EDISON

Drug delivery platforms

The unsung heroes of future drug discovery

Edison themes

28 November 2022

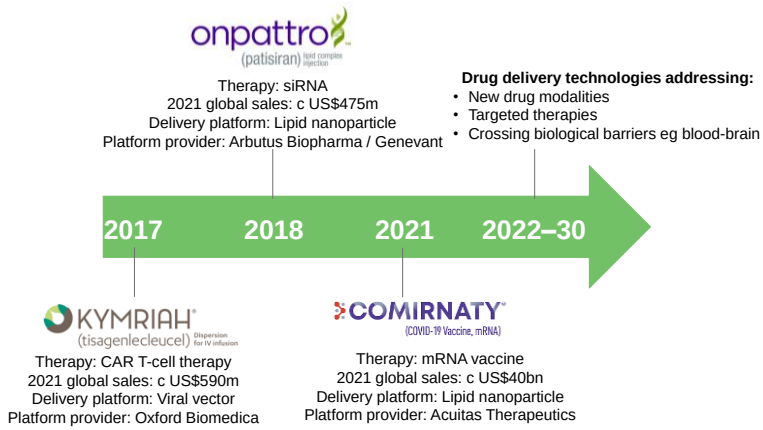
The therapeutic landscape is rapidly changing as clinical investigators continue their efforts to discover the next generation of leading pharmaceutical products. With the emergence of new therapies, such as gene and RNA therapies, there is a need to develop more sophisticated ways of delivering these complex drug modalities to targeted areas in the body. In our view, advancements in drug delivery technologies are as critical as drug discovery, after all, efficacy heavily relies on timing and presence of a drug at the right place. COVID-19 brought a surge of intensified research and funding in delivery platforms, forging new partnerships and, in our view, has primed big pharma pipelines to deliver a raft of new drug candidates that will heavily rely on platforms derived from highly specialised biotechs.

Delivery as valuable as discovery

When assessing the clinical pipeline, there is perhaps a tendency to solely focus on a drug's blockbuster potential with less consideration for the underlying drug delivery technology or where such a platform is derived from. We believe such an attitude represents an oversight and that delivery platforms are, and will continue to be, a critical key to unlocking the true value of new drugs. Some of the latest clinical breakthroughs have only been realised because of delivery platforms, exemplified by the Pfizer/BioNtech COVID-19 vaccine which utilised Acuitas Therapeutics' lipid nanoparticles (LNPs). Unlike Pfizer, Acuitas was not a name making the headlines, yet it played a critical role in the development of a vaccine that helped stem the tide of the pandemic.

Relative to single-asset biotechs, drug delivery companies are somewhat de-risked, in our view, with flexibility to establish diversified partnerships and multiple licensing opportunities that provide upfront access to capital and backend royalties on sales from a single technology platform. Additionally, these technologies can often be applied across a range of indications, uniquely positioning them in the market, and we believe big pharma will ultimately have to turn to them if they are to deliver the therapies of the future.

Exhibit 1: Selected approved drugs utilising new delivery platforms



Source: Edison Investment Research, EvaluatePharma

Advancements in drug delivery continue to rely on highly focused and specialised technologies developed by smaller and nimbler biotech companies. Mechanisms will continue to evolve and fuel advancements in targeted treatments and therapies with more broad-based offerings within large pharma portfolios.

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Companies mentioned in this report (Edison clients in bold)

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Alnylam Pharmaceuticals (ALNY: NASDAQ)
AstraZeneca (AZN: LSE)
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Biogen (BIIB: NASDAQ)
Bristol Myers Squibb (BMY: NYSE)
Eli Lilly (LLY: NYSE)
Gilead (GILD: NASDAQ)
GlaxoSmithKline (GSK: LSE)
Johnson & Johnson (JNJ: NYSE)
Medlab Clinical (MDC: ASX)
Merck & Co (MRK: NYSE)
Novartis (NVS: NYSE)
Novo Nordisk (NVO: NYSE)
Pfizer (PFE: NYSE)
Regeneron (REGN: NASDAQ)
ReNeuron Group (RENE: LSE)
Roche Holding (RO: SIX)
Sanofi (SNY: NASDAQ)
Takeda (TAK: NYSE)

Big pharma is taking notice

The ultimate goal for companies developing drug delivery systems is to create platforms that can incorporate and transport a variety of drugs in a targeted manner, improving safety and efficacy. Conventional drug dosage forms, such as solutions or immediate-release mechanisms, have faced challenges for many drug candidates when administered to patients, eg non-specific tissue distribution and dosing control. These properties can be of particular importance when it comes to approaching regulators who want to see efficacious drugs at lower doses and wider therapeutic windows. We have started to observe a shift occurring in clinical research whereby the development of more sophisticated drug delivery platforms is unlocking the potential of new drug modalities, particularly in the field of cell and gene therapy.

Indeed, we are beginning to see these new therapeutics transition from the clinic to market. The FDA approval of Luxturna (Spark Therapeutics) and Kymriah (Novartis) in 2017 marked two firsts: the first gene therapy to treat an inherited genetic condition and the first CAR-T cancer cell therapy, respectively. Notably, both treatments utilise viral vector delivery technology, a platform that has garnered heightened interest from large cap pharmas. The subsequent takeover of Spark by Roche in a $4.8bn deal and Gilead's $11.9bn takeover of Kite Pharma, whose CAR-T therapies Yescarta and Tecartus were approved in October 2017 and July 2020 respectively, represent some of the industry's most lucrative transactions in the viral vector space.

While viral vectors have been at the forefront of delivering cell and gene therapies, big pharma are also turning their attention to emerging technologies which may be able to deliver the next generation of drugs, establishing partnerships and pencilling deals with smaller companies investigating new delivery platforms (Exhibit 2).

Exhibit 2: Big pharma partnerships with drug delivery technology companies

			Large Pharma								
			Alnylam	AstraZeneca	Boehringer Ingelheim	Bristol Myers Squibb	Eli Lilly	Genentech	Merck	Novartis	Pfizer	Takeda
Selected companies	**Delivery platform**	**Current stage**										
Oxford Biomedica	Viral Vector	Clinical / Commercial		■	■	■				■		
*Medlab	Micelle	Clinical										
**ReNeuron	Exosomes	Preclinical										
Evox	Exosomes	Preclinical					■					■
*Capstan Therapeutics	Lipid-based nanoparticles	Preclinical										
IMV	Lipid-based nanoparticles	Clinical							■			
Acuitas Therapeutics	Lipid-based nanoparticles	Clinical / Commercial									■	
Arbutus Biopharma	Lipid-based nanoparticles	Clinical / Commercial	■									
Starpharma Holdings	Dendrimers	Clinical		■				■	■			
Code Bio	3DNA	Preclinical										■
Voyager Therapeutics	Viral Vector	Preclinical								■	■	

Source: Edison Investment Research, company websites. Note: *Have yet to establish partnerships. **Undisclosed partners.

While some early technologies may take time to progress through the clinic and translate into approved products, they may offer significant growth opportunities. It took nearly 30 years between the first viral vector technology entering the clinic to the approval of the first viral gene therapy, Imlygic, in 2015. Roll forward to 2021 and combined global sales for FDA approved viral vector-

based therapies (Imlygic, Kymriah, Zolgensma, Luxturna, Tecartus, Abecma, Breyanzi, Yescarta) reached c $3.2bn (EvaluatePharma). Approval of Johnson & Johnson's Carvykti, bluebird bio's Zynteglo and Skysona and CSL Behring's Hemgenix in 2022 brought the number of FDA approved viral vector cell and gene therapies to 12, with combined sales estimated to reach c $12.0bn by 2028 (EvaluatePharma). Notably, with a list price of $3.5m, the approval of Hemgenix in November 2022 sets the gene therapy as the world's most expensive drug. Viral vectors have set a precedent, so it is unsurprising that big pharma are paying closer attention to find the next hidden gem of delivery technologies.

Drugs can't always go it alone

While clinical innovations continue, there is a risk that the true therapeutic potential of many drugs goes unrealised. This can be largely due to the inability to deliver them to their site of action in the body. This is particularly true for cancer, where limited drug delivery to tumor microenvironments is one of the major causes of treatment failure, and for major chronic neurological disorders such as Parkinson's and Alzheimer's disease, which require drugs to target the brain. The delivery of drugs to the brain, either for the treatment of neurological conditions or certain cancers, remains a significant challenge with c 98% of newly discovered small molecule drugs unable to cross the blood-brain barrier (BBB). Additionally, efforts to improve drug safety profiles remain paramount as it is estimated that one in three FDA approved drugs exhibit post-market safety issues. New delivery systems must therefore not only demonstrate efficacy but also the ability to safely distribute drugs in patients. With the evolution and development of more complex therapies, such as cell and gene therapies, there is a continued need to develop new delivery platforms to address these clinical challenges. In our view, there are some key characteristics that new delivery technologies need to possess if they are to truly differentiate themselves in the market:

- enhanced drug targeting specificity in the body;
- improved overall drug safety; and
- for those companies investigating gene therapies medicines, the ability to accommodate genetic payloads (eg RNA and/or DNA therapeutics).

Platform companies, not your typical CRO

While biotechs that create and out-license their own pharmaceutical assets may generate a higher return on investment if the drug is successful, those biopharmas that choose to advance their pipelines to the later stages of clinical development internally inherently bear greater financial, regulatory and commercial risk. This is particularly true for biotechs with single asset pipelines. However, delivery platform companies that adopt a technology partnering model may attract more risk averse investors as they may be able to generate immediate and near-term income through multiple technology licensing deals from:

- upfront technology licensing fees;
- research and development consulting revenue on a fee-for-service basis; and
- nearer-term preclinical or clinical milestone payments.

Notably, the market has seen some substantial deals signed with platform companies at the preclinical stages of development. These include Evox Therapeutics' preclinical licensing deals for the company's exosome drug delivery platform with Eli Lilly and Takeda, worth a combined c $2bn in value. The pencilling of such preclinical deals with big pharma players can significantly enhance a biotech's reputation in the market. Additionally, platform companies may be able to validate their technologies to both the biopharma and investment community at the earlier stages of development.

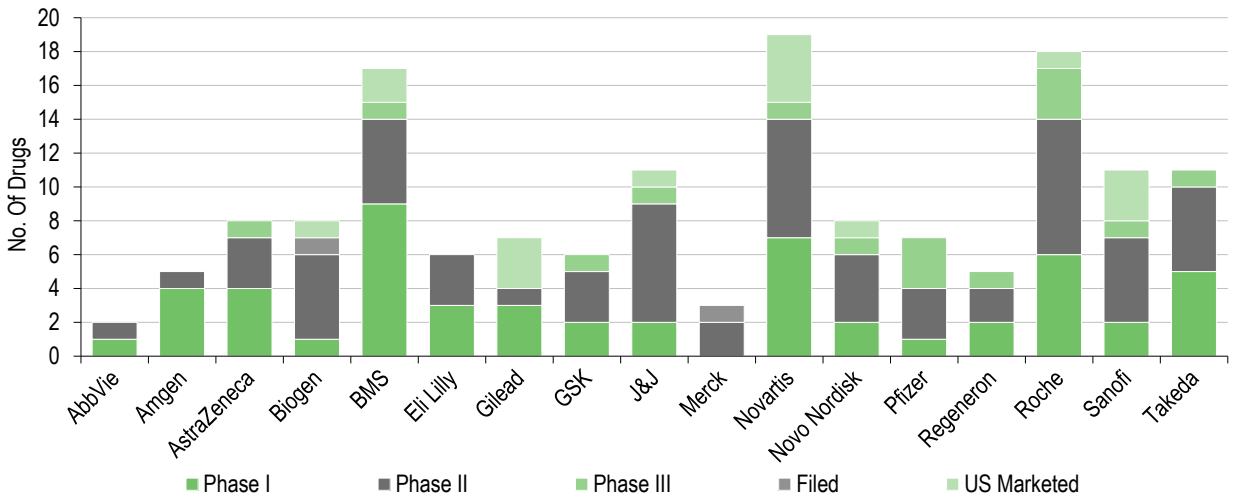
Out-licensing patented technologies can be financially rewarding for smaller companies looking to maintain a competitive advantage by developing new and advanced drug delivery methods. Such a strategy also builds stickiness for platform companies in that they become key technology enablers in the development of a partner's drug with greater value-add than a standard contract research organisation (CRO). In our view, those companies that focus more on becoming critical developmental partners, possessing deep technological know-how in niche areas, may offer greater upside by demanding premium fees for expert research services and higher margins.

ReNeuron Group is an exosome company that is adopting such a 'CRO+' model, aiming to differentiate with its targeted drug delivery exosome platform, CustomEx. The company has reported encouraging preclinical data demonstrating its exosome technology as potential vehicles for targeted drug delivery to the brain, enhanced cellular specificity and drug delivery capabilities (siRNA) over conventional human embryonic kidney-derived (HEK) exosomes used by competitors such as Evox. To date, ReNeuron has established seven discovery stage collaborations with pharma, biotech and academic institutions, through which its proprietary CustomEx platform is being investigated for application in targeted drug delivery.

Unlocking the potential of genetic medicines

While small molecules and antibody therapies will continue to play a critical role in drug discovery, nucleic acid therapeutics, those that utilise DNA or RNA, represent what many perceive as the next generation of pharmaceutical products and big pharma is investing in them (Exhibit 3). One of the major advantages of this drug class is the ability to induce potentially curative responses compared to conventional drugs that target proteins and not the underlying genetic abnormality causing the disease. However, the clinical uptake of nucleic acid therapeutics hinges on sophisticated delivery technologies that help prevent their degradation in the body and can deliver them specifically to diseased cells. Today, we see the most clinically advanced nucleic acid delivery platforms split into two main categories: viral vectors and non-viral vectors (primarily LNPs). However, we are beginning to observe the emergence of new platforms, such as exosomes, transitioning into the clinic that aim to address some of the challenges associated with these existing technologies (Exhibit 4).

Exhibit 3: Big pharma with genetic medicine pipelines



Source: EvaluatePharma. Note: Pipelines represent the following therapeutic categories: gene-modified cell therapies, DNA and RNA therapeutics and gene therapy.

Exhibit 4: Selected drug delivery technologies for nucleic acid therapies

Drug delivery platform	How it works	Advantages	Disadvantages	Selected FDA approved therapies
Viral vectors	Uses modified, inactivated versions of viruses to introduce gene-based therapies (DNA or RNA) into target cells	■ Highly efficient in delivering DNA or RNA ■ High target specificity ■ Can induce effective immune responses	■ Limited to gene therapy payloads ■ Mutagenic safety concerns with certain vector technologies ■ May trigger adverse immunogenic responses and toxicity ■ Issues with re-dosing due to immune response inhibiting efficacy	Imylgic (gene therapy, oncology) Zolgensma (gene therapy, rare disease) Luxturna (gene therapy, ophthalmology)
Lipid nanoparticles (LNPs)	Synthetic nanometre-sized particles consisting of lipids, which encapsulate and deliver therapies to target cells	■ Potentially improved safety profiles over viral vectors ■ Enhance bioavailability and efficacy of non-water-soluble drugs ■ Generally lower cost of manufacturing compared to viral vectors	■ Non-specific tissue distribution of drug outside of the liver ■ Can accumulate in certain tissues including the liver and spleen ■ Challenges associated in sidestepping technology patents	Patisiran/Onpattro (gene therapy, metabolic disorders) Comirnaty (mRNA vaccine, immunology) Spikevax (mRNA vaccine, immunology)
Exosomes	Nano-sized extracellular particles, naturally produced by all cells, which can be manipulated to incorporate therapies and target cells with high specificity	■ Potential to deliver drugs across the BBB ■ Can carry a range of therapeutic payloads ■ Can be used for highly specific, targeted drug delivery with or without modifications ■ Naturally found in the body, which means they are inherently non-immunogenic and offer improved safety profiles	■ Controlled drug release may provide challenges ■ Mechanism of drug delivery and biology not fully elucidated ■ Technology still in its clinical infancy	No existing therapies

Source: Edison Investment Research

Head start for viral vectors but room to improve

Viral vectors use modified versions of viruses to deliver genetic material (DNA or RNA) into target cells to illicit a therapeutic response. In a clinical context, they may be considered as one of the most advanced platforms employed in the development of both cell and gene therapies. To date, the FDA has approved 12 viral vector-based cell and gene therapies, four of which (Zolgensma, Imlygic, Luxturna, Hemgenix) have been approved for direct administration (in vivo) to patients. The public profile of viral vectors received a boost during the pandemic, being the key technology that led to the discovery of the Oxford/AstraZeneca COVID-19 vaccine.

Toxicity concerns highlight what we see as potentially one of the major limitations of viral vector therapies. A number of recent clinical incidents, particularly around Adeno-associated virus vectors, have brought viral vector safety into further question. These include trial pauses for both Pfizer and Astellas' muscular gene therapy treatments and Novartis' FDA approved Zolgensma, which is being further reviewed for potential liver toxicity. While viral vector therapies are expected to share a significant portion of the drug delivery market, particularly for cell and gene therapies, high-profile adverse patient events and increased regulatory scrutiny may hinder overall clinical uptake, opening the door for emerging technologies to differentiate, in our view.

Lipid nanoparticles and RNA therapeutics, hand in hand

RNA-based therapies are a rapidly evolving category of drugs showing much promise as treatments for disease pathways and targets previously considered 'undruggable' through conventional small molecule medicines. Yet the therapeutic benefit of many sophisticated RNA technologies can only be realised through the use of delivery platforms because genetic material rapidly degrades without a specialised delivery vehicle. One of the most advanced vehicles are LNPs.

The FDA approval of Alnylam Pharmaceuticals' Onpattro (Patisiran) in 2018 marked the first-ever RNA interference (RNAi) therapy and provided the clinical breakthrough for the application of LNPs.

Notably, the underlying LNP technology was in-licensed from Arbutus Biopharma in 2012 during the earlier stages of Onpattro's clinical development, with the Canadian biotech profiting from sales royalties and follow-on deals following approval. Arbutus subsequently spun out its LNP delivery platform into the RNA-focused biotech Genevant, which has teamed up with big pharma players Takeda and BioNTech to progress their nucleic acid therapeutic pipelines.

The COVID-19 pandemic marked a further milestone for LNPs, this time in the form of mRNA therapies, acting as critical delivery systems for both the Pfizer-BioNTech (Comirnaty) and Moderna (Spikevax) vaccines. Again, in the case of Comirnaty, the underlying LNP technology originated from a smaller biotech, the privately owned Acuitas Therapeutics. On the back of the vaccine's success, Acuitas entered a strategic partnership with Pfizer with an option to license Acuitas' LNP platform in the development of additional mRNA therapies. Along with Pfizer, BioNTech and AstraZeneca, Moderna became a household name at the heart of the primary COVID-19 vaccination and booster campaigns with its mRNA vaccine Spikevax. While Moderna maintains that Spikevax is developed from its in-house delivery platform, it is currently embroiled in a legal dispute with Arbutus and Genevant, who are seeking damages related to patent infringement on their LNP technology. This emphasises the value smaller biotechs can possess with differentiating technology combined with strong patent estates.

Tissue specificity remains a drawback for LNPs and, unless injected directly into the organ of interest, the technology struggles to deliver therapies to areas in the body other than the liver, inhibiting its application for the treatment of certain diseases. As such, significant effort is now focused on developing organ targeted LNPs that overcome liver accumulation. Capstan Therapeutics is a recently launched US biotech aiming to do just this with its cell-type specific targeted lipid nanoparticle (tLNP) technology. The company is looking to leverage the tLNP platform, combined with mRNA therapeutics, to target various cells in the body, including immune cells for in vivo generation of CAR-T cells in cancer treatment as well as gene editing of diseased cells. The RNA therapeutic pipeline as a whole is poised to deliver further drug candidates, so we view this market as an opportunity for biotechs investing in next-generation drug delivery platforms to target.

Exosomes: The new kids on the block

In our opinion, some of the limitations associated with existing technologies such as viral vectors and LNPs provide an opportunity for new, alternative delivery platforms to address clinically significant challenges. Exosomes are small membrane-bound compartments naturally produced and released by all cells in the body which some companies are attempting to utilise as a new class of drug delivery system. Notably, exosomes can be engineered to incorporate a range of therapeutics and their targeted drug delivery capability can be refined through the modification of proteins on the exosome surface. A major advantage of exosomes is that they have a natural tissue targeting ability based on the parent cell line they are derived from – for example, liver stem cells will produce exosomes that target liver cells. With this, we see the potential market differentiators of exosomes being their ability to:

- specifically target a range of different tissues;
- improve safety profiles;
- cross a range of biological barriers, particularly the BBB;
- protect encapsulated therapies from immune system degradation; and
- incorporate multiple therapeutic payloads.

The most advanced exosome therapies in the clinic are currently derived from HEK293 stem cell lines, aptly named HEK exosomes, and their clinical progression to date is a positive sign in terms of the overall future development of exosomes, in our view. However, the use of only a single HEK293 cell line to produce a single type of exosome may limit the tissues which they can target and result in difficulties when designing therapeutic exosomes to target difficult to reach tissues in the body, such as in the brain. HEK293 is a cell line widely used in the pharmaceutical industry and

exosomes derived from HEK293 are currently being investigated for the treatment of solid tumours (NCT04592484) and liver cancers (NCT05375604). ReNeuron's CustomEx exosomes are derived from seven proprietary stem cell lines: four brain-targeting neural stem cell (NSC) lines (cortex, striatum, hippocampus and ventral mesencephalon) and three stem cell lines from areas outside of the brain (retinal, liver and pancreatic). In our view, ReNeuron's diversification in stem cell lines and ability to produce exosomes designed to provide enhanced natural tissue targeting affinity in preclinical models, particularly NSC lines to target central nervous system (CNS) indications, provides market differentiation from single-cell line competitors. For more information on ReNeuron, please see our recent initiation.

Additionally, in October 2022 ReNeuron announced positive results from a preclinical study in which its CustomEx exosome platform saw a 600% improvement in delivery of a complex RNA therapeutic (siRNA) to the target cells versus competitive HEK exosomes. Targeted drug delivery of siRNA therapies is a significant challenge and overcoming first-pass liver metabolism remains a developmental issue, so we see these results as highly encouraging. However, we recognise that results from preclinical studies may not necessarily translate into patient benefit.

While exosomes represent what we see as an exciting area of clinical research, we acknowledge that the technology is still very much in its infancy, and it may take time before exosome-based products start emerging from the clinic.

Don't underestimate the value of patents

We believe investors should consider the competitive advantages intellectual property (IP) can offer biotechs. Establishing robust IP portfolios is critical in maximising the overall value of a drug or platform, from protection of formulation through to methods of manufacturing. Indeed, big pharma take IP seriously, executing aggressive patenting strategies to extend patent lives, delay competition and keep prices high. A report by I-MAK (the Initiative for Medicines, Access and Knowledge into AbbVie's rheumatoid arthritis blockbuster, Humira (adalimumab), found that, since discovery, a wall of 247 patents had been filed in an effort to protect the drug with market exclusivity for up to 39 years in the United States. We believe the strength of technology patents takes on a heightened importance for drug delivery companies that aim to create a protected and differentiated platform to establish themselves as the go-to drug development partner of choice.

The ongoing legal battle between Arbutus/Genevant and Moderna highlights the benefits a robust IP portfolio can provide to smaller biotech platform companies that often have no tangible marketed products. Arbutus and its spin-off Genevant are seeking damages related to infringement by Moderna on their patented LNP technology, which is claimed to have been used as the delivery platform for Moderna's COVID-19 vaccine, Spikevax. Should a decision fall the way of Arbutus, the biotech's settlement may include significant royalties or licensing agreements tied to the multi-billion-dollar vaccine. In our view, composition of matter patents represent one of the strongest, and most protective, forms of patent a biotech can file, providing a more robust case for demonstrating patent infringement. Notably, it is a key composition claim (US 8,058,069 B2) that forms the basis of Arbutus's litigation case against Moderna.

Exhibit 5: Critical patents for selected drug delivery platform companies

Company	Technology platform	Patent description	Patent status	Patent type	Patent number	Patent expiration
ReNeuron	CustomEx (exosomes)	Exclusivity around using any type of neural stem cell to generate therapeutic exosomes	EU granted US pending	Composition of matter	WO2013150303	2030s
ReNeuron	CustomEx (exosomes)	The protection covers the group's proprietary c-mycER manufacturing technology to generate consistent exosomes	EU granted	Process	WO2014125277	2030s
Medlab	NanoCelle (micelle)	Provides protection over exact composition of NanoCelle technology, possible variations of it and combinations with various active pharmaceutical ingredients	EU granted US granted	Composition of matter	WO2016141069	2030s

Source: Edison Investment Research

ReNeuron has established a patent landscape around its CustomEx technology with management attesting that the group houses the third-largest global patent portfolio in the field of exosomes. We see the true value centering around two main patent families (see Exhibit 5). The first is designed to provide the company with exclusivity around using any type of neural stem cell to generate therapeutic exosomes, most likely for CNS indications, while the second surrounds the group's proprietary exosome manufacturing capabilities. With extensive protection across its conditionally immortalized stem cell lines and patent lives extending beyond 2030, this provides ReNeuron with a distinct competitive advantage and the ability to leverage its IP position to secure future licensing deals and create longer-term value, in our opinion.

Medlab Clinical is an Australian biotechnology company that is developing therapeutics using its proprietary micelle delivery technology, NanoCelle. NanoCelle is Medlab's patented, proprietary drug delivery platform, designed to bypass the digestive tract pathway and first-pass metabolism by allowing drugs to be absorbed via a buccal or nasal spray delivery system. The exact composition, possible variations of it and potential drug combinations are protected by a patent that was first filed in 2016, and now granted in Australia, Europe and Canada, the United States and Singapore. The protection period extends to at least 2036. Medlab has applied the NanoCelle technology in the development of its lead clinical asset, NanaBis, a combination of synthetic cannabidiol (CBD) and dronabinol (synthetic THC), for the treatment of cancer-induced bone pain. The company is now looking to submit an investigational new drug application to the FDA for the commencement of a Phase III study, which is anticipated to commence in FY23. For further information on Medlab please see our initiation.

Delivery platforms hold the value key

It is evident that the discovery of new drugs for the most challenging to treat indications is going to require in tandem advancements in drug delivery technologies. Pharma companies looking to bolster their pipelines by making inroads into the cell, gene or RNA therapeutic markets will have to look to delivery systems to realise their blockbuster ambitions. While some delivery technologies may currently be more advanced than others, it is highly unlikely there will be a 'one glove fits all' technology, and the COVID-19 pandemic has taught us that each platform can find its own way of contributing to the discovery of new medicines. It is sometimes tempting to dismiss emerging technologies and label them as being too risky; however, recent RNA breakthroughs have shown us that getting in on the ground floor with well-positioned smaller biotechs can certainly have its benefits.

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