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Companies covered: **1AD, EX1, OPT**

	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 - May '19)	-2.3%
Year 19 (May '19 - Current)	37.8%
Cumulative Gain	976%
Av. Annual gain (18 yrs)	16.0%

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Blake Industry & Market Analysis Pty Ltd
ACN 085 334 292
PO Box 193
Richmond Vic 3121
AFS Licence No. 258032
Enquiries for *Bioshares*
Ph: (03) 9326 5382
Fax: (03) 9329 3350
Email: info[at}bioshares.com.au

David Blake - Editor/Analyst
Ph: (03) 9326 5382
Email: david[at]bioshares.com.au
Mark Pachacz - Editor/Analyst
Ph: 0403 850 425
Email: mark[at]bioshares.com.au

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Bioshares

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Extract from Bioshares –

Exopharm – Developing a Proprietary Method for Purifying Exosomes

Exopharm (EX1: $0.37) has developed a novel method for the purification of exosomes, which are small extra-cellular vesicles (30-150 nanometres) which have a lipid bilayer containing proteins. Exosomes also carry nucleic acids (DNA, RNA, mRNA and miRNA). Exosomes are secreted by many cells in the body, including adult stem cells.

Exosomes can be regarded as intercellular messengers capable of delivering functional molecules (proteins or DNA etc) or other cells which are capable of generating functional changes at target tissues. An important feature of these exosomes is that they are non-immunogenic, which means they have the potential to be used as an allogeneic therapy.

Exopharm was established in 2013 to resolve manufacturing challenges needed to make exosomes amenable to scalable, pharmaceutical-grade manufacturing processes. In doing so, a related goal of creating a proprietary position from which to create value for investors and the inventors of the technology was also formed.

Exopharm listed in 2018, raising $7 million at 20 cps, which followed a pre-IPO round of $1.4 million. The company has recently raised $4.4 million and has an SPP underway which could potentially raise $2.8 million. The company now employs 19 people, up from two in March 2018.

Exopharm's business plan is to establish manufacturing partnerships for its technology and develop prototype products for licensing to partners.

Rapid Growth in Exosome Research

Exosome research has been driven in part by the research into mesenchymal stem cell therapy. The hypothesis that mesenchymal stem cells exert their (positive) effects through exosomes has become increasingly recognised. This contrasts with the hypothesis that stem cells directly differentiate cells for integration in target tissues as well as replace cells and stimulate tissue repair and growth.

The field of exosome research and its potential as a source of new therapies and diagnostic products is growing, with Pubmed citations for the search term 'exosome', increasing from 287 in 2011 to 2,197 in 2018 and 1,877 this year to date.

However, the number of exosome therapies being investigated in clinical studies is very small. The MD Anderson Cancer Center is sponsoring a 28 patient, Phase I study of mesenchymal-stromal cell-derived exosomes engineered to carry KrasG12 siRNA, for the treatment of metastatic pancreatic cancer patients with the KrasG12 mutation.

The Isfahan University of Medical Sciences is undertaking a trial of allogeneic mesenchymal stem cell-derived exosomes in patients with acute ischaemic stroke.

Exosome therapeutic companies include Codiak Biosciences, Evox Therapeutics, ExCoBio

Cont'd over

and Exogenus Therapeutics, with Codiak possibly being the most advanced of these companies.

Codiak was seeking a Nasdaq listing to raise US$86 million, but withdraw its plans in early July.

Codiak relies on isolating exosomes by using affinity purification techniques (i.e. chromatography) of various proteins that are enriched on their surface. These include: prostaglandin F2 receptor negative regulator (PTGFRN); basigin (BSG); immunoglobulin superfamily member 2 (IGSF2); immunoglobulin superfamily member 3 (IGSF3); immunoglobulin superfamily member 8 (IGSF8); integrin beta-1 (ITGB1); integrin alpha-4 (ITGA4); 4F2 cell-surface antigen heavy chain (SLC3A2); and a class of ATP transporter proteins. *(Source: US patent 10,195,290, Preparation of therapeutic exosomes using membrane proteins)*

Codiak is using proteins such as PTGFRN as a scaffold to which other functional proteins can be attached (e.g. IL-12) creating either fusion proteins, or surface-engineered exosomes, which both can be produced in cell culture manufacturing systems.

In its 2019 IPO filing (S-1), Codiak stated that it had "produced and purified exosomes from cell culture processes up to 250L and have purified exosomes from these cultures using scalable, proprietary chromatography-based methods. The scalable methods have produced exosomes with comparable identity, purity, and functional properties as exosomes purified using unscalable, but high-purity methods, such as ultracentrifugation-based approaches."

The field of exosome therapeutics product development has been challenged by difficulties attached to the extraction and purification of exosomes. This is why there has been such a low number of therapies in development.

Exopharm's patent application (WO 2018/112557) describes these problems:

- Ultracentrifugation is limited in terms of scalability, complexity and the tendency for extracellular vesicles to aggregate.
- Polymer assisted precipitation requires the simultaneous precipitation of protein contaminants as well as the removal of the polymers after precipitation.
- Immunoaffinity capture is limited to the sub-populations of exosomes that can be captured using antibodies, by the lack of a standard marker for exosomes, in addition to the problem of how to remove the antibody that becomes bound to the exosome.
- Tangential flow separation is limited by the requirement to include additional steps to further purify exosomes.

Exopharm's Novel Purification Technology

Exopharm has developed a method for purifying exosomes using affinity chromatography, a widely used method for separating the components of biological liquids.

The method takes advantage of a synthetic polymer substrate that has an array of exosome binding ligands on its surface.

The novelty of the design of the substrate is the degree of separation of the binding ligands are separated, preferably 3.5 to 6 angstroms or 4 to 6 angstroms. The choice of a synthetic polymer overcomes the issue of variability (heterogeneity) that can exist with naturally occurring polymers.

The benefit of the invention is a process that is very specific for exosomes, with other cellular components disregarded, as well as the process being more gentle when compared to centrifuge methods.

Exopharm appears to have little competition as a developer of superior, scalable methods for purifying exosomes. As discussed above, Codiak has developed a scalable, proprietary chromatography-based method. Another rival approach has been developed by researchers at the US National Cancer Institute (WO 2019/133842 A1). This method uses a size exclusion step in conjunction with a resin which comprises an affinity ligand. How scalable this approach is not yet known.

Geelong-based VivaZome Therapeutics, along with Seerpharma and La Trobe University, received $2.2 million in CRC funding in 2017 to develop an advanced manufacturing process for exosomes.

Clinical Studies

Exopharm is seeking to validate its technology through several clinical trials, one using exosomes derived from platelets (Plexaris), the others using exosomes derived from stem cells (exomere). These small studies would aim to demonstrate safety and efficacy.

The Plexaris study recently received ethics approval for a wound healing trial in 20 patients, and will specifically look at wound closure and scarring outcomes.

In addition to wound healing, the company has identified dry age-related macular degeneration and osteo-arthritis as diseases for future clinical studies.

Plexaris is an autologous product, whereas exomere is an allogeneic product.

Summary

Exopharm's proprietary exosome purification technology has the potential to catalyse the field of exosome therapy, once it validates the technology with several proof-of-technology products. The value creation opportunities may be numerous and significant.

Exopharm is capitalised at $34 million.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

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 Health, Pharmaxis, Dimerix, Adalta, Actinogen Medical, Patrys, Cyclopharm, Emvision, Antisense Therapeutics, Heramed, Imugene