Baillieu Holst
Since 1889

Cynata Therapeutics (CYP)

INITIATION OF COVERAGE

Unlimited quantities of potent adult stem cells, no hassles

- **Company description**. Cynata is a player in the emerging field of regenerative medicine. Its Cymerus technology allows virtually unlimited quantities of Mesenchymal Stem Cells (MSCs) to be manufactured for therapeutic use from only a small number of initial donor cells. MSCs are adult stem cells known to be able to facilitate heart repair and rebuild bone and cartilage tissue as well as turn down inflammation. Cynata makes its MSCs from a precursor cell called the mesenchymoangioblast, which was discovered and patented at the University of Wisconsin-Madison in the US. The company is now working on manufacturing process development for its stem cells that involves the use of induced Pluripotent Stem cells (IPS cells). Next year it intends to dose its first patient, in a Graft-versus-Host Disease study.
- **Problem-solving stem cell therapy.** Cynata can solve the key problem in stem cell therapy, which is availability of therapeutically potent stem cells. The science suggests that a single colony of mesenchymoangioblasts can create up to 10^{22} MSCs. However Cynata starts with iPS cells that can differentiate into mesenchymoangioblasts. Since iPSCs can be expanded indefinitely, in effect Cynata can create unlimited number of MSCs.
- **Cynata is a great 'concept stock' for the iPS Revolution.** Induced Pluripotent Stem Cells (iPS), are ordinary adult cells where pluripotency is induced using certain well understood cellular 'reprogramming' techniques. iPS technology is widely expected to make stem cells a medical reality without the ethical controversy that embryonic stem cells created a decade ago. Part of the 2012 Nobel Prize in Medicine went to Japan's Shinya Yamanaka for his invention of iPS cells. In 2013 Cynata became one of the first publicly traded companies in the world to make use of iPS technology. This makes Cynata a great concept stock for investors in the regenerative medicine field.
- **Cynata has strong leadership**. CEO, Ross Macdonald brings years of drug development experience gained at companies such as F.H. Faulding and Stiefel. Executive Chairman, Stewart Washer has broad experience in developing early stage drug and medical device companies.
- **Cynata remains undervalued, on our numbers**. Using a probability-weighted DCF approach, we value Cynata at A$0.93 base case and A$2.25 optimistic case. Our $0.90 target price is derived from our base case. We see Cynata being re-rated to our target price as the company demonstrates the ability to make its stem cells at scale.

INVESTMENT SUMMARY

Year End: 30 June		2012 (A)	2013 (A)	2014 (E)	2015 (E)	2016 (E)
Revenue	$mn	0	0	0	0	9
EBITDA	$mn	-1.4	-1.0	-4.0	-8.7	-0.4
EBIT	$mn	-1.5	-1.0	-4.0	-8.7	-0.4
Reported Profit	$mn	-1.5	-0.9	-4.0	-8.6	-0.1
Adjusted Profit	$mn	-1.5	-0.9	-4.0	-8.6	-0.1
EPS (Reported)	¢	-0.2	-0.1	-0.7	-1.4	0.0
EPS (Adjusted)	¢	-0.2	-0.1	-0.7	-1.4	0.0
EPS Growth	%	N/A	N/A	N/A	N/A	N/A
PER (Reported)	x	N/A	N/A	N/A	N/A	N/A
PER (Adjusted)	x	N/A	N/A	N/A	N/A	N/A
Dividend	¢	0.0	0.0	0.0	0.0	0.0
Yield	%	0.0	0.0	0.0	0.0	0.0
Franking	%	0	0	0	0	0

RECOMMENDATIONS

Rating	**BUY** ▲
Risk	Speculative
Price Target	**$0.90**
Share Price	$0.36

SNAPSHOT

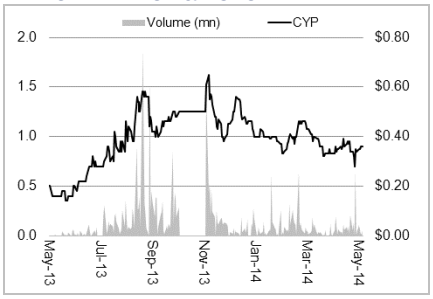
Monthly Turnover	$0.7mn
Market Cap	$16mn
Shares Issued*	45.0mn
52-Week High	$0.68
52-Week Low	$0.14
Sector	Health Care

* Note: In addition to 10.0mn escrowed shares

BUSINESS DESCRIPTION

Cynata is a stem cell company developing the therapeutic potential of a class of stem cell called the mesenchymoangioblast. The company is now working on manufacturing process development for its stem cells. In 2015 it intends to dose its first patient, in a Graft-versus-Host Disease study.

12-MONTH PRICE & VOLUME



RESEARCH ANALYST

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Disclosure
The author owns no shares in CYP.

Financial summary

Code	CYP
Analyst	Stuart Roberts
Date	30 May, 2014
Share price	$0.36
Market capitalisation	$20m
Year end	30 June

Rating	BUY
Price target	$0.90
Upside/downside	153.5%
Valuation	$0.934 / $2.249
Valuation method	Probability-weighted DCF
Risk	Speculative

PROFIT AND LOSS (A$m)

Y/e June 30 (A$m)	FY12A	FY13A	FY14E	FY15E	FY16E
Revenue	0	0	0	1	9
EBITDA	**-1**	**-1**	**-4**	**-9**	**0**
D&A	0	0	0	0	0
EBIT	**-2**	**-1**	**-4**	**-9**	**0**
Net interest	0	0	0	0	0
Pre-tax profit	**-2**	**-1**	**-4**	**-9**	**0**
Tax	0	0	0	0	0
NPAT	-2	-1	-4	-9	0
Minority interests	0	0	0	0	0
Net profit after minorities	-2	-1	-4	-9	0

BALANCE SHEET (A$m)

Y/e June 30	FY12A	FY13A	FY14E	FY15E	FY16E
Cash	1	1	4	15	15
Current receivables	0	0	0	0	0
Inventories	0	0	0	0	0
Other current assets	0	0	0	0	0
Current assets	**1**	**1**	**4**	**15**	**15**
PPE	0	0	0	0	0
Intangible assets	0	0	5	5	5
Other non-current assets	0	1	0	0	0
Non-current assets	0	1	5	5	5
Total assets	1	2	9	20	20
Payables	0	0	0	0	0
Debt	0	0	0	0	0
Other liabilities	0	0	0	0	0
Total liabilities	0	0	0	0	0
Shareholders' equity	1	2	9	20	20
Minorities	0	0	0	0	0
Total shareholders funds	**1**	**2**	**9**	**20**	**20**
Total funds employed	**1**	**2**	**9**	**20**	**20**
W/A shares on issue	190	471	55	72	122

CASH FLOW (A$m)

Y/e June 30	FY12A	FY13A	FY14E	FY15E	FY16E
NPAT plus discontinued ops.	-2	-1	-4	-9	0
Non-cash items	0	0	1	0	0
Working capital	1	0	0	0	0
Other operating cash flow	0	0	0	0	0
Operating cashflow	**-1**	**-1**	**-3**	**-8**	**0**
Capex	0	0	0	0	0
Investments	0	-1	0	0	0
Other investing cash flow	0	0	0	0	0
Investing cashflow	**0**	**-1**	**0**	**0**	**0**
Change in borrowings	0	0	0	0	0
Equity raised	1	2	6	19	0
Dividends paid	0	0	0	0	0
Other financing cash flow	0	0	0	0	0
Financing cashflow	**1**	**2**	**6**	**19**	**0**
Net change in cash	**1**	**0**	**3**	**11**	**0**
Cash at end of period	1	1	4	15	15

EARNINGS (A$m)

Y/e June 30	FY12A	FY13A	FY14E	FY15E	FY16E
Net profit ($m)	-1.5	-0.9	-4.0	-8.6	-0.1
EPS (c)	-0.8	-0.2	-7.2	-12.1	-0.1
EPS growth (%)	N/A	N/A	N/A	N/A	N/A
P/E ratio (x)	-43.8	-182.5	-4.9	-2.9	-326.4
CFPS (c)	-0.4	-0.2	-5.1	-11.5	-0.2
Price/CF (x)	-92.7	-218.2	-7.0	-3.1	-173.8
DPS (c)	0.0	0.0	0.0	0.0	0.0
Yield (%)	0.0%	0.0%	0.0%	0.0%	0.0%
Franking (%)	N/A	N/A	N/A	N/A	N/A
EV/EBITDA	-10.0	-14.5	-3.4	-1.6	-36.1
EV/EBIT	-8.9	-14.5	-3.4	-1.6	-35.2

PROFITABILITY RATIOS

Y/e June 30	FY12A	FY13A	FY14E	FY15E	FY16E
EBITDA/revenue (%)	-434.7%	-2800.0%	-16196.0%	-868.8%	-4.0%
EBIT/revenue (%)	-488.6%	-2802.9%	-16196.0%	-869.3%	-4.2%
Return on assets (%)	-151.6%	-51.1%	-43.8%	-43.6%	-0.7%
Return on equity (%)	-180.6%	-55.8%	-45.0%	-44.1%	-0.7%
Return on funds empl'd (%)	-180.6%	-55.8%	-45.0%	-44.1%	-0.7%
Dividend cover (x)	N/A	N/A	N/A	N/A	N/A
Effective tax rate (%)	0.0%	0.0%	0.0%	0.0%	0.0%

LIQUIDITY AND LEVERAGE RATIOS

Y/e June 30	FY12A	FY13A	FY14E	FY15E	FY16E
Net debt/(cash) ($m)	-1	-1	-4	-15	-15
Net debt/equity (%)	-116.3%	-68.0%	-46.8%	-75.8%	-73.6%
Net interest cover (x)	N/A	N/A	N/A	N/A	N/A
Current ratio (x)	6.2	7.7	18.6	65.9	32.7

INTERIMS

Y/e June 30 ($m)	2H12A	1H13A	2H13A	1H14F	2H14F
Revenue	0	0	0	0	0
EBITDA	**-1**	**0**	**-1**	**-2**	**-2**
D&A	**0**	**0**	**0**	**0**	**0**
EBIT	**-1**	**0**	**-1**	**-2**	**-2**
Net interest	**0**	**0**	**0**	**0**	**0**
Pre-tax profit	-1	0	-1	-2	-2
Tax	**0**	**0**	**0**	**0**	**0**
NPAT	-1	0	-1	-2	-2
Minority interests	**0**	**0**	**0**	**0**	**0**
Net profit after minorities	-1	0	-1	-2	-2

VALUATION

	Base	Optim.
Osteogenesis imperfecta (A$m)	16.5	55.5
Multiple Sclerosis (A$m)	36.6	110.7
Acute Coronary Syndrome (A$m)	51.8	120.5
Value of Cynata technology	104.8	286.6
Value of tax losses	3.7	3.7
Underlying R&D cost	-9.6	-9.6
Cash now (A$m)	5.7	5.7
Cash from options and cash to be rai	24.4	24.4
Total value (A$m)	129.0	310.9
Total diluted shares (million)	138.2	138.2
Value per share	$0.93	$2.25
Valuation midpoint	$1.59	
Share price now (A$ per share)	$0.355	
Upside to midpoint	348.2%	

Ten reasons to own Cynata at current prices

- **The era of regenerative medicine and stem cells is here.** With science having learned a great deal about stem cells and regenerative medicine over the last 15 years, and the first regenerative medicine products now in late stage trials or gaining regulatory approval, the field is set to become increasingly important in modern medicine. We therefore see strong upside for stem cell companies as investors seek to gain exposure to this relatively new treatment paradigm.
- **Problem-solving stem cell therapy.** Cynata can solve a key problem in stem cell therapy, which is availability of stem cells. Cynata is based on a mesenchymal precursor called the 'mesenchymoangioblast'. The science suggests that a single colony of mesenchymoangioblasts can create up to 10^{22} mesenchymal stem cells. However Cynata starts with iPS cells that can differentiate into mesenchymoangioblasts. Since iPSCs can be expanded indefinitely, Cynata can, in effect, create unlimited number of MSCs. This abundance of stem cells points the way towards low-cost cellular therapy.
- **Ample therapeutic possibilities.** Mesenchymal stem cells have powerful therapeutic possibilities. They have the ability to facilitate the repair of damaged or diseased cardiac tissue. They can rebuild bone and cartilage. And they have well-characterised anti-inflammatory properties. Further, the relative lack of immunogenicity on the part of the stem cells also points to their potential to be used as 'off the shelf' products.

Cynata is a great concept stock for the rise of iPS cells.

- **Cynata is working with world leaders in regenerative medicine.** Professor Igor Slukvin of the University of Wisconsin-Madison, who invented the Cymerus technology, is considered a thought leader in stem cells through his work on systems for making blood and angiogenic cells from human pluripotent cells. Wisconsin-Madison is a hotbed of stem cell development thanks largely to one of Slukvin's co-inventors, Professor James Thomson, who famously derived the first human embryonic stem cell line in 1998.
- **Cynata is a great 'concept stock' for the rise of iPS cells.** iPS cells, or induced Pluripotent Stem Cells, are ordinary adult cells where pluripotency is induced using certain well understood cellular 'reprogramming' techniques. iPS technology is widely expected to make stem cells a medical reality without the ethical controversy that embryonic stem cells created a decade ago. Part of the 2012 Nobel Prize in Medicine went to Japan's Shinya Yamanaka for his invention of iPS cells. Cynata is one of the first publicly traded companies in the world to make use of iPS technology. This makes Cynata a great concept stock for investors in the regenerative medicine field.
- **From technology to practice.** Cynata is working towards reducing its technology to practice, with Waisman Biomanufacturing in Madison now working on process development, validation and documentation as well as the manufacture of product for pre-clinical and clinical work. While further work from a major contract manufacturer will be needed in order for Cynata's cells to be made at the 10,000 litre bioreactor level, we see the completion of scale-up to pilot plant as providing evidence that the technology works as expected.
- **Favourable data.** The research data looks good, with evidence that mesenchymoangioblasts can make a serious difference in Critical Limb Ischemia (CLI) and in Graft versus Host Disease (GvHD). GvHD represents an Orphan disease condition with great unmet medical need and provides a good 'proof of concept' testbed for Cynata.
- **A Phase I trial in GvHD is planned soon.** Cynata is currently preparing for a small trial that will evaluate the ability of its stem cells to blunt GvHD. Given evidence from many studies that mesenchymal stem cells can be effective in this setting, we expect good things from Cynata's maiden clinical study.
- **Cynata has strong leadership.** CEO, Ross Macdonald brings years of drug development experience gained at companies such as F.H. Faulding and Stiefel. Executive Chairman, Stewart Washer has broad experience in developing early stage drug and medical device companies.
- **Cynata remains undervalued, on our numbers.** Using a probability-weighted DCF approach, we value Cynata at A$0.93 base case and A$2.25 optimistic case. We see Cynata being re-rated to our target price as the company demonstrates the ability to make its stem cells at scale, and as the early pilot trials of the technology take place.

Cynata can help you prepare for the Stem Cell Revolution

- **Cynata is well placed for the impending revolution.** We argue that companies like Cynata, currently working on stem cells for regenerative medicine, are part of a forthcoming revolution in modern medicine which, through highly favourable patient outcomes in areas of unmet medical need, will help transform healthcare from the second half of this decade. We see a reasonable chance that multiple companies with capitalisations of over a billion US dollars will arise out of this Stem Cell Revolution. Today, however, you can get some of these potential future champions for under US$20m. We suggest that stem cells today are where monoclonal antibodies, the subject of the last medical revolution, were in the mid-1990s.
- **What is regenerative medicine?** Regenerative medicine involves repairing or replacing organs and tissues than have been lost or damaged due to age, disease, damage or congenital defects. When people talk about regenerative medicine they are often talking about the use of stem cells, which are cells that have this regenerative capacity.
- **What are stem cells?** Stem cells are the 'mother cells' of the body, being 'undifferentiated' cells which the body uses to create and repair organs and tissues through the differentiation of the stem cells into specialised cell types. There are three kinds of stem cell:
  - **Embryonic Stem Cells (hESCs)** – stem cells that come from eggs that have been fertilised *in vitro*, and are pluripotent, that is, capable of differentiating into any specialised cell type. The first human embryonic stem cell lines were created in 1998;
  - **Adult stem cells** – stem cells that the body carries throughout life that are multipotent, that is, capable of differentiating into some but not all specialised cell types. An important class of adult stem cell is the 'mesenchymal' stem cell (MSC) found in the bone marrow as well as other tissues including adipose tissue. MSCs can form adipose tissue, bone and cartilage tissue and they are potent immunomodulators; and
  - **Induced Pluripotent Stem Cells (iPS cells)** – adults cells that are already specialised but that have been 'reprogrammed' so that they are pluripotent. iPS cells were first invented around 2007 and won Japan's Shinya Yamanaka a Nobel Prize in 2012.
- **Why can stem cells be revolutionary in medicine?** Stem cells could potentially treat the underlying biology of many diseases, which involves lost or damaged tissue, whereas many current therapies deal more with symptoms. For example, a stem cell treatment for heart failure could repair heart tissue whereas current therapies such as drugs, defibrillators and pacemakers only slow down the rate of tissue damage. It is therefore reasonable to expect that good data for a stem cell product will enjoy annual sales in the billions.
- **Is the Stem Cell Revolution close at hand or far off**? A good question given that embryonic stem cells were first isolated 15 years ago. We believe the Revolution will kick off some time in the second half of this decade, since:
  - The early ethical issues have been bypassed, with adult stem cells showing promise in the clinic but not requiring the embryo destruction that made embryonic stem cell research so controversial in the years after 1998;
  - There is now substantial mid-stage clinical evidence that stem cells work in areas of unmet medical need, much of which has only emerged in the last five years;
  - There are various stem cell products in development that work allogeneically, meaning that the patient receives stem cells sourced from someone else's body. As a general rule, allogeneic therapies are cheap because they can be 'off-the-shelf' whereas autologous therapies (use of the patient's own cells) are expensive; and
  - Stem cells can now be made at industrial scale under the Good Manufacturing Practice that regulators require of drug makers.
- **How will Cynata benefit from the Stem Cell Revolution?** Cynata can solve a key problem in stem cell therapy, which is availability of stem cells. Cynata is based on a multipotent mesenchymal precursor called the 'mesenchymoangioblast'. The science suggests that a single colony of mesenchymoangioblasts can create up to 10^{22} mesenchymal stem cells. However Cynata starts with iPS cells that can differentiate into mesenchymoangioblasts. Since iPSCs can be expanded indefinitely, in effect Cynata can create unlimited number of MSCs. This ability to make abundant stem cells will become highly valuable as the Revolution draws near.

Cynata aims to help pioneer low-cost cellular therapy.

If antibodies were big, stem cells will be even bigger

Monoclonal antibodies provide the template for the Stem Cell Revolution

- **Monoclonal antibodies are now a >US$60bn product class.** Monoclonal antibodies are regular antibodies of the kind that our immune system employs to keep us healthy, but formulated so that each antibody in a drug batch is identical. Monoclonal antibodies are great drugs because they can hit, with exquisite sensitivity and low side effects, a highly specific disease target. They are, in effect, Paul Ehrlich's famous 'magic bullet' against disease[1], which is why, after the first one gained FDA approval in 1997[2], the class boomed to about US$27bn in global sales a decade later and to >US$60bn in net sales in 2013. This means that antibodies today are a massive 5% of the entire world pharmaceutical market. There are now 14 monoclonal antibody blockbusters[3], with six of them in the world's 20 biggest selling drugs[4], and pharma and biotech company pipelines have hundreds of antibodies in development. It took, however, 22 years and a few true believers to get the revolution started.
- **For a long time monoclonal antibodies as drugs were considered a pipe dream.** The hybridoma technology for producing monoclonal antibodies was invented way back in 1975[5], and had won its inventors the Nobel Prize for Medicine in 1984[6]. But in the 1980s and 1990s there were multiple clinical failures that made the field look bad[7]. The main problem was the need to humanise antibodies, since murine antibodies from the hybridomas were unsuitable for use in people. The first humanisation technology was developed around 1988[8] but the first humanised antibodies didn't go to the clinic until the 1990s.
- **The backing of an established company helped the first humanised monoclonal to get over the line.** The November 1997 approval of the non-Hodgkin's lymphoma drug Rituxan effectively started the revolution, but that drug almost didn't get a shot at Phase III. Its developer, Idec Pharmaceuticals, had good Phase II data but only US$22m in cash in March 1995 before Genentech, the world's first successful biotech company, took a chance on the story and agreed to a US$57m funding package to complete the Phase III work. That investment, by a true believer in antibodies, paid off reasonably swiftly – Rituxan was a blockbuster by 2001 – and helped unlock a lot of other value.
- **Once the boom got going, the key players started going for big numbers**. After 1997 new antibodies were being approved at a rate of one or two a year, and existing antibodies increased their sales rapidly. As a result, many of the key players in the Antibody Revolution were eventually acquired for significant price tags:
    - J&J bought antibody drug developer, Centocor for US$4.9bn in 1999 primarily for the anti-inflammatory drug Remicade, which gained FDA approval in 1998;
    - Abbott bought the pharmaceutical business of BASF in 2000 for US$6.9bn in part for D2E7, which became the Rheumatoid Arthritis drug, Humira;
    - In 2003 the merger which formed Biogen Idec[9] valued Idec at US$6.6bn;
    - UCB bought Celltech in 2004 for US$2.6bn, mainly for Cimzia, the Rheumatoid Arthritis drug;
    - Amgen bought Abgenix in 2005 for US$2.2bn, which brought the XenoMouse transgenic mouse – a source of fully human antibodies – and the cancer drug Vectibix;

It took 22 years for the Antibody Revolution to get started.

[1] Paul Ehrlich (1854-1915) of Germany won the Nobel Prize for Physiology or Medicine in 1908 for his discovery of Salvarsan, the first syphilis drug. Ehrlich's magic bullet idea is of a drug that selectively targets disease-causing bacteria.

[2] Technically, the anti-clotting drug ReoPro, generic name abciximab (see www.reopro.com) predates it by three years. However ReoPro is a chimeric human-murine monoclonal (ie 50% mouse) and only works because, since it's only given once or twice, the immune system doesn't react strongly.

[3] Actemra, Avastin, Erbitux, Herceptin, Humira, Lucentis, Prolia, Remicade, Rituxan, Soliris, Stelara, Synagis, Tysabri and Xolair.

[4] Avastin, Herceptin, Humira, Lucentis, Remicade and Rituxan

[5] See Nature. 1975 Aug 7;256(5517):495-7.

[6] The Medicine Nobel that year went to Germany's Georges Köhler (1946-1995) and the UK's César Milstein (1927-2002) for their hybridoma work, as well as Niels Jerne (1911-1994) of Denmark, who had been the first to propose a theory of natural selection for antibody formation.

[7] Consider, for example, the experience of Centocor. In January 1993 that antibody company suspended a trial of its Centoxin antibody in sepsis on an interim analysis showing a higher death rate in the treatment arm. The stock plunged 64% on the news.

[8] See US Patent 5,225,539, priority date 27/3/1986 (the so-called Winter I patent) and Nature. 1988 Mar 24;332(6162):323-7.

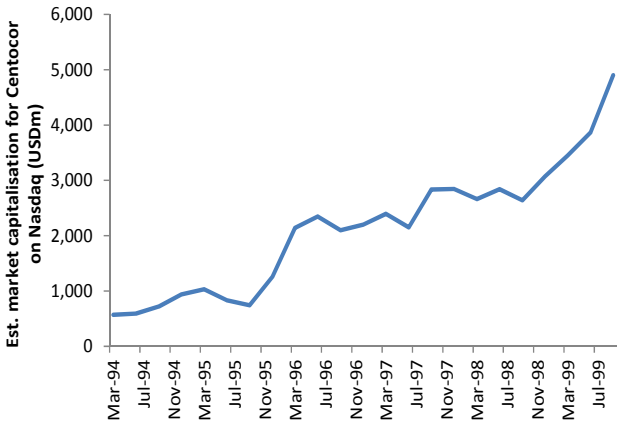
[9] Now the 34th largest pharma company in the world - source: Pharmaceutical Executive magazine.

- AstraZeneca paid US$1.3bn for Cambridge Antibody Technology, which had pioneered phage display for antibody discovery;
- GSK paid US$454m in 2006 for Domantis, pioneer of domain antibodies, when all the acquired company's programmes were pre-clinical;
- AstraZeneca bought Medimmune in 2007 for US$15bn primarily for Synagis, an antibody to prevent RSV infection;
- Genetech purchased Tanox for US$919m in 2007, effectively for the asthma drug, Xolair;
- Eli Lilly bought ImClone Systems for US$6.5bn in 2008, primarily for the cancer drug Erbitux; and
- Bristol-Myers Squibb bought Medarex in 2009 for US$2.4bn, for another transgenic mouse called the 'HuMAb-Mouse' as well as for the cancer antibody Yervoy, then in clinical development.

- **Once the antibody boom got started, Big Pharma started to play**. In the 1990s the early developers of antibodies were mostly emerging .companies such as Centocor, Medimmune and Idec – none of which survived as independent companies. Traditional Big Pharma companies by-and-large didn't play, with the exception of Roche, which in 1990 had bought 60% of Genentech[10]. As the lists of transactions above will have intimated, antibody development became routine for Big Pharma after 1997, to the point where in 2012 the 21 largest drugmakers had 58% of their biological drug pipelines in antibodies[11].

Nowadays antibody drug development is routine at Big Pharma – a decade or so from today stem cell development will be.

FIG.1: CENTOCOR SHAREHOLDERS WERE BENEFICIARIES OF THE ANTIBODY REVOLUTION



Source: Centocor, Baillieu Holst estimates

We think stem cells today are where monoclonal antibodies were in 1995

- **The long wait time parallels that of antibodies in the 1990s.** Like antibodies, stem cells have been through the long waiting period before the 'right' kinds of products can enter clinical development. Once the first human embryonic stem cell lines were isolated in the late 1990s the expectation was that it wouldn't be long until they could go to the clinic given their huge potential. However these kinds of cells were controversial, not only because they required embryo destruction, but also because they came with cancer risk. This slowed the development pace markedly, to the point where it took until October 2010 before the first hESC-derived cells made it into a clinical trial[12], seven years after the relevant pre-clinical

[10] For only US$2bn. The other 40%, acquired in 2009, cost US$46.8bn. That's what a few good antibodies were able to do for Genentech shareholders.

[11] See *Biotech meds are swelling those pharma pipelines* by Ed Silverman, Forbes, 18/11/2013.

[12] See Geron press release dated 11/10/2010 and headlined '*Geron Initiates Clinical Trial of Human Embryonic Stem Cell-Based Therapy*'. The trial was for GRNOPC1, a hESC-derived oligodendrocyte progenitor cell product considered useful in the treatment of spinal cord injury.

data had been published[13]. It took until around 2007 before hESC lines could be readily obtained from single blastomeres without embryo destruction[14], nine years after the first human embryonic stem cell lines. Around the same time the ground-breaking iPS technology was invented[15], but the first iPS clinical trial – now being conducted by Japan's Riken Institute - only started last year[16]. This long wait parallels the period before humanised antibodies supplanted murine monoclonal antibodies in the 1990s. The difference is that Mesenchymal Stem Cells were able to move forward much quicker. Osiris Therapeutics[17] was in a Phase I/II trial of its Prochymal MSC formulation in paediatric bone marrow transplant patients in 2000, while the first autologous clinical study by Mesoblast[18] of its MSCs took place in 2006.

- **Like antibodies, stem cells now have their Nobel laureates.** In 2012 the Nobel Prize for Medicine was jointly awarded to Japan's Shinya Yamanaka for creating iPS cells, and to Britain's Sir John Gurdon, for laying the theoretical foundations for Yamanaka's work by showing that specialisation of cells was reversible[19].

Stem cells won the 2012 Nobel Prizes for Medicine.

- **Like antibodies, stem cells have started to register clinical success**. Consider:
  - **Aastrom Biosciences'**[20] favourable interim results from a randomised, double-blind, placebo-controlled Phase IIb trial in Critical Limb Ischemia (CLI), February 2010[21] - a composite endpoint showed that Aastrom's autologous vascular repair cells were more effective in treating CLI than placebo ($p<0.05$);
  - **Mesoblast's** favourable heart failure data, November 2011[22] - a randomised, placebo-controlled Phase II trial in heart failure patients saw Mesoblast's allogeneic mesenchymal precursors markedly reduce Major Adverse Cardiac Events in the treatment group by 78% over a mean 22 months of follow up ($p=0.011$);
  - **Athersys'**[23] favourable Phase I data in heart attack for its marrow-derived 'multipotent adult progenitor cells', November 2011[24] - Athersys' cells improved ejection fraction and left ventricular stroke volume in the treated patients with strong trends towards significance;
  - **Advanced Cell's**[25] reports of improvement in vision for two patients, one with AMD and one with Stargardt's macular dystrophy, January 2012[26]; the Stargardt's patient went from only being able to see hand motions to having 20/800 eyesight;
  - **Athersys'** favourable Phase I data in GvHD, February 2012[27] - patients undergoing hematopoietic stem cell transplants, mostly for leukaemia, saw a marked reduction in acute GvHD incidence relative to historical experience;
  - **Pluristem's**[28] report that its placenta-derived stem cells had reversed aplastic bone marrow (that is, no HSCs in the marrow), May 2012[29]; and

[13] See *Stem cells enable paralysed rats to walk* by Alexandra Goho, New Scientist, 3/7/2003. The work was later published in J Neurosci. 2005 May 11;25(19):4694-705.

[14] This technology was developed by a US company called Advanced Cell (Marlborough, Ma, OTCBB: ACTC, www.advancedcell.com). See Nat Protoc. 2007;2(8):1963-72.

[15] See Cell. 2007 Nov 30;131(5):861-72.

[16] The Riken (see www.riken.jp) announced in July 2013 that it was launching a pilot study of iPS cells for the treatment of wet AMD. The product is autologous iPS cell-derived retinal pigment epithelium cells.

[17] Columbia, Md, Nasdaq: OSIR, www.osiris.com.

[18] Melbourne, Australia, ASX: MSB, www.mesoblast.com.au.

[19] See J Embryol Exp Morphol. 1962 Dec;10:622-40. Gurdon had replaced the nucleus of a frog's egg cells with the nucleus from a mature frog cell, and the egg turned into a fully functional cloned tadpole. That showed that the mature cell nucleus could still be made pluripotent.

[20] Ann Arbor, Mi., Nasdaq: ASTM, www.aastrom.com

[21] See Aastrom press release dated 24/2/2010 and headlined *'Aastrom Reports Interim Results From Critical Limb Ischemia Trial'*

[22] See Mesoblast press release dated 15/11/2011 and headlined '*Positive Results from Phase 2 Trial of Mesoblast's Adult Stem Cell Therapy Presented at the American Heart Association Annual Meeting*'.

[23] Cleveland, Oh., Nasdaq: ATHX, www.athersys.com.

[24] See the Athersys press release dated November 4, 2011 and headlined '*Athersys Announces Publication of Phase I Data Regarding MultiStem for Treating Acute Myocardial Infarction*'.

[25] Marlborough, Ma., OTCBB: ACTC, www.advancedcell.com.

[26] See Advanced Cell press release dated 23/1/2012 and headlined '*ACT Publishes First Report of Embryonic Stem Cell (ESC)-Derived Cells Transplanted Into Patients*'

[27] See the Athersys press release dated 1/2/2012 and headlined '*Trial Results Could Provide Basis for Accelerating Clinical Development of MultiStem Orphan Drug Candidate*'. It's fair to say that, more recently Athersys had a clinical failure. A Phase II study in ulcerative colitis, results of which were made available in April 2014, saw Athersys' cells failing to show meaningful benefit.

[28] Haifa, Israel, Nasdaq: PSTI, www.pluristem.com.

[29] See the Pluristem press release dated 9/5/2012 and headlined *'Compassionate Use of Pluristem's PLX Cells Saves the Life of a Child after Bone Marrow Transplantation Failure*'.

- **Reneuron's**[30] interim results from a Phase I stroke recovery trial, May 2013[31] - patients experienced sustained reductions in neurological impairment and spasticity out to 12 months compared to baseline.

- **Like antibodies, Big Pharma has been relatively tepid in its support for the new field**. So far in stem cells there have only been three significant partnering deals of note: 1) the Osiris/Genzyme deal of November 2008; 2) the Pfizer/Athersys partnership of December 2009; and 3) and the Mesoblast/Cephalon deal of December 2010. None of these have really planted Big Pharma's flag firmly in the stem cell field:
  - Whilst large[32], the Genzyme deal was unwound in 2012 by Genzyme's acquirer, Sanofi, after a clinical failure in Type I diabetics;
  - Pfizer's arrangement with Athersys was small, at only US$6m upfront and US$105m in milestones for an IBD indication; and
  - Mesoblast's deal with Cephalon, while significant[33], took a long while to translate into clinical progress, with Cephalon's acquirer, Teva, only unveiling a Phase III heart failure trial in October 2013[34].

- **Like antibodies, the equity market has waxed hot and cold on stem cells.** We tracked the performance of a number of stem cell oriented companies over the last ten years and found that the sector had enjoyed only one major bull run in that time, beginning around the time of US President Barack Obama's election (he had campaigned for the liberalisation of Federal funding for stem cell research), and ending shortly after Mesoblast's big November 2010 partnering deal with Cephalon. Stem cells as an investment concept have been trending down since April 2011, more than halving in that time even while biotech generally boomed on Wall Street. Today the entire collection of publicly traded stem cell companies only adds to ~US$4bn[35], a mere 0.6% of the current value of the Nasdaq Biotechnology Index[36].

At the moment you can buy all the stem cell stocks for only ~US$4bn.

- **One difference between antibodies and stem cells is greater speed.** Medical knowledge is, according to one analysis, doubling every eighteen months these days versus a doubling of every seven years at the beginning of the 1980s[37]. The fact that it only took nine years to go from hESC cells to iPS cells, versus 13 years for the murine to humanised antibody transition, tells you that this Revolution is going to happen faster. Also this time around:
  - The biotech industry is more mature in terms of its understanding of how to develop products;
  - The regulators have made the decision to move faster, with the FDA, for example, only requiring a single Phase II and a single Phase III for some regenerative medicine products[38]; and
  - At least one jurisdiction is moving particularly fast on the regulatory front. In November 2013 the Japanese Diet passed amendments to Japan's Pharmaceutical Affairs Law defining new medical products which contain stem cells as 'regenerative medicine products'. This will allow the Japanese Ministry of Health to give conditional approval to such products if their safety is confirmed after Phase II. Japan's is the world's second largest drug market after the US, worth US$96bn in 2012, and nine Japanese companies are in the list of the 50 largest pharma companies in the world[39].

[30] Guildford, UK, LSE: RENE, www.reneuron.com.

[31] See the ReNeuron press release dated 28/5/2013 and headlined *'Interim data from clinical trial of ReNeuron's stem cell therapy for stroke to be presented at leading stroke conference. Longer term data continue to show good safety profile and evidence of sustained reductions in neurological impairment and spasticity'*.

[32] US$130m upfront and potentially US$1.25bn more in milestones.

[33] US$130m upfront, a US$119m equity investment by Cephalon and US$1.7bn in milestones.

[34] See NCT02032004 at www.clinicaltrials.gov.

[35] 15 May 2014 close on Nasdaq and elsewhere.

[36] US$656bn at the 15 May 2014 close on Nasdaq. That's an average of US$5.4bn per company.

[37] See Trans Am Clin Climatol Assoc. 2011; 122: 48-58.

[38] See Mesoblast market release dated 17/10/2005 and headlined *'Mesoblast outlines accelerated timetable for clinical trials and regulatory approvals'*.

[39] Astellas, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Kyowa Hakko Kirin, Mistubishi Tanabe, Otsuka, Shionogi and Takeda

- **We're almost there.** Osiris gained marketing approval for Prochymal in Canada in May 2012 and in New Zealand in June 2012 for paediatric GvHD. Mesoblast, which bought Osiris's stem cell business in 2013, has now taken this product to the FDA on the expectation that there is enough data on clinical effectiveness in serious GvHD to warrant US approval as well. This alone suggests to us that we are on the cusp of the Stem Cell Revolution. Throw in the fact that Mesoblast is now in a number of Phase III trials, while Tigenix is in a Phase III in Crohn's, and the outlook for the start of the Revolution is favourable.

Mesoblast thinks it is close to FDA approval of its stem cells in GvHD.

FIG.2: INVESTORS HAVE WAXED HOT AND COLD ON STEM CELLS

Source: Baillieu Holst[40]

- **Stem cells are going to be a bigger deal than antibodies**. So far the Antibody Revolution has reached US$60m in pa net drug sales. It is reasonable to say that stem cells could be much bigger by Year 15:
  - We noted previously that stem cells could potentially treat the underlying biology of many diseases, which involves lost or damaged tissue, whereas many current therapies deal more with symptoms;
  - Stem cells could go much further than Lucentis in AMD, Tysabri in MS and Xolair in asthma;
  - Antibodies could never treat heart failure and heart attack in the way stem cells can; and
  - Antibodies never made an impact on CNS disorders like Parkinson's, Alzheimer's, ALS, stoke and spinal cord injury, whereas stem cells have shown promise.

Stem cells have shown promise in conditions like spinal cord injury.

[40] The red line in this table is an equally-weighted index of Advanced Cell Technology, Aastrom Biosciences, Athersys, BrainStorm Cell Therapeutics, Bioheart, BioTime, NeuralStem, Cytori Therapeutics, Fibrocell Science, Cellular Dynamics, International Stem Cell, Mesoblast, NeoStem, Osiris Therapeutics, Pluristem Therapeutics, ReNeuron, Regeneus, StemCells, Tengion and Tigenix.

Cynata – The Stem Cell Revolutionary

Unlimited quantities of potent Mesenchymal Stem Cells, no hassles

- **How Cynata does it.** Cynata uses induced Pluripotent Stem cells to make large amounts of Mesenchymal Stem Cells, making it in effect a play on the two most powerful stem cell technologies that have emerged in the last decade:
  - Cynata's mesenchymoangioblasts (MCAs) are a precursor of Mesenchymal Stem Cells, which in turn are adept at differentiating into bone, cartilage, smooth muscle cells and pericytes, as well as turning down inflammation;
  - iPS cell technology allows Cynata to create large amounts of mesenchymoangioblasts, and in turn mesenchymal stem cells, for therapeutic use, thereby overcoming a key limitation of Mesenchymal Stem Cells, which is limits on expansion of those cells.
- **Cynata's MCAs are the precursor of Mesenchymal Stem Cells**. Mesenchymoangioblasts (MCAs) were discovered in the laboratory of Professor Igor Slukvin at the University of Madison-Wisconsion in 2010. The discovery was reported in a key paper in the journal Cell Stem Cell[41] entitled *A mesoderm-derived precursor for mesenchymal stem and endothelial cells*[42]*.* This paper was an important one in the stem cell field because it was the first to reveal the identity of a mesenchymal precursor in the mesoderm layer of embryos[43]. The Slukvin team called these cells 'mesenchymoangioblasts' because they represented a common precursor of mesenchymal and endothelial cells. In effect, Slukvin et. al. went about as far up the river as one can go in the search for a source for MSCs. There are three kinds of mesodermal cells in embryos: intermediate, lateral plate and paraxial. MCAs sat in the lateral plate class. That meant they would be good for turning into vasculogenic cells and cells supporting heart regeneration. Slukvin et. al. didn't publish any *in vivo* data on the efficacy of their MCA-derived MSCs, but they did show that these cells could be markedly increased in number using standard laboratory culture techniques. They didn't start to show senescence until about passage 15 and a single cell was able to expand to up to 10^{22} cells. The patent application around the Slukvin team's work became the basis for Cynata[44], which was backdoor-listed in 2013[45].
- **iPS cells technology allows large amounts of MCAs to be manufactured**. As we noted earlier, iPS cells are simply normal adult cells reprogrammed to have pluripotency. To create an iPS cell various 'transcription factors' are added to a specialised cell to reprogramme it back to the pluripotent state. Once a cell has become pluripotent it can expand in large numbers just as embryonic cells can be. When Cynata was put together to commercialise Slukvin's new cells in 2011 the decision was made to use the relatively new iPS cell technology to be able to mass-produce MCAs.
- **Cynata's iPS-MCA derived MSCs work therapeutically**. The company's various animal studies haven't been published, but Cynata has what it believes is important evidence that MCA-derived MSCs work like other MSCs. Critical Limb Ischemia is a severe blockage in the arteries of the lower extremities. MSCs have been shown to treat CLI by rebuilding blood vessels, and in the standard mouse model of CLI, Cynata's MCA-derived MSCs have been able to restore blood flow in the ischemic limbs, where mice treated with saline have ended up losing those limbs[46].

The early animal evidence has looked good to Cynata's leadership.

- **Cynata is optimising its manufacturing processes.** Cynata is now optimising a manufacturing process to make its iPS-MCA derived MSCs, after which it will go to the clinic. In February 2014 Cynata announced that it had retained a firm in Madison called

[41] A 'sub-journal' of the journal *Cell* focused on – you guessed it – stem cells.

[42] See Cell Stem Cell. 2010 Dec 3;7(6):718-29.

[43] There are the three embryonic germ layers - the endoderm, the mesoderm and the ectoderm.

[44] See *Generation of clonal mesenchymal progenitors and mesenchymal stem cell lines under serum-free conditions*, WO/2011/116117, priority date 1/2/2008. This patent application was filed by the Wisconsin Alumni Research Foundation (WARF), which holds all rights to all the intellectual property created at the University of Wisconsin, and licensed to Cynata. This patent application was granted in the US in November 2009 as No. 7,615,374. Cynata has also licensed two other WARF patent families – *Primate embryonic stem cells*, WO/1996/022362 (priority date 20/1/1995), and *Serum-free cultivation of primate embryonic stem cells*, WO/2001/066697 (priority date 9/3/2000). These two patent families cover the embryonic stem cell line from which MCAs were first derived, and a technique of expanding these cells without fetal bovine serum.

[45] The shell was Ecoquest, ASX Code ECQ.

[46] 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'*.

Waisman Biomanufacturing[47] to work on process development, scale-up and clinical-grade production of its MCA-derived MSCs. Scale-up will allow Cynata to achieve two things:

1) Conduct a single, small proof-of-concept trial, probably in Graft-versus-Host Disease, in order to demonstrate that its MCA-derived MSCs work like other MSCs do. We argue that this study has the potential to unlock considerable shareholder value because of the known power of MSCs – in this case to blunt and inflammatory response - as well as the drawbacks of MSCs; and
2) Allow other academic groups to use, under licence, Cynata's cells in various studies of their own, thereby enlarging the potential pipeline for the cells.

Mesenchymal stem cells are powerful

Mesenchymal stem cells are the reason why Mesoblast is a US$1.4bn company.

- **Menchymal stem cells a particularly hot field within the stem cell area.** One of the areas on which many companies, including Cynata, have chosen to focus is mesenchymal stem cells. The reason for this is threefold
  - **No ethical issues:** Mesenchymal stem cells are adult stem cells of known potency, so they bypassed the ethical issues associated with embryonic stem cells;
  - **The ease with which mesenchymal cells can be sourced:** Many of the cell surface markers which denote a stem cell of mesenchymal lineage are well understood[48], making it easy to extract such cells from culture. Also, such cells can be easily obtained from adipose tissue.
  - **Mid-stage clinical evidence that they work in areas of unmet medical need:** Most of this has only emerged in the last five years.

- **Mesenchymal stem cells have shown efficacy across a wide range of disease conditions,** including acute myocardial infarction[49]; osteogenesis imperfecta[50]; Graft-versus-Host Disease[51], Spinal Cord Injury[52], Multiple Sclerosis[53] and diabetes[54]. It is this efficacy, demonstrated in some cases at Phase IIb, which has allowed Mesoblast, the world's leading MSC research group, to lead the commercial stem cell sector and maintain a market capitalisation of more than US$1.4bn even when the average for its competitors is only US$100-200m.

Mesenchymal stem cells may be powerful, but they come with some drawbacks

- **Mesenchymal Stem Cells have limited expansion potential.** Because mesenchymal stem cells are rare – ie: only around 1 in 100,000 cells in human bone marrow – they have to be 'expanded' *in vitro* before they can be used clinically. That is, a starting population of stem cells obtained from a donor needs to be cultured in growth media so that the cells undergo progressive doublings. Generally this takes place through various 'passages', that is, removals of the cells from the culture vessel in order to stimulate further growth[55]. As with any nucleated cell, there are limitations in terms of population doublings before MSCs undergo 'replicative senescence', that is, lose the ability to divide altogether. However before that point there is evidence that an MSC's ability to differentiate into specialised cell types is affected. These factors suggest limits as to how many therapeutically effective stem cells an MSC batch can create[56]:

[47] See www.gmpbio.org.

[48] The International Society for Cellular Therapy has defined Mesenchymal Stem Cells as cells that are 1) plastic adherent; 2) positive for CD73, CD90 and CD105 and negative for CD34; 3) negative for CD45, CD34, CD11b, CD14, CD79a and HLA-DR and 4) able to differentiate into osteoblasts, adipocytes and chondrocytes *in vitro*. See Cytotherapy. 2006;8(4):315-7.

[49] See, for example, Circ Res. 2013 Jul 5;113(2):153-66. Epub 2013 May 8.

[50] See, for example, Transplantation. 2005 Jun 15;79(11):1607-14.

[51] See, for example, Immunol Invest. 2008;37(1):29-42.

[52] See J Vet Sci. 2007 Sep;8(3):275-82.

[53] See Cell Adh Migr. 2013 Sep-Oct;7(5):404-7. Epub 2013 Oct 30.

[54] See Clin Invest Med. 2008 Dec 1;31(6):E328-37.

[55] A passage occurs when the number of cells has filled up the vessel so that no further doublings of the cell population can take place.

[56] The result can be fewer cells than would be ideal for large patient populations. Consider Osiris' estimate of the expansion potential of its cells – '*The MSCs are selected from the bone marrow and grown in culture so that up to 10,000 doses of Prochymal can be produced from a single donor'* (source: Osiris press release dated 28/9/2012 and headlined '*Swissmedic Invokes Rapid Authorization Procedures for Prochymal Review*'). 10,000 doses from one donor may seem like a lot, but not if you're going after a market like, say, osteoarthritis, where 27 million US adults were affected in 2005 (source: CDC). This would take 2,700 donors assuming one dose was good for one patient per year in this population.

- Wagner et. al. suggested that noticeable replicative senescence for MSCs could show up after only about seven passages, achieving no more than 13 and 25 population doublings, but that the genetic changes which contribute to senescence show up from the initial passage[57];
- Many studies have suggested that only MSCs from earlier passages are really potent[58]; and
- At some point in the expansion process the differentiation potential of MSCs is affected[59], generally after passage ten.

- **MSCs face donor-to-donor and intra-population heterogeneity.** The quality of a starting batch of MSCs will vary depending on where it was sourced. Invariably you need younger donors because they yield more MSCs[60], and more effective MSCs[61].
- **It is difficult to get a 'pure' MSC population**, since there is no universally agreed upon set of markers to identify MSCs. Consequently, cells that express the markers chosen may or may not carry other markers that are relevant for the efficacy of the therapy. Put another way, we don't yet know what markers specify desirable functional attributes in stem cells, so we can't reproducibly generate functionally equivalent MSC populations[62].
- **Cynata doesn't have these issues** because, as we noted above, iPS cells can get you as many MCA cells as are needed.

Cynata is current working on industrial-scale production of its stem cells

Cynata may have completed scale-up before 2014 is out.

- **The ability to make stem cells under GMP at scale is paramount going forward.** GMP is Good Manufacturing Practice, the set of standards that have been laid down by regulators such as the FDA for the production of clinical-grade pharmaceuticals. A key challenge the stem cell sector faces at the moment is making stem cells under GMP. The drug that is given to patients has to be safe, reproducible and efficient. The starting material needs to be defined. The level of cell density in culture needs to be known. The medium used has to be worked out, and preferably it needs to be 'serum free', that is, avoid the use of fetal bovine serum. Finally, analytical methods are needed so that the phenotype, functional potential and microbiological safety of the product is consistent, and that cultured cells remain untransformed.
- **We regard scale-up as critical to value creation at Cynata.** If the company can show that it can make its cells at industrial scale under GMP then it will be in a position to be a genuine Stem Cell Revolutionary, combining the known therapeutic power of MSCs with the low cost of iPS cells. This will suggest to potential commercial partners that they can work with Cynata without having to worry about GMP issues. We understand that the scale-up process is going well and that the manufacturing process is serum-free[63]. The decision to go with Waisman Biomanufacturing on scale-up is, in our opinion, a good one because the company gets access, either directly or indirectly, to the all the stem cell expertise that has congregated in Madison over the last 15 years, including the folks at Cellular Dynamics[64].
- **There are various tricks that the Waisman people can use to get maximum yield from iPS cells**, such as choice of media (both basal and supplementary), cell seeding density, the culture flasks used and the physiochemical environment within the flasks (which involves such variables as dissolved oxygen and carbon dioxide concentrations, temperature, pH, osmolality, and the buffer system). Given this array of tools, scale-up is an engineering process rather than a scientific breakthrough in the making.

[57] See PLoS One. 2008; 3(5): 32213.

[58] See, for example, See Shock. 2006 Dec;26(6):575-80; Neurosci Lett. 2010 Mar 19;472(2):94-8. Epub 2010 Feb 1; and J Tissue Eng Regen Med. 2014 May;8(5):407-13. Epub 2012 Jun 4.

[59] See Tissue Eng. 2007 Jun;13(6):1291-8.

[60] One study found a 10-fold decrease from birth to the teenage years in terms of MSCs per nucleated bone marrow cell, and another 10-fold decrease from the teenage years to old age. See J Pathol. 2009 Jan;217(2):318-24.

[61] One recent animal study found that adipose-derived mesenchymal stem cells from younger donors were much more effective in treating MS than were cells from older donors. See Stem Cells Transl Med. 2013 Oct;2(10):797-807. Epub 2013 Sep 9.

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

[63] Avoidance of fetal bovine serum in manufacturing of biological drugs became important after the first scare over Creutzfeldt-Jakob Disease (ie 'Mad Cow' disease) in the 1990s.

[64] Cellular Dynamics (Madison, Wi., Nasdaq: ICEL, www.cellulardynamics.com) is an industrial-scale manufacturer of iPS cells. It was primarily founded by Slukvin's Madison-Wisconsin colleague Professor James Thomson, with Slukvin himself as a co-founder. Thomson is famous as the man who isolated the first human embryonic stem cell line in 1998 as well as the man who almost beat Yamanaka to the first iPS cell. By 2009 Thomson and colleagues had invented a 'footprint free' technique for reprogramming adult cells into iPS cells that involve the use of episomes to deliver six reprogramming genes (See Science. 2009 May 8;324(5928):797-801. Epub 2009 Mar 26). This provided a way to make clean iPS cells from any individual's blood, and then use them to manufacture differentiated tissue cells in industrial quality, quantity and purity.

- **We expect that Cynata will have a GMP scale-up protocol completed this year**, with, we understand, considerable progress having been made this year.

The iPS cell field is new and untried, clinically speaking – but so what?

- **iPS cells are still somewhat controversial.** The first clinical trial of an iPS cell only started last year, so the technology still has some way to go before iPS cells become 'mainstream' in the regenerative medicine field. People still have three main concerns regarding iPS cells:
  - There are concerns about the cancer-related epigenetic abnormalities that show up during reprogramming of a cell[65];
  - There are concerns that the iPS cell may retain a genetic or epigenetic 'memory' of the kind of cell that it was reprogrammed from, which would restrict its ability to differentiate into different tissue types than its tissue of origin[66]; and
  - There are concerns that iPS cells may prove to be immunogenic[67], because of differential gene expression compared to the cell of origin.
- **We do not think Cynata's use of iPS cells will hinder its reception as a company.** The speed with which the iPS field is developing, and the fact that Cynata's scale-up work is taking place in Madison, Wi., a Centre of Stem Cell Revolutionary Excellence, suggests that Cynata will not ultimately be held back by the concerns described above:
  - The techniques used to create iPS cells are being improved all the time, as evidence by the fact that oncogenes tend to be used less and less in reprogramming, and the emphasis in recent years has been on reprogramming vectors that don't insert into the genome[68]; and
  - The ease with which new cell lines can be created allows the ability to select lines from a cell line library that do not appear to have cancer, unwanted memory or immunogenicity.

The techniques used to create iPS cells are being improved all the time.

Graft-versus-Host Disease can get Cynata started in the clinic

- **GvHD is commonplace in Bone Marrow Transplant**. It is estimated that 35-50% of BMT patients will develop acute GvHD[69] (acute meaning in the first 100 days).
- **GvHD is probably becoming more common** because BMT is on the rise as a therapy for leukaemia and lymphoma – witness the fact that marrow donations facilitated by the US government's 'C.W. Bill Young Cell Transplantation Program' jumped from 2,200 to 6,300 between 2003 and 2013[70].
- **GvHD provides a good testbed for Cynata's cells, for three reasons:**
  - We know from the work of Mesoblast and others that cells of the mesenchymal lineage will work to blunt the inflammation in GvHD;
  - The relevant studies only require small patient numbers and therefore don't require long lead times; and
  - There is the potential for Orphan Drug status for the higher grades.

[65] See Cancer Res. 2010 Oct 1;70(19):7662-73. Epub 2010 Sep 14.

[66] See Nature. 2010 Sep 16;467(7313):285-90.

[67] See Nature. 2011 May 13;474(7350):212-5.

[68] Indeed, new reprogramming techniques have been developed with just this issue in mind - see Methods Mol Biol. 2013;936:295-312.

[69] See Blood. 2013 Nov 7;122(19):3365-75. Epub 2013 Sep 16.

[70] See http://bloodcell.transplant.hrsa.gov.

Valuing Cynata – How we get $0.90 per share

Our basic valuation approach

- We valued Cynata using a probability-weighted DCF approach.
- We assumed payoffs from three theoretical indications relevant to a mesenchymal precursor – osteogensis imperfecta (as a model of an Orphan orthopaedic indication), Multiple Sclerosis (inflammatory) and Acute Coronary Syndrome (cardiovascular). Obviously there can be multiple licensing transactions but we think these three would indicate the potential at this early stage.
- For each indication we modelled around 14 years of commercial exclusivity for the products followed by a negative 3-5% pa terminal growth rate. When we talk about 'Peak sales' we mean sales at year 14.
- Our WACC was 16.3% (Speculative)[71].

Risk weightings

- For each indication we used a 22% probability of success, this being the midpoint of success probabilities in the US between a small molecule in Phase I and a biological product in Phase I[72].

Commercial outcomes

- We assume the following progression of licenses and payoffs for the three theoretical indications:
  - osteogenesis imperfecta licenses in 2016-2017, for US$20-40m upfront, US$50-100m in milestones and 10-14% royalties. We model peak sales of ~US$600-$1,100m.
  - Multiple Sclerosis licenses in 2017-2018, for US$40-80m upfront, US$80-120m in milestones and 12-16% royalties. We model peak sales of ~US$1,600-$2,900m.
  - Acute Coronary Syndrome licenses in 2019-2019, for US$50-120m upfront, US$100-150m in milestones and 14-20% royalties. We model peak sales of ~US$2600-$3,400m.

Further capital

- We assume that the company raises $25m at $0.30 per share in order to move its stem cells into mid-stage clinicals.

The path to $0.90 per share

- We see a number of developments helping to re-rate Cynata to our target price:
  - Licensing for research purposes with academic groups looking into the utility of Cynata's stem cells for various indications;
  - Completion of the manufacturing scale-up process at the Waisman;
  - Engagement with the FDA and EMA as to the appropriate structuring of a proof-of-concept trial, probably in GvHD;
  - Filing of an IND or an equivalent for the trial; and
  - Data from the trial.

[71] For a relevant discount rate, we use WACCs of between 11.9% and 16.3% depending on the risk for Life Science companies. This is derived from a RFR of 4.1%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies like Cynata); and an ungeared beta of 1.1 . We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.

[72] See DiMasi et. al., Clinical Pharmacology & Therapeutics 87, 272-277 (March 2010)

Leadership

- **Dr Ross Macdonald (CEO)** brings decades of leadership and business development experience via large and small companies beginning at Amrad[73] and then at Soltec, the drug delivery unit of the specialty pharma company F.H. Faulding[74] which was ultimately sold to Connetics in 2001. Macdonald acquired his knowledge on the dermatological space at Connetics and at its acquirer, Stiefel, which had dermatologicals as its niche[75]. Subsequent to this career track, Macdonald has led start-ups including Living Cell[76] – his first exposure to cellular therapy – and Hatchtech[77], developer of a new lice control product. We think this diversity of experience, as well as a wide contact base, with serve Cynata well as it seeks to position itself as a Stem Cell Revolutionary.
- **Dr Stewart Washer (Executive Chairman)** has broad experience in drug and medical device start-ups, gained at companies such as Calzada[78] (polymer biomaterials), Phylogica[79] (peptide drugs and vaccines) and iSonea[80] (airway patency diagnostics). We see this background as helping Cynata arrive at the fastest path for commerciality.
- **Dr Kilian Kelly (VP, Product Development**) brings drug development smarts gained through stints at Amgen and AstraZeneca in Regulatory Affairs, and, significantly, at Mesoblast in Regulatory and Clinical.
- **Professor Igor Slukvin (a Cynata co-founder and a member of Scientific Advisory Board)** of the University of Wisconsin-Madison brings substantial scientific credibility to Cynata as well as considerable knowledge of the technology, from his role in inventing MCAs. Slukvin is an acknowledged authority on stem cells, having spent years developing systems to culture blood cells from human pluripotent cells. He has around 70 peer reviewed papers to his name and was a co-founder with James Thomson of the stem cell manufacturer Cellular Dynamics.
- **The Cynata board**, which includes Macdonald and Washer, has enough expertise to keep the company moving forward. Howard Digby brings technology commercialisation smarts gained at IBM, Adobe and Gartner. Peter Webse brings corporate skills.

Professor Igor Slukvin is a world leader in stem cell research

The risks

- **Scale-up.** iPS-derived MCAs may prove too difficult to produce at scale**.**
- **Clinical.** There is the risk that the envisaged Graft-versus-Host Disease trial could be difficult to recruit, or not meet its endpoints.
- **Funding.** More capital will 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.

Major shareholders

- Currently there are no substantial shareholders in Cynata.

[73] Amrad was bought by CSL in 2006 for A$108m mainly for its antibody projects. Macdonald assembled many of its early projects as VP, Business Development.

[74] This company was acquired in 2001 for US$2.4bn by Mayne Group, then primarily known as a private hospital group. Elements of the old Faulding have since shown up in two companies called Mayne Pharma, one of which was bought in 2007 by Hospira for its injectable cancer generic drug business, and another which is currently publicly traded on the ASX, code MYX.

[75] Bought by GSK in 2009 for US$2.9bn.

[76] This company works on transplantation of porcine islet cells for the treatment of diabetes in humans. Auckland, New Zealand, ASX: LCT, www.lctglobal.com.

[77] See www.hatchtech.com.au.

[78] Melbourne, Australia, ASX: CZD, www.calzada.com.au.

[79] Perth, Australia, ASX: PYC, www.phylogica.com.

[80] Melbourne, Australia, ASX: CZD, www.isoneamed.com.

Appendix I – Comparable companies

FIG.3: COMPARABLE COMPANIES TO CYNATA

Company	Location	Code	Market cap (USDm)	Web
Mesoblast	Melbourne, Australia	ASX: MSB	1,459	www.mesoblast.com.au
Osiris Therapeutics	Columbia, Md	Nasdaq: OSIR	539	www.osiris.com
NeuralStem	Rockville, Md	NYSE MKT: CUR	390	www.neuralstem.com
Pluristem Therapeutics	Haifa, Israel	Nasdaq: PSTI	234	www.pluristem.com
BioTime	Alameda, Ca.	NYSE MKT: BTX	197	www.biotimeinc.com
NeoStem	New York, NY	Nasdaq: NBS	195	www.neostem.com
Cytori Therapeutics	San Diego, Ca.	Nasdaq: CYTX	188	www.cytori.com
Cellular Dynamics	Madison, Wi.	Nasdaq: ICEL	182	www.cellulardynamics.com
Advanced Cell Technology	Santa Monica, Ca.	OTCBB: ACTC	172	www.advancedcell.com
Tigenix	Leuven, Belgium	Euronext Brussels: TIG	142	www.tigenix.com
Athersys	Cleveland, Oh.	Nasdaq: ATHX	133	www.athersys.com
Fibrocell Science	Exton, Pa.	NYSE MKT: FCSC	123	www.fibrocellscience.com
ReNeuron	Guildford, UK	LSE: RENE	90	www.reneuron.com
StemCells	Newark, Ca.	Nasdaq: STEM	81	www.stemcellsinc.com
Regeneus	Sydney, Australia	ASX: RGS	63	www.regeneus.com.au
BrainStorm Cell Therapeutics	Petah Tikvah, Israel	OTCBB: BCLI	49	www.brainstorm-cell.com
Aastrom Biosciences	Ann Arbor, Mi.	Nasdaq: ASTM	30	www.aastrom.com
International Stem Cell	Oceanside, Ca.	OTCBB: ISCO	24	www.internationalstemcell.com
Bioheart	Sunrise, Fl.	OTCBB: BHRT	10	www.bioheartinc.com
Tengion	Winston-Salem, NC	OTCBB: TNGN	4	www.tengion.com

Source: Company data[81]

- **Aastrom Biosciences.** This company's proprietary automated system allows key beneficial cell types in a cardiovascular patient's bone marrow to be expanded over a 12-day period, and then returned to the patient. The resulting product, called ixmyelocel-T, is in Phase IIb in ischemic dilated cardiomyopathy after favourable Phase IIa results. The company had been focused on Critical Limb Ischemia as its lead indication, and in Phase II had seen a statistically significant improvement in the time to first treatment failure[82], however with Phase III taking too long to enrol, the company has chosen to focus on dilated cardiomyopathy instead. In April 2014 Aastrom acquired Sanofi's small Cell Therapy and Regenerative Medicine business for US$6.5m.
- **Advanced Cell Technologies.** This company's technology allows stem cells to be sourced from embryos without embryo destruction[83]. The company has focused on ophthalmic indications for its first clinical use of its cell lines, with evidence that the cells can rebuild retinal pigment epithelium at the back of the eye. Phase I studies are proceeding in Dry AMD and in a rare disorder called in Stargardt's Macular Dystrophy[84].
- **Athersys.** This company's multipotent adult progenitor cells are in Phase II in ischemic stroke, while there are also clinical programmes ongoing in inflammatory bowel disease, stroke, GvHD, AMI and solid organ transplants. A Phase II study in ulcerative colitis showed no benefit for the treated patients in results reported in April 2014. Pfizer partnered with Athersys over the inflammatory bowel disease indication in December 2009, in a deal worth US$6m upfront and US$105m in milestones. The company generated favourable clinical data on GvHD in February 2012 and on AMI in November 2011[85].
- **Bioheart**. This company uses muscle cells sourced from a patient's thigh to repair the damage done by a heart attack. An interim analysis on the first 23 patients in a 330 patient Phase II/III trial in heart failure patients saw treated patients improving their six-minute walk distance by 91m versus 4m for placebo, however this only represented a 'trend towards significance[86]'.
- **BioTime.** This company is being built on two core technologies - a stem cell manufacturing technology called PureStem and a delivery system called HyStem. PureStem allows more

[81] 29 May close on Nasdaq and elsewhere

[82] See Mol Ther. 2012 Jun;20(6):1280-6. Epub 2012 Mar 27.

[83] *Nature*. 2006 Nov 23;444(7118):481-5. Epub 2006 Aug 23..

[84] For an early case report in each indication see Lancet. 2012 Feb 25;379(9817):713-20. Epub 2012 Jan 24.

[85] See Circ Res. 2012 Jan 20;110(2):304-11. Epub 2011 Nov 3.

[86] See Am Heart J. 2011 Oct;162(4):654-662.e1. Epub 2011 Sep 9.

than 200 purified, identifiable and scalable human cell progenitors to be sourced from embryonic stem cells, while HyStem hydrogels provide an injectable matrix that allows new tissue to grow from grafted cells. In late 2013, BioTime picked up where Geron left off in terms of Geron's pioneering embryonic stem cell programmes[87].

- **Brainstorm Cell.** This company's technology allows autologous, marrow-derived mesenchymal stem cells to be transformed so that they secrete neurotrophic factors useful in the treatment of CNS disorders such as Amyotrophic Lateral Sclerosis (ALS) and Parkinson's Disease. The company started Phase II work in ALS in 2013.
- **Cellular Dynamics.** This company, founded by James Thomson and Igor Slukvin among others, is an industrial-scale manufacturer of fully functioning human cells, mainly used for research purposes by academic labs and biotech and pharma companies. It is fair to say that Cellular Dynamics is the world leader in iPS cell development and manufacture.
- **Cytori Therapeutics.** This company's Celution System allows the extraction of 'adipose-derived regenerative cells' (ADRCs) from a patient's fat tissue, for use in treating cardiovascular disease and repairing soft tissue defects. In AMI, Celution-sourced ADRCs have reduced injury to the heart and improved the heart's pumping capacity out to 18 months[88]. In chronic ischemic heart failure, cardiac mortality has gone down and cardiac functional capacity has gone up over 18 months[89].
- **Fibrocell.** This company's technology allows the fibroblasts which form the extracellular matrix in tissue to be cultured for autologous use in patients with problems in skin or connective tissue. The company's azficel-T product is being applied in the first instance to restrictive burn scarring and vocal cord scarring.
- **International Stem Cell.** This company can make functionally pluripotent stem cells through 'parthenogenesis', involving chemical stimulation of oocytes (human egg cells) so that they divide into blastocysts from which stem cell lines can be harvested[90]. The company is working on parthenogenetic stem cells for Parkinson's Disease and liver damage as well as corneal transplant.
- **Mesoblast.** Mesoblast is the world leader in stem cell therapies in terms of having advanced products in the clinic and and multiple Phase II and III programmes ongoing. The company has been built on technology for obtaining and expanding Mesenchymal Precursor Cells from donors so that they can be stored and then used as an 'off the shelf' therapy. Mesoblast is at the regulatory stage with a therapy for acute GvHD and in Phase III in Crohn's disease, Bone Marrow Transplantation (BMT) and Heart Failure. Mesoblast's 2010 partnering deal with Cephalon helped put stem cells on the map commercially. Teva inherited this programme and is funding the Phase III study in Heart Failure.
- **NeoStem.** This company combines a contract development and manufacturing service business with various proprietary cell therapy products in development. NeoStem is a player in cell-based immunotherapy as well as in stem cells through programmes in ischemic repair and tissue regeneration. The company's AMR-001 product, which is autologous bone marrow derived cells expressing the CXCR4 receptor, has shown potential to preserve heart function after a severe heart attack - the product is currently in Phase II[91].
- **Neuralstem.** This embryonic neural stem cell company is in Phase II in ALS with its NSI-566 product, which is a formulation of human spinal cord stem cells. A second trial in ischemic stroke started in late 2013. NSI-189, a neurogenerative small molecule drug, is in Phase I for Major Depressive Disorder.
- **Osiris Therapeutics.** This company was built on technology for isolating mesenchymal stem cells, but sold its business in this area to Mesoblast in 2013 in a transaction worth up to $100 million including provision for royalty payments on future sales of products utilising the technology. The company's Grafix and Ovation three-dimensional cellular matrixes are used for acute and chronic wound care. Cartiform is a viable cartilage mesh for cartilage repair while OvationOS is a viable bone matrix.

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

[88] See the company's 8 June 2011 press release.

[89] See the company's 14 April 2014press release.

[90] See Cloning Stem Cells. 2007 Fall;9(3):432-49.

[91] See Eur Heart J. 2014 Feb 25. [Epub ahead of print]

- **Pluristem Therapeutics.** This company's PLX cells are 'mesenchymal-like' stromal cells sourced from human placentas manufactured using 3D cell expansion techniques. The company is in Phase II with a condition called Intermittent Claudication, which is crampy leg pain caused by a blockage in the femoral artery. Under a partnership with United Therapeutics[92] a Phase I trial has now commenced in pulmonary hypertension. Other Pluristem targets include Critical Limb Ischemia and repair of gluteal muscle after total hip arthroplasty.
- **Regeneus**. This company's field is adipose-derived stem cells. An autologous product called HiQCell has been used to treat human arthritic joints in clinical trials. An allogeneic product for canine osteoarthritis, called Cryoshot, is currently in field trials.
- **ReNeuron.** This company takes human cell lines and immortalises them using the c-MycER fusion protein so that therapeutic quantities of the cells can be created. They are encapsulated so as to allow them to be used allogeneically. ReNeuron is focused on neural cells in particular. A Phase I in a stroke recovery trial, delivering a neural stem cell line called CTX, saw sustained reductions in neurological impairment and spasticity in most patients. The company is now moving to Phase II in stroke recovery and to Phase I in Critical Limb Ischemia.
- **StemCells Inc.** This company is developing HuCNS-SC, an embryonic neural stem cell line. This line is in Phase I clinicals in spinal cord injury (the trial was fully recruited as at April 2014), in Pelizaeus-Merzbacher disease, a mostly-paediatric myelination disorder, and in AMD. Other indications in Alzheimer's and stroke are planned.
- **Tengion.** This company's tissue engineering platform allows the creation of new tissues and organ from a patient biopsy, through a process which harvests the cells necessary to catalyse regeneration. It then grows those cells on a bioabsorbable scaffold shaped like the organ or tissue required. The result is 'neo tissues' and 'neo organs'. The first two indications being worked on by Tengion, both in Phase I, are a 'neo-urinary conduit' for patients that have had their bladder removed, and a 'neo kidney augment' for patients with chronic kidney disease.
- **Tigenix.** This company's original product was ChrondoCelect, an autologous stem cell therapy indicated for the repair of defective knee cartilage which gained European approval in 2009. Through its 2011 acquisition of the Spanish company Cellerix, which was focused on adipose-derived mesenchymal stem cells, the company inherited two key programmes, one in the treatment of complex perianal fistulas associated with Crohn's disease, now in Phase III[93], and another in Rheumatoid Arthritis which generated favourable Phase II data in 2013.

[92] NASDAQ: UTHR, Silver Springs, Md, www.unither.com. Pluristem received US$7m upfront and will receive US$55m in milestones as well as a royalty from this June 2011 deal.

[93] For Phase I/II data see Int J Colorectal Dis. 2013 Mar;28(3):313-23. Epub 2012 Sep 29

Appendix I - A Cynata glossary

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

Angiogenic – Capable of forming blood vessels.

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

Cymerus – Cynata's core technology for manufacturing mesenchymoangioblasts for clinical use.

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

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

Fibroblasts - Cells which synthesise the extracellular matrix and collagen.

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

Good Manufacturing Practice (GMP) – The set of standards that have been laid down by regulators such as the FDA for the production of clinical-grade pharmaceuticals.

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

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

hESC – Human embryonic stem cell.

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

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

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

Mesenchymoangioblast – A mesodermal precursor identified by Vodyanik et al. in 2010.

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

MSC – Mesenchymal stem cells.

Multipotent – Capable of differentiating into in multiple cell types.

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

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

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

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

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