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Cynata Therapeutics Limited (CYP-AU)

Initiating Coverage

Healthcare

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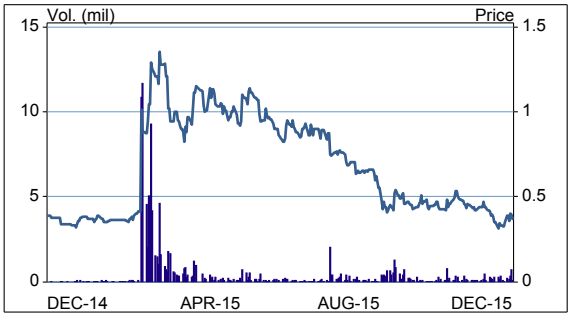
Powering Production of Stem Cells; Initiating Coverage at Buy with A$1.00 Price Target

Stock Data	12/04/2015
Rating	Buy
Price	AUD0.37
Exchange	ASX
Price Target	AUD1.00
52-Week High	AUD1.44
52-Week Low	AUD0.31
Enterprise Value (MM)	AUD22
Market Cap (MM)	AUD27
Public Market Float (MM)	56.6
Shares Outstanding (MM)	72.7
3 Month Avg Volume	189,022
Balance Sheet Metrics	
Cash (MM)	A$8.10
Total Debt (MM)	A$0.03
Total Cash/Share	A$0.11
Book Value/Share	A$0.13

EPS Diluted			
Full Year - Jun	2014A	2015A	2016E
1st Half	--	--	(0.02)
2nd Half	--	--	(0.02)
FY	(0.07)	(0.06)	(0.07)

Revenue (M)			
Full Year - Jun	2014A	2015A	2016E
FY	AUD0.00	AUD0.00	AUD1.00



Scalability and sustainability in stem cell manufacturing. We initiate coverage on Cynata Therapeutics Ltd. with a Buy rating and 12-month price target of A$1.00 per share. Cynata is an Australian stem cell-focused firm with a proprietary platform, Cymerus™, which provides a high-throughput, sustainable solution for the production of mesenchymal stem cells (MSCs). These cells have been shown in various clinical settings to have substantial applicability across various indications, including cardiology, regenerative medicine, autoimmune disorders and cancer. We believe that Cynata could position itself as a potential partner of choice for companies seeking to develop MSC-based therapeutics.

Capital-efficient business model. In our view, Cynata possesses a cost-effective approach to the development of its stem cell platform, choosing to position itself as a manufacturing portal rather than simply a drug developer. The company is planning to conduct relatively capital-efficient proof-of-concept clinical studies to establish the validity of its stem cell production platform, then partner with more established companies for therapeutics development.

Precedent transactions set favorable benchmarks. A slew of recent partnerships and M&A activity in the stem cell domain set an attractive set of benchmarks for Cynata. Notable such transactions include the $307M acquisition of Cellular Dynamics International by Fujifilm, the $50M investment made by Novartis into the privately-held Israeli firm Gamida Cell; and the $130M upfront payment-based licensing deal between Mesoblast Ltd. and Cephalon, now part of Teva Pharmaceutical Industries. In our view, Cynata could easily sign several partnership transactions, each with upfront payments of $5 - 10M and total milestones of $50 - 100M, along with potential future royalties on net sales of products using the Cymerus™ platform.

Valuation methodology leaves ample room for upside. We have employed a discounted cash flow (DCF)-based approach that assigns a total value of ~A$81M to Cynata's technology platform, based only on potential collaborations focusing on the cardiology, regenerative medicine and oncology domains. If the firm were to ink additional partnerships in other areas, further upside could be unlocked. We do not value the potential for Cynata to develop its own proprietary therapeutics at this juncture. Our valuation translates into a price per share of A$1.00, taking into account roughly A$12M in cash and 90M fully-diluted shares outstanding as of end-2016.

Investment Thesis

Cynata Therapeutics, Inc. is an emerging company in the stem cell domain, developing next-generation approaches to the sustainable manufacturing of mesenchymal stem cells (MSCs) using its proprietary Cymerus™ production platform. Currently, commercial-scale manufacturing of MSC-based products presents a substantial practical and regulatory challenge, due to several factors: (i) reliance on donors (different donors = different stem cells = different products); (ii) invasiveness (e.g., stem cells need to be obtained via bone marrow extraction); (iii) limited expansion potential of MSCs in culture, thereby creating a supply constraint; (iv) impure MSC populations, which can cause immunogenicity—hypersensitivity reactions and autoimmune side effects can result, compromising patient safety. As a whole, the existing standard production methodologies in the MSC domain are associated with inconsistency in terms of clinical trial data, low achievable gross margins and a high degree of regulatory uncertainty.

Cynata's Cymerus™ platform, on the other hand, facilitates the commercial-scale production of a consistent, reproducible end-product. The firm's approach allows for theoretically unlimited expansion of MSCs using a production process based on inducible pluripotent stem cells (iPSCs) isolated from a single unique donor. Accordingly, in our view, Cynata represents a potentially best-in-class stem cell manufacturing firm and could present an intriguing strategic collaboration partner for a broad array of biopharmaceutical and healthcare firms operating in the stem cell arena. In addition, Cynata has the ability to develop and advance its own proprietary candidates based on the Cymerus™ technology platform, which can target multiple disease indications.

We are initiating coverage of CYP.AX with a Buy rating and a 12-month price target of A$1.00 per share, which assumes a firm value of A$93 million based on a risk-adjusted NPV analysis and approximately 90 million fully-diluted shares outstanding as of end-calendar 2016. In our view, Cynata represents an underrated entity in the stem cell domain with an attractive technology platform that has the added advantage of little to no near-term binary event risk. We believe an investment in Cynata Therapeutics shares may entail above-average risk and volatility.

We believe that major near-term catalysts for Cynata include the near-term finalization of a clinical development protocol for its most advanced therapeutic program, putatively in graft-vs.-host disease (GvHD), and the initiation of a proof-of-concept trial within the next 12 – 15 months. Potential transformative collaboration agreements with more established companies could provide substantial upside catalysts for the stock.

Table 1: Near-Term Catalysts and Upcoming Events

Projected Event	Timing
Completed	
Completion of institutional private placement	**3Q15**
Presentation of data at stem cell-focused Meeting on the Mesa	**4Q15**
Establishment of collaboration with Dr. Khalid Shah at Massachusetts General Hospital	**4Q15**
Anticipated	
Clarification of development path forward for lead candidates in U.S. via discussion with FDA	**Early 2016**
Development of schedule for formal graft-vs.-host disease (GvHD) trial	Mid-2016
Data from preclinical program and proof-of-concept study in GvHD model	Mid-2016
Consummation of initial transformational partnerships with potential R&D collaborators	**Mid- to late 2016**
Initiation of proof-of-concept clinical trial in GvHD indication	Late 2016 / Early 2017
Completion of enrollment in proof-of-concept GvHD trial	Late 2017
Additional transformational licensing transaction on Cymerus™ technology platform	**2017 / 2018**
Top-line data from GvHD proof-of-concept clinical trial	**Early 2018**

Source: Company reports and Rodman & Renshaw estimates.

Valuation

We utilize a platform-based risk-adjusted Net Present Value (rNPV) analysis in order to value Cynata's shares. Specifically, a discounted cash flow (DCF)-based assessment is applied to the valuation of future cash flows derived from milestone- and royalty-based payments on future products utilizing the Cymerus™ platform. The projected cash position of A$12 million is based on the estimated end-3Q 2015 cash position of A$8.1 million and factors in A$6.3 million in warrant exercise proceeds (strike price A$0.80 and A$1.00) and $2.5 million in option exercise proceeds (strike price A$0.40), plus $5 million in upfront payments from the first licensing transaction using the Cymerus™ platform and a 12-month burn rate of roughly A$6 million. We have utilized a 12% discount rate based on the fact that Cynata's Cymerus™ platform has been extensively validated and has tangible advantages vs. existing manufacturing methods for producing therapeutic stem cells, while our 70% probability of success reflects the fact that there are already stem cell-based products on the market or in late-stage clinical trials with positive proof-of-concept data that could be produced using the Cymerus™ approach. Our analysis shows that Cynata's stock could be worth A$1.00 per share within the next 12 months.

Table 2: Discounted Cash Flow Valuation

Cynata Therapeutics Ltd. Valuation	
Peak sales[1]	510MM
Launch[2]	2022 - 2024
Peak sales year	2030
Protection expires[3]	2032 / 2034
Discount rate	12%
Royalty rate[4]	10% - 16%
Probability of success[5]	70%
Risk-adjusted NPV[6]	$81MM
NPV per share	AUD 0.90
Estimated net cash position (end-calendar 2016)	$12MM
Total firm value	$93MM
Shares outstanding (end-calendar 2016)	90MM
Present value-derived price target	AUD 1.00

Notes on assumptions:

[1] Total sales of stem cell-based products manufactured using Cymerus™ technology

[2] Launch year

[3] Protection expires (based on 12 years of exclusivity for biologics in the U.S. and 10 years in Europe)

[4] Royalty rate based on partnership agreements

[5] Probability of success based on existing proof-of-concept generated with mesenchymal stem cells

[6] Risk-adjusted Net Present Value based on discount rate, 30% effective tax rate and probability of success

Source: Rodman & Renshaw estimates.

The above valuations and the projected cash position lead to the target price of A$1.00 per share. Though Cynata is likely to remain unprofitable for the foreseeable future, we believe our price target could be achieved in an approximate 12-month time frame. We currently do not include specific contributions from development of product candidates utilizing Cynata's platform for indications beyond cardiology, autoimmune disorders and oncology in our valuation. Furthermore, we note that various precedent transactions that have recently occurred in the stem cell sector, which we discuss in greater detail later in this report, have carried upfront payments alone ranging from $10 – 130 million. Accordingly, there may be upside based on the actual structure of the licensing transactions that Cynata may be able to consummate.

Market Model

We have assumed that Cynata Therapeutics would pursue the realization of commercial value for aspects of the applications for its Cymerus™ technology platform primarily through the establishment of strategic partnerships with other, more mature companies in the biopharmaceutical arena. These collaborations would be anticipated to generate revenue in the form of upfront payments, milestones based on the achievement of specific development-, regulatory- and sales-related objectives, and potentially royalties on net sales of products that are manufactured using the Cymerus™ platform. While Cynata has not yet entered into any such strategic partnerships, there is significant impetus for such agreements to be consummated in the near future. Firstly, Cynata represents a unique and sustainable approach to the manufacturing of mesenchymal stem cells (MSCs), arguably the most broadly applicable therapeutic stem cells. Second, there has been a series of such strategic partnerships, with various examples such as the Athersys-Chugai collaboration, the Celgene investment into Mesoblast, and the Novartis investment in Gamida Cell having been inked within the past year. Finally, we anticipate that partnering interest in Cynata would likely increase as the firm generates proof-of-concept human data with its stem cells, which we expect to occur within the next six to 12 months.

Our market model assumes that Cynata would be able to ink three partnership transactions—either with the same company on multiple products or with different firms for different products targeting distinct markets—within the next 12 – 15 months. We believe that these partnerships would each involve upfront payments of $5 million, which we consider conservative given the upfront payments of $10 – 130 million seen in prior technology-based licensing agreements involving other development-stage stem cell-focused companies in recent years. Milestone payments prior to commercialization were projected at $15 – 20 million per indication, while the royalty rate was estimated as a tiered, double-digit royalty ranging from 10% to 16% on net sales of the products in question. We have projected total peak annual sales of these products at roughly $510 million in 2030, which we consider conservative given the projected size of the overall stem cell therapeutics market. Various estimates have indicated that the global stem cell therapeutics market could exceed $10 billion by 2020[1]. Our market model does not assume the payment of specific sales threshold-based milestone payments, which may also be conservative.

The partnership-driven business model provides for attractive economics to Cynata, which would therefore not incur significant SG&A expenses associated with forward integration. We believe that there could be a possibility for Cynata to charge a markup on the cost of product that it manufactures for other companies, but that the more likely scenario would involve licensing of the Cymerus™ technology to Cynata's licensees so that they would be responsible for the upfront capital expenditures needed to establish commercial-scale manufacturing capacity. Accordingly, therefore—while the bulk of the revenues generated by the therapeutic products developed using Cynata's technology platform would accrue to the firm's licensees—the royalty- and milestone-based payments to Cynata should constitute a high-quality income stream. We have projected that the products likely to generate income for Cynata should be launched in the 2022 – 2024 time frame, and that they would benefit from a 12-year market exclusivity period in the U.S. and a 10-year exclusivity period in Europe, where all projected sales would likely be generated. While we have not selected specific disease indications for these products, we believe that our projections in the three general therapeutic areas for which we have forecasted sales are relatively conservative. For example, in the case of cardiology, peak annual sales for Mesoblast's lead stem cell product CCEP-41750 (formerly Revascor™) are projected at over $4 billion[2], while we have estimated peak annual sales for a Cynata-derived product in this area at only $100 million. In autoimmune disease, we have projected peak annual sales of roughly $100 million, while total projected sales in this area for Prochymal® alone, an existing older-generation MSC-based product aimed at graft-vs.-host disease (GvHD), are estimated to be $84 million by 2025[3].

[1] Syed and Evans, Nature Reviews Drug Discovery (2013).
[2] Edison Investment Research (2014).
[3] Visiongain Market Research (2014).

Table 3: Cynata Therapeutics Stem Cell Products Market Model

	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Cardiology ($ MM)		5		10		10	5	25.1	57.4	89.3	106.2	125.7	132.6	158.7	175.5	191.1
Autoimmune disease ($ MM)			5		5		10	5	9.8	21.3	36.8	47.5	54.1	72.3	88.5	102.3
Oncology ($ MM)				5		10		15	5	18.6	65.5	98.9	126.4	141.7	182.5	216.5
Total stem cell-based product sales ($ MM)								25.1	67.2	129.2	208.5	272.1	313.1	372.7	446.5	509.9
Total milestone-based revenues ($ MM)		5	5	15	5	20	15	20	5							
Royalty rate	0%	0%	0%	0%	0%	0%	0%	10%	11%	12%	13%	14%	15%	15%	16%	16%
Total royalty-based revenues ($ MM)								2.5	7.4	15.5	27.1	38.1	47.0	55.9	71.4	81.6
Total revenues to Cynata ($ MM)	0	5	5	15	5	20	15	22.5	12.4	15.5	27.1	38.1	47.0	55.9	71.4	81.6

Discount rate	12%
Effective tax rate	30%
Probability of success	70%
Risk-adjusted NPV ($ MM)	59.5
Australian to U.S. $ exchange rate	1.36
Risk-adjusted NPV (A$ MM)	**81.0**

Source: Rodman & Renshaw estimates.

Investment Highlights

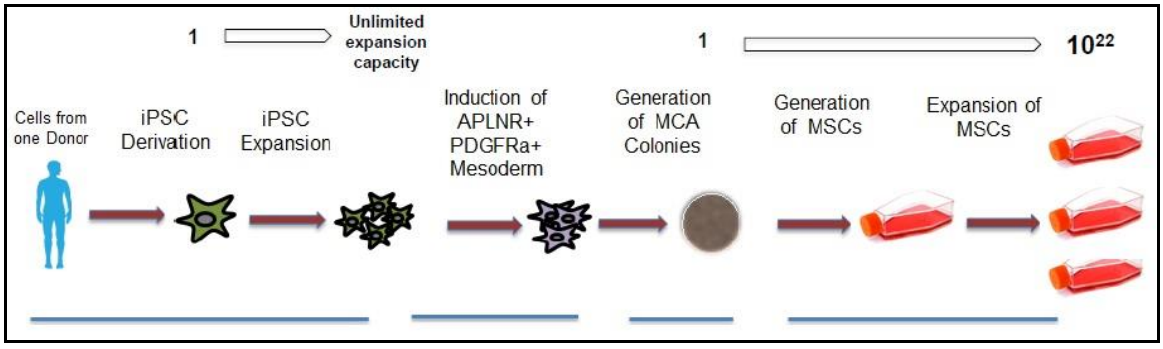
1. Company snapshot

Cynata Therapeutics, Ltd. is an Australian stem cell technology-focused firm advancing a therapeutic stem cell technology platform, Cymerus™, originally developed based on research conducted at the University of Wisconsin-Madison (UWM). UWM is a world-renowned leader in stem cell research, including the work carried out by Prof. James Thomson's group, which included the first successful isolation of human embryonic stem cells in 1998, and the derivation of induced pluripotent stem cells (iPSCs) from human adult cells in 2007. Prof. Igor Slukvin, a co-founder of Cynata, was also a member of the team that conducted UWM's iPSC research. Cynata's Cymerus™ platform stem cell technology is based upon a specific population of versatile stem cells known as mesenchymoangioblasts (MCAs). These cells are known to be precursors of mesenchymal stem (or stromal) cells (MSCs), which are at the forefront of a new generation of treatments being investigated for such devastating diseases as osteoarthritis, Crohn's disease and heart disease. Cynata's proprietary technology utilizes iPSCs originating from an adult donor as the starting material for generating MCAs and in turn manufacturing the MSC-based therapeutic product. Cynata aims to deploy the proprietary Cymerus™ technology to address a critical shortcoming in existing methods for the production of MSCs for therapeutic use, which is the ability to achieve economic manufacturing at commercial scale. In our view, this could open a wide range of therapeutic and manufacturing possibilities on which Cynata could capitalize, as the potential of MSC-based biotech products has long been recognized.

2. Groundbreaking platform for stem cell-based therapeutics production

The Cymerus™ technology has several characteristics which makes it advisable for the development of cell-based therapeutics. First and foremost, the Cymerus™ manufacturing process ensures that cells for therapeutic use can be produced in virtually limitless quantities. This means that Cynata does not constantly need to identify and screen donors of fresh stem cells in order to fuel its manufacturing demands. This has the potential to create a new standard in the emergent arena of stem cell therapeutics and provides Cynata with both a unique differentiator and favorable competitive positioning.

Figure 1: Cymerus™ Manufacturing Technology



Source: Cynata Therapeutics corporate presentation.

A seminal paper published in *Cell Stem Cell* originally demonstrated in 2010 that an expansion/throughput level (power) of 10^{22} can be achieved using the Cymerus™ process[4]. The implication of this finding is that if Cynata were to push its cells to their currently-published expansion limit—indeed, other manufacturers using bone marrow MSCs already do expand to the limits of cell viability—a single vial of 1 million iPSCs could generate 10^{28} MSCs, or 10^{20} typical clinical doses. For the avoidance of doubt, that is 100,000,000,000,000,000,000 doses.

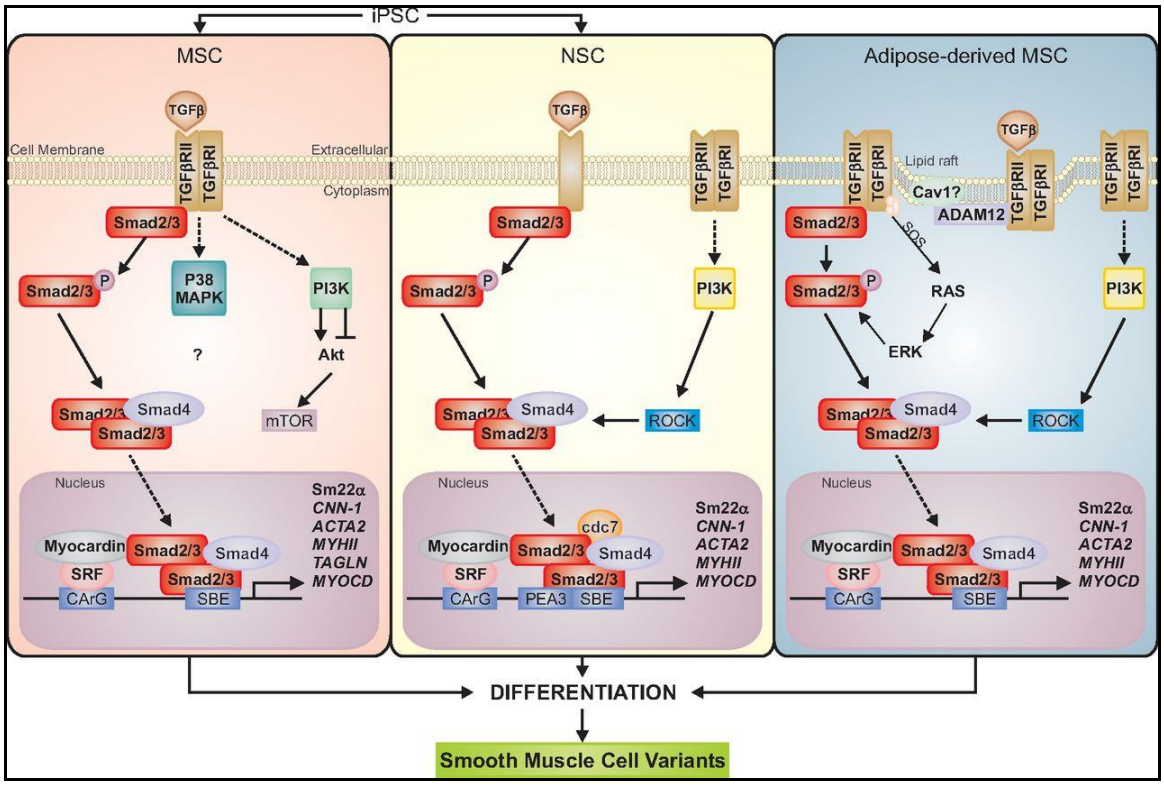
[4] Vodyanik *et al.*, Cell Stem Cell 7: 718 – 729 (2010).

While Cynata does not actually expand its MSCs to that extent, on the grounds that excessive expansion has been shown in the published literature to adversely affect the efficacy of MSCs, even significantly lower orders of expansion can yield substantial amounts of therapeutic material. Unlike BM-MSC processes, Cynata does not have to excessively expand its MSCs to generate a vast number of doses. Even with the minimal expansion levels that the company currently employs, an effectively limitless number of MSC doses can be generated by harnessing the expansion capacity of iPSCs; for example, it has been shown that iPSCs can be expanded by a factor of 10^{72} in culture[5], providing a sustainable supply of stem cells for therapeutic use.

From our perspective, the Cymerus™ technology platform is the first approach to truly address the manufacturing "bottleneck" in MSC production, and may be the sole solution to making MSCs commercially viable. Cynata can generate theoretically unlimited MSCs from a single donor, with reproducible and clinical-grade MSCs being generated in a batch-to-batch uniform manner. As shown in the process workflow for the Cymerus™ platform (Figure 1), the crucial difference between Cynata's methodology and earlier-generation processes is the usage of iPSCs as the source of MSCs, rather than isolating MSCs directly from primary donor sources.

A second advantage of the Cymerus™ platform is flexibility. As shown below, iPSCs can be manipulated in order to derive various types of stem cell populations, including MSCs. The characterization of multiple complex signaling pathways underlying the differentiation of this stem cell population has enabled researchers to pinpoint ways to induce the production of certain highly specialized cell types from MSCs. The example below illustrates this in the case of smooth muscle cell variants. Unlike other competing production platforms, the Cymerus™ approach allows facile switching between different end-products—e.g., muscle cells (myocytes), skin cells (melanocytes), or bone cells (osteoblasts)—that can be produced from the same starting material.

Figure 2: iPSC Derivation of Differential Stem Cell Types



Source: Firth and Yuan, American Journal of Physiology 304: 287 – 288 (2013).

[5] Lei *et al.*, Proceedings of the National Academy of Sciences of the U.S.A. 5039 – 5048 (2013).

A third advantage involves production costs and reproducibility. Given the nature of the Cymerus™ system, which obviates all need for human donors, manufacturing costs are substantially cheaper compared to processes that source MSCs from donor-derived materials such as bone marrow, adipose tissue or placentae. The latter require substantial costs in attracting, screening and obtaining consent from multiple donors. There are further downstream costs associated with processing the derived materials in order to yield the desired starting population. Cell culture costs are, of course, similar across the various processes, but competing approaches must incur the costs of comparability studies and the intrinsic risks associated with having to fail batches/donors if comparability cannot be seen between donor-derived material from different sources. The Cymerus™ process need not contend with any of these issues.

The fourth advantage is on the regulatory front. Here, Cynata also possesses an advantage because of the fact that its production platform is based on the use of a well-characterized cell line. The iPSC line was derived from a blood donation collected in the U.S. from a healthy adult donor, who passed normal eligibility requirements for donating blood in the U.S., and more rigorous additional screening and testing that was put in place for the purpose of selecting donors for iPSC production. The donor explicitly consented to a wide range of uses for the iPSCs produced from the donated tissue, including their use in the manufacture and commercialization of therapeutic products. The adult source of the cell line and the broad consent given obviates any bioethics issues. Cynata's iPSC Master Cell Bank was produced in the U.S., using a transgene-free, viral-free and feeder-free reprogramming procedure under conditions that meet relevant FDA cGMP guidance. A comprehensive traceability system is in place. The iPSC line was subjected to extensive testing to confirm its suitability for manufacturing therapeutic products, including identity, microbial/viral contamination, and other safety tests, and confirmation of pluripotency. These specifications have been discussed with the FDA and other regulatory authorities, none of whom raised any concerns with the specifications or requested additional testing. This iPSC line was used during the successfully-completed technology transfer of the Cymerus™ process to Waisman Biomanufacturing (Madison, WI), and in every manufacturing run since. Consequently, Cynata has generated evidence that this iPSC line can be used in the Cymerus™ process to consistently produce large numbers of MSCs. The finished product (i.e., Cymerus™ MSCs) has been demonstrated to conform to the relevant published guidelines and criteria. Accordingly, we believe that firms seeking to produce therapeutic MSC-based products should have a strong incentive to partner with Cynata because of the preference regulatory authorities are likely to show for a cell line-derived therapeutic product.

3. Validating near-term licensing deals—precedents set attractive benchmarks

In our view, the fact that Cynata possesses a next-generation manufacturing platform for a particularly desirable stem cell type implies that the company's technology platform should be viewed as strategically attractive by potential licensing partners. We note—as discussed in greater detail in a subsequent section of this report—that recent precedent transactions have set the benchmark parameters of potential future licensing deals that Cynata may enter at attractive levels. In certain circumstances, the transaction in question involved a wholesale acquisition of the company in question; in other cases, the deal involved a regional license to a specific product candidate for a particular indication.

Whichever the format, we believe that Cynata could potentially enter into multiple licensing transactions with different partners among the more established companies in the biopharmaceutical sector that could validate its technology platform and provide various sources of near- and long-term revenue. The company's relatively low burn rate and focus on optimizing manufacturing rather than capital-intensive product development should permit multiple value-driving milestones to be attained near-term without the likelihood of financing-driven dilution. We anticipate that Cynata could benefit from growing interest among established biopharmaceutical firms in stem cell-based technologies, since there is a clear need to optimize manufacturing methodologies for such therapeutics and Cynata possesses a truly sustainable approach.

Production Process Comparison Overview

In this section, we provide an assessment of the quantitative advantages of using the Cymerus™ production process vs. bone marrow-derived processes for generating mesenchymal stem cells (MSCs). In our view, the substantial differences between the Cymerus™ platform and traditional donor material-based approaches represent the strongest rationale for potential strategic partners to enter into collaboration agreements with Cynata. All MSC production processes involve three high level stages: (i) sourcing of starting material; (ii) isolation/derivation of MSCs; and (iii) expansion of the MSC population of cells for therapeutic use. A summary of each of these stages, for both the Cymerus™ process, and conventional BM-MSC processes, is provided below.

Table 4: Production Process Comparison

Stage	Cymerus™ MSCs	BM-MSCs
1. Sourcing of starting material	Retrieve vial of iPSCs from freezer	• Advertise, recruit, consent, screen and test prospective donors • Compensate donors for their time/inconvenience/expenses • Harvest bone marrow (procedure performed by a specialist physician) • Perform QC testing on bone marrow
2. Isolation/ derivation of MSCs	Expand iPSCs and then differentiate to MSCs using specific culture media and conditions	Isolate MSCs using density gradient separation followed by culture and plastic adherence and/or active selection (e.g. using magnetic beads)
3. Expansion of MSCs	Culture expansion. # of population doublings: 10 Average doubling time: 24-30 hrs	Culture expansion. # of population doublings: varies Average doubling time: 40 hrs initially, but slows as culture progresses, to 60 hours+

Source: Company reports, Rodman & Renshaw research.

Product Quality Implications

MSC expansion using the Cymerus™ process involves just 10 population doublings, as there is no need to excessively expand Cymerus™ MSCs in order to produce a vast number of doses, and there is a convincing body of evidence in the literature that suggests excessive expansion adversely impacts MSC functionality. The extent of expansion involved in producing BM-MSCs varies significantly between processes, and most other companies developing MSC-based products do not disclose what the extent of expansion is in their processes. However, assuming that the initial yield from a bone marrow donation is 20,000 MSCs, and that a clinical dose consists of 100 million MSCs, the number of population doublings that are required to produce any given number of doses can be calculated. For example:

- 12 population doublings would be required to produce 1 dose
- 22 population doublings would be required to produce 1,000 doses
- 26 population doublings would be required to produce 10,000 doses

There is no publicly available evidence that as many as 10,000 doses of MSCs can be produced from a single bone marrow donation without impairing functionality of the cells. Osiris Therapeutics previously claimed they could manufacture 10,000 doses of their BM-MSC product (Prochymal®), but they did not define how many cells per dose this calculation was based on, and clinical doses of MSCs have varied significantly. Furthermore, at least two Phase 3 clinical trials with this product failed to meet their primary endpoints, and it has been suggested that this might be a consequence of excessive expansion of the MSCs.

It has also been reported that BM-MSCs enter senescence after between 13-25 population doublings. In other words, these cells effectively enter "old age" and no longer exhibit viability in culture. Expanding BM-MSCs to produce just five doses per donation appears to adversely affect their efficacy, in comparison to minimally expanded MSCs.

Cost Implications

As no information is in the public domain regarding the costs of manufacturing BM-MSCs, it is not possible to quantify the cost differences between the processes. However, it is possible to establish an indication of the relative costs of each approach. The costs of Stage 1 (sourcing starting material) are negligible with the Cymerus™ process, but could be substantial with BM-MSC processes, especially when the cost of comparability studies—and the likely need to reject a proportion of batches due to comparability failure—is considered. As such, there can be no question that this stage of the Cymerus™ process is significantly less costly than the equivalent stage of BM-MSC processes. The specific activities involved in Stage 2 (isolation/derivation of MSCs) vary substantially between processes—even between different BM-MSC processes. However, it seems reasonable to assume that differences in costs at this stage between processes would not be significant in the context of the overall production costs. The most significant driver for the costs at Stage 3 (expansion of MSCs), and indeed for the whole process, is the time taken to complete expansion, which is a function of the average doubling time and the number of population doublings involved. Since the Cymerus™ process involves significantly fewer population doublings, with a significantly faster doubling time, it is clear that the costs associated with this stage of the Cymerus™ process would be much lower than with a BM-MSC process. For example, 10 population doublings at an average doubling time of 30 hours would take 12.5 days, while 26 doublings at an average doubling time of 60 hours would take 65 days.

Logistical/Regulatory Implications

Even if it were possible to produce 10,000 MSC doses from a single bone marrow donation without adversely affecting cell functionality, a continuous supply of new donors would still be required at commercial scale. This is associated with significant logistical and regulatory challenges. For example, if each donation could produce 10,000 doses, then in order to supply 1 million doses per year, it would be necessary to obtain an average of two new bone marrow donations every week. It is unclear whether a sufficient number of willing donors could be found to make manufacture at that scale feasible, even if all other challenges could be overcome.

Even if sufficient numbers of donors can be found, comparability testing will be required on the final product each time a new bone marrow donation is used, as it is a regulatory requirement to demonstrate that product manufactured from the new donation is comparable to product manufactured from the original donation. It is likely that such comparability testing will have to include *in vivo* data (in animals and/or humans), in addition to *in vitro* testing, as *in vitro* tests alone have not yet been shown to accurately predict *in vivo* functionality of MSCs. Consequently, each comparability study will be costly and time consuming (at least several months), and it is unclear how it would be feasible to conduct 100 such studies almost concurrently.

It is important to note that regulatory authorities would typically always exhibit a preference for an allogeneic (i.e., "off-the-shelf") solution in the domain of cell-based therapy, rather than an autologous or donor-driven solution that cannot demonstrate batch-to-batch comparability and that by default is not standardized. The Cymerus™ production platform, being based on a well-defined cell line, provides exactly the kind of controllable, tractable and exhaustively characterized basis for stem cell therapeutics that regulatory agencies are seeking. Given the stringent nature of regulatory requirements for the market authorization of human medicinal products, we believe that developers of MSC-based therapeutics would be forced to choose the Cymerus™ process because it provides the greatest probability of regulatory success. Cynata can give its partners flexibility because of the malleable nature of the iPSC line, which is proprietary to Cynata through its license from Cellular Dynamics International (CDI), along with the ability to provide regulators with the documentation and comparability data they seek.

Precedent Stem Cell Strategic Transactions

In the past several years, a number of strategic collaborations and partnerships have been consummated between certain established biopharmaceutical companies and emerging firms in the stem cell therapy arena. In our view, these transactions provide potential benchmarks for future partnerships that Cynata may be able to consummate and also demonstrate how larger firms in the healthcare sector are beginning to increasingly involve themselves in the stem cell domain. In many ways, they have begun to realize that this area of research and therapeutics development is too fundamentally important and potentially valuable for them to ignore.

The table overleaf depicts a selection of recent transactions that we believe constitute valid benchmarks for Cynata's partnering efforts. While we do not anticipate that Cynata would successfully ink a partnership transaction similar in scale or scope to the largest of these deals described below, we believe that an initial validating event such as an early R&D collaboration agreement with an established firm would advance the recognition of Cynata's technology platform and possibly pave the way for a network of licensing transactions to be established.

Athersys—Chugai
On March 2, 2015, Athersys inked a partnership and license agreement with Chugai Pharmaceutical Co., Ltd., to exclusively develop and commercialize MultiStem® cell therapy for the treatment of ischemic stroke in Japan. As part of the collaboration, Chugai will be responsible for the development and commercialization of MultiStem® for ischemic stroke in Japan, and Athersys will have responsibility for product supply. Under the terms of the agreement, Athersys received an up-front cash payment of $10 million from Chugai and was slated to receive additional payments as the program advanced further. Athersys is eligible to receive milestone payments from Chugai of up to $45 million upon the achievement of certain development and regulatory milestones, and sales milestones of up to ¥17.5 billion (approximately $150 million based on the then-prevailing exchange rate). Athersys would also receive from Chugai tiered, double-digit royalties on any net sales, as well as payments for product supplied to Chugai. While the Phase 2 trial of MultiStem that Athersys was running at the time of the licensing transaction subsequently failed to meet its primary and secondary endpoints in April 2015, we note that the high value of this transaction for what was a regional partnership (only involving Japanese rights) provides a solid recent benchmark for supporting the valuation of Cynata's technology platform.

Cellular Dynamics—Fujifilm
On March 30, 2015, Cellular Dynamics International, Inc. (CDI) announced that Fujifilm would acquire CDI via an all-cash tender offer, to be followed by a second-step merger. Fujifilm was to acquire all issued and outstanding shares of CDI's common stock for $16.50 per share or approximately $ 307 million on a fully-diluted basis. The offer represented a premium of 108% to CDI's closing price on March 27, 2015. Cellular Dynamics, founded in 2004, was considered a pioneer in the development of inducible pluripotent stem cells (iPS cells). The company developed and optimized an episomal reprogramming process that utilizes circular DNA vectors to deliver the pluripotency genes. Episomal reprogramming has been hypothesized to hold benefits over other reprogramming methods, especially for clinical applications. We note that certain elements of Cynata's intellectual property (IP) estate are licensed from CDI. Fujifilm, which originally became known as a purveyor of photographic equipment, processing services and raw materials, has over the past decade signaled a keen interest in various life sciences fields, including the stem cell arena.

Kyoto University—Takeda Pharmaceutical Co. Ltd.
On April 17, 2015, Takeda announced that it had inked a 10-year partnership agreement with Kyoto University to develop potential stem cell treatments for a range of diseases, committing up to $270 million to the effort. Under the scope of this collaboration arrangement, Takeda and the school's Center for iPS Cell Research Application (CiRA) will collaborate on projects using induced pluripotent stem cells to discover new therapies. The pair plans to use stem cells both as

potential treatments in their own right and as tools for ferreting out new small-molecule drugs, planning to pursue about 10 projects at a time once up and running. CiRA Director Shinya Yamanaka, a Nobel laureate for his work in stem cells, will lead the effort, which will take an early focus on heart failure, diabetes, CNS disorders and cancer immunotherapy. Takeda has promised to allocate about $170 million in basic research funding over the course of the next decade, hosting CiRA scientists at its Shonan Research Center in Fujisawa and planning to put about 100 minds to the project. In addition, Takeda is committing an additional $100 million in research support, including equipment and R&D services, over the life of the collaboration.

Mesoblast Ltd.—Celgene Corp.

In our view, the transactions involving Mesoblast Ltd. are perhaps the most intriguing in the stem cell arena, as these have thus far comprised the largest dollar value amounts allocated thus far, in addition to involving the most well-known companies to enter the stem cell fray from among the entities in the biotechnology domain. Furthermore, both of the transactions that Mesoblast inked involved the acquisition of substantial equity stakes in Mesoblast by its collaborators—a feature that thus far has been specific only to Mesoblast among stem cell companies consummating licensing transactions in recent years. In a transaction announced April 12, 2015, Celgene paid A$3.82 per share for 15.3 million shares of Mesoblast—a 19% premium to Mesoblast's closing price of A$3.21 on April 10, 2015 and a stake representing roughly 4.5% of Mesoblast's total outstanding equity. Celgene thereby gained a six-month right of first refusal on Mesoblast's stem-cell product candidates for conditions including inflammatory bowel disease and certain oncological ailments. The two companies were discussing global rights excluding Japan, where JCR Pharmaceutical Co. already holds rights to Mesoblast's technology. Currently, Mesoblast has several candidates in the final phases of clinical testing. One product is for treating acute graft versus host disease, a complication that can occur after a stem-cell or bone-marrow transplant and another is for refractory Crohn's disease.

Mesoblast Ltd.—Cephalon Inc.

The original transaction between Mesoblast and Cephalon was announced December 8, 2010, shortly before Cephalon became the subject of a bidding war between Valeant Pharmaceuticals International and Teva Pharmaceutical Industries. Eventually, Teva acquired Cephalon in May 2011 for $6.8 billion. Cephalon originally took a 20% stake in Mesoblast Ltd., for which it paid $220 million, and also bought the rights to market the Australian company's adult stem-cell therapies for cardiac and nervous system conditions. Cephalon was also slated to provide Mesoblast with as much as $1.7 billion in pre-commercial payments based upon the attainment of specific development-related milestones. Initially, Mesoblast received $130 million upfront from Cephalon for the therapy rights, and was to pay for and conduct some clinical trials while Cephalon was to fund and perform other later-stage tests. Mesoblast was to hold the rights to manufacturing commercial supplies of the stem-cell products to be marketed by Cephalon. Under the terms of the agreement, Mesoblast retained the rights to develop and market stem cell treatments for diabetes, eye diseases and orthopedic, inflammatory and immunological conditions.

Gamida Cell—Novartis AG

In October 2015, the privately-held Israeli stem cell firm Gamida Cell announced that the Swiss pharmaceutical company Novartis had elected to invest up to an additional $15 million in Gamida Cell in exchange for a further equity stake, with an initial $5 million being invested for 2.5% of the outstanding equity in Gamida Cell to add to the original 15% of the firm that Novartis originally acquired in 2014 for $35 million. The total amount Novartis invests could reach $600 million if the Swiss firm were to exercise a buyout option that expires in 2016. The final $10 million of the tranche announced in October 2015 is to be deployed contingent upon an equity financing transaction to fund the late-stage development of Gamida Cell's most advanced program, NiCord. This financing transaction would need to be completed before the end of 2017. NiCord is an experimental treatment for patients with high-risk hematological disorders, including both sickle cell disease as well as various forms of leukemia and lymphoma. While Novartis retains the option to acquire Gamida Cell wholesale, under the terms of this investment the Swiss firm is not obtaining any licensing rights to Gamida Cell's technology platform or product candidates.

Table 5: Recent Stem Cell Transactions

Stem Cell Entity	Licensee / Acquirer	Lead Candidate	Lead Indication	Upfront ($ MM)	Pre-Commercial Milestones ($ MM)	Sales-Based Milestones ($ MM)	Equity Stake	Equity Price ($ MM)	Royalty Rate
Athersys	Chugai	MultiStem®	Ischemic stroke	10	45	150	NA	NA	tiered, double-digit
Cellular Dynamics	Fujifilm	iCell® / MyCell®	Myocardial infarction	307	NA	NA	100%	NA	NA
Gamida Cell	Novartis	NiCord™	hematological disorders	NA	NA	NA	17.5%	50	NA
Kyoto University	Takeda	various	various	170	100	NA	NA	NA	NA
Mesoblast Ltd.	Celgene	various	various	NA	NA	NA	4.5%	45	NA
Mesoblast Ltd.	Cephalon	various	cardiac, CNS diseases	130	1700	NA	20%	220	NA

Source: Company reports; Bloomberg BDRUG database.

Stem Cell Research Overview

The stem cell domain has been the subject of intense focus over the past 10 to 15 years as advances in cell culture, fate specification, and implantation have led to a surge in hope that stem cells could represent the next important class of therapeutic agents in biotechnology. Historically, biotechnology and pharmaceuticals have relied upon, initially, traditional small molecules (orally bioavailable pills), and, subsequently, biologic drugs (protein macromolecules that cannot be swallowed but instead dosed via injection). However, as the number of novel receptor targets that can be screened with small molecule or protein drug candidates diminishes, and as the regulatory environment grows tougher with respect to the demands being placed on the risk/benefit profiles of new drugs, biotech and pharmaceutical companies are now searching ever-more avidly for new classes of therapeutics. Some of the types of therapeutic approaches currently in vogue include gene therapy (the insertion, alteration, or removal of genes within an individual's cells to repair a mutation that causes a genetic disease), RNA interference (introduction of short double-stranded RNA segments into the cells to silence the expression of specific genes by preventing a specific messenger RNA species from producing a protein), and stem cell therapy.

In our view, stem cells are perhaps the most promising of these because of their vast potential. Stem cells represent the human body's own natural reservoir for replenishing tissue, skin, and organs. Therefore, we believe they hold promise as the key to regenerative medicine, in which the aim is to re-grow or replace damaged tissue or organs inside the body of a patient. Furthermore, stem cells can be used as a novel form of biologic drug, since administration of certain types of stem cells systemically, or in a targeted manner, create a kind of "cytokine storm" that can actually change the function of a patient's immune system or enhance endogenous repair. Many repair pathways in the human body—particularly in patients suffering from autoimmune diseases like lupus, multiple sclerosis, or rheumatoid arthritis—are actually driven by specific forms of inflammation. Administration of stem cells can induce these inflammatory pathways, leading to cytokine release and induction of endogenous repair.

Cells maintain normal physiological function in healthy individuals by secreting or metabolizing substances, such as sugars, amino acids, neurotransmitters, and hormones, which are essential to life. When cells are damaged or destroyed they no longer produce, metabolize, or accurately regulate those substances. Cell loss or impaired cellular functions are leading causes of degenerative diseases, and some of the specific substances or proteins that are deficient in some of these diseases have been identified. Although administering these substances or proteins has some advantages over traditional pharmaceuticals, such as specificity, there is no existing technology that can deliver them effectively. Cells, however, may do all this naturally. Thus, where failing cells are no longer producing needed substances, or where there has been irreversible tissue damage or organ failure, transplantation of stem or progenitor cells may enable the generation of new functional cells, thus restoring organ function and the patient's health.

Stem cells have two defining characteristics: (i) they produce mature cells that make up particular organs; and (ii) they self-renew—i.e., some of the cells developed from stem cells are themselves new stem cells, thus perpetuating the process. Stem cells are known to exist for the blood and immune system, the nervous system (including the brain), the skin, bone, and even hair. They are thought to exist for other systems, including the liver and pancreas endocrine systems, gut, muscle, and heart. Stem cells are responsible for organ regeneration during normal cell replacement and, to a greater or lesser extent, after injury. Naturally-derived stem cells are rare and only available in limited supply, whether from the patients themselves or from donors. Also, stem cells can often be obtained only through significant surgical procedures. Therefore, in order to develop stem cell therapeutics, three key challenges must be overcome: (i) identification of stem or progenitor cells of a particular organ and testing them for therapeutic potential; (ii) creation of processes to enable use of these rare cells in clinical applications, such as expanding and banking them in sufficient quantities to transplant into multiple patients; and (iii) demonstration of the safety and efficacy of these potential therapeutics in human clinical trials.

Research in the stem cell field grew out of findings by Ernest A. McCulloch and James E. Till at the University of Toronto in the 1960s. The two main types of mammalian stem cells are embryonic stem cells that are isolated from the inner cell mass of blastocysts and adult stem cells that are found in adult tissues. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells, but they also maintain the normal turnover of regenerative tissues, such as blood, skin, or the intestinal lining.

Stem cells can now be grown and transformed into specialized cells with characteristics consistent with cells of various tissues, such as muscles or nerves, through cell culture. Highly plastic adult stem cells from a variety of sources, including umbilical cord blood and bone marrow, are routinely used in medical therapies. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies.

The classical definition of a stem cell requires that it possess two properties:

- Self-renewal: the ability to go through numerous cycles of cell division while maintaining the undifferentiated state.
- Potency: the ability to differentiate into specialized cell types. In the strictest sense, this requires stem cells to be either totipotent or pluripotent—able to give rise to any mature cell type, though multipotent or unipotent progenitor cells are sometimes referred to as stem cells.

Two mechanisms exist to ensure that the stem cell population is maintained:

1) Obligatory asymmetric replication: a stem cell divides into one daughter cell that is identical to the original stem cell and another daughter cell that is differentiated.
2) Stochastic differentiation: when one stem cell develops into two differentiated daughter cells, another stem cell undergoes mitosis and produces two stem cells identical to the original.

Pluripotent embryonic stem cells originate as inner mass cells within a blastocyst. The stem cells can become any tissue in the body, excluding a placenta. Only the morula's cells are totipotent, able to become all tissues and a placenta. Potency specifies the differentiation potential (ability to differentiate into different cell types) of the stem cell.

- Totipotent (also called omnipotent) stem cells can differentiate into embryonic and extra-embryonic cell types. Such cells can construct a complete viable organism. These cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent.
- Pluripotent stem cells are the descendants of totipotent cells and can differentiate into nearly all cells—i.e., cells derived from any of the three germ layers.
- Multipotent stem cells can select multiple fates, but only those of closely-related cell families.
- Oligopotent stem cells give rise to only a few cell types—e.g., lymphoid or myeloid stem cells. There is a limited range of cell fates these cells can select.
- Unipotent cells can produce only one cell type, their own, but have the property of self-renewal, which distinguishes them from non-stem cells (e.g., muscle stem cells).

The practical definition of a stem cell is the functional definition: a cell that has the potential to regenerate tissue over a lifetime. For example, the gold standard test for a bone marrow or hematopoietic stem cell (HSC) is the ability to transplant one cell and save an individual without HSCs. In this case, a stem cell must be able to produce new blood cells and immune cells over a long term, demonstrating potency. It should also be possible to isolate stem cells from the transplanted individual, which can themselves be transplanted into another individual without HSCs, demonstrating that the stem cell was able to self-renew.

The properties of stem cells can be illustrated *in vitro* using methods such as clonogenic assays, where single cells are characterized by their ability to differentiate and self-renew. In addition, stem cells can be isolated based on a distinctive set of cell surface markers. However, *in vitro* culture conditions can alter the behavior of cells, making it unclear whether the cells will behave in a similar manner *in vivo*. Considerable debate exists whether some proposed adult cell populations are truly stem cells, as they may not necessarily possess the ability to self-renew indefinitely. Furthermore, they may not have defined capacity to differentiate into specific cell types, making them poor candidates for therapeutic applications because their differentiation cannot be tightly controlled. There is no consensus yet among biologists on the prevalence and physiological and therapeutic relevance of stem cell plasticity. More recent findings suggest that pluripotent stem cells may reside in adult tissues in a dormant state. Below, we describe the different distinct populations of adult stem cells and the extent to which they can give rise to multiple cell types within their respective lineages.

- Hematopoietic Stem Cells (HSCs) are found in the bone marrow and give rise to all the blood cell types. They have proven particularly useful in the treatment of various hematological cancers, particularly leukemia, in which one potential therapeutic approach is to ablate abnormal cells using chemotherapy and then reconstitute the immune system using autologous transplantation of the patient's own endogenous hematopoietic stem cells derived from his or her bone marrow, harvested prior to the administration of chemotherapy.
- Mammary Stem Cells provide the source of cells for growth of the mammary gland during puberty and gestation and play an important role in carcinogenesis of the breast. Mammary stem cells have been isolated from human and mouse tissue as well as from cell lines derived from the mammary gland. Single such cells can give rise to both the luminal and myoepithelial cell types of the gland and can regenerate the entire organ in mice.
- Mesenchymal Stem Cells (MSCs) are of stromal origin and may differentiate into a variety of tissues. MSCs have been isolated from placenta, adipose tissue, lung, bone marrow and blood, Wharton's jelly from the umbilical cord, and teeth (perivascular niche of dental pulp and periodontal ligament). MSCs are attractive for clinical therapy due to their ability to differentiate, provide trophic support, and modulate innate immune response.
- Neural Stem Cells (NSCs) are commonly cultured *in vitro* as so-called neurospheres—floating heterogeneous aggregates of cells containing a large proportion of stem cells. They can be propagated for extended periods of time and differentiated into both neuronal as well as glia cells; they therefore behave as stem cells. However, this behavior may be induced by the culture conditions in progenitor cells, the progeny of stem cell division that normally undergo a strictly limited number of divisions in vivo. Further, neurosphere-derived cells do not behave as stem cells when transplanted back into the brain. Neural stem cells share many properties with HSCs.
- Olfactory Adult Stem Cells have been successfully harvested from the human olfactory mucosa cells, which are found in the lining of the nose and are involved in the sense of smell. Given the right chemical environment, these cells have the same ability as embryonic stem cells to develop into many different cell types. Olfactory stem cells, in contrast to neural stem cells, can be harvested with ease without harm to the patient. Thus, they are easily obtained from any subject, including older patients who need them most.
- Neural Crest Stem Cells—hair follicles contain two types of stem cells, one of which appears to represent a remnant of the stem cells of the embryonic neural crest. Similar cells have been found in the gastrointestinal tract, sciatic nerve, cardiac outflow tract, and spinal and sympathetic ganglia. These cells can generate neurons, Schwann cells, myofibroblast, chondrocytes, and melanocytes.
- Testicular-Derived Stem Cells are multipotent cells with a claimed equivalency to embryonic stem cells have been derived from spermatogonial progenitor cells found in the testicles of laboratory mice by scientists in Germany and the U.S., and researchers from Germany and the UK subsequently confirmed the same capability using cells from the testicles of humans. The extracted stem cells are known as human adult germline stem cells (GSCs). Multipotent stem cells have also been derived from germ cells found in human testicles.

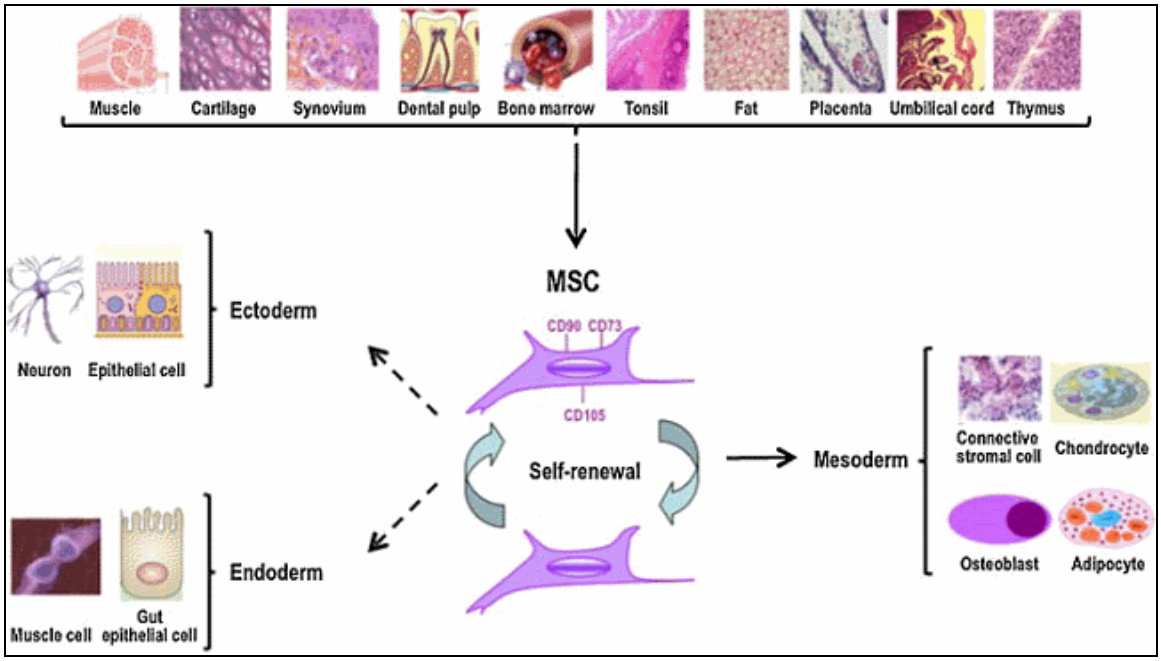
Mesenchymal Stem Cells Overview

In this section, we provide a description of the origins of mesenchymal stem cells (MSCs), their differentiation potential, and their relative advantages and disadvantages from a medical perspective, as well as recent advances in development of therapeutic products utilizing MSCs. Mesenchymal stem cells (MSCs) were first discovered in the bone marrow. Friedenstein described these ‘‘osteogenic stem cells’’ as clonal and fibroblastic stromal cells that formed adherent colonies in culture and had robust osteogenic potential. These cells were first termed ‘‘mesenchymal stem cells’’ by Caplan, and their multi-lineage differentiation potential into bone, cartilage, and fat was further characterized around the turn of the millennium. Since the discovery of MSCs in bone marrow, the identification of cells with similar characteristics has been reported in many adult and fetal tissues.

Although there has been significant progress in the field of MSC biology, there is ongoing controversy and debate over the cell surface epitope profile that uniquely identifies MSCs *in vitro* and *in vivo*. Expression of cell surface epitopes is highly dependent on the soluble and insoluble components of the extracellular milieu and on their physical properties and spatial orientation, as well as interactions with neighboring cell populations. Moreover, the dynamic interactions of stem cells with their microenvironment have a direct consequence on stem cell fate, whether it is self-renewal, differentiation, or immunomodulation. For these reasons, it is critical to identify the components of the extracellular environment of MSCs, or what is termed as the stem cell ‘‘niche.’’ MSCs also possess immunosuppressive or immunomodulatory properties and can modulate their local tissue environment for repair and regeneration through both direct and indirect means.

The figure below depicts the differentiation potential of MSCs, indicating how a broad array of tissue types can be derived from this stem cell population. MSCs are found in various adult tissues, including the muscle, cartilage, bone marrow, dental pulp, and thymus, and can be differentiated into cell types representing all three different layers of tissue in the body—namely, ectoderm, mesoderm and endoderm. As such, therefore, these cells constitute a pliable and tractable population with which to work in order to develop regenerative medicine therapeutics.

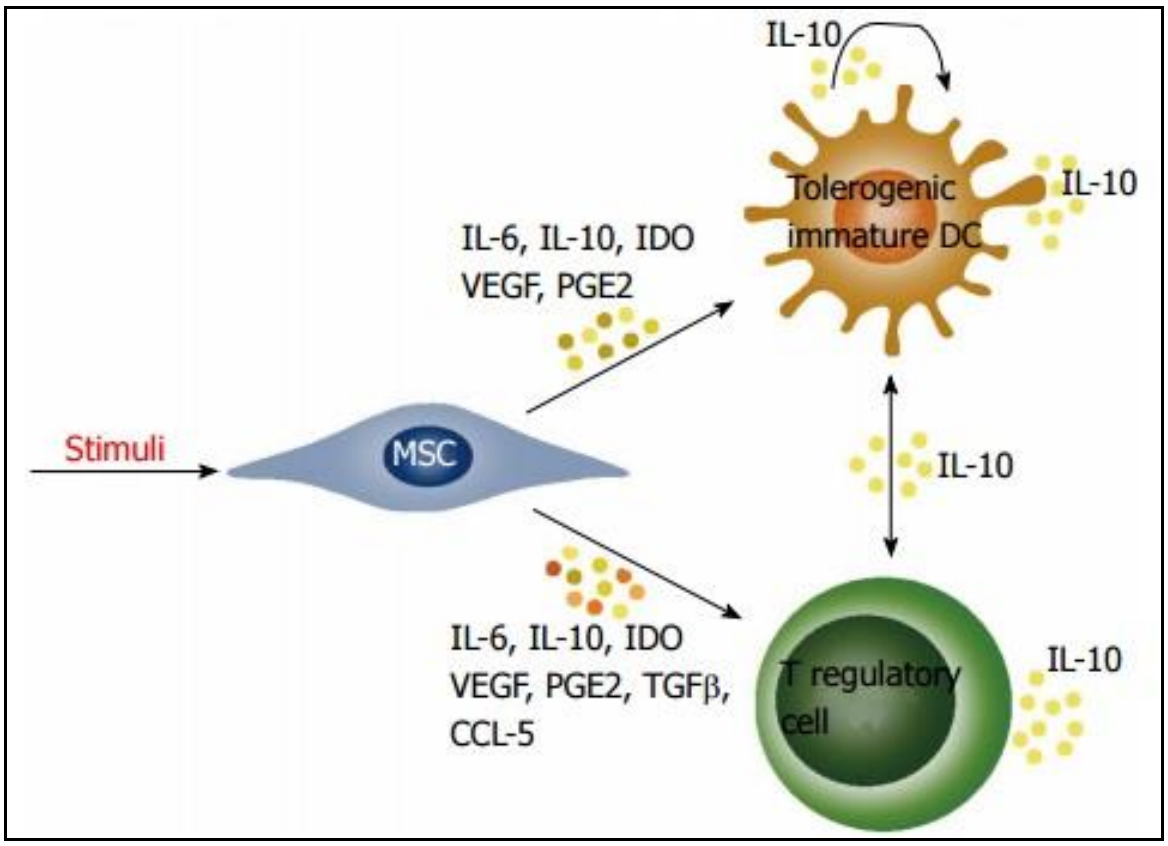
Figure 3: Mesenchymal Stem Cell Origins; Differentiation Potential



Source: Cancerlink.ru.

The figure below depicts two distinct therapeutic modalities via which MSCs can act beneficially in disease contexts. The first is termed the "repair" model, in which MSCs can actively regenerate damaged tissue or replace lost cells within tissues afflicted by pathological conditions. In this model, MSCs actively differentiate into distinct adult cell populations, driven by the endogenous presence of trophic factors. The second "chronic inflammation" model involves the unique immunomodulatory and immunosuppressive characteristics of MSCs, which can impact the immune response through their secretion and production of various cytokines. While the feedback loop between immune cells and MSCs is bidirectional in nature, under pro-inflammatory or chronic inflammatory conditions MSCs are known to drive the production of immunomodulatory and anti-inflammatory factors, including the well-known canonical Th2 cytokines IL-6 and IL-10.

Figure 4: Immunoregulatory Pathways Regulated By Mesenchymal Stem Cells



Source: Kyurkchiev et al., World Journal of Stem Cells 6: 552 – 570 (2014)

Due to their immunoregulatory properties, MSCs are posited to have therapeutic potential in a wide range of autoimmune and chronic inflammatory conditions[6], including graft-vs.-host disease (GvHD), Crohn's disease (CD), ulcerative colitis (UC), and multiple sclerosis (MS). These cells are also hypothesized to have applicability in various inflammatory lung disorders, most notably chronic obstructive pulmonary disease (COPD), asthma and idiopathic pulmonary fibrosis (IPF)[7]. In our view, the most likely near-term commercial manifestations of MSC-based therapeutics are probably in these contexts, since the use of these cells as a novel class of immunomodulatory biologic agents appears more feasible than their deployment as a platform for true regenerative medicine. We note that the broader theme of cell-based immunotherapy has taken on a prominent role in recent years, particularly within the context of oncology; as such, therefore, the deployment of cellular modulators of immune responses seems very reasonable.

[6] Singer and Caplan. Annual Review of Pathology 6: 457 – 478 (2011).
[7] Iyer and Rojas. Panminerva Medica 51: 5 – 16 (2009).

Financial Review and Outlook

Revenue. We do not forecast any sales revenues for 2015 and 2016, respectively. Management does not provide guidance.

Gross margins. Cynata is a development-stage firm, and therefore has no historical cost of goods sold. Should products based on Cynata's Cymerus™ technology platform succeed in pivotal clinical trials, we anticipate gross margins exceeding 80%, which could enable healthy cash flow generation. In our view, Cynata itself is most likely to generate revenue based on milestone payments and royalties on net sales of products that are manufactured using its technology platform, which should enable margins to be kept fairly high.

Operating expenses. For 2015, we estimate operating expense levels to be higher than that of 2014 as Cynata may elect to conduct various proof-of-concept clinical studies. We expect R&D expenses to increase as Cynata continues the validation of its Cymerus™ platform.

Taxes. While we do not anticipate the firm attaining profitability in the near future, we expect that the statutory Australian corporate tax rate would apply in the future. We have assumed an effective tax rate of 30% in our DCF analysis.

Share count. In July 2015, the company sold approximately 6.67 million shares at A$0.75 a share for net proceeds of A$4.7 million, in which H.C. Wainwright & Co. acted as sole placement agent. As of September 30, 2015, there were 72.7 million shares outstanding. Conversion of all outstanding warrants and options could add an additional 13.3 million shares. Given the company's cash position and strategic goals, a share repurchase program is unlikely, in our view.

EPS. We forecast a net loss of (A$0.07) per share for 2016, and a net loss of (A$0.11) for 2017. We do not anticipate that Cynata could attain profitability in the near term, although the company may be able to obtain meaningful upfront payments from licensing agreements going forward.

Balance sheet. The firm had roughly A$8.1 million in cash and investments after the recent financing. We believe this amount to be sufficient to fund operations into early calendar 2017.

Cash flow. We estimate that Cynata is likely to have negative operating cash flows for the foreseeable future.

Management Team

Ross MacDonald, Ph.D.
Managing Director, Chief Executive Officer
Dr. Macdonald has over 20 years' experience in biotechnology. His career history includes positions as CEO of Hatchtech Pty Ltd, Vice President of Business Development for Sinclair Pharmaceuticals Ltd, a UK-based specialty pharmaceuticals company, Vice President of Business Development for Connetics Corporation (Palo Alto, CA), and Vice President, Corporate Development for Stiefel Laboratories Inc., the largest independent dermatology company in the world and acquired by GlaxoSmithKline in 2009 for £2.25 billion. Dr. Macdonald has also served as Vice President of R&D of F.H. Faulding & Co., Ltd., and CEO of Living Cell Technologies, Ltd. His other positions have included non-executive director roles at iSonea Ltd, Telesso Technologies Ltd., Hatchtech Pty Ltd., and Relevare Pharmaceuticals Ltd. Dr. Macdonald currently serves as a member of the Investment Committee of UniSeed Management Pty Ltd. He holds a Ph.D. in Biochemistry from Monash University, a Graduate Diploma in Business Administration from Swinburne University, and is a member of the Licensing Executives Society.

Stewart Washer, Ph.D.
Executive Chairman
Dr. Washer has 20 years of executive and board experience in medical technology, biotech and agricultural firms. In addition to his current position as Chairman of Cynata, he is also Chairman of Orthocell Ltd, a firm focused on the culturing of cells to repair damaged tendons, and Chairman of Minomic International Ltd., a firm with a non-invasive test for prostate cancer. He was previously the CEO of Calzada Ltd. (ASX:CZD; not rated), the founding CEO of Phylogica Ltd. (ASX:PYC; not rated) and before this was CEO of Celentis, the commercial arm of AgResearch, where he managed the commercialization of intellectual property from AgResearch in New Zealand with 650 scientists and $130 million in revenues. He was also a founder of a NZ$120 million New Zealand-based life science fund and Venture Partner with the Swiss-based Inventages Nestlé Fund. He also holds the position of Investment Director with Bioscience Managers. Dr. Washer has held a number of board positions as the Chairman of iSonea Ltd (ASX:ISN), Resonance Health Ltd (ASX:RHT; not rated) and Hatchtech Pty. Ltd., a Director of iCeutica Pty. Ltd., Immuron Ltd (ASX:IMC; not rated) and AusBiotech Ltd. (Private). He was also a Senator with Murdoch University and is currently the Chairman of Firefly Health (Private).

Kilian Kelly, Ph.D.
Vice President, Product Development
Dr. Kelly has over 15 years of experience in pharma/biotech R&D. His previous appointments include Senior Director, Drug Development at Biota Pharmaceuticals (BOTA; not rated), Vice President, Regulatory and Clinical at Mesoblast Limited (ASX:MSB; not rated), and positions with Kendle International (now INC Research), Amgen (AMGN; not rated) and AstraZeneca (AZN; not rated). He has a Masters in Pharmacy from Robert Gordon University, Aberdeen, Scotland, and a Ph.D. in Pharmaceutical Sciences from Strathclyde University, Glasgow. He is a member of the Royal Pharmaceutical Society, The Organization for Professionals in Regulatory Affairs (TOPRA) and the Regulatory Affairs Professionals Society (RAPS).

Igor I. Slukvin, M.D., Ph.D.
Co-Founder
Prof. Slukvin, who co-founded Cynata on the basis of research originally conducted within the group headed by Prof. James Thomson at UWM, is Associate Professor in the Department of Pathology and Laboratory Medicine at the University of Wisconsin School of Medicine and Public Health. Prof. Slukvin's research focus is the development of systems to culture hematopoietic precursors and red blood cells from human pluripotent cells. Prof. Slukvin holds M.D. and Ph.D. degrees from the Kiev Medical Institute in Ukraine. He completed his medical residency at the University of Wisconsin, has published over 70 scientific papers in various peer-reviewed periodicals, and is a co-founder of Cellular Dynamics International (ICEL; not rated).

Investment Risks

Financial outlook. Cynata has been unprofitable since inception and may require additional capital in order to drive the future clinical development of its pipeline and finance the acquisition of other products and pipeline candidates. Thus, the company's stock could experience above-average risk and volatility. While the firm recently raised a total of AUD5 million in gross proceeds from an institutionally-led private placement of common stock and five-year options to purchase common stock, which is anticipated to provide sufficient operational runway for the next 12 – 15 months, further capital may be required to fund continuing operations beyond this time frame. Additional capital may come from debt or equity financings, warrant exercises or non-dilutive grant-based financing. Cynata may not be able to raise cash at all.

FDA unpredictability. New therapeutics development is a multi-year process that requires human clinical trials prior to FDA approval. The amount of additional clinical data that may be required to support regulatory filings on Cynata's stem cell-based therapeutic candidates may change over time, making it impossible to predict the precise timing of market entry and revenue generation. The FDA could also ask for additional data on Cynata's candidates prior to granting formal approval. The period of FDA review may take longer than originally expected.

Competitive landscape. Cynata is likely to face competitors with greater financial resources and larger organizations for marketing, sales, distribution, and service, assuming that the firm's candidates successfully obtain regulatory approval. Some of these companies include much larger entities, such as Celgene Corporation, Cellular Dynamics International, Gamida Cell, Mesoblast Ltd., and Osiris Therapeutics. Many of Cynata's peers may have substantially greater financial resources, which may allow them to establish more favorable strategic relationships and commercial infrastructure than Cynata.

Partnership risk. Cynata lacks commercial experience and could eventually find itself having to rely upon partners to establish sales and marketing support for its products if they reach the market. If so, the company is likely to be dependent on such sub-licensees to execute on the commercialization of proprietary therapeutic products employing Cynata's production technology. In addition, certain elements of Cynata's intellectual property and drug candidate ownership rights are licensed from third parties. Should these third parties revoke the rights that they originally provided to Cynata, the company may be unable to further develop its candidate drugs or realize profits from their commercialization.

Intellectual property. Cynata relies on patents and trade secrets to protect its products from competition. The pharmaceutical industry is litigious, and lawsuits are considered to be a normal part of doing business. A court might not uphold Cynata's intellectual property rights, or it could find that Cynata infringed upon another party's property rights. The company is also dependent in part upon the continued validity of intellectual property in-licensed from third parties.

Industry risks. The securities of emerging biotechnology and specialty pharmaceuticals companies are inherently volatile and increasingly subject to development and regulatory risk. Meeting or missing commercial milestones may result in changes in the perception of the firm and the stock price. We do not anticipate volatility to subside near-term.

For additional risk considerations, please refer to the company's formal filings with the Australian Securities and Investments Commission (ASIC).

Table 6: Cynata Therapeutics, Inc. (CYP.AX) – Historical Income Statements, Financial Projections

FY end June 30
$ in thousands, except per share data

			2016E					2017E					
	2014A	2015A	1QE	2QE	3QE	4QE	2016E	1QE	2QE	3QE	4QE	2017E	2018E
Revenue													
Collaboration revenue	-	-	-	-	500	500	1,000	1,000	1,000	1,000	1,000	4,000	6,000
Net sales	-	-	-	-	-	-	-	-	-	-	-	-	-
Cost of sales	-	-	-	-	-	-	-	-	-	-	-	-	-
Gross income (loss)	-	-	-	-	-	-	-	-	-	-	-	-	-
Operating expenses													
Research & development	503	1,920	600	750	900	1,050	3,300	1,100	1,200	1,300	1,500	5,100	6,000
Selling, general and administrative	602	831	300	350	400	450	1,500	550	600	650	700	2,500	3,200
Share-based compensation expense	1,303	429	100	105	115	120	440	200	200	200	200	800	1,000
Total expenses	2,408	3,180	1,000	1,205	1,415	1,620	5,240	1,850	2,000	2,150	2,400	8,400	10,200
Gain (loss) from operations	(2,408)	(3,180)	(1,000)	(1,205)	(1,415)	(1,620)	(5,240)	(1,850)	(2,000)	(2,150)	(2,400)	(8,400)	(10,200)
		-					-					-	-
Other income (expense)													
Other expenses	(632)	(459)	-	-	-	-	-	-	-	-	-	-	-
Depreciation and amortization	0	(448)	-	-	-	-	-	-	-	-	-	-	-
Other income (expense)	-	375	8	7	6	5	26	3	7	11	10	31	42
Interest income (expense)	-	-	-	-	-	-	-	-	-	-	-	-	-
Total investment income and other	(632)	(532)	8	7	6	5	26	3	7	11	10	31	42
Net income (loss)	(3,039)	(3,712)	(992)	(1,198)	(1,409)	(1,615)	(5,214)	(1,847)	(1,993)	(2,139)	(2,390)	(8,369)	(10,158)
Net income (loss) per share (basic)	(0.07)	(0.06)	(0.01)	(0.02)	(0.02)	(0.02)	(0.07)	(0.02)	(0.03)	(0.03)	(0.03)	(0.11)	(0.11)
Net income (loss) per share (diluted)	(0.07)	(0.06)	(0.01)	(0.02)	(0.02)	(0.02)	(0.07)	(0.02)	(0.03)	(0.03)	(0.03)	(0.11)	(0.11)
Weighted average number of shares outstanding (basic)	44,959	60,655	72,738	72,738	72,763	72,813	72,763	76,221	76,246	77,963	84,430	78,715	89,311
Weighted average number of shares outstanding (diluted)	44,959	60,655	73,038	73,038	73,063	73,113	73,063	76,521	76,546	78,263	84,730	79,015	89,611

Source: Company reports and Rodman & Renshaw estimates.

Table 7: Cynata Therapeutics, Inc. (CYP.AX) – Historical Balance Sheet Data

FY end June 30
$ in thousands, except per share data

	12/31/14A	12/31/15A
Assets		
Current assets:		
Cash and cash equivalents	6,156	4,704
Restricted cash	-	-
Trade receivables	43	48
Inventories, net	-	-
Other prepaid expenses and current assets	-	-
Total current assets	6,200	4,751
Property and equipment, net	-	-
Intangibles	4,822	4,374
Total Assets	11,021	9,125
Liabilities and shareholder equity		
Current liabilities		
Trade and other payables	185	314
Borrowings	-	33
Provisions	22	29
Total current liabilities	207	375
Derivative liability	-	-
Deferred revenue, long term	-	-
Total Liabilities	207	375
Shareholder's equity		
Option reserves	3,212	3,276
Foreign currency translation reserve	4	4
Shares yet to be issued	681	-
Issued capital	23,614	24,460
Accumulated deficit	(16,698)	(18,991)
Total shareholder's equity	10,814	8,750
Total liability and shareholder's equity	11,021	9,125

Source: Company reports and Rodman & Renshaw estimates.

Public companies mentioned in this report:

Amgen Inc. (AMGN; not rated)
AstraZeneca PLC (AZN; not rated)
Biota Pharmaceuticals (BOTA; not rated)
Calzada Ltd (ASX:CZD; not rated)
Celgene Corporation (CELG; not rated)
Cellular Dynamics International (ICEL; not rated)
Chugai Pharmaceutical Co., Ltd. (CHGCF; not rated)
Fujifilm Holdings Corporation (FUJIF; not rated)
GlaxoSmithKline plc (GSK; not rated)
Immuron Ltd. (ASX:IMC; not rated)
iSonea Ltd (ASX:ISN; not rated)
Merck & Co. Inc. (MRK; not rated)
Mesoblast Ltd. (MSB.AX; not rated)
Novartis AG (NVS; not rated)
Osiris Therapeutics (OSIR; not rated)
Phylogica Ltd. (ASX:PYC; not rated)
Resonance Health Ltd (ASX:RHT; not rated)
Roche Holding AG (RHHBY; not rated)
Takeda Pharmaceutical Co., Ltd. (TKPHF; not rated)
Teva Pharmaceutical Industries (TEVA; not rated)
Valeant Pharmaceuticals International (VRX; not rated)

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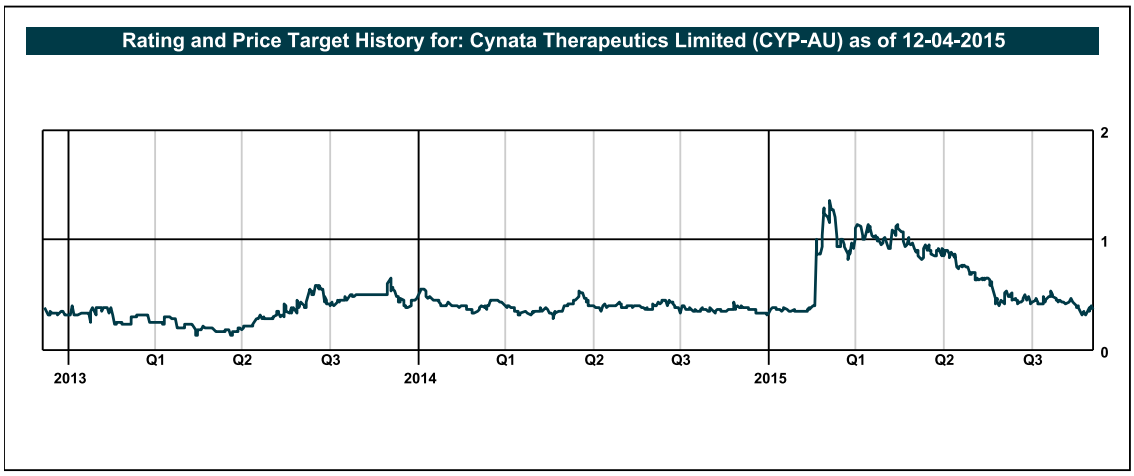
RETURN ASSESSMENT

Market Outperform (Buy): The common stock of the company is expected to outperform a passive index comprised of all the common stock of companies within the same sector.

Market Perform (Neutral): The common stock of the company is expected to mimic the performance of a passive index comprised of all the common stock of companies within the same sector.

Market Underperform (Sell): The common stock of the company is expected to underperform a passive index comprised of all the common stock of companies within the same sector.



Related Companies Mentioned in this Report as of //					
Company	Ticker	H.C. Wainwright Rating	12 Month Price Target	Price	Market Cap

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Distribution of Ratings Table				
			IB Service/Past 12 Months	
Ratings	Count	Percent	Count	Percent
Buy	134	95.71%	43	32.09%
Neutral	5	3.57%	1	20.00%
Sell	0	0.00%	0	0.00%
Under Review	1	0.71%	0	0.00%
Total	140	100%	44	31.43%

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