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In Vivo Gene Therapy for Mainstream Diseases

Making Inroads Beyond the Rare and Orphan

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FIRST PRINCIPLES
ADVISORY GROUP

The past 18 months have provided a glimpse of the promising future of in vivo gene therapy. The US launches of LUXTURNA® and ZOLGENSMA®, and high-profile acquisitions suggest this field will forge ahead into new indications and continue to break boundaries. The continued growth and change indicates that invested parties need to revitalize perspectives. A holistic view of the market, agencies and competitors is needed to truly optimize a portfolio and maintain a favorable market presence. We review where in vivo gene therapy stands today, examine the potential shift in indications, from monogenic to complex, and discuss why it is time to review market and portfolio analyses in the field.

In Vivo Gene Therapy Now Approved In Two US Indications

On May 2019, ZOLGENSMA® (onasemnogene abeparvovec-xioi) became the second in vivo gene therapy (genes are directly inserted into the body) approved by the US Food and Drug Administration (FDA). In this therapy, a single dose intravenous infusion of the SMN1 gene is administered directly in vivo to children less than two years of age who are diagnosed with spinal muscular atrophy (SMA). That approval followed on the heels of LUXTURNA (voretigene neparvovec-rzyl), approved in December 2017 as a one-time delivery of a functional gene for patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. In the second half of 2019, across multiple indications, nine industry sponsored, late stage trial readouts are expected.

In addition to the approvals, several large deals exemplify the expectation of significant therapeutic and commercial value from this emerging technology. Over the last 12 months $14.5B in acquisitions occurred in this landscape: AveXis ($8.7B), Spark Therapeutics ($4.8B), NightStar Therapeutics ($800M), and Myonexus Therapeutics ($165M).[1-4] See table in appendix for details.

QUESTIONS EXAMINED IN THIS PAPER

- **How far has in vivo gene therapy advanced? What is driving the change and how quickly is the market evolving?**
- **What is the potential for in vivo gene therapy in both orphan and common indications? How competitive is in vivo gene therapy within indications and compared to existing therapies?**
- **How will it affect standard of care? How might this affect current and future portfolios?**

Over 700 gene therapies are in development and in vivo gene therapies comprise about 55% of them.[6] Most clinical in vivo gene therapies are targeting monogenic diseases, however several are for large, polygenic and complex indications such as in oncology and neurodegenerative disorders such as Parkinson's and Alzheimers.

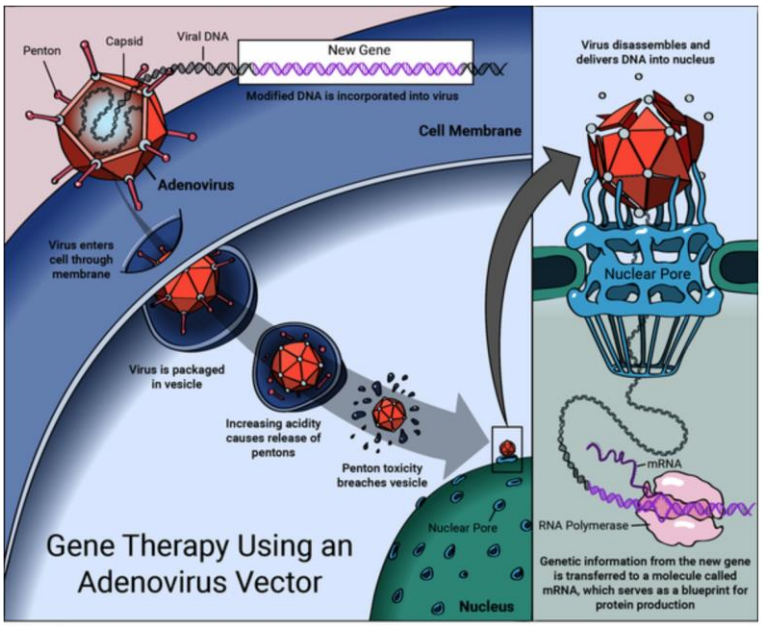
As these therapies move from monogenic diseases to become part of the broader therapeutic landscape and the regulatory environment becomes more favorable, the in vivo gene market has potential to experience greater growth and drive disruption.

It is time to re-examine existing assumptions and frameworks to develop a clearer understanding of this dynamic, evolving treatment and its impact on life science company strategies, portfolios, and competitive positions.

A Long Road to Approval

In vivo gene therapy transfers a working copy of a gene(s) into a patient's body using a viral or non viral vector. Unlike ex vivo, in vivo therapy is administered directly into cells of the body. The AAV (adeno-associated virus) is the most common vector used for in vivo therapy today, largely due to safety and long-term expression.[8]

Culminating more than forty years of research and development,[5] current in vivo gene therapy advances are finally ushering in a surge of successes. After set-backs in the late 1990s, safer, more effective vectors were integrated and a steady flow of trials ensued. Now, successful applications in inherited retinal disease, hemophilia, thalassemia, sickle-cell anaemia and spinal muscular atrophy are emerging.



The US regulatory agencies have also signaled a shift in thinking. After decades of close scrutiny and redundant oversight on the field, the FDA, NIH (National Institutes of Health) and IOM (Institute of Medicine) have streamlined the review process for new applications, removed some regulatory barriers and started incorporating gene therapy oversight into existing systems[22]. The FDA announcement that some gene therapies will receive less arduous review for diseases with high unmet demonstrates the FDA's commitment to relatively fast regulatory path[23].

US and EU Approved in Vivo Gene Therapies

Date	Therapy and Indication	Approval Agency
July 2012	Glybera® for hereditary lipoprotein lipase deficiency (LPLD).	European Medicines Agency (EMA)
December 2017	LUXTURNA® for Leber's congenital amaurosis	FDA
November 2018		EMA
May 2019	ZOLGENSMA® for SMA	FDA

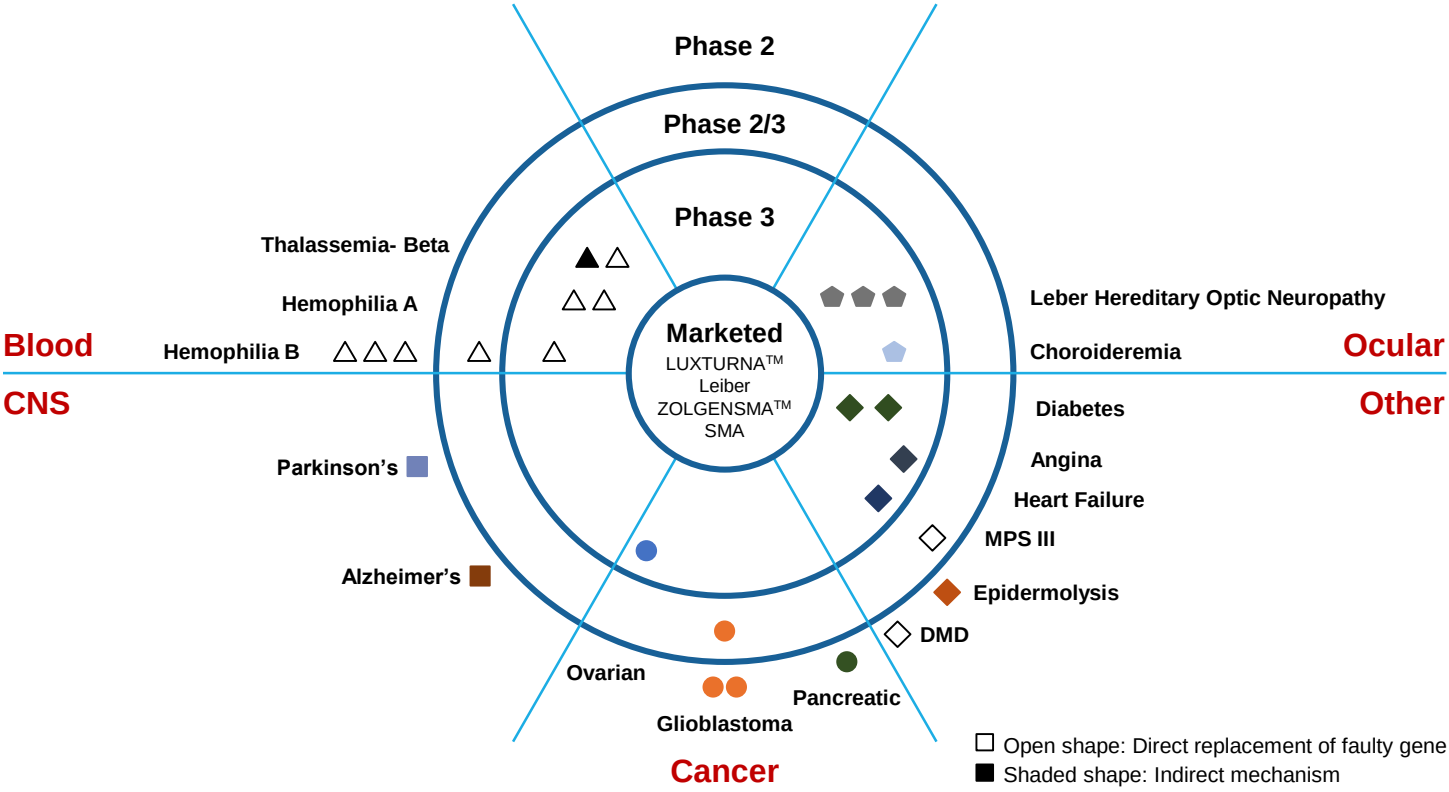
Note: Additional therapies have been approved globally.

> ***I believe gene therapy will become a mainstay in treating, and maybe curing, many of our most devastating and intractable illnesses.***
>
> ***Former FDA Commissioner Scott Gottlieb, M.D.*** *(Dec. 2017-LUXTURNA approval)*

The Pipeline Is Large with Many Different Indications

The targeted indications for in vivo gene therapy demonstrate a breadth of potential applications. The number of preclinical to pre-registrational gene therapy programs tripled from 2014 to 2018. Globally, as of May 2018, 400+ in vivo gene therapies are in development, with an estimated 160 focused on AAV-based delivery.[6]

There are ~80 current in vivo clinical trials in the US7. Overall, more than 30 disorders are represented in the current pipeline. Nine commercial therapies are currently in US phase III clinical trials and eleven more are in phase II clinical trials. Additionally, seven molecules in phase III trials have a planned primary completion date of 2019, potentially leading to multiple approvals in the next two years.



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Current clinical-stage therapies focus on two primary categories: those that directly replace a missing or malfunctioning gene, and those that affect a broad cellular mechanism unrelated to specific mutated genes. While much of the focus has been on direct gene replacement in monogenic indications, the greater potential may lie in how gene therapy impacts complex indications without clear genetic causes.

Monogenic Gene Replacement Therapies Dominate the Pipeline and Acquisitions (~75% of US trials)

The currently approved in vivo gene therapies are for rare and orphan monogenic diseases. Glybera (EMA) is approved for familial lipoprotein lipase deficiency, LUXTURNA® (FDA,EMA) for blindness due to mutations in the RPE65 gene and ZOLGENSMA® (FDA) for SMN1 gene correction in SMA. The potential number of monogenic diseases applicable for in-vivo gene therapy is not known. With advances in early genomic detection, and a broad pipeline of programs in development, additional monogenic applications are highly likely.

Monogenic diseases are caused by errors or mutations in a single gene that impacts the body's ability to make a necessary protein. According to the World Health Organization, over 10,000 human diseases are known to be monogenic.[9] With the exception of blood disorders such as hemophilia and thalassemia, monogenic diseases tend to be rare. Eighty percent of rare diseases are caused by a single faulty gene.

In the United States alone, an estimated 30 million people are living with a rare disease, defined as affecting 200 thousands or fewer patients.[15] However, for any particular rare disease, the incidence and prevalence will be low. For example, Leber congenital amaurosis, a genetic condition corrected by LUXTURNA, affects about 2 thousand individuals in the US, compared with heart disease that affects around 5 million adults.

Rare, monogenic diseases can also be challenging to diagnose, which takes an average of eight years.[15] Patients are often diagnosed after long-term damage to their health has already taken place, which may limit the efficacy of gene therapy. Both LUXTURNA and ZOLGENSMA aim to treat very young patients, highlighting the importance of administering gene therapy as early as possible.

The combination of challenging diagnosis, low prevalence and incidence makes finding appropriate patients for trials and eventual treatment a challenge in the monogenic space. Yet, as demonstrated by the current approved therapies, quality of life is vastly improved for those that benefit.

Spark Therapeutics LUXTURNA™
First in-vivo Gene Replacement Therapy for monogenic disease approved by the FDA (2017)

LUXTURNA™ approved for retinal dystrophy caused by biallelic mutations in the RPE65 gene. A one-time treatment for patients >12 months with viable retinal cells.

The approval of LUXTURNA™ marked an inflection point in the US:

- **Set New Standard of Care:** Created a best-in-class treatment for patients with no other therapeutic options
- **New gene-based market segmentation:** Segmented the retinal dystrophy market by gene mutations (identification of genetic mutations are imperative for patients to receive LUXTURNA™)
- **First approved FDA in vivo gene therapy:** Forged a new regulatory pathway and benchmark for gene-directed treatments

However, adoption is a challenge:

- **Limited Access:** Seven hospitals in the U.S. are qualified to offer this treatment, and only a single center has two full time surgeons, there is a backlog of patients waiting and patients often must travel long-distances to receive treatment.10
- **Limited Market:** Treatment should be as early as possible after 12 months of age, to preserve the most potential eyesight, so many current patients are not considered candidates for therapy. Only ~ 1-2 thousand people in the US have the RPE65 mutation.
- **High Cost:** It costs $850K to treat both eyes, and was the most expensive medicine in the US before the approval of Zolgensma. Spark has offered rebates if certain visual thresholds are not met after treatment, though it is unclear what those rebates will be.
- **More Competition:** MieragTx also offers an adenovirus based in vivo gene therapy for replacing defective RPE65 genes (A001), is currently enrolling in a phase 1/2 clinical trial, and has received orphan status from both the FDA13 and the EMA. MieragTx also benefits heavily from being the second to market in this instance, as the regulatory path and appropriate medical facilities were created by LUXTURNA's approval.

Newborn Screening May Be Key to Finding Patients with Rare, Monogenic Diseases

Enhanced newborn screening could aid in pediatric identification of patients and to determine risk of adult onset of a specific disease. In the United States, newborn screening is determined at the state level, is not uniform, and can vary from fewer than 30 diseases to over 60 diseases screened.[16] In 2015, the National Institutes of Health's Newborn Sequencing in Genomic Medicine and Public Health (NISGHT) launched a newborn screening project called BabySeq. The study goal is to generate insights on how best to use genomics in clinical pediatric medicine. In this project, each newborn is profiled with whole exome sequencing techniques to generate a genomic sequencing report, examining >5000 genes that are strongly linked to childhood-onset disease. This has been expanded to also include adult onset diseases (under certain conditions).[17]

The ability to diagnose both pediatric and adult onset diseases from newborn testing would potentially allow a greater number of diseases to get identified before damage has occurred.

Much Greater Opportunity From Non-direct Mechanisms? (~25% of US trials)

Monogenic disorders such as hemophilia, thalassemia and ocular disorders currently have the largest and most advanced clinical pipelines for in vivo gene therapy. However, about a quarter of all clinical trials are for larger, complex indications, such as various cancers, Alzheimer’s Disease and Parkinson’s Disease. In these competitive indications, gene therapy provides another mechanism of action for slowing, halting or reversing disease progression, that can be used alone or in conjunction with more traditional therapies.

Many gene therapy candidates in this arena have more general mechanisms of action than targeting one malfunctioning gene. Several therapies for cancer are not looking at the specific malfunctioning genes, but instead are aiming more broadly at activating ubiquitous mechanisms that will lead to cell death, with a variety of different targets and delivery mechanisms. For example, gene therapies are being employed to have cells produce their own 5-fluorouracil (Toca 511), produce chimeric receptors that induce apoptosis (VB-111), or wild-type versions of p53 that can induce apoptosis (SGT-53).

If these gene therapies continue to show efficacy and specificity, the potential application for gene therapy will be greatly enhanced. These therapies will no longer be limited to diseases where biology is well understood, and a single malfunctioning gene has been identified as causative.

Case Study: VB-111 (Ofranergene obadenovec) Gene Therapy

VBL Therapeutics VB-111 (Ofranergene obadenovec)
Phase 3 trials for platinum resistant ovarian cancer
Non-Direct Gene Therapy

VB-111 is a late stage contender in a new class of in vivo gene therapies that only replicate in specific cell types and that target general cell mechanisms to affect disease course.

- **Another treatment option:** Gene therapy advancing in a crowded and competitive field targeting a sizable indication.
- **A therapy that does not require a diagnostic biomarker:** For platinum resistant patients, many new therapies, such as rucaparib and olaparib, are only available for patients with specific genetic mutations. VB-111 is available to all patients regardless of mutation or biomarker status.
- **Gene therapy delivery via peripheral infusion:** VB-111 is easily delivered and requires no special facilities, training or equipment.
- **Tumor specific targeting:** The promoter used in VB-111 allows specific targeting to cancer cells. The gene will not be inserted, or replicate, outside of cancer cells. This mechanism could allow for much higher level of specificity for gene therapy over traditional therapies, potentially decreasing adverse events.
- **Navigable FDA approval path:** VB-111 could follow in the footsteps of both aped in vivo gene therapies, LUXTURNA® and ZOLGENSMA®.

Market potential is high

- **Widespread access:** Delivered via infusion, so any chemotherapy unit will be able to treat patients with VB-111.
- **Open, but competitive, market**: VB-111 is not limited to mutation positive patients, so can be used in all-comers population, however will need to compete with several clinical or marketed candidates in this space.
- **High cost therapies common for ovarian:** It is unclear how much VB-111 will cost, however current therapies, pembrolizumab, rucaparib, olaparib, are hundreds of thousands of dollars for treatment.

Time to Update Market Perspectives

The combination of recent approvals, shifts in regulatory agencies, acquisitions, and a large pipeline of growing clinical programs marks an inflection point for in vivo gene therapy as a competitive therapy across a number of indications. Market change is already underway and the impact is being felt. Whether looking across the in vivo gene therapy market as a disruptor, competitor or investor, it is timely to re-examine assumptions and impact. Current key areas of impact include:

Elevates Standard of Care

- For monogenic diseases, these may provide one of few therapy options and, in some cases, may sustainably address the underlying causes of the diseases
- For non-direct gene therapy diseases, in vivo gene therapy presents a new mechanism of action which could as a stand-alone or in combination to offer improved outcomes. Some early read-outs show promise of improved efficacy in advanced cancers.

Adds to Competitive Intensity

- Companies are not just pursuing monogenic or greenfield market options.
- Gene therapies are now clinically-staged alternatives for a number of large indications, with a variety of different MOAs that could affect broad cellular processes. As the field grows and evolves, gene therapy will add to the competitive intensity in these indications.
- Gene therapy companies are well funded, allowing them to move to clinical trials faster and better compete in crowded indications.

Repositions Pharma Portfolios

- Recent acquisitions demonstrate the desire to have specific indications and/or platforms incorporated into portfolios. The acquisitions have been complementary in nature.
- For some companies the timeline from formation to acquisition has been very short. Further in vivo gene therapy market acquisitions are widely cited as highly likely even for 2019.

Favorable FDA Environment

- The FDA is committed to streamlining approval process, publishing more guidance documents and working to advance gene therapy approvals.
- Proof of concept strategies often aimed at getting quick FDA feedback

Beyond these considerations, gene therapy is already challenging existing paradigms in newborn screening, trial design (endpoints), payer models and patient access, and will continue to do so as it moves into new indications. Ultimately, it has the potential to significantly change previous assumptions on how disease is managed.

> ***Gene therapy products now have the potential to cure intractable diseases, and fundamentally alter the trajectory of many other vexing illnesses.***
>
> ***Former FDA Commissioner Scott Gottlieb, M.D. and CBER Director Peter Marks, M.D., Ph.D. (Jan 2019***

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APPENDIX: Acquisitions as Complements

Acquisition rationale has been primarily based on complementary indications within a portfolio. With the exception of the acquisition within the in vivo gene therapy market, others have focused on late stage assets proved assets.

Summary of In Vivo Gene Therapy Acquisitions 2018-2019

Gene Therapy Company	Acquired By	Latest Phase in Portfolio	Purchase Price	Acquisition Rationale
NightStar Therapeutics (Public Company valued at $393M at IPO on Sep 27, 2017; raised $175M prior to IPO)	Biogen Idec March 2019	Phase 3	$800 million	▪ Two potentially first-in-class mid- to late-stage clinical assets as well as preclinical programs ▪ Lead asset NSR-REP1 is in Phase 3 development for choroideremia ▪ Ophthalmology is an emerging growth area for Biogen
Spark Therapeutics (Public Company valued at $352M at IPO on January 30, 2015; raised $123M prior to IPO)	Roche February 2019	Marketed product (Luxturna)	$4.8B	▪ First biotechnology company that has successfully commercialized a gene therapy for a genetic disease in the U.S ▪ Spark's hemophilia A program
Myonexus Therapeutics (Private Company; raised $63M prior to acquisition)	Sarepta Therapeutics February 2019	Phase 1/2a	$165 million	▪ Five gene therapy candidates to treat limb-girdle muscular dystrophy ▪ Serepta micro-dystrophin gene therapy and the Myonexus programs have much in common
AveXis (Public Company valued at $430M at IPO on Feb 11, 2016; raised $75M prior to IPO)	Novartis May 2018	Marketed product (Zolgensma)	$8.7B	▪ First-ever one-time gene replacement therapy for spinal muscular atrophy (SMA) ▪ AveXis offers a valuable gene therapy platform and scalable manufacturing to accelerate potential future programs and launches

Excludes companies that have taken a significant stake in a gene therapy company or announced a significant licensing deal.

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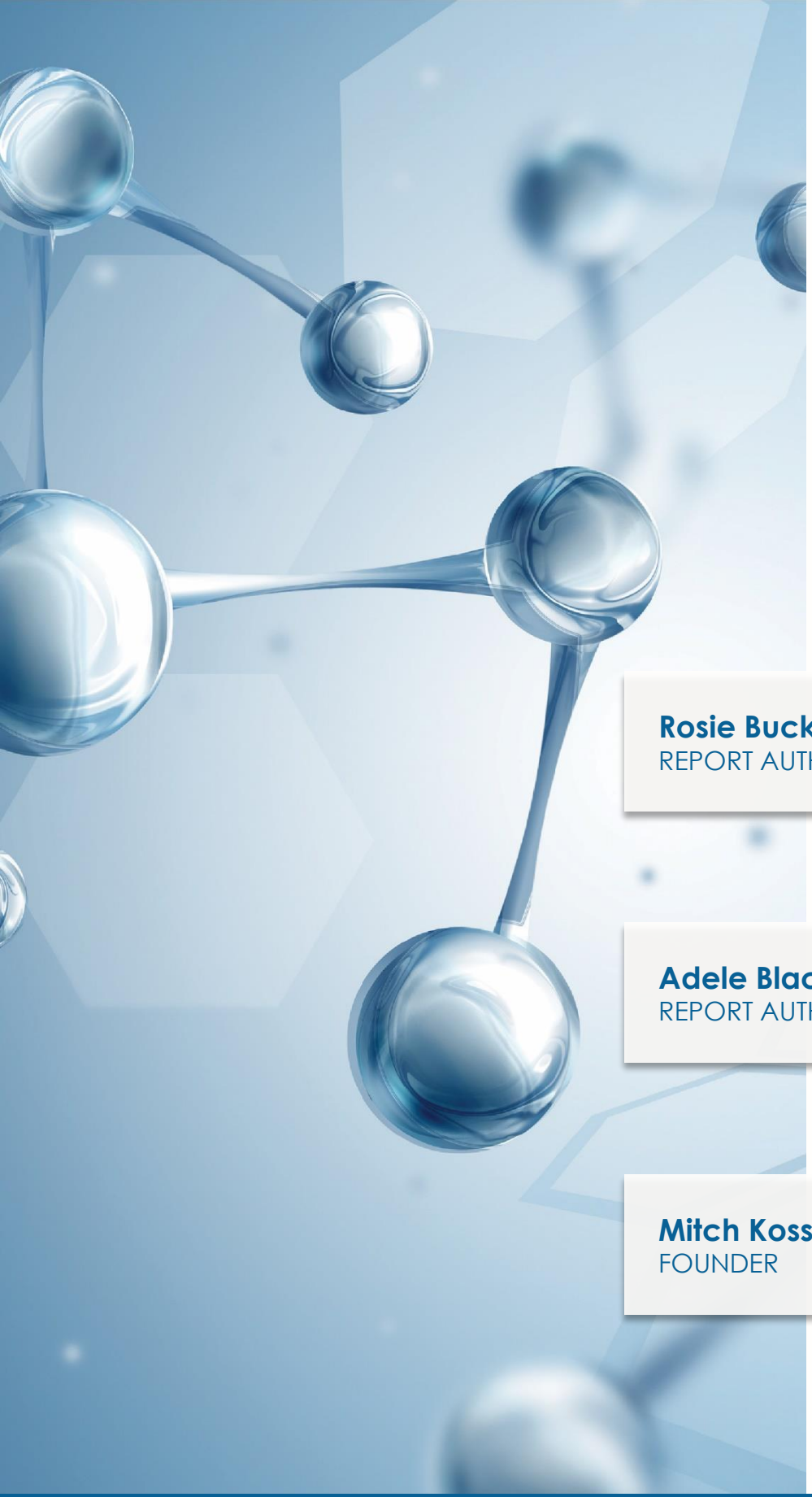

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