NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

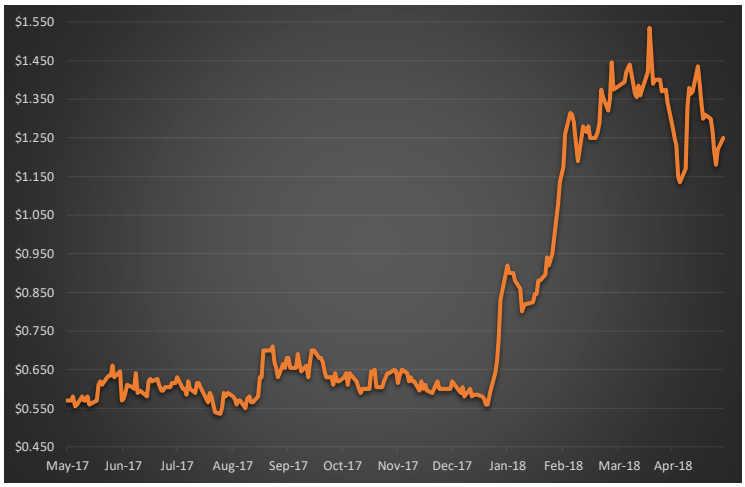
Cynata Therapeutics (ASX: CYP)

Update note – Friday 22 June 2018

Clinical evidence that Cymerus works

This note updates our 24 July 2017 note headlined 'The Swiss Army Knife of cellular remedies'. Enrolment of the second cohort of patients in Cynata Therapeutics's Phase 1 trial of its CYP-001 stem cell product in steroid-refractory Graft-versus Host Disease has now completed, after the first cohort, which was dosed at 1 million cells per kilogram of body weight, showed that the therapy is safe and well-tolerated. The first cohort generated early evidence that CYP-001 can blunt the severe and life-threating inflammation associated with GvHD, with all eight patients seeing their GvHD reduced by at least one grade of severity and four showing complete resolution of GvHD by 100 days post-treatment. In the second cohort, Cynata's investigators have dosed at 2 million cells / kg and generated an encouraging Complete Response in four of seven evaluated patients at Day 28. Now that Cynata is nearing the completion of its maiden clinical study, we see strong potential for Fujifilm to exercise the option over Cymerus in GvHD which it negotiated in January 2017. Fujifilm, now a global leader in cellular medicine, is Cynata's second largest shareholder, with 9% of the company. Further clinical success for Cynata in the second patient cohort will considerably enhance the appeal of this regenerative medicine company. With just one study in GvHD, Cynata has demonstrated the value of its unique Cymerus platform, and the broad applicability and efficacy of its MSCs. Cynata has the only platform in the world to produce unlimited quantities of Mesenchymal Stem Cells without requiring multiple donors or massive expansion of the MSCs themselves. With this note we are increasing our share price target from $2.00 to $2.40.

Rating	Risk	Current price	Target price
Buy	Medium	$1.37	$2.40



Stock details

Daily Turnover: ~A$146,000
Market Cap: A$130.2m
Shares Issued: 95.1m
52-Week High: $1.54
52-Week Low: $0.51

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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.

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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'.

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

In this report

Cynata Therapeutics – first evidence that Cymerus works

Who is Cynata Therapeutics? Cynata Therapeutics is a Melbourne-based regenerative medicine company whose technology allows the creation of virtually unlimited quantities of Mesenchymal Stem Cells (MSC). A significant body of knowledge from the last two decades has shown that MSCs are very useful across a range of disease conditions and, importantly, can act as potent anti-inflammatories. A potential challenge for companies working on MSC-based therapies is being able to source MSCs in therapeutically and commercially significant quantities at low cost. Cynata believes that it has solved this problem with its Cymerus™ technology. The Cymerus process was developed around a precursor cell called the mesenchymoangioblast, which was discovered and patented by the University of Wisconsin-Madison and exclusively licensed to Cynata. Early *in vitro* work had shown that a single colony of mesenchymoangioblasts could produce up to 10^{22} MSCs. Cynata took these energetic MSC factories and enabled them to be produced by iPS cells, which are ordinary cells from the body reprogrammed so that their ability to expand and turn into any cell type in the body is virtually unlimited. A maiden clinical study of Cynata's Cymerus-sourced MSCs, that product being designated the code name CYP-001, is now underway in steroid refractory Graft-versus Host Disease. The early data from the first cohort in that study is encouraging. In January 2017 Fujifilm, a global leader in regenerative medicine, optioned Cynata's cells for GvHD, and the availability of the report describing the clinical data from this study brings into focus a 90-day window in which Fujifilm can exercise its option. Should Fujifilm exercise, it will pay Cynata US$3m in cash, fund all further development of Cymerus in GvHD and potentially pay Cynata AUD$60m in downstream milestones, plus double-digit royalties.

Cynata needs just one study to show that its Cymerus platform has value. Cynata's strategic intention from the time of its 2013 ASX listing was to demonstrate, firstly, that it could manufacture Cymerus-sourced MSCs at scale under GMP, and, secondly, that its MSCs would work in the clinic as MSCs were widely expected to do. Taken together, these achievements would reasonably show, to investors and the pharmaceutical industry, that the Cymerus platform had significant value in the new era of regenerative medicine into which the world was moving. The manufacturing part of this strategy was achieved in early 2015. Cynata then proceeded to the clinical stage. It chose Graft-versus-Host Disease for the maiden study of its MSCs because MSCs have known anti-inflammatory properties, and only small numbers of patients would be needed to show that the MSCs had the desired treatment effect. Cynata's CYP-001 Cymerus MSCs were granted Orphan Drug designation by the FDA in March 2018 for GvHD.

CYNATA NEEDS JUST ONE STUDY TO SHOW THAT ITS PLATFORM HAS VALUE

Cynata has generated favourable data from its maiden clinical study. Cynata's study, which dosed its first patient in May 2017, has recruited 16 patients with steroid-resistant acute GvHD (Grades II-IV) in hospitals in the UK and Australia. In addition to assessing safety, the study is tracking complete and partial responses on Cymerus therapy, as well as survival at Days 28 and 100[1].

[1] See NCT02923375 at www.clinicaltrials.gov.

- **The first cohort** of eight patients was dosed at 1 million cells per kilogram of body weight[2] in two doses one week apart. This cohort had been recruited by November 2017, after which an independent Data Safety and Monitoring Board (DSMB) looked at the data to check for any untoward adverse events. The DSMB reported back to Cynata's investigators that the trial could proceed as planned in January 2018. This was encouraging for two reasons: Firstly, Cymerus at 1 million cells /kg was judged safe and tolerable. Secondly, all eight patients saw the severity of their GvHD fall by at least one grade. A further report in February 2018 added to this bright picture, showing a Complete Response Rate at Day 100 of 50% (ie four of eight patients) and Overall Survival at day 100 of 87.5%, with one of the eight patients having died of pneumonia. This death was not judged by the DSMB as a treatment-related adverse event as pneumonia is a frequently-seen cause of death in GvHD patients[3]. It is important to put these promising results into the context of the clinical outlook of these patients, which is extremely poor with very high mortality rates. At the six-month mark in June 2018 the survival rate remained 87.5% and the safety profile remained favourable.
- **The second cohort** of this study enrolled another eight patients for a dose of at 2 million cells / kg, with two doses being administered as in the first cohort, 7 days apart. Recruitment in Cohort B was completed in May 2018 and the first batch of data at Day 28, reported on 21 June, showed an Overall Response Rate of 86% (six of seven evaluated patients[4]) where the GvHD severity improved by at least one grate. The Complete Response Rate of 57%, reflected the fact that four of the seven evaluated patients experienced complete resolution of their symptoms. This latter outcome was encouraging because for Cohort A only one patient had had a Complete Response by Day 28.

COHORT B OF THE GvHD STUDY HAS NOW FULLY RECRUITED

Fujifilm's period to license Cynata's MSCs in GvHD will be coming up soon. Under the January 2017 option deal with Fujifilm, that company, which already owns 9% of Cynata, can execute a global licensing deal over the GvHD indication for Cymerus at any time, with that option concluding 90 days after Cynata finalises the study report describing the Phase 1. If Fujifilm chooses to license it will pay US$3m cash upfront and up to AUD$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. It is notable that Fujifilm have publicly announced that they expect peak sales of a Cymerus GvHD product to reach US$300m pa[5]. 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 2021.

After the GvHD 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

[2] Up to 100 million cells.
[3] Bone Marrow Transplant. 2003 Sep;32(5):515-22.
[4] The eighth patient in this cohort was excluded from analysis because a of a medical complication that occurred after recruitment but before treatment.
[5] Source: Fujifilm Corporate Presentation, December 2016.

Therapy status for these cells[6]. Consequently, if Fujifilm chooses to exercise its option it can act quickly to move this product into multiple markets.

After GvHD, what's next for Cynata? With GvHD helping to establish clinical proof-of-concept, there are plenty of other opportunities for Cynata's MSCs. Over the last few years the company have generated favourable pre-clinical data in Critical Limb Ischemia, asthma, Acute Myocardial Infarction and Idiopathic Pulmonary Fibrosis. Moreover, the laboratory of Professor Khalid Shah at Harvard has shown that modified MSCs derived using the Cymerus process can be used to treat brain tumours, while the University of Massachusetts Amherst has shown that Cynata's MSCs can be used to blunt the potentially fatal 'cytokine storm' often associated with CAR-T therapy for the treatment of cancer. We expect that Cynata will look to build out its pipeline following completion of the GvHD study. Let's look at some recent developments for Cymerus MSCs in CAR-T, cancer and asthma.

AFTER GvHD THERE ARE MANY MORE OPPORTUNITIES FOR CYMERUS

Cynata may help make CAR-T a kinder, gentler therapy

One of the significant developments in cancer treatment over the last ten years has been the emergence of CAR-T, short for 'Chimeric Antigen Receptor T-Cell therapy'. CAR-T is a form of adoptive T cell therapy, in which a patient's own T cells are engineered to increase their cancer-fighting properties. In CAR-T the T cells are engineered to carry Chimeric Antigen Receptors, these receptors being a combination of antibodies and T cell signalling molecules that tell the immune system where to send a storm of antigen-destroying T cells[7]. CAR-T has shown massive potential in recent clinical studies in various blood cancers.

- The major pharma company Gilead paid US$11.9bn in August 2017 to acquire a CAR-T pioneer called Kite Pharma, off the back of a clinical study showing a 54% complete remission rate in refractory or relapsed large B-cell lymphoma when these patients were treated with Kite's leading CAR-T[8]. That product, called Yescarta[9], gained FDA approval in October 2017.
- A Novartis CAR-T called Kymriah[10], originally developed at the University pf Pennsylvania[11], gained FDA approval in August 2017 for the treatment of paediatric patients and young adults with refractory or relapsed B cell precursor acute lymphoblastic leukemia. In the study which led to this approval the overall remission rate within 3 months was 81%[12].

[6] See the Cynata market release dated 5 July 2017 and headlined '*FDA meeting provides clear path for Cynata US development plans*'.
[7] Mol Cancer. 2018 Feb 15;17(1):32.
[8] N Engl J Med. 2017 Dec 28;377(26):2531-2544. Epub 2017 Dec 10.
[9] Generic name Axicabtagene Ciloleucel, see www.yescarta.com.
[10] Generic name tisagenlecleucel, see www.kymriah.com.
[11] Novartis started collaborating with the laboratory of Carl June at the University of Pennsylvania on CAR-T in 2012. The product that became Kymriah, originally CTL019, gained Breakthrough Therapy Designation from the FDA in July 2014 for relapsed/refractory acute lymphoblastic leukemia.
[12] N Engl J Med. 2018 Feb 1;378(5):439-448.

The trouble with CAR-T in terms of potential adverse events are the 'cytokine storms' in which massive numbers of cytokines from the immune cells affected by the immunotherapy are unleashed inside the patient's body. As with any serious inflammation, this so-called Cytokine Release Syndrome can be fatal[13], but the patient more often than not experiences it as fever, nausea, headache, rash, rapid heartbeat, low blood pressure, and difficulty breathing. This is virtually the norm in CAR-T – in the Kymriah study in ALL CRS occurred in 77% of patients, 48% of whom had to be treated with the Roche anti-inflammatory Actemra[14]. That drug, best known as a Rheumatoid Arthritis therapy, for which it gained FDA approval in 2010, was granted FDA approval for a CAR-T indication at the same time as Kymriah's approval[15].

CYMERUS MSCs CAN COMBAT CAR-T CYTOKINE STORMS

Cynata's MSCs may emerge as a better alternative to Actemra and other anti-inflammatories in CAR-T-induced CRS. Cynata announced in April 2018 that it had filed for patent protection over the use of its Cymerus MSCs in CAR-T-induced CRS after favourable pre-clinical work in mouse models done by collaborators at the University of Massachusetts Amherst.

The commercial upside in CRS may be significant. The CAR-T therapies are likely to be among the more high-priced interventions in cancer, if the initial US$475,000 price for Kymriah in the US market is any guide[16], and if CAR-T can expand its reach beyond the blood cancers it's reasonable to expect the market to be in the billions given the favourable treatment outcomes. Consequently, CRS could be a US$0.5bn opportunity for effective drugs with strong anti-inflammatory properties. Cynata's opportunity here would be for Cymerus MSCs to be selected by the CAR-T developers for use in one of its early studies.

Progress with Cynata's engineered cells

Cymerus MSCs can allow for targeted cancer therapies. One of the more recent fields of research endeavour related to MSCs is their use in treating cancer. It has long been known that MSCs can migrate to the site of tumours. This was generally assumed to be favourable to the cancer[17], although more recently evidence has started to emerge of the putative anti-cancer properties of MSCs[18]. Various groups are now seeking to harness the migratory properties of MSCs to deliver therapeutic payloads into the tumour microenvironment[19]. One such group is led by Dr Khalid Shah[20], who directs the Center for Stem Cell Therapeutics and Imaging at Harvard Medical School and who has a strong research focus on brain tumours. In 2009 the Shah lab showed that, in vivo, that MSCs engineered to express a pro-apoptotic protein called TRAIL could work in glioma[21], while in 2014 the Shah lab showed that MSC could deliver TRAIL-expressing oncolytic viruses in an animal model of glioblastoma[22].

[13] See *Cancer immunotherapy company tries to explain deaths in recent trial* by Roni Dengler, Science Magazine, 16 November 2017
[14] Generic name tocilizumab, see www.actemra.com.
[15] Oncologist. 2018 Apr 5. pii: theoncologist.2018-0028. [Epub ahead of print]. The indication of for severe or life-threatening CAR-T induced CRS where the patients are over the age of two.
[16] See *Patient advocate says Novartis' $475,000 breakthrough should cost just $160,000* by Matthew Herpe, Forbes, 8 February 2018.
[17] Curr Cancer Drug Targets. 2015;15(2):88-98.
[18] Mutat Res. 2014 Oct;768:98-106. Epub 2014 Feb 7.
[19] Stem Cells Dev. 2016 Sep 7. [Epub ahead of print]
[20] Adv Drug Deliv Rev. 2012 Jun 1;64(8):739-48. Epub 2011 Jun 29.
[21] Proc Natl Acad Sci U S A. 2009 Mar 24;106(12):4822-7. Epub 2009 Mar 5.
[22] J Natl Cancer Inst. 2014 May 16;106(6):dju090. Print 2014 Jun.

Importantly, the Shah lab had devised a method of encapsulating their MSCs in a biodegradable synthetic extracellular matrix so as to protect the stem cells from destruction by the TRAIL they were delivering[23]

The early lab work looks good. Cynata announced in February 2018 that the Shah lab had been able to engineer Cymerus MSCs to express various proteins of diagnostic and therapeutic interest, with stable expression and persistence of the cells *in vivo* for long enough to have a therapeutic effect. The Shah lab will now look to generate in vivo data in their animal models, presumably of glioblastoma, with results available later this year.

ENGINEERED CYMERUS MSCs MAY BE USED TO TREAT CANCER

Why Cymerus MSCs would make great anti-cancer drug delivery vehicles. Targeted cancer therapy started to mainstream with the arrival of the monoclonal antibody drugs from the late 1990s.However it is the ability of interventions to hit multiple targets at one, and to function in the tumour microenvironment, that is more of interest to the field rather than just hitting one particular cancer antigen. MSCs engineered to express multiple anti-cancer proteins could represent an efficient solution particularly if, like Cymerus MSCs, they are available in very large quantities at very low cost.

Cymerus MSCs may represent a new treatment option for asthma

Cymerus MSCs can significantly knock down airway hyper-responsiveness in asthma. In 2016 a group at Monash University in Melbourne led by Drs Chrishan Samuel and Simon Royce evaluated Cymerus MSC in an animal model of chronic allergic airways disease and found that the cells could reduce airway hyper-responsiveness by 60-70% in the standard ovalbumin challenge test[24]. This decrease was statistically significant ($p<0.01$)[25]. Samuel and Royce published their study in The FASEB Journal in June 2017, showing in that paper that Cymerus MSCs would also act on inflammation and airway remodelling, again with statistical significance ($p<0.05$)[26]. What was exciting here was that pathogenic collagen deposition was completed reversed with intra-nasal delivery of the MSCs.

Cymerus MSCs can work with steroids, and is better than steroids alone, in asthma. Following on from this early work Samuel and Royce took the same animal model and compared Cymerus MSCs to the corticosteroid dexamethasone, commonly used to treat asthma exacerbations. Cynata was able to announce in August 2017 that both Cymerus MSCs as a monotherapy, and Cymerus MSCs plus dexamethasone could reduce airway hyper-responsiveness by a greater amount than dexamethasone alone. This finding had statistical significance ($p<0.01$). A confirmatory animal study announced in December 2017 repeated these findings.

CYMERUS MSCs ARE BETTER THAN STEROID MONOTHERAPY IN ASTHMA

[23] See WO/2015/089280, *Stem cell delivered oncolytic Herpes Simplex Virus and methods for treating brain tumors*, invented by Khalid Shah, priority date 11 December 2013.
[24] 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.
[25] See the company's market release dated 17 October 2016 and headlined '*Cynata's MSC technology demonstrates significant efficacy in preclinical asthma study*'.
[26] FASEB J. 2017 Sep;31(9):4168-4178. Epub 2017 Jun 16.

The asthma field is ripe for the Next Big Thing. Around 7% of US adults and 9% of US children have asthma[27].The mainstay of asthma treatment since the 1990s, and the basis of significant franchises for GSK and AstraZeneca – US$8bn for GSK's Advair in 2013 US$3.8bn for AstraZeneca's Symbicort in 2014 - has been long-acting beta agonists with corticosteroids. We argue MSCs could reasonably be the Next Big Thing in an environment where the biologic drugs are starting to emerge at the rate of one a year – witness GSK's Nucala[28] (2015), Teva's Cinquair[29] (2016) and AstraZeneca's Fasenra[30] (2017) – but where there remains further progress to be made on airway remodelling and fibrosis. We expect that a key challenge for Cynata in moving into the clinic in asthma will be developing stable formulations of Cymerus MSCs that are patient-friendly.

Background to Cynata

CYNATA IS PART OF A REVOLUTION IN MODERN MEDICINE

Cynata is part of the next Revolution in modern medicine. Over the last three decades or so medicine has passed through a series of what can reasonably be called Revolutions, where new technologies have enabled 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 exquisitely 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[31] 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$86m. 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

[27] Source: CDC, 2014 National Health Interview Survey.
[28] Generic name mepolizumab, see www.nucala.com.
[29] Generic name reslizumab, see www.cinquair.com.
[30] Generic name benralizumab, see www.fasenra.com.
[31] 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.

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*[32]. Slukvin et. al. showed[33] 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[34]. 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[35]. At that time, there wasn't any *clinical* 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.

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[36], 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[37]. 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[38]. 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, Wisconsin. called Waisman Biomanufacturing[39] 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:

CYNATA CAN MAKE ITS CELLS AT SCALE

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.

[32] A 'sub-journal' of the journal *Cell* focused on stem cells.
[33] 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.
[34] The shell was Ecoquest, ASX Code ECQ.
[35] 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.
[36] 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.
[37] And often arises in diabetics as a complication of their underlying diabetes.
[38] 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*'.
[39] See www.gmpbio.org.

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 is completing its first 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 was the first time a patient anywhere in the world was treated with an allogeneic, iPSC-derived MSC therapy. This study saw favourable outcomes for the patients in the first cohort and we expect to see first data from the second cohort to be announced shortly.

CYNATA DOSED ITS FIRST GvHD PATIENT IN MAY 2017

Updating our valuation of Cynata

We value Cynata using a probability-weighted DCF-based approach where we value the potential payoff in GvHD, Acute Myocardial Infarction and asthma. We refer readers to our 24 July 2017 note for the details of our approach. At that time, we valued Cynata at $1.03 per share base case and $2.77 per share optimistic case, using a probability-weighted DCF method. This put our target price at $2.00 per share, around the mid-point of our valuation range. With this note our valuation range changes to $1.36 base case and US$3.47 optimistic case. The main factors involved in the change are as follows:

- our Australian dollar forecasts have increased by around 1.7% since July 2017, thanks to the stronger rates prevailing in late 2017.
- Cynata recently raised A$5.2m in a placement to global investment giant, Fidelity, at A$1.275 per share.
- We changed the risk weighting on the GvHD project from 21% to 38% to reflect the favourable Cohort A data. 38% is the historic probability of a large molecule drug in Phase 2[40].
- We raised the 'earliest approval' date assumption for the GvHD project from 2023/2024 to 2021/2022 to reflect the potential of Fuji moving this project swiftly once the current study completes.
- We raised the 'earliest approval' date assumption for the AMI and asthma projects. For AMI we moved this forward from 2026/2027 to 2023/2024. For asthma we moved from 2028/2029 to 2024/2025. In each case our thinking was shaped by the relative speed with which Phase 2 studies could initiate – possibly 2019 in the case of AMI, 2020 in the case of asthma given the reformulation required for that product – followed by the Japanese regulatory fast track.

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

Our new price target of $2.40 is the midpoint of our new valuation range. We continue to 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'.

Valuation – Project parameters

Figure 1: GvHD project parameters

	Base case	Optimistic case
CYP 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	2022	2021
Peak sales (USDm)[41]	400	600

Figure 2: AMI project parameters

	Base case	Optimistic case
CYP 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	2024	2023
Peak sales (USDm)[42]	700	1,200

[41] 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.
[42] 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 3: Asthma project parameters

	Base case	Optimistic case
CYP 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	2025	2024
Peak sales (USDm)[43]	1,400	2,400

Figure 4: Our valuation of Cynata.

	Base	Optim.
GvHD (A$m)	44.6	81.4
AMI (A$m)	46.6	133.8
Asthma (A$m)	54.1	156.4
Total programme value	145.2	371.6
Value of tax losses	9.1	9.1
Corporate overhead	-32.0	-32.0
Cash now (A$m)	13.5	13.5
Cash to be raised (A$m)	0.0	0.0
Option exercises (A$m)	9.5	9.5
Total value (A$m)	145.3	371.7
Total diluted shares (million)	107.0	107.0
Value per share	$1.357	$3.472
Valuation midpoint	$2.415	
Share price now (A$ per share)	$1.370	
Upside to midpoint	76.2%	

Re-Rating Cynata

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

- 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;
- *In vivo* data on other Cymerus MSC indications.

[43] 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.

Risks related to Cynata

Risks specific to Cynata. We see three 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.
- **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.

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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.

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