EXOPHARM

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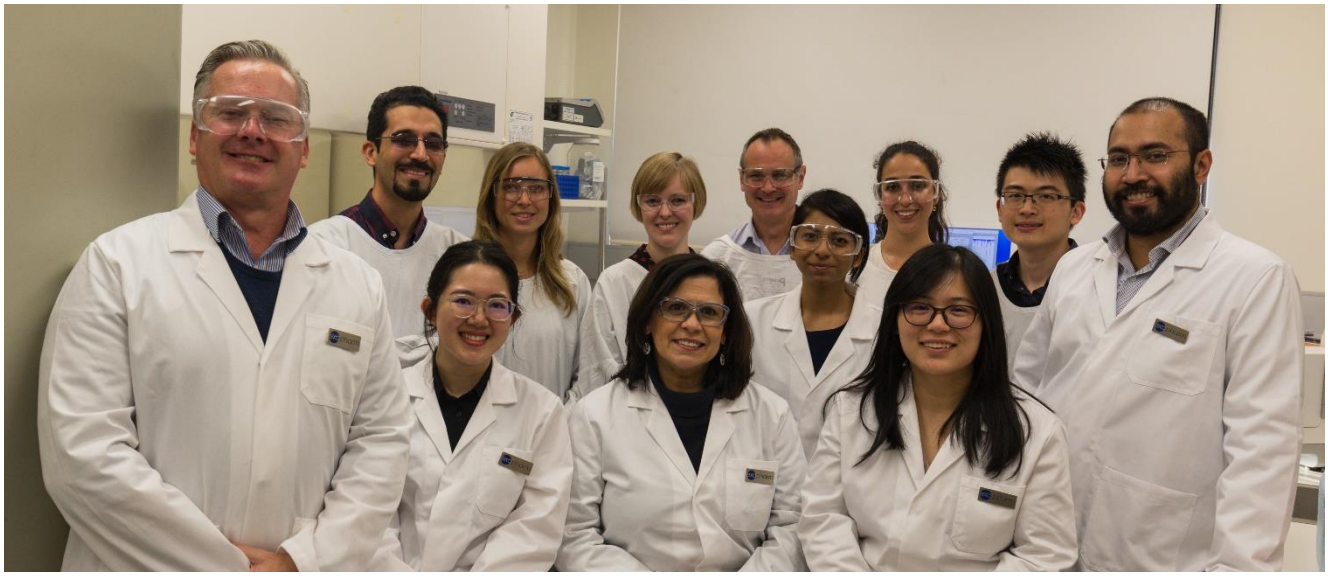
Introduction

Over the past 20 years, stem cells have been in the spotlight as a new therapeutic medium with potential for success in a wide range of biomedical fields. However, over the past decade, this ceiling of potential has been lowered due to some underwhelming results in clinical trials, safety concerns and increasing questions around how they functioned. With more and more research, it has been revealed that the commonly desired therapeutic effect of stem cells is heavily dependent on certain biological factors that are released from the cells.

Exosomes have been identified as a key biological factor in promoting cellular and functional regeneration. Exosomes are nanometre sized particles which have been shown to be essential in shuttling biologically active molecules from one cell to another. They are understood to be pivotal in defending the body against disease and conserving good health. An increasing number of studies and publications would suggest they could be the driving force behind the regenerative and health sustaining actions that were once associated with stem cells. Finding an effective and efficient way to cultivate and harness exosomes for use as a therapeutic treatment could produce the "limitless" applications once promised by stem cells.

Here at **Exopharm** we aim to do exactly that. We have centred our business and research around exosomes as regenerative therapeutics. As one of the first companies to embrace this modality, we are in a great position to be a market leader in the exosome field. We are working to determine if exosomes could be used to increase a person's span of good health (health span) and to treat a variety of life altering conditions and medical issues.



Our ever growing laboratory-based team coming together for a group photo.

Recent News in the Exosome Field

As exosome therapies progress through the clinical pipeline, demand for pharmaceutical-grade exosomes in ever-larger amounts continues to grow. Meanwhile, Maryland-based stem cell company RoosterBio[1] received a US$300,000 research grant for extracellular vesicle (EV) manufacturing. RoosterBio will use the funds to help address the "critical need for an economical biomanufacturing process capable of generating the EV numbers necessary to meet the demand for clinical doses," said Taby Ahsan, the company's senior director of development.

Future Promise and Challenges

In therapeutic research, exosomes continue to show their rich promise. Premature babies' delicate lungs could benefit from therapeutic exosomes derived from stem cells, US researchers have reported[2]. These regenerative exosomes could shift the babies' lung cells from a pro-inflammatory to a pro-healing status. Separately, an international research team[3] showed exosomes' ability to freely roam the body could be used to selectively deliver drugs across the blood-brain barrier into the brain – potentially targeting neurodegenerative diseases. And in Germany, researchers found further evidence[4] that the whole-body benefits of physical exercise may be mediated by exosomes released by a range of body tissues during a workout. Therapeutic exosome populations might be identified that can recreate this effect.

Although research linking exosomes to potential therapeutic benefits continues to flood in, challenges on the path to market remain. Last month, Cambridge, Massachusetts-based exosome therapeutics firm Codiak Biosciences cancelled its initial public offering[5], citing unfavourable market conditions.

On the Front Line of Applications

In more positive news, the US Food and Drug Administration granted breakthrough device designation[6] to Minneapolis-based Bio-Techne for its ExoDx Prostate IntelliScore test. The test, designed to detect aggressive prostate cancer from biomarkers in urine samples, is the first exosome-based liquid biopsy to receive breakthrough status, which should accelerate the regulatory review process. Meanwhile, two university teams showed exosome analysis could be used as an early warning for complications of pregnancy, including preeclampsia[7] and gestational diabetes[8]. And California company Biological Dynamics[9] received a Bill & Melinda Gates Foundation grant to develop exosome-based health diagnostic tools for low- and middle-income countries.

Exopharm News

PLEXOVAL - Exosome Wound Healing Human Study Begins!

As outlined in our ASX announcement on the 26th of August, we have now entered into a Phase 1 human clinical study, that involves exosomes being used for wound healing. This trial will evaluate the safety, tolerability and biological activity of Plexaris in humans, while also assessing potential benefits within wound healing rates, wound tensile strength and scar tissue formation. This is a very exciting time for Exopharm as this is one of the first steps in our journey to creating commercially available exosome-based therapeutics that aims to improve the lives of many.

Exo-Offsite Celebration Event

In the month of June, we had our first Exo-Offsite event where our staff, executives, partners and financial collaborators got together for an evening of meet and greets. It was a fantastic opportunity for us to celebrate and express our gratitude for all the great work that has occurred over the past few years. The night was a huge success and while the next event of a similar nature is a long time away, it is already being looked forward to.

From Interns to Employees

Over the April-June period, we had the pleasure of having three interns working with us, for the purpose of them gaining both lab and business-orientated work experience. This was Exopharm's second foray into the world of internships and the overall experience was nothing short of fantastic. During this time, our interns garnered various degrees of knowledge and experience from a variety of our senior staff who were more than willing to impart their years of wisdom. Our interns assimilated into the team with ease and were set tasks from the get-go to which they approached with tenacious intent. The intern program was a success and we were fortunate enough to be able to take on two as permanent team members!

Journal Club

An initiative set by one of our newest staff members, is bringing our team together with the common appreciation for interesting science. A monthly Journal Club has been set up where the staff can get together to listen to a team member talk about and elaborate on a scientific paper within any scientific discipline that they find interesting. This event is not only about the social aspect but also about expanding each other's scientific horizons and potentially opening new ways of thinking and problem solving that can benefit us as scientists and as a company. Our most recent journal club was led by our CEO, Ian Dixon who presented an immensely interesting paper on human endogenous retroviruses (HERVs) which was well received by all.

Running for Charity

The Exopharm Team joined together to participate in the annual Run Melbourne charity event on the 28th of July. Run Melbourne is a fantastic fun run held every year and over the past 12 years it has raised in total over $16.5 million dollars for various charities. Exopharm were more than happy to stand behind such a brilliant community event. Our team were split between the 5km and 10km events. This event was not only an opportunity to show our company in a public setting but was also great way to get our staff involved in wider community events.

Woman in Science

The BioMelbourne Network's Connecting Women Lunch in June brought together researchers to celebrate the achievements of women in the biotechnology, medical technology and pharmaceutical sectors in Victoria. Two members of our team attended to expand their networks, spread the word on the good work we are doing and to support their fellow women in science. Now in its 11th year, the annual lunch is renowned for providing rewarding networking and mentorship opportunities for its attendees. Thought provoking discussions, led by Catherine Fox, an award-winning journalist and commentator on women in the workplace, flowed into a networking session paired nicely with a glass of champagne.

Employee Focus: Sam Law

Sam Law joined the Exo-Team in February this year as an engineer in our manufacturing department. He studied at Pennsylvania State University, completing his honours in Biotechnology, before moving to Melbourne to pursue higher level research. He undertook a PhD at the University of Melbourne focused on improving the microalgae biofuel manufacturing process, an emerging technology that could help address the global energy crisis. After completing his PhD, he applied to Exopharm, intrigued by the unique position description set for 'Biotechnology Innovators', which required a very high level of problem solving and technical abilities. Always up for a challenge, he thought the role would suit him well, especially with his passion for emerging technology and the biotechnology field.

He was hired without hesitation and there couldn't have been a better fit for the role. Six months on, Sam is loving his work with the Exopharm team, where there is never a dull moment with many opportunities for problem resolution and innovative thinking. He was quick to make his mark within the Exopharm team and has cemented himself as a vital piece to our company.

Sam's interest in the isolation process and application of exosomes really drives him as he sees the limitless potential that is slowly being uncovered. Being a natural pioneer, he is eager to play a role in unlocking the full potential of exosomes for therapeutic applications. His position in the manufacturing department allows him to do just that. He is excited about the future

of exosome-based technology, believing that one day soon we may be able to harness the potential of exosomes and develop 'designer' exosomes for any therapeutic use.

Outside of work he enjoys all things coffee, taking the technical skills he uses during the day and applying it to roasting his own coffee beans, perfecting espresso extraction, and tinkering with his coffee machine. On the weekend, he likes to relax with his family by cooking and watching movies.

We are very fortunate to have him as a part of our team and look forward to the incredible work to come from him in the future.

Informative Q and A with Dr. Andrew Coley, Manager, ExoHUB Innovation

Exosomes are a new therapeutic modality in the pharmaceutical industry. In short, what are some of the advantages of exosomes?

- Exploitation of a natural inter-cellular communication mechanism;
- Able to be manipulated to create novel pharmaceuticals;
- Can be incorporated into diagnostic technologies;
- Lots of intellectual property (IP) space for new inventions; and
- Opportunity to make significant contributions to our field and extend human health span.

In your opinion, what is the biggest challenge currently facing the exosome field?

From a therapeutic perspective, the most obvious challenge is the consistent and reliable manufacture of an exosomal 'drug product'. In cell therapy, the manufacturing process is a critical component of the 'product'. This is because cells behave in different ways depending on how they are grown and stored. As exosomes are an intrinsically normal cellular phenomenon, they are subject to the same issues. Therefore, the manufacture of a therapeutic exosome drug product requires a similar approach. In addition, as there are several different 'types' of exosomes the manufacturing process must reproducibly and consistently select identical exosomes irrespective of the scale of manufacture. These are not trivial issues, but they are currently being successfully addressed at Exopharm with the application of our Ligand-based Exosome Affinity Purification (LEAP) technology. LEAP allows for the purification of exosomes based on their biophysical properties and therefore is reproducible and importantly, scalable. Most other exosomal therapy developers use a combination of exosome size, density and antibody affinity chromatography to isolate exosomes with the result being products of unsatisfactory purity, reproducibility and scalability, and in the case of antibody affinity chromatography the introduction of additional biological components into the process.

From a research perspective, we still have a way to go to understanding the biology surrounding exosomes; the cellular control of their generation and secretion, and the selective qualities surrounding the messages they communicate between cells. Answers to many of these questions will provide opportunities for additional therapeutic avenues and fine-tuning of our approach to exosomal therapy.

There has been a lot of interest in "designer" or engineered exosomes for drug delivery. What is the reason for this interest and which therapeutic field do you see exosomes being most heavily involved in?

It is difficult to say which therapeutic field exactly but taking mesenchymal stem cell (MSC) therapeutics as a guide, Graft Versus Host disease (GVHD) could present an exciting opportunity to use both engineered and 'naive' exosomes. Additionally, any degenerative disease indication is fair game. Exosomes may have utility, for example, in an age-related ocular setting and in degenerative arthritis. We may also be able to regenerate damaged tissues and organs, so post-infarct myocardial ischemic disease or renal failure might be within the realms of possibility. All of these approaches (and many, many more) could be taken with either naive or engineered exosomes. This is in line with our company goal of producing therapeutics to extend one's period of good health.

The very attractive property of exosomes is our ability to harness the 'natural' therapeutic benefits of 'naive' exosomes and simultaneously incorporate (or engineer) additional beneficial features into them. For example, we could generate exosomes that have a targeting molecule on their surface to direct them to specific cell types. Or supplement the intra-exosome cargo with an enzyme or nucleic acid to modify the metabolic activity of the target cell. All of this is possible by engineering the cells that produce the exosomes such that the modifications are incorporated into the exosomes they produce.

Not all exosomes are equal - what are some differences between types of exosomes and how can we capitalise on this for therapeutic benefit?

The answer to this question is not completely known. We know that different cell types produce exosomes with different 'cargo' and that identical cells cultured in different conditions generate qualitatively and quantitatively different exosomes. Possibly the most effective method of resolving these issues is by generating empirical data from a carefully considered experimental approach; also called 'suck it and see'. If we have a reasonable idea of what we require from a therapeutic exosome preparation, we can design experiments using our established knowledge to address that need. Therefore, it is critical to develop purification techniques that permit the reproducible generation of an exosome product, so any qualitative or quantitative differences between exosome preparations are not the result of the purification process but are bona fide differences in the exosomes prior to purification.

How exciting to you is the emergence of the exosome-based field, and what interests you most about it?

We have exploited natural cell communication techniques in the past by developing hormonal (e.g. hormone replacement therapy, anabolic steroids and insulin), growth factor (e.g. human growth hormone and granulocyte-colony stimulating factor) and immunological (e.g. antibodies and CAR-T cell) therapeutics. Exosomes are the most recent inter-cellular communication phenomenon described and offer immense promise in tackling some diseases not easily treated by conventional interventions. It's clear to many experts now that MSC therapy is not mediated by the proliferation and differentiation of therapeutic MSCs in situ, but the therapeutic effect is dependent on the administered MSCs secreting exosomes, which 'reprogram' resident tissues to regenerate. Therefore, there is the possibility to fulfil the promise of MSC therapy in a more practical and 'dosable' fashion, in addition to the exciting opportunities provided by engineered exosomes. The exosome field is becoming more lucid by the week with new discoveries being published regularly. The developers that adopt those discoveries and translate them into potential drug products will be the real winners in this very new sector. The opportunity to help develop an entirely new therapeutic modality for the benefits of patients and investors presents itself only very occasionally and is enormously exciting. But it's not for the faint-hearted.

Notable Recent Publications List

Marban E. The Secret Life of Exosomes: What Bees Can Teach Us About Next-Generation Therapeutics. J Am Coll Cardiol. 2018; 71(2): 193-200.

Jafari D et al. The relationship between molecular content of mesenchymal stem cells derived exosomes and their potentials: Opening the way for exosomes-based therapeutics. Biochimie. 2019; 165:76-89.

Colombo M, Raposo G and Théry C. Biogenesis, secretion, and intracellular interactions of exosomes and other extracellular vesicles. Annu Rev Cell Dev Biol. 2014; 30:255-289.

Cabral J et al. Extracellular vesicles as modulators of wound healing. Adv Drug Deliv Rev. 2018; 129:394-406.

Kojima R et al. Designer exosomes produced by implanted cells intracerebrally deliver therapeutic cargo for Parkinson's disease treatment. Nat. Commun. 2018; 9: 1305.

Luan X et al. Engineering exosomes as refined biological nanoplatforms for drug delivery. Acta Pharmacol. Sin. 2017;38(6):754–763.

Sterzenbach U et al. Engineered Exosomes as Vehicles for Biologically Active Proteins. Mol Ther. 2017;25(6):1269–1278.

Upcoming Biotech/Exosome Related Events

AusBiotech Trade Show

30th October-1st November - Melbourne, Australia

Circulating Biomarkers, Exosomes & Liquid Biopsy

30th October-1st November - Rotterdam, Netherlands

Glossary:

Chromatography: a laboratory technique for separating mixtures of substances. Chromatography could form part of a scalable protocol for purifying exosomes for clinical applications

Exosome: a type of extracellular vesicle, typically 40 and 200 nanometres in diameter, that plays an essential role in cell-to-cell communication.

Extracellular Vesicle: a varied group of biomolecule-filled particles released by most cells, which form by budding off from a cell's lipid membrane.

Senescence: the point at which cells become so aged, stressed or damaged that they are no longer able to grow and divide. Regenerative exosomes could help repair and reactivate senescent cells, combating age-related diseases.

Stem cell: a cell which has the potential to give rise to another cell of the same type or become a specialised cell with specific functions.

Other Resources Mentioned:

1. https://www.prweb.com/releases/roosterbio_receives_grant_from_maryland_stem_cell_research_fund_to_commercialize_msc_ev_technology/prweb16376824.htm
2. https://link.springer.com/article/10.1007/s40124-019-00198-1
3. https://www.nature.com/articles/s41598-019-44569-6#Sec1
4. https://www.tandfonline.com/doi/full/10.1080/20013078.2019.1615820
5. https://www.nasdaq.com/news-and-insights
6. https://investors.bio-techne.com/press-releases/detail/144/fda-grants-breakthrough-device-designation-to-bio-technes
7. https://www.mdpi.com/1422-0067/20/12/2972/htm
8. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0218616
9. https://www.businesswire.com/news/home/20190628005073/en/Biological-Dynamics-Receives-Grant-Award-Funding-Advance