016 and headlined '*Takeda and TiGenix enter into licensing agreement for ex-U.S. rights to Cx601 for the treatment of complex perianal fistulas in patients with Crohn's Disease*'.
[140] With US$11.1bn in 2016 revenue - source: Pharmaceutical Executive magazine.
[141] *Nature*. 2006 Nov 23;444(7118):481-5. Epub 2006 Aug 23.
[142] For an early case report in each indication see Lancet. 2012 Feb 25;379(9817):713-20. Epub 2012 Jan 24.
[143] Athersys, BioTime, Brainstorm Cell Therapeutics, Cytori Therapeutics, Fibrocell Science, International Stem Cell, Mesoblast (from its 2015 Nasdaq IPO), Neuralstem, Pluristem Therapeutics, TiGenix, US Stem Cell and Vericel.
[144] America's 44th President had campaigned for increased stem cell research funding during the 2008 campaign.

Figure 8: Stem cell stocks versus the Nasdaq Biotechnology Index

The pace of stem cell research and development today is faster than for antibodies thirty year ago. Our troves of medical knowledge double every 18-months or so. Compare this to the 1980s when such knowledge doublings took seven years[145]. A good example to highlight this increase in pace is to compare the two major breakthroughs of stem cells and antibodies. The transition from using mouse antibodies to humanised antibodies took 13 years, while transition from using human Embryonic Stem Cells to Yamanaka's induced Pluripotent Stem Cells took nine. That's an improvement of four years. The Stem Cell Revolution will happen faster.

The regulatory environment for regenerative medicine is favourable. Add to the knowledge base a relaxed regulatory stance in the world's largest pharmaceutical market designed to encourage new stem cell therapies. The FDA has for over a decade now only requires a single Phase 2 and a single Phase 3 for some regenerative medicine products[146]. More recently the 21st Century Cures Act, signed into law by President Obama in December 2016, embodied specific provisions for accelerated approval and priority review for products designated by the FDA as Regenerative Medicine Advanced Therapies[147]. Notably Cynata has received advice from the FDA that its GvHD product, CYP-001, is suitable for this mechanism.

AMERICA'S 21ST CENTURY CURES ACT BODES WELL FOR THE REGENERATIVE MEDICINE FIELD

The Revolution's start date is getting closer. Marketing approval was given to Osiris' Prochymal for paediatric GvHD in Canada in May 2012 and in New Zealand a month later. In October 2013 Mesoblast bought Osiris's stem cell business[148] and Prochymal (as 'Temcell') has since been approved in Japan (September 2015) and entered a

[145] See Trans Am Clin Climatol Assoc. 2011; 122: 48-58.
[146] See Mesoblast market release dated 17/10/2005 and headlined *'Mesoblast outlines accelerated timetable for clinical trials and regulatory approvals'.*
[147] See *With 21st Century Cures Act, the future of regenerative medicine is "inject and see"* by Megan Moltini, *Wired,* 6 December 2016.
[148] For US$50m in cash and stock and up to US$50m more in milestones.

60-patient Phase 3 in the US ahead of potential FDA approval in 2018[149]. The progress of Prochymal alone suggests to us that we are on the cusp of the Stem Cell Revolution. Combine this with Mesoblast's many other Phase 3 trials, and Tigenix's Phase 3 trial in Crohn's, and the start date for the Revolution is arguably getting close.

A final word on stem cells and monoclonal antibodies. As we mentioned above, stem cells, as a therapy, work with the body, rather than against it; modulating the immune response in GvHD, rather than suppressing it with steroids, is a good example. This heralds the idea that stem cells could go much further than Lucentis in AMD, Tysabri in MS and Xolair in asthma. Antibodies could never treat heart failure and heart attack in the way stem cells can. They haven't been able to be used in complex Central Nervous System disorders like Parkinson's, Alzheimer's, ALS, stoke and spinal cord injury, whereas stem cells have shown promise.

Appendix II – A Cynata glossary

Acute Myocardial Infarction (AMI) – The medical term for a heart attack, that is, a blockage of blood supply to the heart muscle (the myocardium).

Acute Respiratory Distress Syndrome (ARDS) – The rapid build-up of fluid in the air sacs in the lungs, preventing oxygen to reach the bloodstream.

Allogeneic – A type of bone marrow or stem cell transplant in which the donor and recipient are genetically dissimilar. Stem cells that can be used allogeneically are commercially important because they can become 'off the shelf' products.

Angiogenic – Capable of forming blood vessels.

Autologous – A type of bone marrow or stem cell transplant in which the recipient receives his or her own cells.

Cymerus – Cynata's core technology for manufacturing Mesenchymal Stem Cells from pluripotent cells for clinical use.

CYP-001 – Cynata's cell product for GvHD, now in a Phase 1/2 clinical study.

DSMB – The Data Safety Monitoring Board, an independent group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing.

Ectoderm – The outermost germ layer of an embryo, which give rise to the nervous system, among other things.

Endoderm – The innermost germ layer of an embryo, which give rise to the epithelial lining of various organs, among other things.

Fibroblasts – Cells which synthesise the extracellular matrix and collagen.

[149] This study (see NCT02336230 at www.clinicaltrials.gov) passed an interim futility analysis in November 2016. The product was granted Fast Track designation by the FDA in March 2017.

Germ layers – The three layers of an embryo: ectoderm (outermost), mesoderm (middle) and endoderm (innermost).

Glioblastoma – A rare brain cancer that begins in the glial cells that surround and support neurons.

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.

Graft-versus-Host Disease (GvHD) – The severe immune reaction a patient undergoing a bone marrow transplant can experience when that patient receives donated Hemopoietic Stem Cells from an unrelated recipient and the immune system of the patient seeks to throw out the cells that it has recognised as 'non-self'. The symptoms can be skin rash, jaundice and abdominal pain among others, but sometimes the condition is so severe patients die.

Haemopoietic stem cells – Stem cells that help build the body's blood supply.

hESC – Human embryonic stem cell.

induced Pluripotent Stem cells (iPS cells) – Stem cells derived from adult cells that have been transformed, through the transfection of various genes, into cells having the pluripotency of embryonic stem cells.

Lateral plate – Mesodermal cells that give rise to the circulatory system and blood.

Mesenchymal Stem Cells (MSCs)– Stem cells found in the bone marrow which can give rise to bone, cartilage, adipose and connective tissues.

Mesenchymoangioblast – A mesodermal precursor identified by Vodyanik et al. in 2010 and the key cell on the pathway from pluripotent cell to MSC.

Mesoderm - The middle germ layer of cells of an embryo, which gives rise to skeletal and connective tissues as well as the heart wall and blood vessels.

MSC – See Mesenchymal Stem Cell.

Multipotent – Capable of differentiating into in multiple cell types.

Passage –. The removal the cells from the medium they're growing in, because there are too many cells and the growth rate is slowing down.

Pluripotent – A cell capable of turning into almost all cell types. Embryonic stem cells are pluripotent.

Regenerative medicine – The process of creating living, functional tissues to repair or replace tissue that has been lost due to age, disease, damage, or congenital defects.

Stem cells – Cells that can differentiate into many different cell types when subjected to the right biochemical signals.

Stromal cells – The cells that make up the connective tissue of an organ. Mensechymal stem cells come primarily from marrow stromal cells.

Appendix III – Cynata's IP position

Cynata's core intellectual property is covered by four patent families owned by the Wisconsin Alumni Research Foundation (WARF)[150], and licensed to Cynata.

- *Serum-free cultivation of primate embryonic stem cells*, WO/2001/066697, priority date 9 March 2000, invented by James Thomson.

This patent family covers a technique of expanding embryonic stem cell lines, including the line from which mesenchymoangioblasts were first derived, without fetal bovine serum.

- *Primate embryonic stem cells,* WO/1996/022362, priority date 20 January 995, invented by James Thomson.

This patent family covers the method of deriving the embryonic stem cell line[151] from which Cynata's mesenchymoangioblasts were first derived.

- *Generation of clonal mesenchymal progenitors and mesenchymal stem cell lines under serum-free conditions*, WO/2011/116117, priority date 18 March 2010, invented by Maksym Vodyanyk and Igor Slukvin[152].

This patent family covers Cynata's mesenchymoangioblasts.

- *Methods and materials for hematoendothelial differentiation of human pluripotent stem cells under defined conditions*, WO/2014/165131, priority date 13 March 2013, invented by Igor Slukvin and Gene Uenishi.

This patent family covers a new co-culture system for Cynata's mesenchymoangioblasts, which does away with the mouse bone marrow stromal cell line, OP9, for the cell feeder layer, in favour of feeder layers suitable for manufacturing a product for use in humans.

More patent families coming: In addition, Cynata has filed patent applications covering inventions made during the course of developing the Cymerus technology, potentially adding a further layer of protection.

Appendix IV - Major shareholders

Cynata currently has only one substantial shareholder:

- Fujifilm (TYO:4901), the Japanese company involved in healthcare, highly functional materials and document management, which owns 9% of Cynata. Fujifilm is now a major player in regenerative medicine through its 2013 acquisition of Cellular Dynamics.

FIJUFILM OWNS 9% OF CYNATA

[150] Holder all rights to all the intellectual property created at the University of Wisconsin.
[151] It was based on the word which Thomson et. al. did to isolate rhesus monkey embryonic stem cells in 1995 - see Proc Natl Acad Sci U S A. 1995 Aug 15;92(17):7844-8.
[152] This patent application was granted in the US in November 2009 as No. 7,615,374

Appendix V – Key relevant papers

Vodyanik et. al. (2010), *A mesoderm-derived precursor for mesenchymal stem and endothelial cells*. Cell Stem Cell. 2010 Dec 3;7(6):718-29.

- This paper reported the isolation of Cynata's mesenchymoangioblast cell line.

Koch et. al. (2016), *Mesenchymoangioblast-derived mesenchymal stromal cells inhibit cell damage, tissue damage and improve peripheral blood flow following hindlimb ischemic injury in mice*. Cytotherapy. 2016 Feb;18(2):219-28. Epub 2015 Dec 28.

- This paper reports in vivo data on the effectiveness of mesenchymoangioblasts in treating peripheral artery disease.

Royce et. al. (2017). *Intranasal administration of mesenchymoangioblast-derived mesenchymal stem cells abrogates airway fibrosis and airway hyperresponsiveness associated with chronic allergic airways disease*. FASEB J. 2017 Jun 16. [Epub ahead of print]

- This paper shows in vivo that Cymerus MSCs can reduce airway hyper-responsiveness by 60-70% in an animal model of chronic allergic airways disease.

THE *IN VIVO* DATA ON CYMERUS MSCS IN ASTHMA HAS BEEN PUBLISHED

Appendix VI – Cynata's capital structure

		% of fully diluted	Note
Ordinary shares, ASX Code CYP (million)	90.1	89.3%	
Unlisted options (million)	10.8	10.7%	Average exercise price 66.3 cents, average expiry date 21-Jun-2019
Fully diluted shares	100.9		

Current market cap:	A$54.5 million (US$43.2 million)
Current share price	$0.605
12-month trading range	$0.29 - $0.805
Average turnover per day (last three months)	$131,000

Appendix VII – Comparable companies

Company	Location	Code	Market cap (USDm)	Web
Mesoblast	Melbourne, Australia	ASX: MSB	667	www.mesoblast.com.au
BioTime	Alameda, Ca.	NYSE MKT: BTX	333	www.biotimeinc.com
Tigenix	Leuven, Belgium	Euronext Brussels: TI	276	www.tigenix.com
Athersys	Cleveland, Oh.	Nasdaq: ATHX	184	www.athersys.com
Asterias Biotherapeutics	Menlo Park, Ca.	NYSE MKT: AST	172	www.asteriasbiotherapeutics.com
Pluristem Therapeutics	Haifa, Israel	Nasdaq: PSTI	118	www.pluristem.com
BrainStorm Cell Therapeutics	Petah Tikva, Israel	OTCBB: BCLI	101	www.brainstorm-cell.com
NeuralStem	Rockville, Md	NYSE MKT: CUR	68	www.neuralstem.com
ReNeuron	Guildford, UK	LSE: RENE	66	www.reneuron.com
Caladrius Biosciences	Basking Ridge, NJ	Nasdaq: CLBS	37	www.caladrius.com
Cynata			43.2	

Asterias Biotherapeutics. This company is developing the human embryonic stem (hES) cell lines originally developed by Geron. The company is in Phase 1/2 in spinal cord injury with AST-OPC1, a hES cell-derived neural cell line.

Athersys. This company's multipotent adult progenitor cells are in Phase 2 in ischemic stroke, while there are also clinical programmes ongoing in a range of neurological, cardiovascular, inflammatory and orthopaedic indications. In September 2016 the FDA agreed with Athersys on a Special Protocol Assessment (SPA) for a planned Phase 3 in ischemic stroke.

BioTime. This company is being built on two core technologies - a stem cell manufacturing technology called PureStem and a delivery system called HyStem. PureStem allows more than 200 purified, identifiable and scalable human cell progenitors to be sourced from embryonic stem cells, while HyStem hydrogels provide an injectable matrix that allows new tissue to grow from grafted cells. In late 2013, BioTime picked up where Geron left off in terms of Geron's pioneering embryonic stem cell programmes[153], vending them into the abovementioned Asterias Biotherapeutics.

BrainStorm Cell Therapeutics. This company's NurOwn technology allows Mesenchymal Stem Cells to be converted into cells that secrete a variety of neurotrophic factors. NurOwn has completed Phase 2 in Amyotrophic Lateral Sclerosis (ALS) and is now seeking to initiate a Phase 3.

Caladrius Biosciences. This immunotherapy company has been built on a platform to obtain and enhance the patient's own Regulatory T cells in order to turn off an immune response. Its lead candidate, CLBS03, is in Phase 2 recent onset type 1 diabetes. The company's PCT subsidiary is a contract manufacturer of cellular therapies.

Mesoblast. This company is the world leader in stem cell therapies in terms of having advanced products in the clinic and multiple Phase 2 and 3 programmes ongoing. The company has been built on technology for obtaining and expanding Mesenchymal Precursor Cells from donors so that they can be stored and then used as an 'off the

[153] In October 2013 BioTime acquired from Geron all its stem cell assets and programmes, including an ongoing Phase 1 trial for a human embryonic stem cell treatment for spinal cord injury which was one of the earliest stem cells to go to the clinic. Geron had announced it was getting out of stem cells in late 2011.

shelf' therapy. Mesoblast is at the regulatory stage with a therapy for acute GvHD and in Phase 3 in advanced chronic heart failure and chronic low back pain due to degenerative disc disease.

NeuralStem. This company is developing Central Nervous System stem cells. NSI-566, a spinal cord-derived neural stem cell line, is under development for treatment of ALS and chronic spinal cord injury.

Pluristem Therapeutics. This company's PLX cells are 'mesenchymal-like' stromal cells sourced from human placentas and manufactured using 3D cell expansion techniques. The company's lead PLX-PAD product is in Phase 3 in Critical Limb Ischemia.

ReNeuron. This company takes human cell lines and immortalises them using the c-MycER fusion protein so that therapeutic quantities of the cells can be created. They are encapsulated so as to allow them to be used allogeneically. ReNeuron is focused on neural cells in particular. A Phase 1 in a stroke recovery trial, delivering a neural stem cell line called CTX, saw sustained reductions in neurological impairment and spasticity in most patients. The company now has positive data from the PISCES II Phase 2 clinical trial of CTX in stroke disability. CTX is in Phase 1 in Critical Limb Ischemia.

Tigenix. This company's original product was ChrondoCelect, an autologous stem cell therapy indicated for the repair of defective knee cartilage which gained European approval in 2009. Through its 2011 acquisition of the Spanish company Cellerix, which was focused on adipose-derived Mesenchymal Stem Cells, the company inherited a key program in the treatment of complex perianal fistulas associated with Crohn's disease. This has now successfully completed Phase 3 and in 2016 the ex-US rights were licensed to Takeda.

Risks related to Cynata

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

- **Scale-up**. iPS-derived MCAs may prove too difficult to produce at final commercial scale.
- **Clinical**. There is the risk that the envisaged Graft-versus-Host Disease trial could be difficult to recruit in a reasonable time period, or not meet its endpoints.
- **Funding**. More capital may be needed to get iPS-MCA derived MSCs into mid-stage clinicals.
- **Regulatory**. Regulators may err on the side of caution with regard to the new field of iPS cells, which may slow Cynata's corporate and clinical development.

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 Cynata.

General Advice Warning, Disclaimer & Disclosures

The information contained herein ("Content") has been prepared and issued by NDF Research the business name of Stuart Dean Roberts, ABN 11 209 563 517) ("NDF Research"), an Authorised Representative (no: 1245466) of Bellmont Securities ABN 47 119 852 890 AFSL 331625. All intellectual property relating to the Content vests with NDF Research unless otherwise noted.

Disclaimer

The Content is provided on an as is basis, without warranty (express or implied). Whilst the Content has been prepared with all reasonable care from sources we believe to be reliable, no responsibility or liability shall be accepted by NDF Research for any errors or omissions or misstatements howsoever caused. Any opinions, forecasts or recommendations reflect our judgment and assumptions at the date of publication and may change without notice. NDF Research will not accept any responsibility for updating any advice, views, opinions or recommendations contained in this document.

No guarantees or warranties regarding accuracy, completeness or fitness for purpose are provided by NDF Research, and under no circumstances will any of NDF Research, its officers, representatives, associates or agents be liable for any loss or damage, whether direct, incidental or consequential, caused by reliance on or use of the Content.

General advice warning

The Content has been prepared for general information purposes only and is not (and cannot be construed or relied upon as) personal advice nor as an offer to buy/sell/subscribe to any of the financial products mentioned herein. No investment objectives, financial circumstances or needs of any individual have been taken into consideration in the preparation of the Content.

Financial products are complex, entail risk of loss, may rise and fall, and are impacted by a range of market and economic factors, and you should always obtain professional advice to ensure trading or investing in such products is suitable for your circumstances, and ensure you obtain, read and understand any applicable offer document.

Disclosures

NDF Research has been commissioned to prepare the Content. From time to time, NDF Research's representatives or associates may hold interests, transact or hold directorships in, or perform paid services for, companies mentioned herein. NDF Research and its associates, officers, directors and employees, may, from time to time hold securities in the companies referred to herein and may trade in those securities as principal, and in a manner which may be contrary to recommendations mentioned in this document.

NDF Research will receive fees from Cynata, for research services and other financial services or advice we may provide to that company. The analyst has received assistance from the company in preparing this document. The company has provided the analyst with communication with senior management and information on the company and industry. As part of due diligence, the analyst has independently and critically reviewed the assistance and information provided by the company to form the opinions expressed in the report. Diligent care has been taken by the analyst to maintain an honest and fair objectivity in writing this report and making the recommendation.

Where NDF Research has been commissioned to prepare this content and receives fees for its preparation, please note that NO part of the fee, compensation or employee remuneration paid will either directly or indirectly impact the Content provided.

Recommendations

NDF Research issues a BUY recommendation in case of an expected total shareholder return (TSR, share price appreciation plus dividend yield) in excess of 25% within the next twelve months, an ACCUMULATE recommendation in case of an expected TSR between 5% and 25%, a HOLD recommendation in case of an expected TSR between -5% and +5% within the next twelve months and a SELL recommendation in case of an expected total return lower than -5% within the next twelve months.

As at the date of this report the expected TSR for Cynata is 331%.