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Bioshares

14 September 2018
Edition 761

Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies

Companies covered: **BNO, CYP, IMU, MEB, MSB, TLX**

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - May '13)	3.1%
Year 13 (May '13 - May '14)	26.6%
Year 14 (May '14 - May '15)	23.0%
Year 15 (May '15 - May '16)	33.0%
Year 16 (May '16 - May '17)	16.8%
Year 17 (May '17 - May '18)	-7.1%
Year 18 (May '18 - current)	8.8%
Cumulative Gain	770%
Av. Annual gain (17 yrs)	17.1%

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Medibio Reports Mediocre Trial Result

Medibio (MEB: $0.089) has reported results from its pivotal 'confirmatory' study for its depression diagnostic aid. Unfortunately the results were not as confirmatory as expected, with accuracy below the previous MACH-3 study completed in August last year.

This most recent study assessed 230 patients across eight clinical sights, seeking to accurately detect major depressive disorder. The results showed that the company's algorithm, which interprets sleeping patterns, was 70% sensitive in detecting depression after four assessments, and was 71% specific. The results were not statistically significant. This is well enough below the MACH-3 study results, which showed the technology was 84% sensitive and 78% specific.

Using only the one assessment, the Medibio diagnostic aid was only 60% sensitive and 63% specific.

The technology is an improvement on reported accuracy assessments by medical practitioners of between 48% - 64%. However, to gain widespread clinical adoption as a diagnostic aid for depression, it can be argued that higher accuracy levels, above 80%, will be required.

Medibio submitted its application for regulatory approval with the FDA in July for its Medibio-DX test to be cleared for sale in the US, with the company anticipating approval in early 2019.

To increase its diagnostic's accuracy, the company would need to conduct additional trials that would likely involve improvements in the data processing algorithm.

Medibio has a market value of $18 million and held cash of $6.1 million at the end of June.

Bioshares recommendation: **Sell**

Medibio Trial Results in Depression Diagnosis

Date	Retrospective or Prospective	Nº Subjects	Sensitivity	Specificity
September 2018	Prospective (after 4th scan)	230	70%	71%
August 2017	Prospective	220	78%	84%
December 2016	Retrospective	26	80%	82%
November 2016	Retrospective	889	88%	82%

Bionomics Update – Market for Agitation Treatment in Elderly

In May this year, Bionomics (BNO: $0.53) started a clinical trial in the fourth indication for its lead drug candidate, BNC210.

It completed a Phase II study in Generalised Anxiety Disorder in 2016 with positive results, and positive results in a Phase I simulated panic trial. Results from a 193 patient study in post-traumatic stress disorder with BNC210 are to be announced this month.

And in May this year, Bionomics commenced a Phase II study in Australia to explore the effect of that compound for the treatment of agitation in the elderly in a 40 patient trial.

This week Bionomics hosted a conference call to discuss the need for a treatment for agitation in the elderly, with a key opinion leader in the field, Dr Paul Rosenberg from the Johns Hopkins University School of Medicine who is a geriatric psychiatrist that specialises in Alzheimer's disease. He is currently running trials for the treatment of Alzheimer's disease and trials to treat associated aspects of this disease, including agitation and apathy.

Dr Rosenberg said that people used to think of Alzheimer's as a pure cognitive disorder. But in recent years, it has been understood that the biology of the disease affects psychiatric symptoms. The most common of these are agitation, depression and apathy. Around 40% - 50% of patients with Alzheimer's will have one of these symptoms during the course of the disease.

One of the symptoms of agitation is excess motor activity, which can include pacing up and down or rummaging through draws, which Dr Rosenberg said many patients will spend a lot of the day doing.

Dr Rosenberg said this is not only non-productive and tiring for the patient, but it is exhaustive for care givers and there is a major need for supervision. In assisted care living, the first priority is that the door must be locked.

The other two characteristics of agitation in Alzheimer's disease are verbal aggression and physical aggression. This leads to more rapid institutionalisation of patients and has a huge economic cost. Another issue people with Alzheimer's disease have is addressing pain as they struggle to articulate the source of their discomfort, whether it is constipation of a urinary tract infection from ongoing sedation.

Distraction is the main non-pharmaceutical intervention but is often difficult to maintain. And whilst language communication falls away with disease progression, it is of interest that the appreciation of music appears to be less interrupted by disease progression.

When non-pharmaceutical interventions are insufficient or hard to implement, pharmaceutical treatments are prescribed. But currently there are no approved treatments for agitation in Alzheimer's in the US.

Current Pharmaceutical Treatments for Agitation

Dr Rosenberg said that benzodiazepines are used to treat agitation, but they resolve the issue only in the short term and have not solved the overall problem. The use of benzodiazepines has greater side effects than benefits. They also put the patient at risk of worse cognitive impairment, as well as making patients more susceptible to falls, which is an issue that troubles Dr Rosenberg the most with respect to the use of this class of drugs.

Anti-psychotics are widely used and they sometimes work. But it is hit or miss. In Europe only risperidone is approved for the treatment in patients with dementia. But the issue with anti-psychotics is that they have a mortality risk, even if it is not a large risk. Anti-convulsants can sometimes work.

Dr Rosenberg is currently studying THC (active from cannabis - dronabinol approved by the FDA for other indications) which may work, but nothing has been approved in the US. Dr Rosenberg believes the FDA is heading towards classing agitation as a separate indication.

Dr Rosenberg has also done some work with SSRI drugs. While there is some success with this class of drugs, they are only effective in 40% of cases. A number of drugs are also in clinical trials that should be reporting soon.

All of the above drugs are prescribed in the treatment of agitation in Alzheimer's disease but they do not work consistently and have adverse events. Dr Rosenberg, who spends 40% of his time treating patients, said that these are some of the most frail patients he works with, because of their combined declining physical and mental states. This makes them heavily impacted by side effects.

Dissatisfaction due to Adverse Events

A lot of the dissatisfaction with existing drugs is due to adverse events, and not the inconsistent efficacy across different patients. This has caused a major change to the prescription of anti-psychotics, because of their mortality risk. Of the drugs that are being repurposed for the treatment of agitation, Dr Rosenberg believes that SSRIs are the safest class, although do have drug interaction issues.

Agitation and other symptoms of Alzheimer's also cost a lot of money said Dr Rosenberg, both real money and virtual money (from the care giver).

Bionomics CEO Deborah Rathjen said that the company expects rapid recruitment into the Phase II agitation trial which will treat patients for only five days.

Results will be available in early 2019. It will be a blinded, placebo-controlled study. The immediate action of BNC210, as seen in the Phase II generalised anxiety trial, differentiates BNC210 from anti-psychotic drugs that need to be explored in longer 12 week trials to gain effect.

BNC210 evaluated in 430 subjects

At the end of this agitation treatment study, BNC210 will have been evaluated in nine clinical studies involving around 430 sub-

Continued over

Bioshares Model Portfolio (14 September 2018)

Company	Code	Price (current)	Price added to portfolio	Recommend-ation	Cap'n ($M)	Date added
Clinuvel Pharmaceuticals	CUV	$18.13	$4.15	Spec Hold A	$868	December 2014
Bionomics	BNO	$0.530	$0.295	Spec Buy A	$256	March 2016
Volpara Health Technologies	VHT	$0.900	$0.375	Spec Buy A	$161	June 2017
Opthea	OPT	$0.630	$0.160	Spec Buy A	$128	November 2014
Somnomed	SOM	$1.945	$0.94	Buy	$121	January 2011
Pharmaxis	PXS	$0.315	$0.260	Spec Buy A	$113	December 2016
Cogstate	CGS	$0.625	$0.515	Spec Buy A	$74	August 2018
Osprey Medical	OSP	$0.210	$0.695	Spec Hold B	$71	September 2015
AirXpanders	AXP	$0.105	$0.745	Spec Buy B	$59	September 2015
Micro-X	MX1	$0.340	$0.38	Spec Buy A	$49	May 2017
Factor Therapeutics	FTT	$0.056	$0.041	Spec Buy B	$47	March 2018
Visioneering Technologies	VTI	$0.170	$0.435	Spec Hold B	$39	March 2017
Acrux	ACR	$0.235	$0.31	Spec Buy A	$39	July 2017
Adalta	1AD	$0.280	$0.23	Spec Buy A	$33	July 2017
Rhinomed	RNO	$0.205	$0.320	Spec Buy B	$24	December 2015
Dorsavi	DVL	$0.090	$0.480	Spec Buy B	$15	December 2016
Adherium	ADR	$0.085	$0.495	Spec Buy A	$15	May 2016

Portfolio Changes – 14 September 2018

IN:
No changes

OUT:
No changes

– Bionomics cont'd

jects. It has shown a rapid effect on anxiety from a single dose, no safety issues, no effect of sedation and no addictive characteristics.

The primary endpoint in the PTSD study, which is due to readout shortly, is a decrease in PTSD symptoms as measured by the CAPS-5 assessment. Secondary endpoints include a reduction in anxiety levels and a reduction in depression.

Rathjen said that the company would need a partner to conduct the larger and longer studies for major indications such as depression, bipolar disorder, social anxiety and general anxiety. However the company would like to remain involved with progressing BNC210 for smaller markets such as PTSD and agitation.

Bionomics is capitalised at $256 million. It held cash of $25 million at the end of June.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Telix Pharmaceuticals Acquires Atlab Pharma

Telix Pharmaceuticals (TLX: $0.83) has acquired Atlab Pharma, for US$10 million in cash and scrip, to secure intellectual property (and other) assets relating to TLX-591, its prostate cancer therapeutics program

Telix is commercialising three main assets which combine the use of radiopharmaceuticals for molecular targeted therapy in oncology and diagnosis.

Its lead program is TLX-250, which is being developed to initially image kidney cancer (ccRCC) and then also as a therapeutic for kidney cancer.

Last month the company filed an application to start its Phase III imaging trial in Europe, which will seek to recruit 250 patients. That trial will be conducted also in the US and Australia. For the imaging study the company will attach the antibody to the radioisotope zirconium-89.

Its second program is with the TLX-101, which is a therapeutic being developed for the treatment of glioblastoma. The company received ethics approval this month to start a Phase I/II study in Vienna.

TLX-101 is a small molecule (iodinated phenylalanine) that targets LAT-1 which is highly expressed on this cancer. TLX-101 has been used as an imaging agent and will be used in conjunction with external radiation. Other study sites in Europe and Australia will be added.

The third asset is TLX-591, which is being developed for the treatment of prostate cancer (mCRPC). This week the company announced that it had acquired Atlab Pharma to access additional intellectual property around this asset, including the antibody huJ591. This transaction was forecast in the company's prospectus last year.

TLX-591 is an improved version of the antibody, huJ591, which has been studied in 200 patients in 12 clinical trials. It targets the prostate-specific membrane antigen (PSMA).

However huJ591 generates bone marrow toxicity at high doses. Telix's version of the antibody, TLX-591, which was licensed from Abzena, is an improved version of the original antibody, with a half-life that is one tenth of huJ591, whilst still delivering the same level of radiation to the tumour.

The reason the Atlab acquisition is important to Telix is because of surrounding IP, including the combination use of the anti-PMSA drugs with anti-androgen compounds, as well as IP around synergistic imaging of patients with treatment, which can assist in patient selection and tracking PSMA levels to coordinate therapy. Androgen deprivation therapy is known to drive PSMA levels in the early stages of treatment.

Atlab has also developed important knowledge about how lower and more frequent dosage of the antibody against PSMA can reduce side effects.

Competition to TLX-591 comes from small molecule compounds that target the same antigen, PSMA. The leading company in this area is Endocyte, which in May started a Phase III study in 750 patients with prostate cancer with its small molecule drug, PSMA-617, that is conjugated with the radioisotope lutetium-177. Telix, through its joint venture Kyzeo, is supplying imaging products for that study.

CEO of Telix Pharmaceuticals, Chris Behrenbruch, said that while small molecules against PSMA clear quickly from the body, they also target healthy tissue, such as the saliva gland and pancreas, unlike antibodies against the target. TLX-591 is conjugated to the same radioisotope, 177Lu.

Telix held cash of $42 million at the end of June. The company is capitalised at $178 million.

Bioshares recommendation: **Not formally covered**

Bioshares

Imugene Prepares for Phase IIa Study

Imugene (IMU: $0.023) announced that it has completed recruitment into its Phase 1b study with its cancer vaccine, HER-Vaxx, for patients with HER2 positive gastric cancer. Around 12 patients have been recruited, exploring three different doses of the vaccine to establish the optimum biological dose for the Phase IIa study.

Data from the study is expected towards the end of this year, with initial data showing all patients had developed internally produced antibodies against the HER2 protein which is involved with tumour growth. The other primary endpoint is to determine the optimum dose for the next phase of development. Secondary endpoints include changes in tumour size.

Once the optimum dose is established, Imugene will move into a Phase IIa study in the same indication, seeking to enrol 68 patients. The first patient in the Phase Ib study was dosed in August last year.

Imugene CEO Leslie Chong said that momentum from existing sites has increased recruitment rates into the study. The company is trialing the novel therapy in Asia and Eastern Europe where access to the HER2 antibody therapies Herceptin and Perjeta is challenging for patients.

The Phase IIa trial will be an open study, with one arm receiving HER-Vaxx plus standard-of-care chemotherapy and the second arm receiving chemotherapy alone. The company is currently arranging clinical trial sites for the study. Although recruitment has been slow in the Phase Ib trial, positive safety data to date should allow more rapid recruitment into the Phase IIa study.

Imugene has a market capitalisation of $83 million. The company held cash of around $27 million at the end of June, including $20.1 million raised in July at $0.027 per share.

Bioshares recommendation: **Not formally covered**

Bioshares

A Comparison of Two Cell Therapy Companies – Mesoblast and Cynata Therapeutics

Below we compare Mesoblast and Cynata Therapeutics. This comparison is by no means complete e.g. it does not include data on the cost of manufacturing of either company's products, which is arguably the most important information required to meaningfully compare both companies. While we compare features of each company's respective Graft versus Host Disease (GvHD) programs, other Mesoblast clinical programs have not been included. Note that Mesoblast took on the GvHD program through its acquisition of Osiris in 2013, which began its first of four GvHD trials in 2005 in the USA. Cynata commenced its GvHD trial in 2016.

	Mesoblast	**Cynata Therapeutics**
Founded	2004	2011
Listing (ASX)	2007	ECQ investment 2012; Change to CYP, 2013
Description	Developing medicines based on mesenchymal precursor cells (MPCs) and their progeny, mesenchymal stem cells (MSCs)	Developing a technology (Cymerus) which uses induced pluripotent stem cells (iPSCs) to produce a type of MSC precursor, called mesenchymoangioblast (MCA). Cymerus is a platform designed to fit the pharmaceutical product business model and deliver economies of scale.
Sourcing of cells	Allogeneic (but multiple donors)	Allogeneic (Single donor)
Manufacture	A single master cell bank can source many production runs, which in turn can produce up to thousands of doses of a given product, depending on the dose level.	A single master cell bank of iPSCs – derived from a single donor. Cymerus eliminates the need to repeatedly source, screen and qualify new donors.
Shares (M)	482.64	95.66
Share Price	$1.68	$1.265
Capitalisation ($M)	$811	$121
Accumulated Losses ($M)	US$380	$33
Top Shareholders	M&G Investment Group - 14.4% Silviu Itescu -14.3% Capital Research Global Investors - 8.8% Thorney Holdings - 5.1%	FIL - 10% Fujifilm - 8.5%
Cash (June 30, 2018) ($M)	US$38.8 million Pro forma in respect of Novaquest funding below: US$77.8 million	$12.2
Funding Facilities	**March 6, 2018**: loan and security agreement with Hercules, for a US$75.0 million non-dilutive, four-year credit facility, with first tranche of US$35.0 million at closing.	
	June 29, 2018: loan and security agreement with NovaQuest for a $40.0 million non-dilutive, eight-year term credit facility, repayable from net sales of MSC-100-IV in pediatric patients with srGVHD, in the US and other geographies (excluding Asia), with the first tranche of $30.0 million on closing.	
Comm. Revenues		
2018	US$3.6 million	
2017	US$1.4 million	
2016	US$37.9 million	
R&D Spend		
2018	US$65.9 million	$3.2 million
2017	US$58.9 million	$3.5 million
2016	US$50.1 million	$4.2 million
Employees		
2018	81	2
2017	75	2
2016	108	2

Continued over

	Mesoblast	**Cynata Therapeutics**
Clinical programs	remestemcel-L (MSC-100-IV) (acute steroid refactory GVHD) **[Phase III]** MPC-06-ID Chronic Low Back Pain **[Phase III]** MPC-150-IM (Class II-IV Chronic Heart Failure) **[Phase II]** MPC-300-IV (inflammatory conditions) **[Phase II]**	CYP-001 (GVHD) **[Phase I]** Planning for chronic limb ischemia (CLI) Phase II trial
Non-clinical programs		Has achieved positive results in pre-clinical models showing the effectiveness of Cymerus MSCs in asthma, heart attack and chronic limb ischemia (CLI). Ready to begin CLI Phase II. Is investigating Cymerus MSCs in pre-clinical models of coronary artery disease (CAD) (with UNSW), acute respiratory distress syndrome (ARDS) and diabetic wounds (with CRC for Cell Therapy Manufacturing).
Clinical Results - GvHD	**Acute steroid refactory GVHD** **Pediatric- Grade C/D** remestemcel-L (MSC-100-IV) Day 100 results demonstrated 87% survival rate for Day 28 responders to remestemcel-L treatment (33/38), and an overall survival rate of 75% (41/55)	**Acute steroid refactory GVHD** **Adults- Class II-IV** Overall Response rate by Day 100 was 93% 14 out of 15 patients showed an improvement in GvHD severity by at least one grade compared to baseline Complete Response rate by Day 100 was 53% GvHD signs and symptoms completely resolved in 8 out of 15 patients Overall survival at Day 100 was at least 87% All treated patients received two infusions of CYP-001. Patients in Cohort A received a dose level of 1 million cells per kilogram of bodyweight, up to a maximum of 100 million cells per infusion. Patients in Cohort B received 2 million cells per kg of bodyweight, up to a maximum of 200 million cells per infusion. The overall response rate by day 100 in Cohort B was six out seven (86%), and the Complete Response rate was four out of seven (57%).

Continued over

	Mesoblast	**Cynata Therapeutics**
Products on market via licensees	TEMCELL (Japan) JCR Pharmaceuticals (for GvHD)	
	Alofisel (Europe) Takeda (for fistulae)	
Active Licensee, Partners and Collaborations	**JCR Pharmaceuticals**: Rights to MSCs in two fields for the Japanese market: exclusive in conjunction with the treatment of hematological malignancies by the use of HSCs derived from peripheral blood, cord blood or bone marrow (milestones and escalating double-digit royalties in the twenties); and non-exclusive for developing assays that use liver cells for non-clinical drug screening and evaluation.	**Fujifilm** holds licence option for GvHD – will pay all costs of all further development and commercialisation plus $60m in milestone payments plus royalties if exercised. US$3m would fall due on exercise.
	Dec 2017: TiGenix, a subsidiary of **Takeda Pharmaceutical Company** Limited was granted exclusive worldwide access to certain Mesoblast's patents to support global commercialization of its adipose-derived mesenchymal stem cell product Alofisel, previously known as Cx601, for the local treatment of fistulae. Mesoblast to receive up to €20.0 million in payments, as well as single digit royalties on net sales of Alofisel	Development partnership with Royal College of Surgeons in Ireland (RCSI) to focus on demonstrating the therapeutic potential of Cynata's Cymerus mesenchymal stem cells to treat sepsis
	July 2018: Tasly Pharmaceutical Group China rights to MPC-150-IM for the treatment or prevention of chronic heart failure and MPC-25-IC for the treatment or prevention of acute myocardial infarction. Mesoblast to receive $40.0 million on closing, $25.0 million on product regulatory approvals in China, double-digit escalating royalties on net product sales and is eligible to receive six escalating milestone payments upon the product candidates reaching certain sales thresholds in China.	
	May 2018: Cartherics Pty Ltd To develop allogeneic off-the-shelf CAR-T cells armed with multiple targeting receptors for use in solid cancers	

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating "Take Some Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A

These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B

These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C

These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

Corporate Subscribers: Cogstate, Bionomics, LBT Innovations, Opthea, ResApp, Pharmaxis, Dimerix, Cyclopharm, Adalta, Medibio, Pharmaust, Actinogen Medical, Patrys

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