PITT STREET RESEARCH

Exopharm Ltd

Share Price: A$0.66

Game-changing potential in drug delivery

Exopharm is a Melbourne-based clinical-stage company developing exosome-based medicines. Extracellular vesicles (EVs) such as exosomes are tiny bubbles secreted naturally from almost all cells, where those EVs traffic molecules from cells of one tissue to another to regulate vital cellular processes. A lot of exosome research has shown that exosomes from adult stem cells provide the regenerative effect of adult stem cells in animals. However, in the last couple of years exosomes have started to be thought of more as drug delivery tools for precision medicine. Exopharm is now a key part of that trend. With its foundation LEAP technology, Exopharm arguably has the world's best tools for manufacturing exosomes. Until recently it was developing various 'naïve EVs' (NEVs) with regenerative applications. And it has now pivoted into drug delivery with new technologies for the creation of 'engineered EVs' (EEVs) that would allow exquisite targeting of therapeutic agents.

Pharma is now betting on exosomes for drug delivery

We believe Exopharm has the capability to create a high number of EEV variants suitable for hard-to-treat diseases. Further, the EEV space is garnering attention from big pharmaceutical players and Exopharm is in a strong position to enter into lucrative partnerships. Recent partnering deals by exosome pioneers Codiak Biosciences and Evox Therapeutics, with milestones in the billions, underly the present opportunity Exopharm is going after.

LEAP makes Exopharm a key player

One of the key challenges hindering the commercialisation of exosome-based medicines is purification of sufficient quantities of exosomes from biological materials. This is where Exopharm's LEAP technology comes into play. With Exopharm now actively marketing LEAP we see considerable value from licensing and other commercial opportunities.

Valuation range of A$2.80 – $4.71 per share

Using a probability-weighted DCF methodology, we value Exopharm at $2.80 per share base case and $4.71 per share bull case. On Exopharm's EEV pipeline products, we attempt to model payoffs for Fortrexo, Cognevo and Plexodox. In addition, we also model licensing revenues as a result of the out-license of the LEAP technology. Please see our valuation chapter below for more detail. Key risks include: 1) clinical risk; 2) timing risk; and 3) funding risk.

ASX: EX1

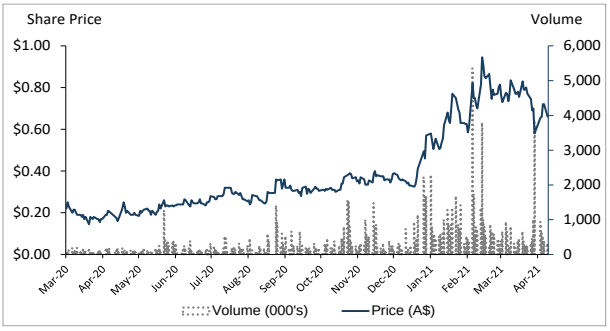
Sector: Healthcare

13 April 2021

Market Cap. (A$ m)	92.0
# shares outstanding (m)	139.4
# shares fully diluted (m)	143.9
Market Cap Ful. Dil. (A$ m)	95.0
Free Float	60.9%
52-week high/low (A$)	0.96 / 0.16
Avg. 12M daily volume ('1000)	400.8
Website	www.exopharm.com

Source: Company, Pitt Street Research

Share price (A$) and avg. daily volume (k, r.h.s.)



Source: Refinitiv Eikon, Pitt Street Research

Valuation metrics	
Probability-weighted DCF (A$)	2.80 – 4.71
Discount rate	14.4%
Assumed terminal growth rate	None

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Introducing Exopharm, ASX: EX1

Exopharm is a Melbourne-based clinical-stage company developing exosome-based medicines. Exosomes are extracellular vesicles (EV), that is, tiny bubbles secreted naturally from almost all cells, where those EVs traffic molecules from one cell to another to regulate vital cellular processes. A lot of exosome research has shown that exosomes from adult stem cells provide the regenerative effect of adult stem cells in animals. The cellular trafficking function of exosomes led to many research groups to explore their use as drug delivery tools for precision medicine, and in the last couple of years that research interest has gained momentum. Exopharm is now a key player in the field of extracellular vesicles as drug delivery agents. With its foundation LEAP technology, it arguably has the world's best tools for manufacturing exosomes. Until recently it was developing various 'naïve EVs' (NEVs) with regenerative medicine applications. And it has now pivoted into drug delivery with new technologies for the creation of 'engineered EVs' (EEVs) that can allow exquisite targeting of therapeutic agents and improved loading.

What is an exosome? Exosomes are a type of extracellular vesicle (EV) or tiny bubble secreted naturally by practically all cells. These exosomes are nano-sized (30–100 nanometers) and contain proteins, DNA and RNA of the cells that discharge them. These EVs are taken up by distant cells, where they can affect cell function and behaviour. Exosomes therefore act as a key communications intermediary in delivering a distinct set of lipids, proteins and nucleic acids across cells.

Why have exosomes been thought of as the 'evolution' of regenerative medicine? For many years adult stem cells such as Mesenchymal Stem Cells have been investigated as promising agents to heal human tissue. At first the general line of inquiry related to the apparent ability to differentiate and proliferate into the type of tissue needed[1]. Later the focus was on the known anti-inflammatory properties of such cells by their secretions[2]. Since stem cells were known to secrete various growth factors, cytokines and exosomes, it was assumed that the long-lasting therapeutic power of stem cells lay in exosomes because of their known role in intracellular signalling with nucleic acids and long-lasting changes in the recipient cell[3]. Exopharm was founded with this approach in mind and this approach guided its original work in Naïve EVs.

Exosomes can get drugs through the cell membrane to better hit internal targets of interest

Why are exosomes now being looked at more as drug delivery agents? One of the emerging big themes in 21st Century medicine is the targeting of intracellular targets that are difficult to reach with conventional drugs, be they large or small molecules or nucleic acids (e.g. siRNA, mRNA). Since exosomes are designed by nature to pass through cell membranes, the last few years have seen various research groups experiments with their use as drug delivery vehicles, with some success. That success has in turn promoted some large partnering deals. So while exosomes remain interesting as a regenerative medicine play, pharma companies are increasingly starting to see the potential of EVs as drug delivery tools. Unlike other delivery means, exosomes are not seen as 'foreign' and can act as a 'Trojan horse' to protect a drug as it travels from the site of administration to inside the target cell. The body metabolises or clears many drugs unless the drug is protected – and exosomes offer that protection.

[1] Wiley Interdiscip Rev Syst Biol Med . Jul-Aug 2009;1(1):97-106
[2] Front Immunol. 2019; 10: 1191.
[3] Drug Des Devel Ther . 2019 Oct 24;13:3693-3704.

The more potent a drug the more important it is to deliver the drug selectively to diseased cells only – e.g. cancer cells. Exosomes can be 'engineered' to target certain cell types.

What's the difference between Exopharm's EEVs and its NEVs? Exopharm has worked on two types of EVs that have applications in human therapeutics – Engineered EVs (EEVs) and Naïve EVs (NEVs). While the EEVs act as tools to deliver active drugs as precision medicines to treat infectious diseases, neurological diseases and cancer, the NEVs are unaltered EVs from stem cells and platelets with applications in regenerative medicine. NEVs were Exopharm's first attempt at showing EVs could work as medicine. EEVs are now the main focus of Exopharm's from a pipeline sense as it pivots into drug delivery.

Exopharm can help pharmaceutical companies unlock value in stranded assets. The company provides a full spectrum of solutions to pharmaceutical companies, from platform to product. Through its EEV programme, Exopharm plans to help pharmaceutical companies unlock value of drugs that have demonstrated potential in laboratories but have been shelved due to delivery issues.

LEAP, LOAD and EVPS technologies provide competitive edge and additional revenue streams

Unique proprietary technologies lend Exopharm a significant edge. Taking EV medicines forward into larger clinical trials and commercial use demands a cost-effective and scalable purification technology. Exopharm's 100% owned purification technology, called LEAP, has demonstrated the ability to overcome challenges regarding scalability and processing costs and is the subject of patent applications in 12 jurisdictions. LEAP is fully compatible with GMP-compliant bioprocessing manufacturing equipment to provide access to large quantities of high-purity EVs for research and clinical use, and can be scaled for commercial manufacturing of EEV and NEV products. In addition, Exopharm has exclusive international rights to two technologies called LOAD and EVPS. While LOAD helps in the insertion of custom nucleic acids into EVs, EVPS enables the attachment of custom proteins to the surface of EVs. These technologies underpin Exopharm's EEV programme with the potential for deal-based revenue and licensing fees.

Recent advances in EV medicines are a driving force for Exopharm. The COVID-19 vaccines by Moderna and Pfizer deliver RNA through Lipid Nanoparticles (LNPs), which are essentially artificial EVs. However, LNPs have delivery issues that Exopharm's EVs can overcome. Adoption of EVs to deliver nucleic acid medicines by pharmaceutical companies provide a growth opportunity to Exopharm. Through its novel proprietary technologies such as LEAP, Exopharm can help pharmaceutical companies scale their EV medicines beyond phase II trials and into broad use.

Why Exopharm is currently undervalued? We believe that given its proprietary technologies and significant opportunities in key target markets, the business is currently undervalued by investors. In our view, a re-rating is possible, driven by a) the emerging use of EVs as a drug delivery technology; b) positive news on partnerships with pharmaceutical companies; and c) licensing deals with biomanufacturing/bioprocessing companies.

Nine reasons to look at Exopharm

1) **Exopharm's technical know-how and manufacturing capability to develop EEVs** positions the company at a crucial point in time to capitalise on the rising interest in exosomes and their role in precision medicine.
2) **EEVs offer a targeted delivery solution** for diseases that were earlier untreatable due to delivery issues. Thus, Exopharm is able to provide big pharmaceutical companies with solutions to delivery problems of their key drug candidates.
3) **Exopharm has started to build its pipeline of EEV products**, starting with Fortrexo CoV, a potential prophylactic for COVID-19 infection, and Cognevo for brain diseases.
4) **The company has a strong portfolio of novel proprietary technologies – LEAP, LOAD and EVPS** – which underpin its EEV programme. One of the major challenges in using exosomes in medicines is the purification of biological materials at a commercial scale, which Exopharm is able to provide via its LEAP technology.
5) **LEAP provides a cost-effective way to commercialise drugs in the clinical stage.** The technology has demonstrated its ability to produce a billion EVs for just A$10. The company plans to further bring down this cost to less than 5 cents per billion EVs. Given that cost is an important component for determining the feasibility of emerging exosome applications, we believe that LEAP can act as an important driver for growth.
6) **The company's robust position in the EEV space prepares the ground for lucrative partnership opportunities** given that this space has witnessed several high-value partnerships involving big pharmaceutical companies in the recent past by Codiak Biosciences (Nasdaq: CDK) and Evox Therapeutics, where the total values have been reported as above US$1bn.
7) **The company's business model provides multiple revenue generation channels** – licensing its technology for commercial use, transferring its technical know-how to Pharma/biotech companies, selling LEAP columns to researchers and sale of its own EEV products.
8) **Exopharm boasts an experienced management team** with significant technical and industry knowledge. Dr. Ian Dixon, the CEO and founder, is the driving force behind some of Exopharm's proprietary technologies and has a track record of successfully commercialising medical technologies.
9) **We believe Exopharm is undervalued** at its current market value. Our valuation using a probability-weighted DCF methodology yields A$2.80 per share base case and A$4.71 per share bull case, representing significant upside to the current share price.

Exopharm's massive opportunity in Engineered EVs

Over the past three years there have been five 'billion dollar deals' deals done by less than a handful of Exopharm's competitors in the Engineered EV space

Engineered EVs have taken over from Naïve EVs as Exopharm's main focus. Targeted and non-targeted Engineered EVs are seen by the biopharma industry as a highly differentiated platform with the potential to enhance tissue delivery for a variety of payloads like mRNA and proteins – part of the global market for drug delivery systems – growing at a compound annual growth rate (CAGR) of 5% and valued at perhaps US$200bn currently. For some medicines, EVs are seen as an alternative and superior means for delivery in the body – alongside technologies such as Lipid Nanoparticles (LNP), cell penetrating peptides, viral vectors, liposomes etc. Over the past three years there have been five 'billion dollar deals' deals done by less than a handful of Exopharm's competitors in the Engineered EV space, each with significant cash upfront payments of around US$50m each and each based upon preclinical (i.e. not in clinical trials yet) Engineered EV products.

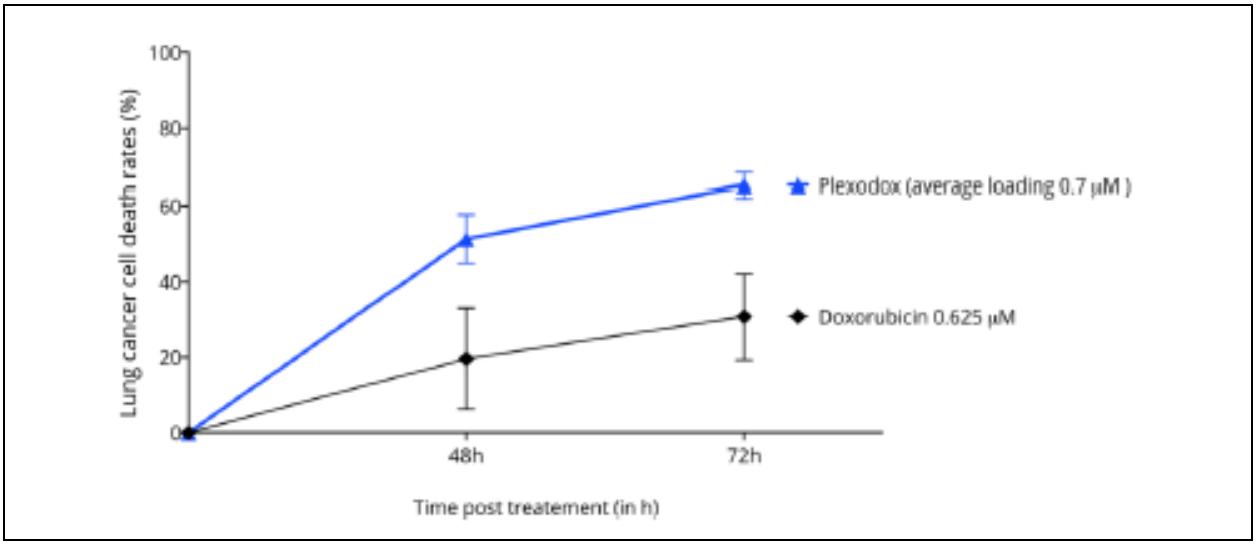
The humble exosome can make a great drug delivery tool. By 2018, when Exopharm was being taken public, it was well appreciated in the exosome field that naïve Extracellular Vesicles could potentially be useful not just in regenerative medicine, but also in drug delivery[4]. Not only are exosomes tiny, and therefore able to penetrate deep tissue[5], they also have long circulation times[6], the ability to slip through cell walls due to their membranous origins[7] and low immunogenicity[8]. All it takes to make exosomes the ideal drug delivery tool is the ability to load the drug of interest into the exosome, and the ability to engineer the exosome so that it naturally targets the cell of therapeutic interest. From around 2011 the literature around exosomes as drug delivery vehicles had been growing[9], and by 2018 both these problems – the cargo-loading and the targeting – had potential solutions, opening up the field of Engineered Extracellular Vesicles or EEVs.

EEVs are being tested as delivery vehicles for active cargo drugs to treat cancer, and infectious and neurological diseases

Exopharm's Plexodox product provides a basic illustration of how exosomes can be engineered as drug delivery vehicles. Plexodox, created in 2019, is Exopharm's EV carrier for the chemotherapy drug doxorubicin. A drug like doxorubicin can be loaded into exosomes by simply treating relevant cells in culture[10] or already-isolated exosomes[11], with doxorubicin. Exopharm's Plexodox product has been shown, *in vitro*, to be more potent than doxorubicin alone (Figure 1). Doxorubicin is a widely used drug in chemotherapy but can cause adverse effects such as myelosuppression, cardiotoxicity, alopecia, nausea and vomiting. Therefore, its dosage is limited to contain toxicity and prevent harm to healthy cells. Plexodox offers a special targeting mechanism that enables a higher dosage of the drug without the side effects.

[4] For a good review paper from about that time see J Nanobiotechnology. 2018 Oct 16;16(1):81.
[5] Adv Drug Deliv Rev. 2016 Nov 15;106(Pt A):148-156. Epub 2016 Feb 27.
[6] J Biomed Nanotechnol. 2016 May;12(5):1101-14.
[7] Wiley Interdiscip Rev Nanomed Nanobiotechnol. Jul-Aug 2012;4(4):458-67. Epub 2012 May 30.
[8] Cell Mol Immunol . 2020 Apr;17(4):323-334. Epub 2020 Mar 19.
[9] In that year a team at Oxford proved exosomes' potential as drug carriers in a mouse model of Parkinson's disease – see Nat Biotechnol. 2011 Apr;29(4):341-5. Epub 2011 Mar 20.
[10] Int J Hyperthermia. 2015;31(5):498-506. Epub 2015 May 8.
[11] Int J Nanomedicine . 2019 Nov 1;14:8603-8610.

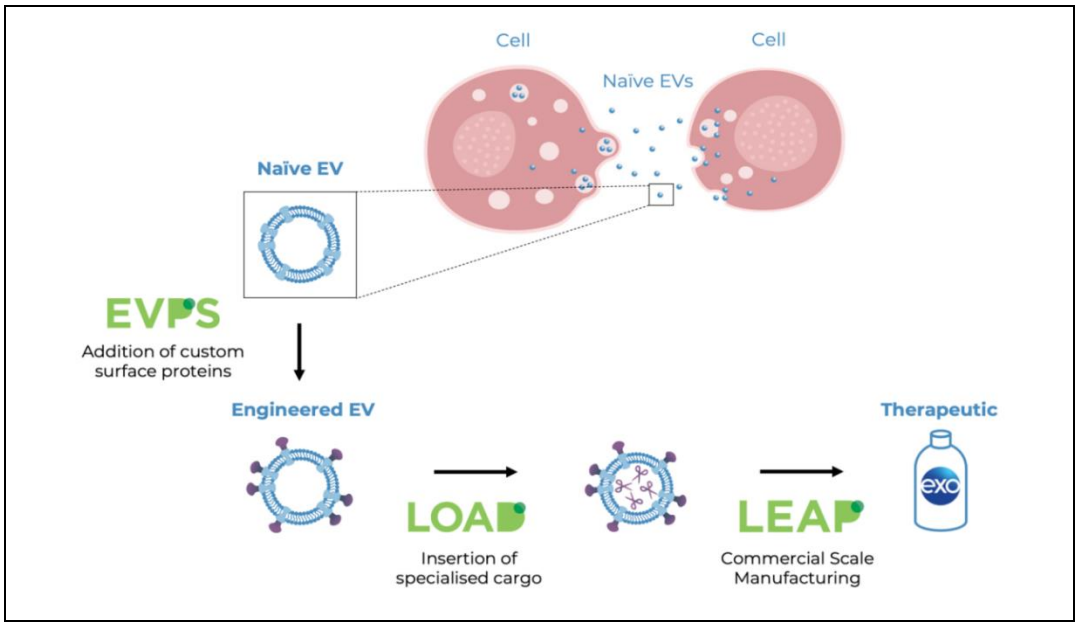
Figure 1: Plexodox increases doxorubicin's potency



Source: Company

The need for LEAP as a vital tool to manufacture therapies cost effectively. One issue that had been holding the exosome field back, with the potential to hinder its transition to being a drug delivery tool of choice, is the issue of how to make enough EV product cost-effectively. As we explain below, Exopharm believes with its LEAP technology that it has solved this problem, making it easy to potential partners to work with Exopharm on Engineered EVs. Moreover by making LEAP available for other EV developers to license, the company may potentially own the industry standard for EV manufacturing.

Figure 2: Exopharm's NEV to EEV transformation



Source: Company

Exopharm unveiled its core Engineered EV technologies in June 2020

Exopharm's mid-2020 EEV pivot was sudden. In June 2020 the company simultaneously announced the in-licensing of what it considered the ideal combination of technologies for EV engineering – LOAD for the loading of RNA-based drug payload into the exosome, and EVPS for the exosome targeting[12]. In each case Exopharm took exclusive global rights.

- **LOAD was developed in the laboratory of Dr Juliane Nguyen at the University at Buffalo**[13] in upstate New York. The technology has its origins in the observation that cells will often sort non-coding RNA into exosomes[14], as well as messenger RNAs to make proteins and microRNAs to regulate the expression of genes. The Nguyen laboratory used the tools of bioinformatics to select RNA sequences that specifically package into pure exosome populations in multiple different cell types. They called their sequences 'EXO-Codes' and, by attaching their EXO-Codes to drug cargo – in this case strings of RNA that would be therapeutically useful – they were able to get that therapeutic RNA into the cells as well. In some cases the loading of the therapeutic RNA was enhanced by EXO-Codes up to 100-fold. The University of Buffalo filed for patent protection over this approach in 2018[15]. Exopharm advanced EXO-Code technology into a process it refers to as LOAD, referring to the fact that it is Leveraging Oligonucleotides to Alter Diseases.
- **EVPS was developed in the laboratory of Dr Bill Lu at Santa Clara University** in Santa Clara, California. EVPS is based on VSV-G, a glycoprotein from a particular virus that mostly targets animals and insects[16]. Many viruses have glycoproteins that help them enter cells, and the VSV-G glycoprotein does this by spanning the membrane of that cell. Lu and colleagues found that when they fused VSV-G to a 'reporter' protein[17], this combination would incorporate into exosomes, and that such exosomes would subsequently slip in to multiple recipient cell types. The beauty of this system is that the portion of VSV-G that sticks out of the EV (so-called 'ectodomain') can be exchanged for a targeting protein of choice, thereby offering the opportunity to control what kinds of cells the EV would go for[18]. Santa Clara University filed for patent protection over this approach in 2017, with the first granted patent being issued in 2020[19]. In 2019 the Lu lab had shown that its VSV-G technology allowed delivery of the correct enzyme that would treat Gaucher disease[20]. Exopharm called the VSV-G technology EVPS because it was based on an Extracellular Vesicle Positioning System.
- **Now add LEAP to LOAD and EVPS**. The ability of LEAP to be able to mass-produce EVs suggests the potential high value Engineered EVs at low cost.

Exopharm is both a 'platform technology' and 'product company' with the potential to ride the wave up as Engineered EVs become a part of the biopharmaceutical industry. Exopharm sees that near-term platform technology partnering revenue will start to come in from two streams:

- Multiple deals from out-licensing its LEAP and other bioprocessing technologies and know-how to allow others to purify EVs; and

[12] See the ASX market release dated 12 June 2020 and headlined *'Added Intellectual Property empowers Exopharm's engineered exosome pipeline'.*
[13] Nguyen is now an Associate Professor at the University of North Carolina at Chapel Hill.
[14] Noncoding RNA Res. 2016 Oct;1(1):3-11. Epub 2016 Jul 1.
[15] See WO/2018/209182, *Compositions and methods for loading extracellular vesicles with chemical and biological agents/molecules*, priority date 11 May 2017, invented by Juliane Nguyen and Scott Ferguson.
[16] The Vesicular Stomatitis Virus, these days called the Indiana Vesiculovirus, is a virus similar to Rabies that can infect insects, cattle, horses and pigs.
[17] Such as Green Fluorescent Protein, so called because of its bright green fluorescence when exposed to light in the blue to ultraviolet range.
[18] Int J Nanomedicine. 2017 Apr 18;12:3153-3170.
[19] See US2019/0015333, *Engineered exosomes for the delivery of bioactive cargo using transmembrane VSV-G*, priority date 12 July 2027, invented by Biao Lu, Conary Meyer, Joseph Losacco and Zachary Stickney. US Patent No. 10,617,768 was granted in April 2020 and US Patent No. 10,758,486 in September 2020
[20] Sci Rep. 2019; 9: 17274.

- Collaborations with bioprocessing companies to create EV-specific product and service offerings.

Exopharm is commercialising its Engineered EV products in two models:

- Enabling biopharma to improve delivery of their drug candidates
- Designing and testing new Engineered EV medicines themselves. Some Engineered EV products will be partnered/out-licensed as preclinical assets (i.e. before clinical trials are run), whilst other Engineered EV products will be taken by Exopharm into clinical trials and towards registration before partnering.

Whilst early revenue can come from enabling the success of others, substantial future upside can come from Exopharm's own products that it designs, makes, owns and tests under its own investment.

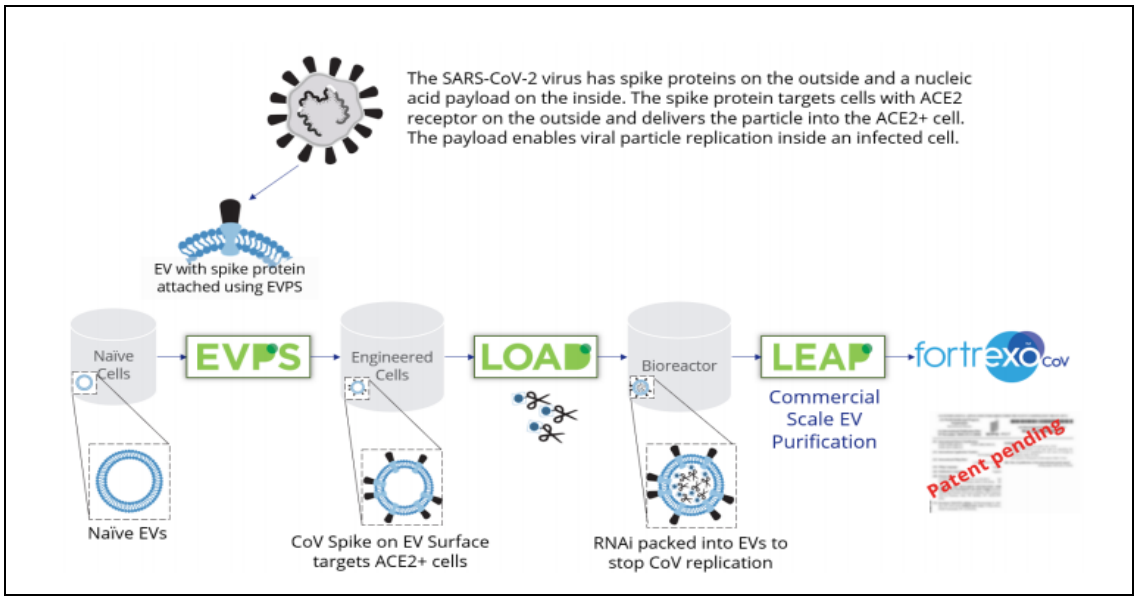
Exopharm's Engineered EV for Covid-19 infection was developed in-house

Fortrexo-CoV: An anti-COVID agent as a prototype Engineered EV. Given that the world was in the middle of a Coronavirus Pandemic in 2020, it seemed natural for Exopharm to use its newly in-licensed LOAD and EVPS technologies to create a COVID-19 therapeutic. The result was Fortrexo-CoV, and the product was designed (and patented) in-house by Exopharm's own team in Melbourne. Although it is not a vaccine, Fortrexo-CoV is not unlike the Pfizer and Moderna vaccines currently being deployed around the world in that those vaccines deliver RNA from the virus wrapped in artificial Lipid Nanoparticles (LNPs). In some ways we argue that it's better than those vaccines:

- Fortrexo-CoV is 'smarter', as it targets cells with the ACE2 receptor, as does SARS-2[21], using the 'Spike' protein, which is the glycoprotein that allows SARS-2 to get into cells via that receptor. Exopharm's scientists used the EVPS technology to fuse the Spike protein to the outside of the natural (non-immunogenic) Lipid Nanoparticles (i.e. the EVs from human cells and purified using LEAP). The manufacture of the Fortrexo-CoV EEVs also uses the Exopharm LOAD technology to more heavily 'load' designer siRNA (silencing RNA) into the EVs that 'silences' or blocks viral replication.
- When given to a patient, the Fortrexo-CoV will preferentially target cells that are prone to SARS-2 infection (ACE2 positive cells) and deliver the antiviral siRNA to 'silence' or block viral replication inside cell. Blocking viral replication inside vulnerable cells would decrease the viral load and then end the infection without relying upon a host immune response or a vaccine.
- We know that vaccines are vulnerable to virus mutation and are more effective in healthy young people than older and less healthy people, meaning that it is not fully protective for those most vulnerable. Fortrexo-CoV has been designed to overcome these limitations and could be designed to 'silence' any variant of SARS-2 or indeed any virus.
- Exopharm is building *in vitro* evidence that Fortrexo-CoV would be an effective therapeutic and is progressing toward animal studies and then potentially clinical trials. But Fortrexo can be rapidly designed against any existing (e.g. EBV) or emerging virus (e.g. SARS-3).

[21] COVID-19's 'correct name' is SARS-CoV-2

Figure 3: SARS-CoV-2 and Fortrexo



Source: Company

Engineered EVs can make great drug delivery vehicles for brain disorders

Cognevo: Engineered EVs for treating neurological diseases. Whilst many important neurological conditions remain to be treated, the blood–brain barrier (BBB) prevents the delivery of most pharmaceuticals into the Central Nervous System/brain[22]. Treating neurological conditions such as MS, ALS, Parkinson's is a natural area for which Engineered EVs could be deployed given the ability of exosomes to slip through the blood-brain barrier. Indeed, already two big deals have been done by pharma companies over the past 36 months to enable development of EEVs to treat CNS conditions.

- Exopharm's partnering discussions have highlighted certain CNS cell types of interest and certain 'cargos', so Exopharm's scientists are creating various Cognevo Engineered EVs to address these needs – harnessing the power of EVPS and LOAD technologies to cross the blood brain barrier, target specific CNS cell types and deliver nucleic acid medicines (e.g. mRNA, miRNA) into cells.
- Cognevo EEVs can be designed and made in many variations to meet partnering needs and new product opportunities. With EVPS the external EVPS protein can target surface proteins on neurons and other cellular elements of the CNS such as glial cells. With the LOAD technology Exopharm can load into EVs higher concentrations of nucleic acid medicines such as mRNA or miRNA. Exopharm has already demonstrated that it can load small molecule drugs into EVs, so Cognevo could also rescue existing drugs that have failed due to delivery problems. So far it has been able to show high uptake and delivery of Cognevo EEVs into these cells types *in vitro*. The next steps will be testing Cognevo variants in animal models of CNS medical conditions such as Alzheimer's Disease.

Established pharma companies have recently started to discovered Engineered EVs. Five recent deals highlight how attractive Engineered EVs are to Big Pharma as well as emerging pharma companies:

- **Jazz Pharmaceuticals / Codiak Biosciences, January 2019.** Jazz Pharmaceuticals[23] is a leading specialty pharma company focused on

[22] J Cereb Blood Flow Metab. 2012 Nov;32(11):1959-72. Epub 2012 Aug 29.
[23] Dublin, Ireland, Nasdaq: JAZZ, jazzpharma.com.

sleep medicine and haematology/oncology. The company enjoyed US$2.4bn in 2020 revenue. In 2019 this innovative company partnered with Codiak on five hitherto undruggable cancer targets. Codiak received US$56m upfront, and each target came with up to $200 million in milestones[24].

- **Takeda / Evox Therapeutics, March 2020. Takeda is the world's 10th Largest Pharma company**[25]. The Takeda/Evox collaboration will see the two companies work on various rare diseases using protein replacement and mRNA therapies. The first of these will be a preclinical programme in Niemann-Pick disease type C. The deal is worth up to US$882 million in upfront, development, and commercial milestone payments, of which US$44m is near-term in nature[26].
- **Eli Lilly / Evox Therapeutics, June 2020.** Eli Lilly is the world's 14th Largest Pharma company[27]. This collaboration involves the delivery of RNA interference and antisense oligonucleotide constructs for neurological disorders. The price tag was US$20m upfront and US$1.2bn in milestones[28]
- **Sarepta Therapeutics / Codiak Biosciences, June 2020**. Sarepta[29] is the gene therapy company famous for its ground-breaking Exondys 51 (eteplirsen), an 'exon-skipping' therapy for Duchenne Muscular Dystrophy that gained FDA approval in 2016.
- **Takeda / Carmine Therapeutics[30], June 2020**. Carmine Therapeutics uses red blood cell Extracellular Vesicles as vehicles for delivery of gene therapy. Takeda is evaluating this technology for two gene therapy programmes worth US$900 in milestone payments. Takeda also made a small equity investment in the company[31].

The partnering deals for Engineered EVs have featured milestones in the billions of US dollars

The first two of these transactions were pivotal to shaping Exopharm's thinking about the future of exosomes lying in the Engineered EV space. The important thing to remember about these transactions is that they related to pre-clinical programmes and the upside lay above or close to US$1bn in milestones. That is unusually high even in pharma partnering terms and reflects the enormous optimism around Engineered EVs as an ideal delivery system. With LEAP, EVPS and LOAD, Exopharm is well positioned to participate in this deal flow. The other interesting point is that Takeda has now done EEV deals with two EEV companies – so the number of EEV companies available to do deals is smaller than the number of Big Pharma players seeking to do EEV deals.

Investment dollars are starting to flow into Engineered EVs. Witness the US$83m IPO of Codiak Biosciences in October 2020, where the lead programme was only headed into a Phase 1/2 study in advanced solid tumours. Codiak is now capitalised on Nasdaq at in excess of US$300m. Earlier, Mantra Bio, a San Francisco–based exosome start-up founded in 2016[32], was able to raise US$25m in Series A financing in August 2020. In February 2021 Evox Therapeutics, a British company based in Oxford and still

[24] See the 3 Januaru 2019 press release headlined *'Jazz Pharmaceuticals and Codiak BioSciences Announce Strategic Collaboration to Research, Develop and Commercialize Engineered Exosomes to Create Therapies for Hard-to-Treat Cancers'*.
[25] Source: Pharmaceutical Executive, Pharm Exec's Top 50 Companies 2020, published 9 July 2020.
[26] See the 26 March 2020 press release headlined *'Evox Therapeutics and Takeda Sign Multi-target Rare Disease Collaboration'*.
[27] Source: Pharmaceutical Executive, Pharm Exec's Top 50 Companies 2020, published 9 July 2020.
[28] See the 9 June 2020 market release headlined '*Evox Therapeutics Announces a Multi-target RNAi and Antisense Research Collaboration and License Agreement With Lilly*'.
[29] Cambridge, Ma., Nasdaq: SRPT, sarepta.com.
[30] Cambridge, Ma., carminetherapeutics.com.
[31] See the press release dated 30 June 2020 and headlined '*Carmine Therapeutics and Takeda Collaborate to Discover and Develop Rare Disease Gene Therapies Using Novel Red Blood Cell Extracellular Vesicles Platform'*.
[32] See mantrabio.com.

privately held[33], raised US$95.4 million in an over-subscribed financing round. Recently Capricor Therapeutics[34] started moving into the Engineered EV space. As well as an Engineered EVs for Covid-19 at pre-clinical, the company is also evaluating other Engineered EVs to augment its lead programme in cardiosphere-derived cells in Duchennes. That company is current capitalised in Nasdaq at >US$100m.

Where does Engineered EVs fit in large pharma industry trends? We see four main reasons why Engineered EVs will grow in importance in the pipelines of major pharmas:

- **Increasing interest in hard-to-hit intra-cellular drug targets**. Probably more than 80% of potential drug targets are intracellular[35], where traditionally they haven't been reachable with large molecules, due to the difficulty of getting such drugs through the cell membrane. Engineered EVs could provide a solution for better drugging of hard-to-hit intracellular targets[36].

Engineered EVs are important in a world where RNA medicine is important

- **The rise of the RNA-based therapies.** The last decade or so has seen a lot of progress in the use of RNA and more generally nucleic acid medicines as a therapeutic option – but targeted delivery in the body is still a holdup. There are the single-stranded antisense oligonucleotides (ASOs) and double-stranded RNA interference (RNAi) molecules where the target is nucleic acids; the RNA aptamers that target proteins; and the mRNA therapies that encode proteins and an emerging field of microRNAs (miRNA). The speed with which the world got mRNA Covid-19 vaccines within 12 months of the start of the Pandemic has advanced the understanding and acceptance of RNA, but also the limitations of the present delivery and formulation technologies.
- **The willingness of pharma to re-engage in the CNS space.** One of the hardest areas of drug development in recent decades has been CNS disorders such as Alzheimer's and Parkinson's. With exosomes offering a new way to deliver targeted therapies through the blood-brain barrier, we expect increased licensing interest, particularly now that drug developers are exploring new targets beyond the traditional beta amyloid and tau proteins and have new nucleic acid medicines under development.

Exosomes may help progress the field of gene therapy beyond the use of viral vectors

- **The potential for use of exosomes as a safer way to do gene therapy.** There is evidence that exosomes would make a for better, less dangerous vector for gene therapy constructs than the viruses currently used. Viral vectors have the limitation that they can only be used a maximum of once in a person. With gene therapies for inherited immune disorders, haemophilia, eye and neurodegenerative disorders, and lymphoid cancers now approved in United States and Europe, the search is on for the next generation of deliver vectors. That search could reasonably include exosomes.

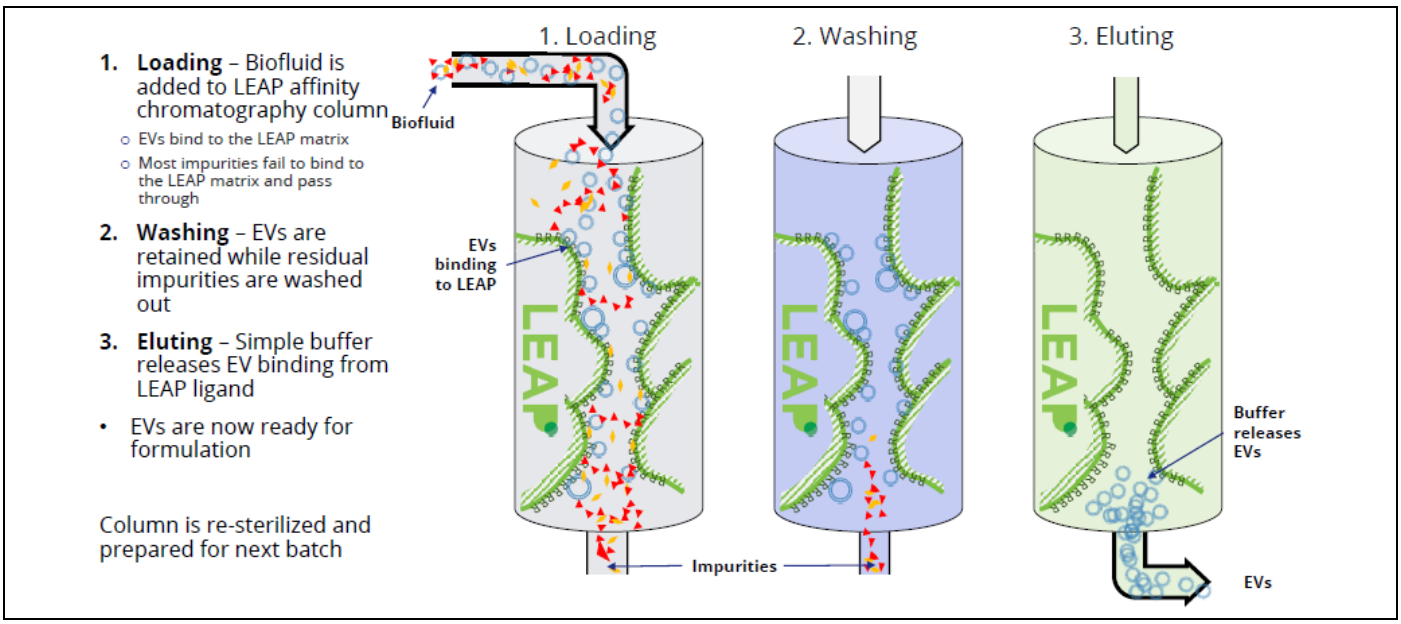
All of these trends suggest, potentially, a ~US$200bn market opportunity in which Engineered EVs are important players.

Can 2021 or 2022 see a partnering deal for Exopharm in Engineered EVs? We believe that the LEAP advantage, when combined with enough data on the potential of EVs engineered using LOAD and EVPS, can potentially attract a collaboration like those from Codiak and Evox we noted above. Exopharm will need to generate more *in vitro* and *in vivo* data on the actual EEVs, but LEAP

[33] See evoxtherapeutics.com.
[34] Los Angeles, Ca., Nasda: CAPR, capricor.com.
[35] Nat Rev Drug Discov. 2006 Dec;5(12):993-6.
[36] See, for example, Nat Commun. 2016 Jul 22;7:12277.

will likely open the doors to a lot of partnering discussions given concerns that the pharma companies will have about scale of manufacture, cost of goods and consistency of properties.

Figure 4: LEAP uses a three-stage purification process



Source: Company

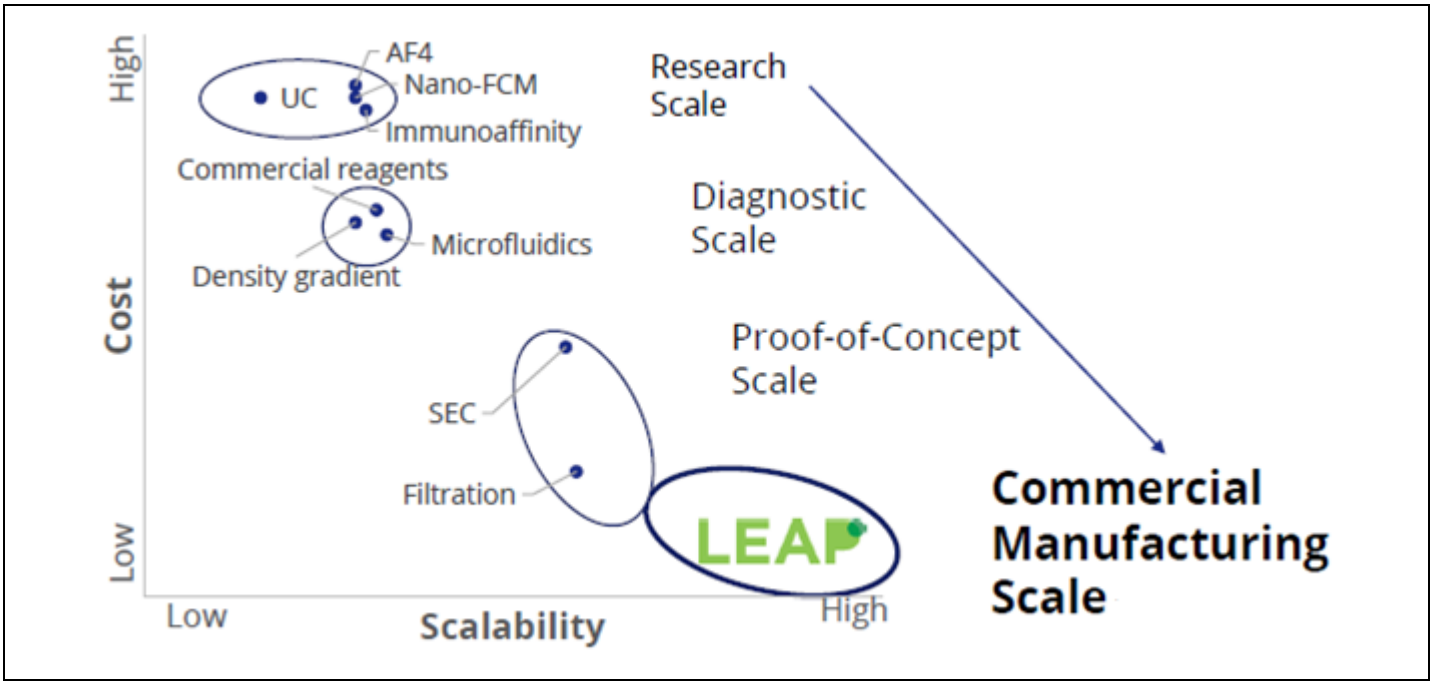
LEAP – Commercial-scale EV purification technology

One of the main barriers to using exosome-based medicines is purifying sufficient quantities of EVs from biological materials. LEAP, a chromatography technique, was invented by the founder of Exopharm and is currently the only commercial-scale EV purification technology. Exopharm intends to use this technique in-house and license it to other researchers and pharmaceutical companies.

Provides access to large quantities of high-purity EVs for research and clinical uses

How does the LEAP technology work? Biological materials are put through LEAP affinity chromatography columns. The entire purification process is divided into three phases: loading, washing and eluting; and each stage utilises the LEAP matrix (Figure 4). The first stage is loading where bind (a solution containing exosomes and contaminates) is passed through a column. The column is lined with the LEAP matrix, which grips the exosomes while most impurities simply pass through. The next step is washing, where impurities are removed by passing a fresh inert solution through the column, leaving behind the EV material. The final step is eluting, which simply releases the EVs left attached to the LEAP ligands.

Figure 5: LEAP allows better scalability while maintaining cost effectiveness

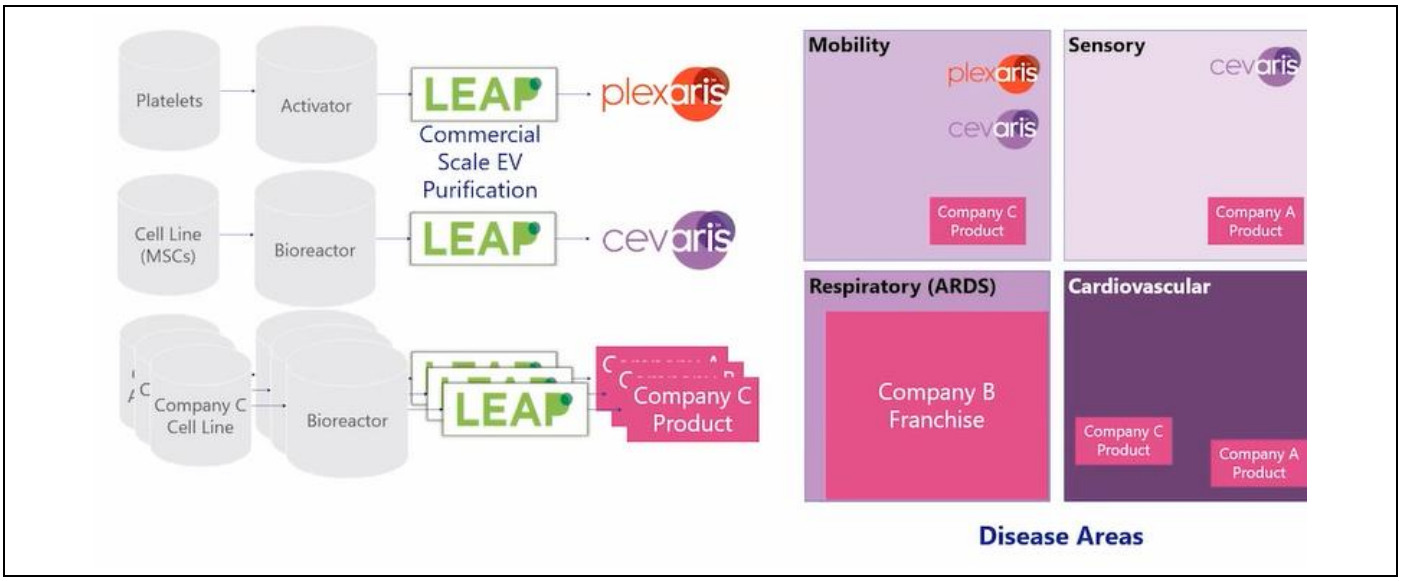


Source: Company

LEAP has the potential to scale production of clinical-grade exosomes in sufficient quantities that can be used in human clinical studies and in off-the-shelf therapeutic products. Key merits of the technology include the following:

- **Yield:** LEAP is based on affinity chromatography, which has been proven in terms of yield, i.e. exosomes extracted per unit of biological material.
- **Gentle:** The process of extracting exosomes using LEAP retains most of their natural biological properties vs. other methods such as ultracentrifugation (UC).
- **Scalability:** Affinity chromatography is suitable for scaling production beyond thousands of doses (Figure 5).
- **Consistent:** Output is much more homogenous, as LEAP manufacturing introduces specificity and selectivity in isolating biological materials.
- **Acquainted:** LEAP does not have any extraordinary prerequisites and uses standard bio-manufacturing equipment and processes.
- **Cost:** At present, the cost of LEAP is ~A$10 per billion EVs and the company targets to reduce this to <A$0.05 per billion EVs.
- **Lower contamination:** The final product is less contaminated than simple filter processes.
- **Reusable consumables:** Another addition to the low-cost attractiveness of this technology stems from its ability to reuse consumables.

Figure 6: LEAP will be used internally and is likely to be licensed to other pharmaceutical firms



Source: Company

LEAP presents multiple revenue paths

At present, the management has identified four distinct paths to generate revenue from the LEAP technology (Figure 6).

- **Internal programmes:** Involves the use of LEAP in manufacturing its own EV-based medicines. For instance, Fortrexo and Cognevo (both Exopharm's proprietary EEVs) use LEAP manufacturing to purify EVs from biological material at a commercial scale. This strategy offers a significant advantage but involves product development from scratch and is therefore slower to monetise (more than three years).
- **Licensing potential:** The management is keen on licensing the technology, and such deals are expected to be a significant initial revenue generator until its EEV and NEV portfolio comes to market. Early potential partnerships include blood products companies. This is likely to be a major long-term revenue stream (more than four years), and Exopharm is currently exploring future partners.
- **Technology transfer:** Interest among pharmaceutical firms for EEVs as an ideal drug delivery solution is gaining traction. As previously established, only a handful of technologies exist that can harness exosomes from biological fluids and none compare to the cost effectiveness of LEAP. This path is likely to be a medium-term option, i.e., 1–3 years.
- **Researchers:** License fees from established bioprocessing equipment companies selling branded LEAP columns to academic researchers is another option available to the company. Though the deal size in this case may be small, it will have quick monetisation potential, i.e., less than one year. Exopharm is currently exploring OEM partners for this option.

Multiple commercialisation paths being explored for LEAP

We believe Exopharm is in a unique position, wherein it has not only a number of EV products in the pipeline but also a revolutionary technology to facilitate its own production. Besides using the LEAP technology for its in-house production, Exopharm can leverage it as an early revenue opportunity by inking licensing/partnership deals with pharmaceutical

companies, particularly those with a significant interest in EEVs. In fact, in order to facilitate international partnerships, Exopharm has established a wholly owned Swiss entity ExoSuisse GmbH. In our view, this is a positive move, as it will improve the company's visibility in the global market and enhance its credibility among potential partners/collaborators.

Why EEVs like Exopharm's can address a US$200bn market opportunity

Drug delivery is evolving beyond just patient convenience. Traditionally biotech and pharma companies innovated around delivery of small molecule Active Pharmaceutical Ingredients mainly for more for patient convenience. The aim of the game was to develop ways to reduce the number of times a month drug needed to be administered by the existing routes, or allow delivery in a way that was more convenient for the patient. It was this need which drove the growth of companies like ALZA back in the 1970s, for example. More recently it has allowed the founding and growth of companies like Endo Pharmaceuticals, Alkermes, Impax Laboratories and Nektar Therapeutics. What companies like this had in common is the need to deliver existing small molecules by better routes, such as transdermally, or sub-lingually.

Today drug delivery is grappling with bigger issues. The issue with drug delivery today is that new generation drugs have no easy of getting to the cells where they are therapeutically active. As we noted above, either they are too large to get through the cell wall or the blood-brain barrier (large molecules such as peptides), or based on nucleic acids and therefore in need of appropriate packaging (DNA, miRNA etc) or delivered by vectors that are immunogenic as well as have inefficient tropism to areas of damaged tissue (gene therapy).

Many drugs today rely on drug delivery systems, making for a US$200bn market

'21st Century drug delivery' is a ~US$200bn market opportunity. About 20 years ago roughly 8% of all marketed drugs came with a drug delivery system[37]. We estimate the figure is more like 15% today[38], which represents a combination of life cycle management of older drugs as well as the arrival of newer generation drugs. 15% of the global US$1.25 trillion pharma market[39] represents US$190bn in value attributable to drug delivery.

siRNA and miRNA opens up this US$200bn opportunity for EVs. The recent rise of RNA therapeutics has been dramatic. Take Spinraza (nusinersen), from Biogen, as a good example. That product, for the treatment of Spinal Muscular Atrophy, only gained FDA approval in December 2016 but did US$2.1bn in sales in both 2019 and 2020. With RNA therapeutics now in the blockbuster category the search will be on for new ways to deliver them.

EEVs have advantages allowing them to better address the market opportunity. EVs are not the only way to deliver drugs efficiently through the cell wall. There's also liposomes and Lipid Nanoparticles, as well as cell penetrating peptides such as PYC Therapeutics (ASX: PYC) is working on. And viral vectors benefit from decades of research in improving their usefulness. The competing systems all come with drawbacks. The viral vectors, for example, have well understood immunogenicity issues[40]. Liposomes are also

[37] Source: Presentation by John Rountree of Novasecta to Photocure Capital Markets Day 2007.
[38] For background here see Pharmaceutics. 2018 Dec 6;10(4):263.
[39] Source: IMS Health, Statista.
[40] Mol Ther. 2020 Mar 4;28(3):709-722. Epub 2020 Jan 10.

immunogenic and have run up against toxicity issues[41]. Cell penetrating peptides potentially have stability issues because of the difficulty of sourcing such rare peptides that also have a robust structure[42]. And the LNPs that have performed valiant service in the Covid-19 vaccines, while they can do the delivery job, are still subject to the endocytic recycling pathways in the cell that chews up a lot of the payload[43]. Exopharm believes that its EEVs are superior to all these alternatives.

Codiak Biosciences shows how attractive a publicly-traded Engineered EV company can be.

Codiak Biosciences is a >US$300m company on Nasdaq

The best public company comparable for Exopharm is Codiak Biosciences, which raised a net US$74m in its 2020 IPO and another $62m in net proceeds in February 2021. Codiak currently has a market capitalisation on Nasdaq in excess of US$300m.

Codiak Biosciences has moved fast in the Engineered EV space. This company, founded in 2015[44] and public on Nasdaq as of late last year, was built out of the pioneering work on exosomes done by Jan Lötvall at the University of Gothenburg in Sweden[45] and Raghu Kalluri at the MD Anderson Cancer Center in Houston[46]. The company's core technology is engEx, has been designed to allow EVs to be engineered for both payload and tropism, and then manufactured at scale.

Codiak can engineer EVs to display therapeutically important proteins on their surface as well as hold drug cargo. Codiak's technology is based on two scaffold proteins, called PTGFRN and BASP1, that are preferentially sorted into EVs and that allow various molecules to be displayed in the EV surface or held internally[47]. This platform is more-or-less equivalent to the LOAD and EVPS technologies of Exopharm. The company can manufacture its EVs under GMP but Exopharm believes its LEAP technology will ultimately give it a cost advantage.

Codiak proprietary molecules are just getting into the clinic now. The company's lead Engineered EV products are exoSTING and exoIL-12. In each case the products are designed to prompt an inflammatory response to cancer. Interleukin-12 has long been known about as a potential immuno-oncology agent[48], as has STING[49]. Codiak's lead products deliver these molecules via Engineered EVs and they are now in Phase 1/2 studies – exoIL-12 in various indications including Triple Negative Breast Cancer, exoSTING in advanced solid tumours.

The early data with exoIL-12 is promising. In December 2020 Codiak reported positive initial safety data for exoIL-12 in healthy volunteers. IL-12 has never translated from promising pre-clinical studies due to dose-limiting toxicities[50]. Codiak with its EV-delivered IL-12 is able to avoid the systemic

[41] Nanomaterials (Basel). 2020 Feb; 10(2): 190.
[42] Bioconjug Chem. Jan-Feb 2007;18(1):50-60.
[43] Nat Biotechnol. 2013 Jul; 31(7): 653–658.
[44] If you're wondering about the name, one of Codiak's original investors is the Alaska Permanent Fund, which invented US$80m into the company in November 2015. Kodiak is an island in Alaska (57 degrees North, 153 degrees West) that is home to the famous Kodiak bear.
[45] It was the landmark 2007 paper from Jan Lötvall's laboratory at the University of Gothenburg in Sweden which first identified that exosomes were more than tiny trash sacs that tossed non-coding RNA out of cells – see Nat Cell Biol. 2007 Jun;9(6):654-9. Epub 2007 May 7.
[46] Kalluri became interested in exosomes because of their role in the tumour microenvironment – see J Mol Med (Berl) . 2013 Apr;91(4):431-7. Epub 2013 Mar 22.
[47] Mol Ther. 2021 Jan 21;S1525-0016(21)00020-4. Online ahead of print.
[48] Expert Opin Biol Ther. 2007 Nov; 7(11): 1705–1721.
[49] The STimulator of InterferoN Genes, see Immunol Rev. 2019 Jul;290(1):24-38.
[50] Blood, 1997, vol. 90 7(pg. 2541-2548).

exposure that would notionally cause such toxicity, and specifically target the tumor microenvironment.

The partnering deals indicate the attraction of the engEx platform. We noted above the deals which Codiak did in 2019 and 2020 with Jazz and Sarepta respectively. It's fair to say that the former deal, worth US$56m upfront, helped put Engineered EVs on the map as far as being a 'legitimate' drug delivery strategy.

Beyond Codiak – the competitive landscape

There are companies with an exosome programme among other offerings There are also certain companies that are purely focussing on exosome extraction technologies. While a few exosome companies have entered into partnerships with major pharmaceutical players and/or research institutes, most of their products are in discovery or pre-clinical stages. The products have various applications across the oncology, neurodegenerative disorder and vaccine domains. (Figure 7)

In addition to public entities, there are various private, pure-play exosome companies, most of which have products in pre-clinical or discovery phase. Notably, these private players are also attracting interest from big pharmaceutical companies that want to utilise their proprietary technologies to develop exosome-based medicines. One such case is Evox Therapeutics, which has signed major deals with Lilly and Takeda. The deal with Lilly is for the development of RNAi and antisense oligonucleotide (ASO) drug payloads using Evox's DeliverEX platform, while for Takeda, Evox is developing novel protein replacement and mRNA therapies. (Figure 8).

Figure 7: Diversified public companies in the exosomes space

Company	Domicile	Founded	Exosome Extraction Technology (Y/N)	Key Exosome Partner (Last 2-3 Years)	Deal Value/Date
Avalon GloboCare Corp	US	2014	Y, ACTEX	GE Healthcare	N/A (Jul 2019)
Key Exosome Product Pipeline/Development Phase - **ACTEX** is an advanced platform for deriving clinical-grade, tissue-specific exosomes from different stem cells					
Aethlon Medical Inc	US	1998	Y, Hemopurifier	University of Pittsburgh	US$3.5m (Aug 2020)
Key Exosome Product Pipeline/Development Phase - **Hemopurifier** is designed for rapid depletion of circulating viruses and cancer promoting exosomes					
Capricor Therapeutics	US	2005	N	Lonza	N/A (Jan 2021)
Key Exosome Product Pipeline/Development Phase - **CAP-1002:** "Off-the-shelf" cardiac cell therapy for Duchenne Muscular Dystrophy (DMD) and COVID-19; clinical development stage					
Clinomics Inc	South Korea	2011	Y, CD-Prime	-	-
Key Exosome Product Pipeline/Development Phase - **CD-Prime platform** offers automated protocols for purification of circulating tumour cells, cell-free DNA and exosomes derived from cancer tissues					
PureTech Health plc	US	2005	Y, Orasome	Roche	>US$1bn (Jul 2018)
Key Exosome Product Pipeline/Development Phase - **Orasome platform:** Allows for oral administration of biotherapeutics; instead of using vesicles, the drug is transported via gastro-intestinal tract using milk-derived EVs					
ReNeuron Group plc	UK	1997	N	Major US biotechnology firm	N/A (Jun 2020)
Key Exosome Product Pipeline/Development Phase - **ExoPr0** is a stem cell derived exosome therapy which has demonstrated potential for an efficient drug delivery system; targeted for oncology, vaccines and neurodegeneration; currently in pre-clinical stage					

Source: Pitt Street Research

Figure 8: Private, pure-play exosome companies

Company	Domicile	Founded	Exosome Extraction Technology (Y/N)	Key Exosome Partner (Last 2-3 Years)	Deal Value/Date
Aegle Therapeutics	US	2013	N	-	-
Key Exosome Product Pipeline/Development Phase **- AGLE-102:** Treatment of Dystrophic Epidermolysis Bullosa (DEB) using exosomes containing protein and genetic material cargo; phase 1/2a clinical trials are expected to begin in Q1 2021					
Aruna Biomedical	US	2003	N	-	-
Key Exosome Product Pipeline/Development Phase - **AB126** is both a therapeutic and a delivery vehicle for treating a wide range of neurodegenerative diseases; currently in Investigational New Drug (IND) stage to evaluate potential toxicity - **Delivery platforms AB127** (gene knockdown) and **AB128** (protein delivery) are in proof-of-concept stage - **AB129** used for gene knockdown is in early research stage					
Evox Therapeutics	UK	2016	N	Lilly Takeda University of Oxford (collaboration)	US$1.7bn (Jun 2020) US$1.3bn (Mar 2020) N/A (Nov 2020)
Key Exosome Product Pipeline/Development Phase -**DeliverX** platform is proprietary engineered EV solution for targeted drug delivery system; planning clinical trials					
ExoCoBio	South Korea	2017	Y, ExoSCRT	CHA Biotech	N/A (Jul 2020)
Key Exosome Product Pipeline/Development Phase -**ExoSCRT,** a patented isolation and purification technology for exosomes from stem cells					

Source: Pitt Street Research

Valuing Exopharm

Using a probability-weighted DCF methodology, we value Exopharm at $2.80 per share base case and $4.71 per share bull case (Figure 11).

Our approach is as follows:

- **EEV pipeline products**. We model milestone payments and royalty revenue streams for EEV's pipeline products which include Fortrexo, Cognevo and Plexodox. We note that our ascribed values are highly speculative due to the early stage of those drug programs.
- **LEAP**. We model Exopharm out-licensing its LEAP technology to large pharmaceutical companies at the start of FY22. When and if executed, these licensing arrangements should provide Exopharm with some early cashflows to help fund the development of its EEV pipeline products.

Figure 9: Key valuation parameters for EEV pipeline products

	Product: Fortrexo (EEV)	
	Base case	**Bull case**
Global antiviral drug market (US$B)	34	34
Estimated market share	15%	17%
License date	FY22	FY22
Upfront milestones (USDm)	20	25
Development milestones	200	300
Royalty rate	8%	9%
Product approval	Fy27	FY26
Peak sales (USDm)	408	520
	Product: Cognevo (EEV)	
	Base case	**Bull case**
Global neurodegenerative diseases drugs market (US$B)	36	36
Estimated market share	16%	18%
License date	FY22	FY22
Upfront milestones (USDm)	25	30
Development milestones	250	350
Royalty rate	8%	9%
Product approval	Fy27	FY26
Peak sales (USDm)	454	575
	Product: Plexodox (EEV)	
	Base case	**Bull case**
Global cancer therapy market (US$B)	158	158
Estimated market share	8%	10%
License date	FY22	FY22
Upfront milestones (USDm)	30	40
Development milestones	300	400
Royalty rate	8%	9%
Product approval	Fy27	FY26
Peak sales (USDm)	1011	1422

Source: Pitt Street Research

For EEV deals, our key valuation parameters are shown in Figure 9.

Additionally, we assume the following parameters on valuing EEV products:

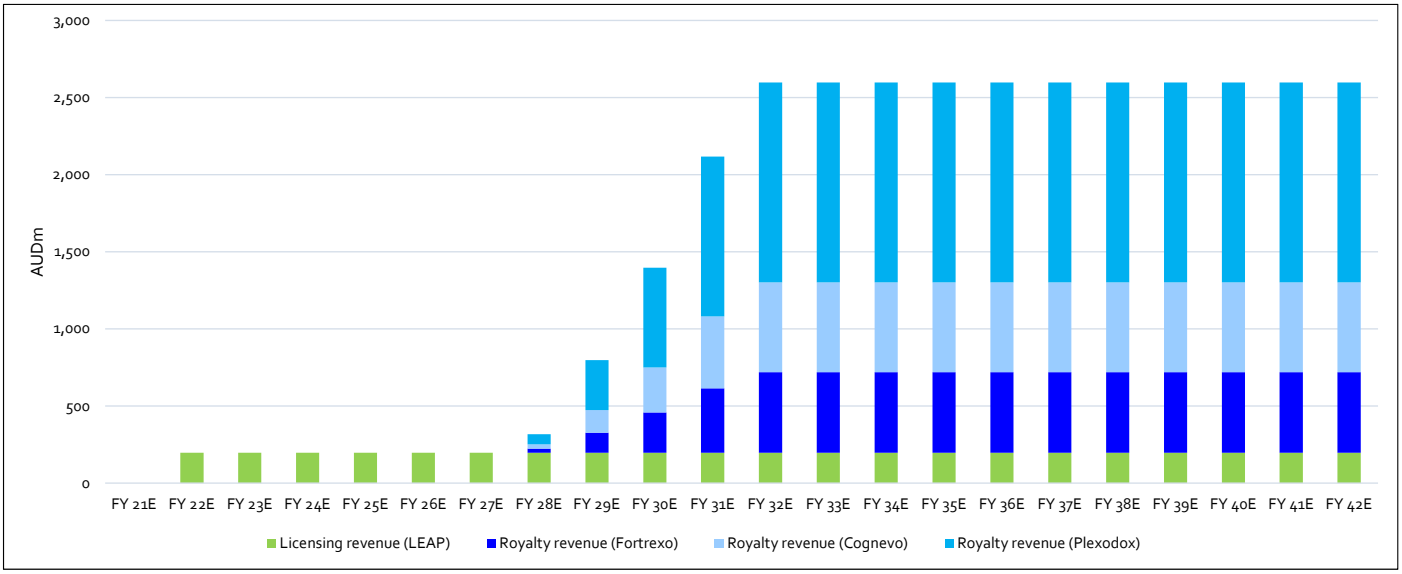
- A high discount rate of 14.4%, appropriate in our view for a 'Speculative' risk rating[51], Exopharm is in pre-revenue phase which we see as more risky than other more commercialised Life Sciences ventures.
- A 20-25% probability in eventually reaching approval.
- In aggregate, licensing deal will include US$75-95M in upfront milestone and US$750M-1.1B in development milestone. We believe these inputs are conservative given that recent EEV deals such as Codiak and Evox have higher potential milestone payments.
- A 15-year commercial exclusivity period with no follow-on revenues.

For LEAP deals, we assume the following:

- Exopharm out-licenses this asset to 2-3 partners at the start of FY22.
- A 50% probability in successfully securing partnerships. Exopharm's set up of its Swiss entity gives us confidence as it not only helps increase the company's presence in the global EV market but also facilitates potential international partnerships.
- A 1.5-2.0% licensing revenue, reflecting the practicality and the vital role of the technology in the manufacturing process of EV-based medicines.
- Licensing revenues to be derived from partners' expected sales of their EV-based medicines, with which we base them off our own forecasts of peak sales for one of the EEV prospects, namely Fortrexo.
- Ongoing licensing renewals between Exopharm and its licensees.

Figure 10 shows our expected combined revenue modelling for Exopharm throughout the commercial lives of Fortrexo, Cognevo and Plexodox.

Figure 10: Revenue modelling for Exopharm's EEV prospects



Source: Pitt Street Research

[51] For a relevant discount rate, we use varying WACCs depending on the risk for Life Science companies. We start with an RFR of the Australian ten-year bond rate (1.7%) and an ungeared beta of 1.1 but use a variable MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies). Ordinarily 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'. We have used a Speculative risk rating for Exopharm considering it is at a pre-revenue stage.

Capital. As at December 2020, Exopharm held c.A$7.9M in cash with a burn rate of c.A$8.3M over FY20. If the company is able to out-license its LEAP technology by the start of FY21 and subsequently earn licensing revenues as per our modelling, we then don't expect further raisings to occur.

Figure 11: DCF summary

DCF Valuation	Base Case	Bull Case
PV of FCF de-risked	400.7	675.0
PV of Terminal FCF	-	-
Enterprise Value	**400.7**	**675.0**
		-
Net debt	(2.7)	(2.7)
		-
Equity value (A$M)	**403.4**	**677.6**
Diluted shares	143.9	143.9
Implied price (A$)	**2.80**	**4.71**
Current price (A$)	0.66	0.66
Upside (%)	*324.7%*	*613.4%*

Source: Pitt Street Research

Re-rating Exopharm

We believe that the current share price of Exopharm does not reflect its true long-term potential. In our view, Exopharm should be re-rated as it achieves its key near- and medium-term milestones, including the following:

- Encouraging safety results from its PLEXOVAL II study – Exopharm completed the first dosing for Plexaris in human trials in January 2021 and the results are expected to be released in the first quarter of 2021.
- Positive news on partnerships with pharmaceutical companies – The company has set up a wholly owned subsidiary in Switzerland and is holding discussions with potential partners for its EVs as well as LEAP technology.
- New scientific research supporting the benefits of EVs compared with stem cells – We believe as new evidence arrives showcasing the relative benefits of exosomes, their acceptance in the pharmaceutical industry will grow in tandem.

Experienced and lean leadership team

The company's current board and management composition is listed below (Figure 12).

Figure 12: Board and management teams

Name	Designation	Affiliations (current and past)
Board of Directors		
Dr. Ian Dixon	Founder and Managing Director, Chief Executive Officer	Cynata, Nyrada, Noxopharm
Jason Watson	Non-executive Director, Chair	Elementary Law
Elizabeth McGregor	Non-executive Director	Governance Institute of Australia
Management team		
Gregor Lichtfuss	Chief Operating Officer	Spinnovator, Cardior Pharmaceuticals GmbH
Chris Baldwin	Chief Commercial Officer	Haemonetics, McKinsey & Company

Source: Company, Pitt Street Research

Board of Directors

Dr. Ian Dixon is the founder of Exopharm, and co-inventor of the LEAP manufacturing technology and Fortrexo (part of EEV pipeline). Before founding Exopharm, Ian co-founded Cynata Inc, the owner of the Cymerus stem cell technology. He was also the Founding Director of Noxopharm Ltd and Non-executive Director of Cell Therapies Pty Ltd. Ian holds a PhD in biomedical engineering from Monash University, an MBA degree from Swinburne University and professional engineering qualifications.

Jason Watson has assisted several companies with licensing deals for various technologies. He heads a legal practice in Melbourne, for which he has been recognised among The World's 1000 Leading Patent Professionals. Jason has a Bachelor of Laws degree and a Bachelor of Commerce degree.

Elizabeth McGregor of the Automic Group, a share registry operator which also provides governance and compliance services, was named a director and Company Secretary in January 2021.

Management Team

Chris Baldwin joined Exopharm in November 2019. He was responsible for Haemonetics' largest and most profitable business unit across Asia Pacific. He previously served banking, pharmaceutical and non-profit clients at McKinsey & Company. He holds a PhD in Chemical Engineering from University of Cambridge.

Gregor Lichtfuss has significant entrepreneurial experience in biotechnology start-ups. He previously worked at Spinnovator, a start-up creation hub where he played a significant role in setting up Cardio Pharmaceuticals GmbH. He holds a PhD in Medicine/Clinical Immunology from Monash University, a Master of Science in International Health from Humboldt University, Berlin, and a Diploma in Biology (Virology and Generics) from Humboldt University.

Other management includes people with experience from companies such as CSL, Bayer, Opthea, PolyNovo and Zoetis.

Appendix I – Glossary

Affinity chromatography – Method of separating biomolecules from a mixture based on a binding interaction between different substances in the mixture.

Allogeneic – Refers to those tissues or cells that are genetically dissimilar and immunologically incompatible but are from individuals of the same species.

Autologous – Process where the donor and recipient are the same individual.

Blood brain barrier (BBB) – A semipermeable membrane separating the blood from the cerebrospinal fluid, and constituting a barrier to the passage of cells, particles and large molecules.

Bone marrow – The soft tissue that lies within the hollow interior of long bones.

Fibroblasts – Type of cell that secretes collagen protein used to maintain a structural framework for many tissues. They are usually found in connective tissues and facilitate wound healing.

Immunomodulatory – Medications that help regulate or normalise the immune system.

RNA interference (RNAi) – Cellular process that uses a gene's own DNA sequence to turn it off. It is an essential process in immune response to viruses and other foreign genetic materials.

Mesenchymal stem cells (MSCs) – Stem cells generally found in the bone marrow that can give rise to bone, cartilage, adipose and connective tissues.

Messenger RNA (mRNA) – Molecule that carries codes from DNA in the nucleus to the sites of protein synthesis in the cytoplasm.

Micro RNA (miRNA) – Molecules that help cells control the kinds and amounts of protein they make.

Multipotency – Refers to stem cells that are capable of self-renewing and developing into multiple specialised cell types.

Ribonucleic acid (RNA) – Facilitates the synthesis of proteins by carrying the instructions from the DNA.

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

Silencing RNA (siRNA) – Refers to a particular gene type that silences or mutes the gene expression, essentially suppressing the normal gene reaction to protect from viruses.

Stem cell – Special cells that have the ability to develop into many different cell types when subjected to the right biochemical signals.

Appendix II – Capital Structure

Class	In millions	% of fully diluted	Note
Ordinary fully paid shares	139.4	96.6%	
Options expiring 9 November 2025	4.5	3.1%	Wtd. avg. exercise price of A$0.40
Performance rights	0.3	0.2%	
Fully diluted shares	**144.3**		

Source: Company

Appendix III – Major Shareholders

Exopharm has one major shareholder – Dr. Ian Dixon (founder) – who owns ~20% stake in the company.

Appendix IV – Comparable Companies

Aethlon Medical Inc. A US-based company, it is involved in the development of immunotherapeutic technologies for application in infectious diseases and cancer. Its Hemopurifier is a clinical-stage immunotherapeutic device that removes cancer-promoting EVs and life-threatening viruses from the human circulatory system. Aethlon Medical is collaborating with the University of Pittsburgh on studies related to head and neck cancer. It also owns a majority stake in Exosome Sciences Inc, which is focussed on the discovery of exosomal biomarkers to diagnose and monitor life-threatening diseases.

Avalon GloboCare Corp. It is a clinical-stage bio-developer focussed on developing immune effector cell therapy, EV technology, and COVID-19-related diagnostics and therapeutics. Its ACTEX offering is an advanced platform for deriving clinical-grade, tissue-specific exosomes from different stem cells, with applications in wound management and neurodegenerative disorders.

Capricor Therapeutics Inc. It is a US-based clinical-stage biotechnology company that develops cell- and exosome-based therapeutics. Its lead candidate, CAP-1002, is an 'off-the-shelf' cardiac cell therapy for Duchenne Muscular Dystrophy (DMD) and COVID-19. The company is developing this drug candidate in collaboration with Lonza.

Clinomics Inc. A South Korean biotechnology company, it provides genome-based cancer and disease diagnostic solutions. The company's liquid biopsy and precision medicine CD-PRIME offers enrichment of circulating tumour cells (CTCs), cell-free DNA and exosomes derived from cancer tissue, which help in the diagnosis and prognosis of cancer.

Codiak BioSciences. It is a clinical stage biopharma company focussed on developing EV-based therapeutics. Its engEx platform is an exosome engineering and manufacturing platform for designing novel exosome therapeutics, and its two lead engEx product candidates are exoSTING and exoIL-12. The company has strategic collaborations with Jazz Pharmaceuticals and Sarpeta Therapeutics for EV-based therapeutics.

PureTech Health plc. A US-based clinical stage bio therapeutics company, it focusses on medicines for intractable cancers; lymphatic, gastrointestinal and CNS disorders; and inflammatory and immunological diseases. Its Orasome platform allows for oral administration of bio therapeutics instead of using

vesicles. The drug is transported via the gastro-intestinal tract using milk-derived EVs.

ReNeuron Group plc is a clinical-stage, stem cell therapy developer based in the UK. It is currently engaged in the development of CTX stem cell therapy, its flagship product for stroke disability and human retinal progenitor cell therapy. It is also developing CTX-derived exosomes which is a targeted drug delivery system.

Appendix V – Exopharm's In-House Intellectual Property

WO 2018, 112557, *Methods and compositions for purification or isolation of microvesicles and exosomes,* priority date 23 December 2016, invented by Chacko Joseph, Ian Dixon, Jim Palmer and Gregor Lichtfuss.

- The patent discloses a method to isolate exosomes using an array of synthetic polymers with specific exosome-binding ligands – such as cellufine sulfate, offering a binding efficiency of ~75% and isolation yield up to 98%. The use of synthetic polymers – instead of the highly heterogeneous natural polysaccharides/peptides – and ligands spaced apart by 2–10 angstrom enhances the exosome-binding efficiency and overall yield, thus allowing scalable manufacturing of therapeutics.
- Applications for the patent were filed in the US, Europe, Russia, Australia, Brazil, Canada, China, Japan and South Korea, but approvals have not been granted in any of the countries yet.

WO 2019, 241836, *Methods and compositions for purification or isolation of microvesicles and exosomes,* priority date 18 June 2018, invented by Gregor Lichtfuss, Ian Dixon and Jim Palmer.

- The patent discloses a method to isolate exosomes using affinity media – such as GE Healthcare's Capto DeVirS/CaptoS (comprising an agarose substrate, dextran polymers and sulfate ligands) and Merck's Eshmuno S (comprising a polyvinylether substrate, polyacrylamide polymers and sulfoisobutyl ligands) – with ligands spaced apart by 2–10 angstrom to achieve high efficiencies for exosome binding and elution, thus enhancing the overall yield.
- Applications for the patent were filed in Canada, Australia and Singapore, but approvals have not been granted in any of the countries yet.

Appendix VI – Exopharm's Non-Patent Literature

Johnson et. al. (2020), *Prospective Therapeutic Applications of Platelet Extracellular Vesicles*, Trends Biotechnol. 2020 Nov 4; S0167-7799(20)30268-7.

- The paper pertains to the use of platelet EVs – including exosomes, microvesicles, microparticles and ectosomes – as sub-cellular therapeutics in regenerative medicine and as a substitute for synthetic nanocarriers in drug delivery due to their superior biocompatibility, tissue infiltration ability, and targeting and retention capabilities at pathological sites. It further mentions the use of platelet concentrates – an

established, licensed medicine in most countries derived from platelets collected under the supervision of national regulatory authorities – as a source of EVs to tackle the industrial and regulatory challenges associated with EVs derived from in vitro cultured MSCs.

Appendix VI – Analyst Qualifications

Stuart Roberts, lead analyst on this report, has been an equities analyst since 2002.

- Stuart obtained a Master of Applied Finance and Investment from the Securities Institute of Australia in 2002. Previously, from the Securities Institute of Australia, he obtained a Certificate of Financial Markets (1994) and a Graduate Diploma in Finance and Investment (1999).
- Stuart joined Southern Cross Equities as an equities analyst in April 2001. From February 2002 to July 2013, his research speciality at Southern Cross Equities and its acquirer, Bell Potter Securities, was Healthcare and Biotechnology. During this time, he covered a variety of established healthcare companies, such as CSL, Cochlear and Resmed, as well as numerous emerging companies. Stuart was a Healthcare and Biotechnology analyst at Baillieu Holst from October 2013 to January 2015.
- After 15 months over 2015–2016 doing Investor Relations for two ASX-listed cancer drug developers, Stuart founded NDF Research in May 2016 to provide issuer-sponsored equity research on ASX-listed Life Sciences companies.
- In July 2016, with Marc Kennis, Stuart co-founded Pitt Street Research Pty Ltd, which provides issuer-sponsored research on ASX-listed companies across the entire market, including Life Sciences companies.
- Since 2018, Stuart has led Pitt Street Research's Resources Sector franchise, spearheading research on both mining and energy companies.

Cheng Ge is an equities research analyst at Pitt Street Research.

- Cheng obtained a B. Com in Finance and LL. B from the University of New South Wales, in 2013, and has passed all three levels of the CFA Program.
- Before joining Pitt Street Research, he has worked for several financial services firms in Sydney, where his focus was on financial advice.
- He joined Pitt Street Research in January 2020.

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