Stem cell pioneer

Share Price: A$0.80

Valuation range: A$2.18 - $4.21

ASX: CYP

Sector: Biotechnology

6 November 2020

Cynata is emerging as a world leader in the field of stem cells. The company's Cymerus technology allows the manufacture of large quantities of therapeutic Mesenchymal Stem Cells (MSCs) under Good Manufacturing Practice (GMP) at low cost. This gives Cynata a distinct advantage over other stem cell players as it moves its products into the clinic.

Cynata has done its first partnering deal

In September 2019 Cynata signed an exclusive licensing deal with the Japanese company Fujifilm for global rights to Cynata's CYP-001 product in Graft-versus-Host Disease (GvHD), a complication that occurs after bone marrow transplants. The product had performed well in Phase 1 and Fujifilm will now take it further. This deal is relatively low on milestones, at only US$43m (plus royalties), but provides significant validation for Cynata's technology and manufacturing process.

Cynata is building a stem cell pipeline

Cynata has favourable pre-clinical data in various indications with its MSCs including Critical Limb Ischemia, osteoarthritis and Acute Respiratory Distress Syndrome (ARDS), amongst others. Cynata is planning a large human clinical study in osteoarthritis in Australia. The ARDS indication is particularly attractive in the current climate given the potentially fatal ARDS that can show up in some cases of Covid-19 and is largely responsible for Covid-related mortality. Cynata has approval in Australia to run a clinical study in patients in intensive care with Covid-19 but this study has yet to enrol its first patient due to declining Covid-19 incidence in this country.

The Stem Cell Revolution is almost with us

With widespread clinical data from multiple developers showing that MSCs can be therapeutically beneficial we believe the scene is set for the Stem Cell Revolution in medicine where stem cell therapies are reduced to practice. Cynata with its low cost and reliable manufacturing is well placed to be a leader of this Revolution.

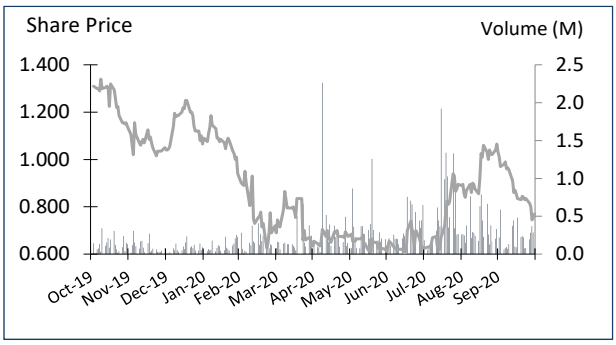
Valuation range of A$2.18 – A$4.21 per share

We value Cynata at $2.18 per share base case and $4.21 per share optimistic case. We valued a range of programmes beginning with the GvHD programme but see considerable upside from programmes we consider too early to value. We see Cynata being re-rated by the market as pre-clinical data emerges on the various programmes in Cynata's pipeline, and as other products move into the clinic.

Market Cap. (A$ m)	93.7
# shares outstanding (m)	117.1
# share fully diluted	118.8
Market Cap Ful. Dil. (A$ m)	95.1
Free Float	100%
12 months high/low (A$)	$1.35 - $0.58
1 / 3 / 12-month performance	-28% / 23% / -41%
Website	cynata.com

Source: Company, Pitt Street Research

Share price (A$) and avg. daily volume (k, r.h.s.)



Source: Thomson, Pitt Street Research

Valuation metrics	
Fair valuation (A$)	$2.18 - $4.21
WACC	15%
Assumed terminal growth rate	-3-5%

Source: Pitt Street Research

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Introducing Cynata (ASX: CYP)

Cynata is a Melbourne-based clinical-stage biotechnology company focused on stem cells. Stem cells are arguably going to be an important part of 21st Century medicine, and after more than 20 years of work the first stem cell therapeutics are now in late stage development. Cynata with its Cymerus technology has been built around a kind of stem cell called the mesenchymoangioblast, which is a precursor to the Mesenchymal Stem Cells (MSCs) generally regarded as being at the forefront of the Stem Cell Revolution. The lead product from Cynata's Cymerus technology, called CYP-001, will soon enter Phase 2 in Graft-versus-Host Disease and has been licensed to the Japanese major Fujifilm. Other clinical candidates are being prepared including one for osteoarthritis now moving into a Phase 3. A large and growing body of preclinical work has shown the utility of Cymerus MSCs. Cynata believes it can become one of the leaders of the coming Stem Cell Revolution thanks to the ease with which its products can reliably be manufactured at scale using induced Pluripotent Stem Cells.

What are stem cells and what do you mean by the term 'Stem Cell Revolution'? Stem cells are specialised cells that have the ability to differentiate into different tissue types, and also secrete various proteins/growth factors/cytokines that are therapeutically useful. Stem cells are becoming increasingly important in medicine because of the evidence that they can modulate the immune system and promote tissue regeneration across a wide range of diseases. The development over the last 20 years of Mesenchymal Stem Cells (MSCs), as well as induced Pluripotent Stem Cells (iPSCs) have allowed the development of stem cells as therapeutics along ethical lines in a way that was not possible when the first human embryonic stem cell line was isolated in 1998 at the University of Wisconsin-Madison. We expect to see the widespread use of stem cells across multiple fields of medicine by the end of the current decade and call this development the Stem Cell Revolution. It is not unreasonable to see many stem cell companies emerge from this Revolution with market capitalisations of over a billion US dollars and Cynata believes it can potentially be one of them.

Many billion-dollar companies can be created by the Stem Cell Revolution

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.[1] 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 [2] and involve ethical and legal considerations[3], MSCs are not only less problematic with regard to these issues but are self-renewing and also exhibit multilineage differentiation[4] – they have the potential to form bone, cartilage, and adipose tissue[5]. More recently, MSCs were discovered to be potent immune system modulators[6], which is where a considerable amount of research interest is being directed to at the moment. They are considered to be safe and generally do not evoke any immune response in allogeneic situations. MSCs were first derived from samples of human bone marrow, however more recently science has

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

pioneered extraction techniques to source them from adipose tissue[7] and dental pulp. All these advantages of MSCs has propelled a Melbourne-based biotech company called Mesoblast (ASX: MSB) into the leading position in the stem cell field today, and led many other companies including Cynata to work on ways to better harness the therapeutic power of MSCs. Cynata believes its unique approach can allow it to take market leadership once the clinical data has sufficiently built up.

What are induced Pluripotent Stem Cells (iPSCs) are why did they help win the Nobel Prize? iPSCs are derived from 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[8]. The 2007 discovery by Japan's Shinya Yamanaka that adult cells could be once again rendered pluripotent was ground-breaking because 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), and can be turned into any type of cell in the body, including MSCs.

Cynata's stem cell production method sets it apart.

Cynata's Cymerus technology involves the use of iPSCs to make large amounts of MSCs. Cynata's stem cell platform technology, which it calls Cymerus, represents a process to create MSCs using iPSCs from a single donation 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*[9]. Slukvin et. al. showed[10] 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[11]. Cynata since proceeded to develop iPSC methods of making these mesenchymoangioblasts at scale, becoming in February 2015 the first company in the world to show that iPSC-based production of MSCs at scale was possible[12]. Since then the company has optimised the production process and validated it in third party facilities and at scale. These achievements are notable because now virtually unlimited quantities of MSCs of consistent quality can be manufactured at low cost.

Cynata's first indication is in Graft-versus-Host Disease. Cynata chose steroid-refractory Graft-versus-Host-Disease as its proof-of-concept indication, and in May 2017 dosed its first patient. This study, which was the first in the world to evaluate an allogeneic, iPSC-derived MSC therapy, read out data in 2018. Japan's Fujifilm licensed the global rights to this indication in 2019.

Cynata now has a pipeline of products in pre-clinical and clinical development. Over the last four years Cynata has built up a body of work showing that its MSCs can work in indications such as Critical Limb Ischemia (CLI), asthma and heart attack. Cynata is now working on bringing these

[7] Obtainable via liposuction, which is a major surgical procedure.
[8] 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.
[9] A 'sub-journal' of the journal *Cell* focused on stem cells.
[10] 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.
[11] The shell was Ecoquest, ASX Code ECQ.
[12] 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.

products into the clinic, along with a clinical trial underway in Covid-19 and a Phase 3 clinical trial shortly to get underway in osteoarthritis.

If Cynata is so good, then why is it currently capitalised at only $93.7m/A$66.8m? Cynata's decision in October 2019 to turn down an offer from Japan's Dainippon Sumitomo, which would have valued the company at A$204m, has likely caused some investors to be wary of the stock in 2020. Also, the recent decision by the FDA to issue a Complete Response Letter to Mesoblast related to its Remestemcel-l product in GvHD has also dampened investor interest in stem cells. In addition to this Cynata may have 'missed the boat' in terms of the opportunity to study its MSCs in Covid-19 given the current low rates of infection in Australia. We see Cynata overcoming all these issues as it moves forward with its pipeline and as Mesoblast advances with its other late stage products.

Ten 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 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 cause the rebuilding of 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 highly consistent, uniform and potent MSCs from the same starting material. Abundance leads the way to low-cost therapy. Cynata has made strong progress in recent years in being able to manufacture in commercial facilities at scale.
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 among the top 10 shareholders. 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.

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 in therapeutic applications, 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.

Cynata's relationship with Fujifilm has worked well and translated into a licensing deal

6. **Cynata has partnered its lead product with Fujifilm**. Fujifilm became a major global player in stem cells after it bought Cellular Dynamics in 2015. In 2018 the Japanese conglomerate licensed the global rights to the use of Cynata's cells in Graft-versus-Host-Disease (GvHD), paying US$3m upfront and up to US$43m in milestones, plus royalties, for the global license. This deal has markedly de-risked Cynata, in our view. Cynata has a vigorous partner outreach so further revenue accretive corporate partnerships will drive value.
7. **Favourable early stage clinical data in GvHD**. A 15-patient Phase 1 trial in steroid-refractory GvHD showed that Cynata's CYP-001 product could blunt the severe immune response associated with GvHD. Fujifilm will now build on that data in the upcoming Phase 2.
8. **A growing pipeline**. Cymerus MSCs have shown *in vivo* that they can work in multiple conditions. A Phase 3 study funded by Australia's NHMRC is planned in osteoarthritis, and Critical Limb Ischemia is also an important potential clinical programme. The data on Acute Respiratory Distress Syndrome suggests the potential to treat Covid-19 and a clinical trial may potentially take place in 2021.
9. **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 Geoff Brooke, Cynata's Chairman, brings valuable experience as a successful VC investor focused on the Life Sciences.
10. **Cynata is currently good value, in our opinion**. We value Cynata at $2.18 per share base case and $4.21 per share optimistic case, using a probability-weighted DCF method. Should the GvHD study show the clinical utility of the Cymerus technology, we see Cynata being re-rated.

Mesenchymal Stem Cells are growing in academic and clinical interest

Cynata is a Mesenchymal Stem Cell company

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. 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 markedly since that time. That research interest has translated into a considerable number of clinical trials - there are currently well in excess of 1,200 clinical studies registered 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:

- **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. Similarly, iPSCs are derived from adult cells.
- **There is clinical evidence that they work, in important areas of medicine.** These areas, such as Graft-versus- Host-Disease and diseases of ageing, 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.

MSCs have the potential to treat a broad range of diseases

And it's not just GvHD - MSCs have the potential to treat a broad range of diseases. Some examples are Acute Myocardial Infarction[13]; osteogenesis imperfecta[14]; Spinal Cord Injury[15]; Multiple Sclerosis[16]; Crohn's disease (fistula)[17]; stroke[18]; and diabetes[19]. This broad potential medical application is a reason that the Australian company Mesoblast[20], which is the world leader in MSCs, and these days ordinarily enjoys a market cap in the billions.

Cynata represents a play on the future popularity of MSCs in regenerative medicine. 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.

[13] See, for example, Circ Res. 2013 Jul 5;113(2):153-66. Epub 2013 May 8.
[14] See, for example, Transplantation. 2005 Jun 15;79(11):1607-14.
[15] See J Vet Sci. 2007 Sep;8(3):275-82.
[16] See Cell Adh Migr. 2013 Sep-Oct;7(5):404-7. Epub 2013 Oct 30.
[17] Cells. 2019 Jul; 8(7): 764.
[18] Cell Transplant. 2018 Dec; 27(12): 1723–1730.
[19] See Clin Invest Med. 2008 Dec 1;31(6):E328-37.
[20] Melbourne, Australia, ASX: MSB, www.mesoblast.com.au.

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[21]. Once those cells are obtained and purified, they then need to be expanded in culture. This is because a typical therapeutic dose requires more than 2 million MSCs for every kilogram of patient body weight[22]. Adipose tissue can yield much greater number of MSCs than bone marrow[23], but beyond sourcing there are other issues to deal with.

MSCs have a limited potential to expand

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[24]. In addition, there is evidence that after many cycles of expansion, the immunomodulatory properties of MSCs and their ability to release cytokines etc, are impaired by excessive expansion[25]. Thus, MSCs created using first generation techniques may have uses that are restricted to diseases with only very small patient numbers, severely limiting their commercial potential.

It has been suggested that the only truly potent MSCs are from the early passages[26]. A 2008 study published in the journal PLOS One[27] 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. These studies indicate a potential issue with the old way of obtaining 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[28], and more effective MSCs[29]. 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 sourced from a different donor effectively becomes a different

Defining the purity of MSCs is difficult

[21] See Biomed Res Int. 2014;2014:951512. Epub 2014 Jan 6 and and Annu Rev Pathol. 2011;6:457-78.
[22] See, for example, Biol Blood Marrow Transplant. 2009 Jul;15(7):804-11.
[23] J Nippon Med Sch. 2009 Apr;76(2):56-66.
[24] 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.
[25] See, for example, Cytotherapy, 2017; 19: 798–807; and Biol Blood Marrow Transplant 18: 557-564 (2012).
[26] 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.
[27] PLoS One. 2008; 3(5): 32213.
[28] 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.
[29] 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.

product, and needs a new 'potency assay' to show that it works as demonstrated when production is scaled up[30].

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 or characteristics 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 the starting point is a single cell bank[31].

The regulators have become concerned about these issues, as evidenced by Meosblast's recent Complete Response Letter from the FDA, which we look at below.

Cynata has the answer to all these production problems with Cymerus because, as we noted above, iPS cells can consistently produce as many uniform 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 can get you all the cells you need, at the quality the regulator wants

Stem cell manufacturing – it's all about scale. A key issue since regenerative medicine started to emerge as a viable therapeutic approach has been scale. Concerns have been voiced over the years about how product developers will be to produce enough cells to meet market needs, at a reasonable price[32]. The basic problem has been taking an starting cell batch and expanding that batch into therapeutic quantities, where the end product is predictably uniform, and where the process can be regarded as having conformed with current good manufacturing practice (cGMP)[33].

Serum-free media is vital in stem cell manufacture

What the regulators want, part 1 – the basics. 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[34]. 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 consistent throughout. That might prove the hard part…

What the regulators want, part 2 – product consistency. The key issues the regulators have grappled with is product characterisation and specification. When you're making a small molecule drug it's easy to characterise the drug on a per-atom basis. With large molecule drugs like antibodies characterisation, while a little more complex, can still be done. The current debate in regulatory circles is how to characterise a stem cell. Given the sheer variety of cells that could emerge in a batch, that's difficult[35]. However for more than a decade now the FDA view has more or less been that products

[30] 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.

[31] See J Cell Biochem. 2012 Sep;113(9):2806-12.

[32] Pigeau et al. *Commercial Scale Manufacturing of Allogeneic Cell Therapy*, Front. Med., 22 August 2018

[33] Abbasalizadeha and Baharvandab, Technological progress and challenges towards cGMP manufacturing of human pluripotent stem cells based therapeutic products for allogeneic and autologous cell therapies, Biotechnology Advances, Volume 31, Issue 8, December 2013, Pages 1600-1623.

[34] 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.

[35] Cell Stem Cell . 2014 Feb 6;14(2):141-5. doi: 10.1016/j.stem.2014.01.013.

for which BLAs have been filed should come with a battery of matching potency assays, that is, *in vitro* tests where, if the cells respond in the way the potency assay predicts, the drug batch can be said to be uniform in terms of quality[36].

Manufacturing quality may not come easy for some stem cell therapies. The trouble with stem cells is what happens as a batch of cells is expanded. There are only a certain numbers of times that a cell can replicate and divide before it cannot divide anymore and dies by apoptosis. It's around 40-60 times and it's called the 'Hayflick limit'[37]. Long before then cells are changing shape and losing their potency, and this has been particularly noted with Mesenchymal Stem Cells[38].

Mesoblast still faces manufacturing challenges even after its clinical successes. Mesoblast has described its manufacturing processing this way: '*Through a proprietary process, Mesoblast selects rare mesenchymal lineage precursor and stem cells from the bone marrow of healthy adults and creates master cell banks, which can be industrially expanded to produce thousands of doses from each donor that meet stringent release criteria, have lot to lot consistency, and can be used off-the-shelf without the need for tissue matching'*[39]. Mesoblast disclosed in August 2020 that for the GvHD indication each donation could treat 'more than 500 patients[40].

Mesoblast's critics have often pointed to this notional limit of 'thousands of doses per donor' as a shortcoming[41]. More significant for that company in the near terms is manufacturing quality. When Mesoblast received its Complete Response Letter for remestemcel-L on 2 October the FDA specifically highlighted the need for further work on potency assays, and this was also in the briefing document that went to the members of the Oncologic Drugs Advisory Committee.

Cynata's mesenchymoangioblasts can satisfy on both the quantity and quality fronts. Since pluripotent cells are immortal they have infinite expansion capacity, so Cynata has no issues on the quantity front. As for quality, the ability to use a single donor cells make the provenance of Cymerus MSCs easy to explain. The company has found in its manufacturing work at desktop and pilot plant scale that the potency assays are reliable regardless of the number of passages its starting cells have undergone.

- For its scale-up, Cynata chose, in February 2014, 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.
- Cynata and Waisman were able to announce an initial validation of the manufacturing process for Cymerus back by February 2015[42];

[36] Stem Cells. 2010 May; 28(5): 996–1004.
[37] Biomaterials. 2007 Sep; 28(26): 3751–3756.
[38] Stem Cell Res Ther 9, 131 (2018).
[39] See, for example, the company's market release of 30 May 2019, in the 'About Mesoblast' section.
[40] "For each manufacturing campaign of DP, 1 container of DCB is used, which following the culture expansion steps, cell harvesting and formulation, will generate on average 120 finish product vials in each finished product lot. Therefore overall, 1 donation of bone marrow can manufacture enough DP to treat more than 500 patients." - Mesoblast Briefing Information for the August 13, 2020 Meeting of the Oncologic Drugs Advisory Committee, page 8.
[41] We understand Mesoblast gave testimony to the Oncologic Drugs Advisory Committee that it was only getting 400-500 doses per donor in the GvHD trial.
[42] See Cynata's market release dated 19 February 2015 and headlined *'Cynata achieves major stem cell manufacturing milestone'*.

- Since 2015 we understand Cynata has greatly optimised the manufacturing process in terms of the choice of medium, temperature and pressure issues, and the matrix in the culture vessels.

Fujifilm is a great partner to have

Fujifilm has been working with Cynata since 2017

Fujifilm licensed the global rights to the use of Cynata's cell product for GvHD, CYP-001, in September 2019, having first optioned the product in January 2017. Fujifilm paid US$3m cash upfront and will pay up to US$43m 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.

- At the time of the option agreement in 2017 Fujifilm took an equity stake in Cynata – investing $4m at ~$0.49 per share (then a 35% premium), and the company remains the second largest shareholder in Cynata, with 6.9% of the stock.
- It is notable that Fujifilm have publicly announced that they expect peak sales of a Cymerus GvHD product to reach US$300m pa[43]. 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.

Fujifilm is a major player in stem cells

Fujifilm is 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 is basically an industrial-scale manufacturer of iPS cells. 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*'[44]. 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[45]. 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.

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. For another, it may lead other partnership opportunities in Japan and elsewhere in the world.

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

Cynata's first clinical evaluation of Cymerus MSCs, in GvHD, was a success

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. It got there in August 2018. While steroid-refractory GvHD incidence is small, we believe it is growing rapidly: some estimates put the occurrence at 35-50% of BMT patients[46]. Bone Marrow Transplant is becoming more common - marrow donations through the 'C.W. Bill Young Cell Transplantation Program', a US Government initiative, have been increasing steadily since 2000[47]. 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[48]. Cynata's CYP-001 product was granted Orphan Drug status by the FDA in acute GvHD in March 2018.

Cynata's pre-clinical data in GvHD looked good

The pre-clinical data for Cymerus MSCs in GvHD 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[49]. Animal studies with larger numbers of animals confirmed this interim data in February 2017[50] and this data was published in February 2019[51].

The survival outcomes for Cynata's Phase 1 GvHD patients were gratifying. For its Phase 1 in GvHD, which was conducted at NHS hospitals in the UK in 2017 and 2018[52], Cynata recruited 15 patients with steroid-resistant acute GvHD and track complete and partial responses on Cymerus MSC therapy, as well as survival at Days 28 and 100[53]. The results of the study, which were published in *Nature Medicine* in September 2020, were particularly encouraging

- 87% of patients had responded by Day 100, with 53% of patients enjoying a Complete Response
- The 100 day survival rate was 87%
- At the two year mark, 63% of patients were still alive.

The last point is particular important. Once GvHD becomes steroid refractory the patient's chances of being alive two years later is understood to be less than one in five[54]. Obviously at only 15 patients it is early days for this programme but the Phase 1 validation bodes well for Fujifilm's upcoming Phase 2. Notably, Cynata's product required only two infusions whereas other MSC products typically require at least 8 infusions to achieve a similar therapeutic benefit. This is very important competitive advantage for Cynata.

[46] See Blood. 2013 Nov 7;122(19):3365-75. Epub 2013 Sep 16.
[47] See http://bloodcell.transplant.hrsa.gov.
[48] See Biol Blood Marrow Transplant. 2012 Mar;18(3):406-13. Epub 2011 Jul 4.
[49] See the company's market release dated 7 April 2016 and headlined '*Compelling results from pre-clinical stem cell study in GvHD'*.
[50] 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*'.
[51] Stem Cell Res. 2019 Mar;35:101401. Epub 2019 Feb 1.
[52] Cynata sought approval to run the Phase 1/2 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 first cohort was enrolled by November 2017 and the DSMB analysis gave the all-clear to proceed with the next 8 patients in January 2018. Good data came back from the first cohort in February 2018. The second cohort completed recruitment in May 2018. Six month data from Cohort 1 was available in June 2018, at the same time as 28 data was available for Cohort B. 100 day patent data for Cohort B was obtained in August 2018. Two year data was available by June 2020.
[53] See NCT02923375 at www.clinicaltrials.gov.
[54] See Westin et. al. (2011), *Steroid-refractory acute GVHD: predictors and outcomes*. Adv Hematol. 2011;2011:601953.

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 related to Cymerus MSCs, and clarified that Cynata could file to for Regenerative Medicine Advanced Therapy status for these cells[55]. Fujifilm is now working to initiate this study. It had hoped to do so in 2020 but we believe the advent of Covid-19 may delay this until 2021. As we note below, the 2020 experience of Mesoblast with its remestemcel-L will now guide Cynata and Fujifilm in their deliberations on clinical trial design.

Mesoblast has validated the use of MSCs in GvHD. When Mesoblast acquired Osiris Therapeutics's culture-expanded stem cell therapeutic business in October 2013 it inherited Prochymal, which went on to gain Japanese approval as 'Temcell' for acute GvHD in children and adults in September 2015 and was launched in that market in early 2016. Mesoblast proceeded to initiate a Phase 3 of Prochymal, now called remestemcel-L, for US approval in paediatric patients. That study yielded good clinical data, with the primary endpoint being met, and the data was regarded with favour by the FDA's advisory committee, but Mesoblast's application still received a Complete Response Letter from the FDA itself.

- **Good clinical data.** The 55-patient open-label Phase 3 saw an Overall Response rate at Day 28 of 70%, markedly better than the protocol-defined historical control rate of 45% (p=0.0003). This data was first reported in February 2018[56] and published in February 2020[57].
- **A favourable response from the Oncologic Drugs Advisory Committee**. That commit, which advises the FDA on all cancer drugs, voted 9-to-1 in favour of approval in August 2020.
- **An unexpected Complete Response Letter from the FDA.** In early October, in a surprise move by the FDA (since it ordinarily follows the lead of its advisory committees), the Agency issued a Complete Response Letter for remestemcel-L. The Agency cited the need for a randomised, controlled study of the product before it could consider approval. Significantly, it also indicated that it would like to see more data linking potency assays of the product to actual performance in patients, expressing concern about that "substantial functional heterogeneity has been observed between MSC batches derived from different donors".

What the October 2020 FDA Complete Response Letter to Mesoblast means for Cynata's programme. We think the Complete Response Letter, while a setback for patients and for Mesoblast, is a net positive for Cynata and Fujifilm, since the developers will now be better prepared in terms of trial design. Importantly, Cynata and Fujifilm will be in a good position to be able to show that the product quality received by all treated patients is consistent.

[55] See the Cynata market release dated 5 July 2017 and headlined '*FDA meeting provides clear path for Cynata US development plans*'.
[56] See Mesoblast's press release dated 21 February 2018 and headlined '*Primary endpoint successfully achieved in Mesoblast's Phase 3 cell therapy trial for Acute Graft versus Host Disease*'.
[57] Biol Blood Marrow Transplant. 2020 May;26(5):845-854. Epub 2020 Feb 1.

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:

Cynata has been building a pipeline with Cymerus

- **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[58].
- **Asthma, Monash University, October 2016**. A group at Monash University in Melbourne led by Drs Chrishan Samuel and Simon Royce had evaluated Cymerus MSCs 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[59]. This decrease was statistically significant ($p<0.01$)[60]. Samuel and Royce published this study in The FASEB Journal in June 2017[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]. A second study in July 2018 showed that Cymerus MSCs would work better in this model than bone marrow MSCs[63], while in September 2020 the Chong lab was able to show that the rate of new blood vessel growth was strong[64].
- **Asthma, Monash University, August 2017**. In this second study the Monash Group looked *in vivo* at how Cynata's cells can work with steroids. This group found that the addition of Cymerus MSC to dexamethasone produced a statically significant reduction in airway hyper-responsiveness compared to dexamethasone alone ($p<0.001$)[65]. This work was published in the FASEB Journal[66] in February 2019[67].
- **Diabetic wounds, May 2018**. The Cooperative Research Centre for Cell Therapy Manufacturing evaluated various MSCs and found that Cynerus MSC closed wounds faster in an animal model of diabetic wounds[68].
- **Cytokine Release Syndrome, September 2018.** The laboratory of Dr Lisa Minter at the University of Massachusetts Amherst was able to show that Cymerus MSCs markedly improved body temperature and clinical scores in murine models of Cytokine Release Syndrome[69].
- **Glioblastoma, Massachusetts General Hospital, October 2018**. Cynata has been collaborating with Dr Khalid Shah of Massachusetts General Hospital in October 2015 on the re-engineering of Cymerus MSCs to secrete cancer-killing toxins. Shah believes that, since MSCs tend to

[58] Cytotherapy. 2016 Feb;18(2):219-28. Epub 2015 Dec 28.
[59] 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.
[60] See the **company's market release dated 17 October 2016 and headlined '*Cynata's MSC technology demonstrates significant efficacy in preclinical asthma study*'.**
[61] FASEB J. 2017 Sep;31(9):4168-4178. Epub 2017 Jun 16.
[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 the Cynata market release dated 31 July 2018 and headlined '*Cymerus MSC treatment leads to improved recovery of cardiac function in preclinical heart attack study*'.
[64] See the Cynata market release dated 24 September 2020 and headlined *'Further data confirms potential utility of Cymerus MSCs in restoring cardiac function following heart attack'*.
[65] See the Cynata market release dated 23 August 2017 and headlined '*Positive data from Cymerus MSCs in second preclinical asthma study*.
[66] The journal of the Federation of American Societies for Experimental Biology.
[67] See FASEB J. 33, 6402–6411 (2019).
[68] See the Cynata market release dated 31 May 2018 and headlined '*Cynata's Cymerus MSCs effective in preclinical model of diabetic wounds'*.
[69] See the company's market release dated 7 April 2016 and headlined '*Compelling results from pre-clinical stem cell study in GvHD'.*

migrate to the site of tumours in response to signals sent out by the cancer, they could become targeted delivery vehicles for cancer drugs[70]. Cynata reported in February 2018 that the re-engineered cells had been produced and were persisting *in vivo*. By October 2018 the first *in vitro* data was available showing that the engineered MSCs could disable glioblastoma and melanoma cells[71].

- **Coronary Artery Disease, UNSW, March 2019**. Cynata announced in June 2018 that it was collaborating with the laboratory of Dr Kris Kilian on the potential use of Cymerus MSCs in promoting angiogenesis to treat Coronary Artery Disease[72]. The Kilian lab showed in March 2019 that it could improve the neovascularisation potential of Cymerus MSCs by changing the cell culture matrix[73].

Cymerus MSCs may be useful against difficult-to-treat conditions such as sepsis

- **Sepsis, Royal College of Surgeons in Ireland, December 2019**. Cynata announced in July 2018 that it was collaborating with Professor Gerard Curley of the Royal College of Surgeons in Ireland on the use of MSCs to reduce the damaging inflammation associated with sepsis[74]. In December 2019 the Curley lab was able to show marked improvements in an animal model of severe pneumonia-induced sepsis[75].
- **Idiopathic Pulmonary Fibrosis, Monash University, September 2020**. Samuel and Royce at Monash used the standard bleomycin mouse model of IPF to show that Cymerus MSCs could improve lung function across a range of measures[76] .

Cynata may be able to move quickly on osteoarthritis

Cynata is, in effect, moving into Phase 3 with osteoarthritis

Cynata is, in effect, moving into Phase 3 with osteoarthritis. In June 2020 a group led by researchers at the University of Sydney announced that they have NH&MRC funding for a Phase 3 study of CYP-004, a Cymerus MSC product indicated for osteoarthritis. This 440-patient study, to take place at various study centres in NSW and Tasmania, will compare Cymerus MSCs with placebo in recovery rates from knee osteoarthritis over a two year period. The Principal Investigator is Professor David Hunter of the University of Sydney.

Knee osteoarthritis is a multi-billion dollar market. Osteoarthritis has a large patient population globally. In the US alone it is estimated that knee osteoarthritis occurs in 10% men and 13% in women aged 60 years or older[77]. Given current treatments are symptomatic only, any regenerative medicine alternatives in this space are likely to gain a global market we estimate to be worth US$2bn p.a.

This Phase 3 could quickly translate into something bigger. The upcoming study will be conducted in Australian under the 'Clinical Trial Notification' system. However its size is such that, should solid data eventuate, it could potentially allow Cynata to go straight to Phase 3 for US regulatory purposes, vi a 'Phase 2'-style lead-in.

[70] See Adv Drug Deliv Rev. 2012 Jun 1;64(8):739-48. Epub 2011 Jun 29.
[71] See the Cynata market release dated 18 October 2018 and headlined *'Engineered Cymerus MSCs demonstrate anti-cancer effects in preclinical studies'*.
[72] See the Cynata market release dated 18 June 2020 and headlined '*Cynata announces research collaboration with University of New South Wales to develop stem cell therapies for Coronary Artery Disease'*.
[73] See the Cynata market release dated 4 March 2019 and headlined '*Cynata's collaboration with University of New South Wales yields positive preclinical data for Coronary Artery Disease'*
[74] See the Cynata market release dated 2 July 2020 and headlined '*Cynata enters development partnership with RCSI'*.
[75] See the Cynata market release dated 5 December 2019 and headlined *'Cymerus MSCs effective in preclinical model of sepsis'*.
[76] See the Cynata market release dated 7 September 2020 and headlined *'Cymerus MSCs demonstrate efficacy in preclinical lung disease study'*.
[77] Clin Geriatr Med. 2010 Aug; 26(3): 355–369.

The Covid-19 opportunity is interesting

MSCs seem to work in Covid-19 infection. On 24 April 2020 Mesoblast reported a remarkable piece of clinical data from Remestemcel-L. Mesoblast's stem cells have long been known to be able to blunt strong inflammation in the body, which made them potentially useful in Covid-19 because in some patients the virus causes Acute Respiratory Distress Syndrome. What's happening is that there's a sudden and widespread inflammation in the lungs as the infected patient's immune system reacts to the virus, resulting in shortness of breath and blueish skin. Which is, potentially, fatal, but possibly less so with Mesoblast's help. Shortly after the pandemic reached New York, Mesoblast took 12 Covid-related ARDS patients at Mt Sinai Hospital in that city and gave them Remestemcel-L. Nine of those patients, or 75%, were able to come off ventilator support within a median ten days, as against maybe 9-12% on standard-of-care. That proof-of-concept was good enough for Mesoblast to start a 300-patient Phase 2/3 trial in Covid-19 ARDS just a week or so later[78].

Cymerus MSCs seem to work in Acute Respiratory Distress Syndrome. Cynata announced in April 2017 that a team at The Prince Charles Hospital in Brisbane called the 'Critical Care Research Group'[79] was evaluating the use of Cymerus MSCs in the treatment of ARDS, in conjunction with the standard ECMO treatment[80]. This group reported in April 2020 the results of a sheep study that showed reduced inflammation, lung injury and circulatory shock when Cymerus MSCs were used[81].

Cymerus MSCs may be useful in Covid-19

Cynata has also looked into clinically evaluating Cymerus MSCs in Covid-19. The evidence from the Critical Care Research Group on ARDS, along with pre-clinical data from studies in sepsis and cytokine release syndrome, motivated the company to initiate its own 24-patient Covid-19 ARDS study, which was opened to patients in late August 2020. However by late August there were very few Covid-19 patients in intensive care in Australian hospitals. As a consequence we are concerned that this study will not progress quickly. Should the Pandemic progress well into 2021 Cynata may look to open new centres for this study.

Valuing Cynata

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 [82] stretching back to the 1960s that have allowed researchers to estimate the probability of success at various stages of development. One estimate[83] has shown that 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

[78] See NCT04371393 at clinicaltrials.gov.
[79] ccrg.org.au.
[80] That is, extracorporeal membrane oxygenation, where the blood is circulated through an artificial lung and back into the bloodstream of the patient. See the Cynata market release dated 11 April 2017 and headlined '*Cynata collaborates with world leading team on Acute Respiratory Distress Syndrome project*'.
[81] Am J Respir Crit Care Med. 2020 Aug 1;202(3):383-392.
[82] Most notably from the Center for the Study of Drug Development at Tufts University in Medford, Ma. (see csdd.tufts.edu).
[83] Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3

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
- Historically the biotechnology industry from the 1980s worked on 'low-hanging fruit' proteins that were easier to develop;
- Large molecules (eg monoclonal antibodies) have tended to be better targeted and therefore safer and more effective.
- 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.

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 four later partnerships in osteoarthritis; Critical Limb Ischemia and sepsis. We used a 71% weighting for GvHD to reflect the reasonable potential that this programme can make it to Phase 3[84], while for the other three programmes we used 32%.

Cost of capital. A key question in developing a DCF model is the cost of capital. For this company we use 13.4%, which would equate to:

- **Risk-Free Rate.** The Australian Ten-Year Bond Rate is currently ~0.8%;
- **Market Risk Premia**. 11.5%.
- **Ungeared beta**. 1.1.

This rate accounts for the de-risking that Cynata effectively underwent when it licensed its GvHD application to Fujifilm.

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.

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

[84] Considering particularly the Mesoblast Phase 3 for Remestemcel-L.

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[85].

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 assumed that the AUDUSD exchange rate converges on 0.7 over the next three years.

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

Further capital. Purely for valuation purposes, we assume another $10m is raised at 70 cents per share.

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

[85] 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.

Valuation parameters

Figure 1 shows our valuation parameters.

Figure 1: Valuation parameters

	GvHD project	
	Base case	Optimistic case
CYP investment required (AUDm)	0	0
License date	2019	2019
License upfront (USDm)	0	0
License milestones (USDm)	43	43
Royalty rate	10.0%	12.0%
Earliest approval	2024	2023
Peak sales (USDm)	600	600

	Osteoarthritis project	
	Base case	Optimistic case
CYP investment required (AUDm)	0	0
License date	2023	2022
License upfront (USDm)	25	50
License milestones (USDm)	100	200
Royalty rate	10.0%	12.0%
Earliest approval	2026	2025
Peak sales (USDm)	1,100	1,500

	Critical Limb Ischemia project	
	Base case	Optimistic case
CYP investment required (AUDm)	10	5
License date	2024	2023
License upfront (USDm)	15	30
License milestones (USDm)	200	300
Royalty rate	12.0%	15.0%
Earliest approval	2027	2026
Peak sales (USDm)	1,400	1,500

	Sepsis project	
	Base case	Optimistic case
CYP investment required (AUDm)	10	5
License date	2025	2024
License upfront (USDm)	50	80
License milestones (USDm)	150	250
Royalty rate	12.0%	15.0%
Earliest approval	2028	2027
Peak sales (USDm)	1,600	1,800

Source: Pitt Street Research

Valuation – Putting it all together

We completed our valuation of Cynata by adding.

- The individual programme DCFs;
- The notional value of the tax losses (ie the A$45m in retained losses as at June 2020 multiplied by the 30% Australian corporate tax rate);
- The current cash on hand (A$12.3m as at September 2020);
- The notional value of A$6m p.a. in corporate overhead, discounted in perpetuity at the discount rate calculated above, and adjusted for tax.
- The $3.1m that can be received from option exercises in 2022 and 20214.

Valuation range $2.18 / $4.21. We value Cynata at $2.18 per share base case and $4.21 per share optimistic case (Figure 2).

Figure 2: Valuation Summary

	Base	Optim.
GvHD (A$m)	85.3	136.8
Osteoarthritis (A$m)	78.8	186.4
Critical Limb Ischemia (A$m)	99.9	190.8
Sepsis (A$m)	19.2	38.9
Total programme value	283.1	553.0
Value of tax losses	13.5	13.5
Corporate overhead	-31.3	-31.3
Cash now (A$m)	12.3	12.3
Cash to be raised (A$m)	10.0	10.0
Option exercises (A$m)	3.1	3.1
Total value (A$m)	290.8	560.8
Total diluted shares (million)	133.1	133.1
Value per share	$2.184	$4.212
Valuation midpoint	$3.198	
Share price now (A$ per share)	$0.800	
Upside to midpoint	299.8%	

Source: Pitt Street Research

Re-Rating Cynata

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

- Completion of the Phase 2 GvHD study (with successful outcomes);
- Commencement of the osteoarthritis study in Australia;
- Potential commencement of a study in Covid-19;
- *In vivo* data on other Cymerus MSC indications;
- Further work on stem cell manufacturing;
- Completion of (a) further corporate partnering transaction(s).

Cynata's leadership team

Dr Ross Macdonald (CEO) has worked in large and small drug development and commercialisation companies including Amrad [86], F.H. Faulding [87], Connetics[88] and Stiefel[89] as well as Living Cell Technologies[90], another cellular therapy company, and Hatchtech [91]. Macdonald's varied managerial experience has enabled Cynata to move rapidly since he joined as CEO in July 2013.

Dr Geoff Brooke (Chairman), who became a director in May 2019 and Chairman in August 2020, brings management skills relevant to early stage biotech companies gained from his years building the respected VC house GBS Venture Partners. That firm has backed numerous Australian Life Science success stories such as Peplin Biotech [92], Spinifex Pharmaceuticals [93] and Elastagen[94].

Dr Paul Wotton (Non-Executive Director), who joined Cynata's board in June 2016 and was Chairman from February 2017 until August 2020, has an enviable resume for a stem cell company, having been CEO of Ocata Therapeutics prior to that company's acquisition to Astellas[95] 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[96], where he was Global Head of Business Development.

Dr Kilian Kelly (Chief Operating Officer) 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.

The Cynata board chaired by Brooke, 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[97]. **Dr Darryl Maher**, a 20-year veteran of the Melbourne-based CSL Ltd (ASX: CSL), brings strong R&D skills.

[86] 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.
[87] 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.
[88] This company bought Soltec in 2001
[89] Bought by GSK in 2009 for US$2.9bn.
[90] This company (Auckland, New Zealand, ASX: LCT, www.lctglobal.com) works on transplantation of porcine islet cells for the treatment of diabetes in humans.
[91] Developer of a new lice control product (Melbourne, Australia, privately held, www.hatchtech.com.au).
[92] Developer of a natural product for the treatment of skin cancer. This company was sold to Denmark's Leo Pharma for US$287.5m in 2009.
[93] Developer of a potential first-in-class oral treatment for chronic pain without CNS side effects. Spinifex was sold to Novartis in 2015 for US$200m plus milestone payments.
[94] Developer of recombinant tropoelastin, useful in aesthetics, scar remodeling and surgical wound repair. This company was sold to Allergan in February 2018 for US$95m plus contingent commercial payments.
[95] Astellas is the world's 21 largest pharma company with US$11.1bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[96] London, UK, LSE: SKP, www.skyepharma.com.
[97] Gained at companies such as Calzada (polymer biomaterials), Phylogica (peptide drugs and vaccines) and iSonea (airway patency diagnostics).

Appendix I – 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.

Critical Limb Ischemia – Severe blockage in the arteries of the lower extremities.

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

Cytokine release syndrome – A large, rapid release of cytokines into the blood from immune cells. Patients undergoing immunotherapy sometimes experience cytokine release syndrome, which can be life threatening.

CYP-001 – Cynata's cell product for GvHD, now licensed to Fujifilm.

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.

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.

Osteoarthritis – Progressive degeneration of bone tissue such as cartilage resulting from inflammation.

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.

Sepsis – Serious and potentially life-threatening inflammation caused by severe infection.

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 II – Cynata's IP position

Cynata's core published intellectual property is covered by four patent families owned by the Wisconsin Alumni Research Foundation (WARF)[98], and licensed to Cynata, and six patent families for which Cynata has filed. Cynata continues to file for patent protection over new IP.

WO/1996/022362, *Primate embryonic stem cells,* priority date 20 January 1995, invented by James Thomson.

- This patent family covers the method of deriving the embryonic stem cell line[99] from which Cynata's mesenchymoangioblasts were first derived.

WO/2001/066697, *Serum-free cultivation of primate embryonic stem cells*, , 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.

WO/2011/116117, *Generation of clonal mesenchymal progenitors and mesenchymal stem cell lines under serum-free conditions*, priority date 18 March 2010, invented by Maksym Vodyanyk and Igor Slukvin[100].

- This patent family covers Cynata's mesenchymoangioblasts.

WO/2014/165131, *Methods and materials for hematoendothelial differentiation of human pluripotent stem cells under defined conditions*, priority date 13 March 2013, invented by Igor Slukvin and Gene Uenishi[101].

[98] Holder all rights to all the intellectual property created at the University of Wisconsin.
[99] 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.
[100] This patent application was granted in the US in November 2009 as No. 7,615,374 and in September 2017 as No. 9,771,561. It was granted in Europe as EP 2 547 763 in August 2018
[101] This patent application was granted in the US in April 2018 as No. 9,938,499 and in Europe as EP 2 970 912 in March 2019.

- 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.

WO/2017/156580, *Colony forming medium and use thereof*, priority date 16 March 2016, invented by Igor Slukvin, Gene Uenishi, Derek Hei and Diana Drier.

- This patent family covers the medium used to culture Cynata's MSCs.

WO/2018/090084, Pluripotent stem cell assay, priority date 16 November 2016, invented by Igor Slukvin, Derek Hei and Diana Drier

- This patent family covers the assay that would allow a uniform iPSC product to be cultured by detecting all undifferentiated cells in culture.

WO/2018/184074, *Method for treating a side effect of Chimeric Antigen Receptor (CAR) T cell therapy*, priority date 7 April 2017, invented by Kilian Kelly and Igor Slukvin.

- This patent application covers the use of Cynata's MSCs in treating cytokine release syndrome in cancer patients being administered a CAR-T product.

WO/2018/227244, *Method for treating a side effect of immunotherapy*, priority date 16 June 2017, invented by Kilian Kelly and Igor Slukvin.

- This patent application is similar to WO/2018/184074 above but covers cancer immunotherapy other than CAR-T.

WO/2019/051536, Method for treating Allergic Airways Disease (AAD) / asthma, priority date 15 September 2017, invented by Chrishan Samuel and Simon Royce.

- This patent application covers the use of Cynata's MSCs in treating asthma and related allergies.

WO/2020/172700, *Method for improving angiogenic potential of a mesenchymal stem cell*, priority date 28 February 2019, invented by Kris Kilian and Sara Romanazzo.

- This patent family covers a way of culturing Cynata's MSCs where the substrate has a matrix protein that leads to MSCs better able to secrete pro-angiogenic factors to treat coronary artery disease and peripheral artery disease.

Appendix III - Major shareholders

Cynata currently has only two substantial shareholders:

- **Fidelity** (9.3%)
- **Fujifilm** (TYO:4901), the Japanese company involved in healthcare, highly functional materials and document management, which owns 6.9% of Cynata. Fujifilm is now a major player in regenerative medicine through its 2015 acquisition of Cellular Dynamics.

Appendix IV – 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, from the Royce laboratory at Monash University, shows *in vivo* that Cymerus MSCs can reduce airway hyper-responsiveness by 60-70% in an animal model of chronic allergic airways disease.

Royce et. al. (2019), *iPSC - and mesenchymoangioblast - derived mesenchymal stem cells provide greater protection against experimental chronic allergic airways disease compared with a clinically used corticosteroid.* FASEB J. 33, 6402–6411 (2019).

- This paper reports the *in vivo* work of the Royce lab at Monash University on reversing airway remodeling in asthma.

Ozay et. al. (2019), *Cymerus™ iPSC-MSCs significantly prolong survival in a pre-clinical, humanized mouse model of Graft-vs-host disease*. Stem Cell Res . 2019 Mar;35:101401. Epub 2019 Feb 1.

- This paper, from the laboratory of Lisa Minter at the University of Massachusetts Amherst, reports Cynata's pre-clinical data on the effectiveness of its Cymerus MSCs in GvHD.

Khan et. al. (2019*), iPSC-derived MSC therapy induces immune tolerance and supports long-term graft survival in mouse orthotopic tracheal transplants*. Stem Cell Res Ther. 2019; 10: 290. Published online 2019 Sep 23.

- This paper, from a group at the King Faisal Specialist Hospital and Research Centre, in the Saudi Arabian capital of Riyadh, shows *in vivo* that Cymerus MSCs can be used for immunosuppression in transplant recipients.

Miller et. al. (2020), Combined Mesenchymal Stromal Cell therapy and Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome. A randomized controlled trial in sheep. Am J Respir Crit Care Med . 2020 Aug 1;202(3):383-392.

- This study showed that Cymerus MSCs could help blunt the severity of ARDS in sheep.

Bloor et. al. (2020), *Production, safety and efficacy of iPSC-derived mesenchymal stromal cells in acute steroid-resistant graft versus host disease: A Phase I, multicenter, open-label, dose-escalation study*, Nature Medicine, 14 September 2020.

- This paper reports the Phase 1 data on Cynata's MSCs in GvHD.

Appendix V – Cynata's capital structure

Class		% of fully diluted	Note
Ordinary shares, ASX Code CYP (million)	117.1	98.5%	
Unlisted options (million)	1.7	1.5%	Weighted average exercise price 181.3 cents, weighted average expiry date 20-Sep-2022
Fully diluted shares	118.8		
Current market cap:	A$93.7 million (US$65.8 million)		
Current share price	$0.800		
Twelve month range	$1.34 - $0.605		
Average turnover per day (last three months)	255,200		

Appendix VI – Comparable companies

Allovir (Cambridge, Ma., Nasdaq: ALVR, allovir.com, market cap US$1.67bn[102]). This company's Virus-Specific T cell (VST) technology allows off-the-shelf treatment and prevention of viral diseases. The company sources PBMCs from donors and then cultures these cells using proprietary methods for a rapid expansion of antigen-specific T cells. Allovir's lead candidates against viruses such as CMV are now in proof-of-concept studies.

Atara Biotherapeutics (South San Francisco, Ca., Nasdaq: ATRA, atarabio.com, market cap US$1.09bn). This company's technology allows rapid expansion of allogenic T cells. The company's lead candidate, Tabelecleucel, is in Phase 3 for patients with Epstein-Barr virus-associated post-transplant lymphoproliferative disease (EBV+ PTLD). Atara is also working on next-generation CAR-T therapy.

Athersys (Cleveland, Oh., Nasdaq: ATHX, athersys.com, market cap US$328m). This company's MultiStem multipotent adult progenitor cells are in Phase 3 in ischemic stroke under a Special Protocol Assessment. In Phase 2 a post-hoc analysis showed that patients who received MultiStem treatment earlier in the treatment window had more robust recovery rates in comparison to placebo and relative to patients who received later MultiStem treatment . After ischemic stroke Athersys is progressing clinical programmes in a range of neurological, cardiovascular, inflammatory and orthopaedic indications.

BrainStorm Cell Therapeutics (New York, NY, Nasdaq: BCLI, brainstorm-cell.com, market cap US$322m). This company's NurOwn technology allows Mesenchymal Stem Cells to be converted into cells that secrete a variety of neurotrophic factors. NurOwn is in Phase 3 in Amyotrophic Lateral Sclerosis (ALS) after a favourable Phase 2 study .

Capricor Therapeutics (Beverly Hills, Ca., Nasdaq: CAPR, capricor.com, market cap. US$90m). This company is working on 'Cardiosphere-Derived

[102] Note, all market capitalisations from 2 November 2020 close on Nasdaq and elsewhere.

Cells' (CDCs), which are cardiac progenitor cells that have potent immunomodulatory properties. Capricor's lead candidate, CAP-1002, is being developed as an off-the-shelf cardiac cell therapy for Duchenne Muscular Dystrophy (DMD) and Covid-19. In Phase 2 data reported in May 2020 CAP-1002 improved performance of the upper arm in treated DMD patients over a 12-month period.

Fate Therapeutics (La Jolla, Ca., Nasdaq: FATE, fatetherapeutics.com, market cap. US$4.14bn). This company's platform uses iPSC cell lines to create off-the-shelf cellular immunotherapies. The company's pipeline is mainly focused on cancer immunotherapy, with a number of iPSC-derived NK cell products in the clinic. Fate's FT500 product, now in Phase 1 in solid tumours, is the first-ever iPSC-derived cell therapy cleared for clinical investigation in the United States.

Gamida Cell (Jerusalem, Israel, Nasdaq: GMDA, gamida-cell.com, market cap US$280m). This company has been built on technology for the *ex vivo* expansion of cord blood cells to maintain 'stemness'. The company's lead Omidubicel product performed well in Phase 3 for advanced hematologic malignancies, with improvements for patients in platelet engraftment, infections and hospitalizations. Gamida Cell intends to file a BLA with the FDA before 2020 is out.

Healios K.K. (Tokyo, Japan, TSEL 4593, healios.co.jp/en, market cap US$980m). This company is based on technology to create gene-modified iPSCs. The company is currently conducting two pivotal studies in Japan in ischemic stroke and acute respiratory distress syndrome (ARDS) with Athersys's Multistem product. In addition, Healios has established a next generation immuno-privileged universal donor iPSC platform and is working on applications in immuno-oncology, ophthalmology, and liver disease.

Medipost (Seongnam, Korea, Kosdaq: 078160, medi-post.com, market cap US$390m). This company runs the largest private cord blood bank in Korea, but, more importantly, it is working on new off-the-shelf, allogeneic cell therapies using MSCs derived from that cord blood. There are clinical programmes ongoing in osteoarthritis and Alzheimer's, among other indications.

Mesoblast (Melbourne, Australia, ASX: MSB, mesoblast.com, market cap US$1.33bn). 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 off-the-shelf. Mesoblast has reached the regulatory stage with a therapy for acute GvHD. The company is in Phase 3 in advanced chronic heart failure and chronic low back pain due to degenerative disc disease. In April 2020 the company showed that its cells were useful in treating Covid-19 infection .

Pluristem Therapeutics (Haifa, Israel, Nasdaq: PSTI, pluristem com, market cap US$248m). 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, while another Phase 3 is evaluating the potential of PLX-PAD for muscle regeneration following hip fracture.

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**. iPSC-derived MSCs may prove too difficult to produce at final commercial scale.
- **Clinical**. There is the risk that the Phase 2 Graft-versus-Host Disease trial being organised by Fujifilm could be difficult to recruit in a reasonable time period, or not meet its endpoints.
- **Funding**. More capital may be needed to get iPSC-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.

Analyst qualifications

Stuart Roberts, lead analyst on this report, has been covering the Life Sciences sector as an analyst since 2002.

- Stuart obtained a Master of Applied Finance and Investment from the Securities Institute of Australia in 2002. Previously, from the Securities Institute of Australia, he obtained a Certificate of Financial Markets (1994) and a Graduate Diploma in Finance and Investment (1999).
- Stuart joined Southern Cross Equities as an equities analyst in April 2001. From February 2002 to July 2013, his research specialty at Southern Cross Equities and its acquirer, Bell Potter Securities, was Healthcare and Biotechnology. During this time, he covered a variety of established healthcare companies such as CSL, Cochlear and Resmed, as well as numerous emerging companies. Stuart was a Healthcare and Biotechnology analyst at Baillieu Holst from October 2013 to January 2015.
- After 15 months in 2015 and 2016 doing Investor Relations for two ASX-listed cancer drug developers, Stuart founded NDF Research in May 2016 to provide issuer-sponsored equity research on ASX-listed Life Science companies.
- In July 2016 with Marc Kennis, Stuart co-founded Pitt Street Research Pty Ltd, which provides issuer-sponsored research on ASX-listed companies across the entire market, including Life Science companies.

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