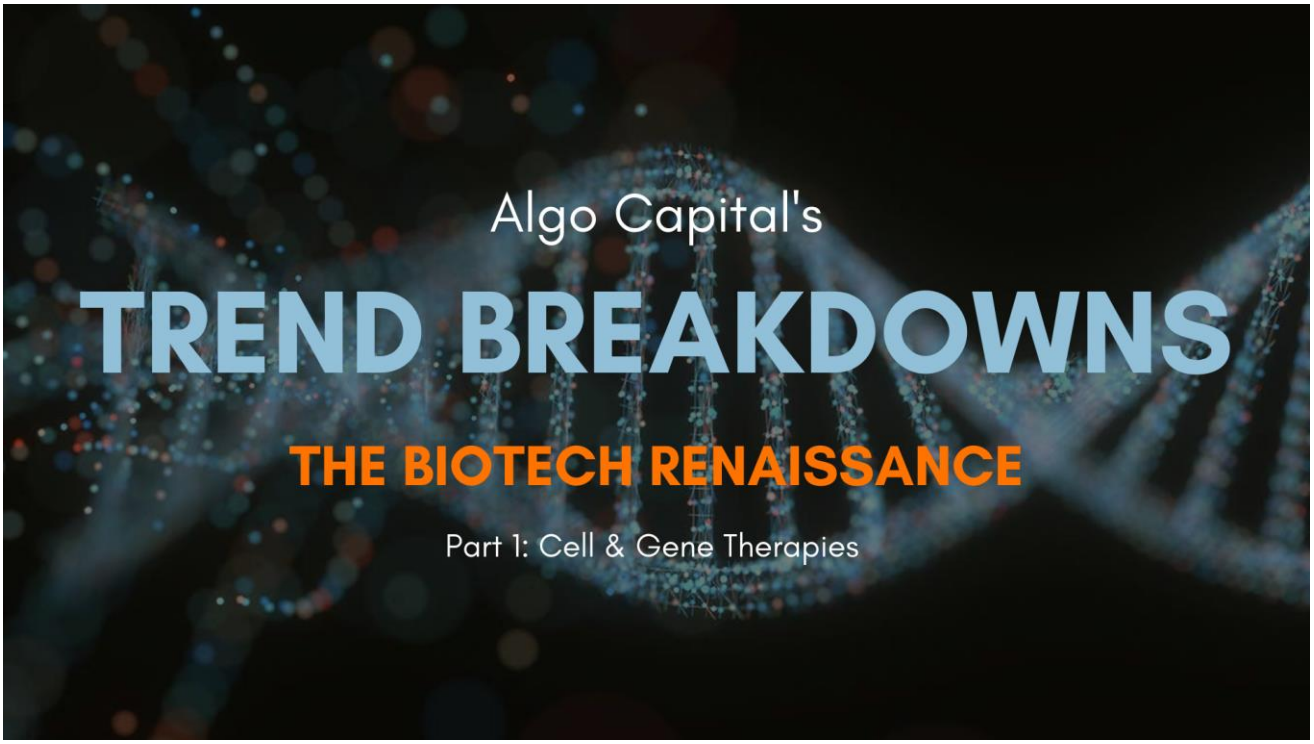


An Introduction to the Series

In today's fast-paced world, our capacity to capture excess returns as investors is heavily resting on our ability to spot new emerging trends well in advance of the market and having the stomach to position our capital accordingly. The linear world that has been so familiar to our parents and grandparents has abruptly taken a turn, jumping on the exponential bandwagon referred to as "Moore's Law". Artificial Intelligence, Space Exploration, 3D Printing, Genetic Engineering… the list goes on and on, but the underlying framework that underpins all of these exciting new trends is the systematic leveraging of data — being it in bits or stored in DNA bases — to re-design the world to be more efficient, cost-effective, and overall improved.

By virtue of our advisory activity at the side of startups, as well as our daily analysis of the public markets, at Algo Capital we are blessed to be constantly exposed to the Cambrian explosion of change that is unfolding. Being able to navigate and sort through the noise, understanding which new technology has merits and which ones are still too young to be relevant, has become essential nowadays if you — like us — aim at operating effectively in the business world.

Through these series of publications titled Trend Breakdowns, we look at breaking down into its constituent parts these exciting new industries. We hope to provide you with a basic understanding of the technologies involved in this incredible wave of innovation as well as some of the companies pushing — the proverbial — envelope. Our objective is to inform and spur discussions that might enable us to learn from you as much as you from us. Being very conscient that we: "don't know what we don't know" we welcome all comments and insights that may arise from this article.

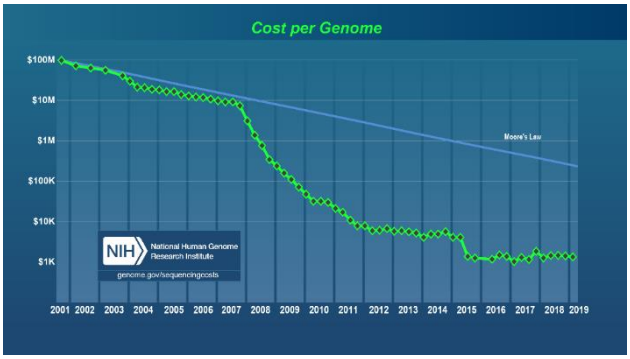
The Biotechnology Renaissance

What is happening in Biotechnology is probably the most exciting opportunity that we ever came across. We believe this is going to be the most significant driver of change of the 21st century. Of course, we might be a bit biased given our passion for the subject, but the amount of innovation unfolding in the healthcare sector and particularly in biotechnology is just staggering. Until recently, the space has been kind of a walled garden, shying away from the spotlight. Maybe the perceived complexity of the underlying technologies and the binary outcomes of investments in biopharmaceutical companies has kept the public eye and non-specialized investors somewhat distant. But not anymore. The unheralded unfolding of the Covid-19 global pandemic has made sure of that. Like never before, the world has realized the critical relevance of the healthcare system and related supply and value chains.

The virus has taught us the importance of preparedness in the face of tail-events, and that complacency can be very costly. On the other hand, it has shown us just how magnificent technology applied to the understanding of the internal mechanics of our bodies is, and the effect it can have on the world. In the span of a few months, we went from utter and black desperation of not seeing the end of this pandemic to having a vaccine with over 90% efficacy. This is just incredible. Innovations such as mRNA vaccines have been in the pipeline for years, and only now we were able to bring their potential to light. Companies such as Moderna and BioNtech, have demonstrated just how important breakthroughs in these areas are, and we are just ecstatic about what this will mean for the next decade of the biotech industry.

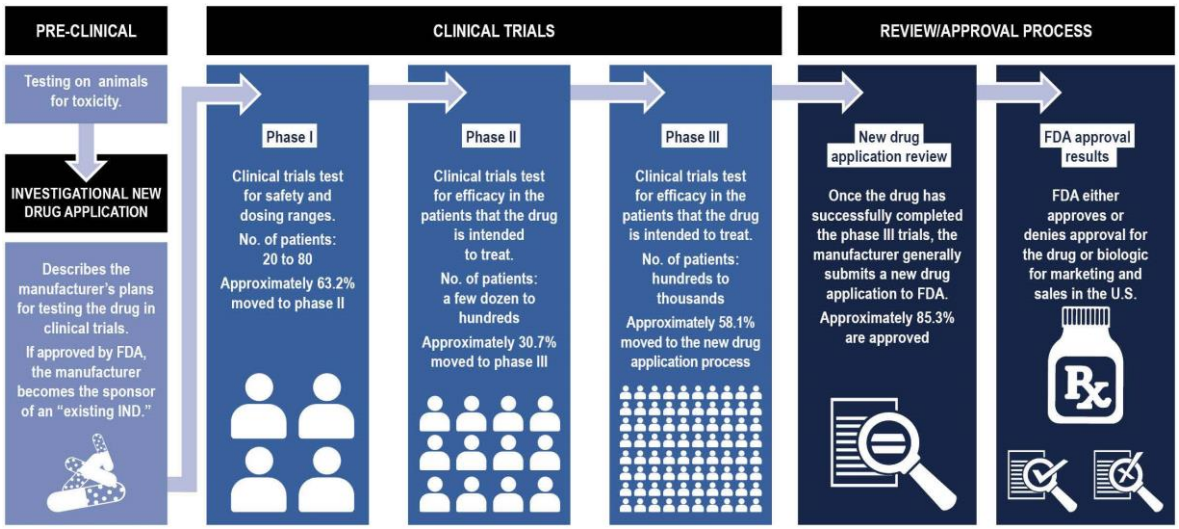
Backdrop:

Thanks to the *Human Genome Project*, which in the '80s set out the bodacious goal to sequence the entire human genome, we now have a much clearer account of the more than 30,000 genes present in our cells. The swift progress made in computing power capabilities starting from the 90's up until today, has exceptionally enhanced our capacity to run analytics, implement big data, and machine learning components on top of this trove chest of data. As never before have we had so much computing capacity dedicated to the understanding of our own biology. The breakthroughs in semiconductors and related technologies have brought down exponentially the costs of genome sequencing from millions of dollars to just a few hundred dollars. Therefore, we are now empowered by much better, much more granular, and much cheaper data, which has set the stage for the inflection point in biology that we are currently experiencing. Below a graphic representation **[1]** of the price decline:



For the past twenty years, Biotechnology companies have masterfully leveraged the superior computing capabilities at their disposal to improve upon their discovery efforts. The billions of dollars of capital invested gave birth to a multitude of technologies that are just now coming into fruition, beginning to get approved by regulators and hence becoming commercially enabled.

Given the high sensitivity and risk associated with administering drugs to patients, biotechnology is highly regulated by specific bodies, such as the *FDA* (*Food and Drugs Administration*) in the USA and *EMA* (*European Medicine Agency*) in the EU. This in turn makes the go to market for biotech companies much more expensive and slower compared with other type of businesses — like SaaS. The lifecycle from new discoveries to marketed drugs has been generally in the range of 10+ years, and often even longer. For those of you unfamiliar with the drug development process, we have attached an intuitive picture [2] of the entire workflow from pre-clinical to approval at the FDA below:



Even the regulatory process will see change in the next decade, thanks to advancements in big data and analytics. We are very cognizant of how governments are slow to change, but even them are powerless in front of technology relentless advance. Slowly but surely, they will adapt and incorporate better digital processes to streamline drug approvals, making them faster, more secure, and safer. This trend is unfolding as we speak, being further accelerated by the Covid-19 pandemic, which saw for the first time much faster rate of approval for specific drugs, as well as highlighting to regulators the importance of speed. We see this as an incredibly positive development, converging with all the breakthroughs in therapeutic drugs coming through clinical trials.

Each of these major technologies will be the topic of discussion of the next few publications of our series. We are going to dive into Cell & Gene Therapies, Stem Cells, Cancer Immunotherapies, mRNA Technology, Gene Editing, and Exosomes.

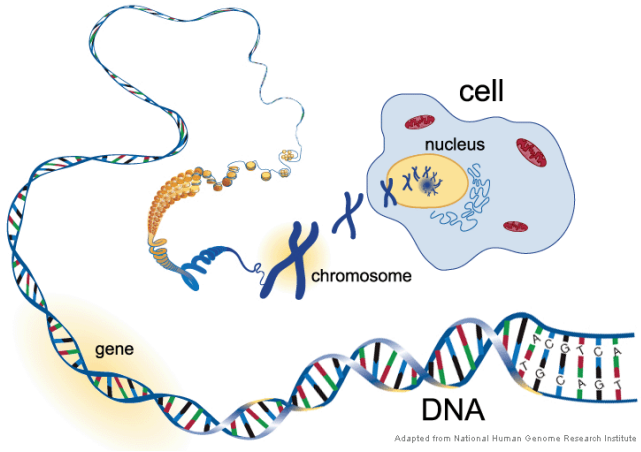
Biology 101

To be able to gain an understanding of the different technologies gaining momentum in biotech, it is necessary to secure a very basic understanding of some of the terminology and processes underpinning basic biological systems. Many of you may not be well versed in the subject, so a very quick rundown is in order.

Disclaimer: We do not hold a Phd in bioengineering, so for the ones among you who does reading this, feel free to point out to any error we might have made!

What is DNA and how are proteins made?

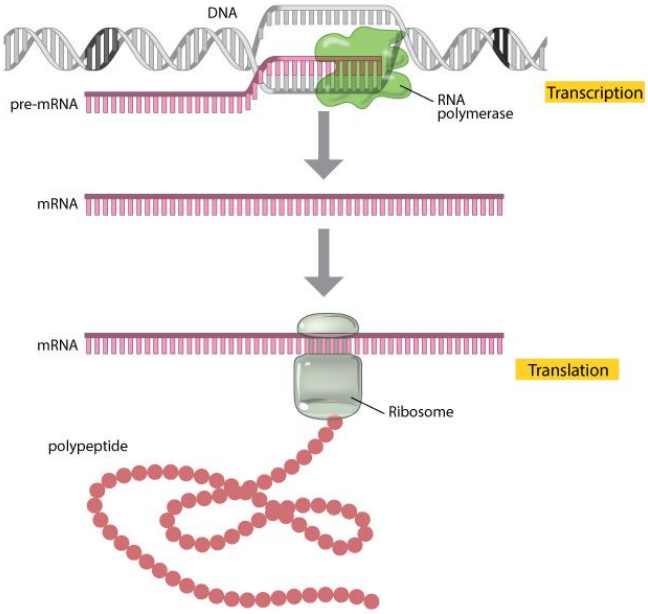
As it is often the case, complex systems are best explained using analogies. A metaphor cleverly employed by the wonderful writer biologist, *Matt Ridley*, in his book *Genome*, is to compare the Genome to a book. There are only 23 chapters called *Chromosomes*, each containing several stories called *genes*. Each gene, instead of being written on paper, is composed by three letter words called *codons* encoded on chains of sugar and phosphate termed *DNA*. Each codon is further broken down in three letters called *bases* or *nucleotides*. There are only four letters in the DNA alphabet, (A) Adenosine, (G) Guanine, (T) Thymine and (C) Cytosine. These four letters, repeated in different combinations, are the language of life. A convenient illustration [3] of the various components below:



Chromosomes are present in the nucleus of most cells in our body and are replicated during cell division. The genome is not like your typical book, in fact it is able to read itself in a process called *translation*, as well as to photocopy itself, in biology's lingo *replication*.

Chromosomes are present in the nucleus of most cells in our body and are replicated during cell division. The genome is not like your typical book, in fact it is able to read itself in a process called *translation*, as well as to photocopy itself, in biology's lingo *replication*.

The whole process starts with *transcription*, where an enzyme called RNA Polymerase reads the text of a specific gene and creates an almost exact copy called *pre-messenger RNA*. RNA is written in remarkably similar language to DNA, there is only a slight change in one letter, (U) Uracil instead of (T). The message is still a rough version though, it goes through a sequence called *splicing* where certain parts of the text, called *introns* get cut out, and other parts, *exons*, are pasted together to form a complete mRNA or *messenger RNA*. This process is vitally important because it allows different mRNAs to be created from the same recipe or gene, depending on the different exon combinations. The next step involves complex biological machines made up protein and RNA called *ribosomes*, which move along the mRNA, reading the different codons (e.g. AAC) and translating them in another language made up of twenty *amino acids*. Each three-letter codon has a corresponding amino acid which is transported by a *transfer RNA* or *tRNA*. The process continues until the whole mRNA has been read and a chain of amino acids, called *poly-peptide chain* has been formed. This chain then folds up in a specific shape. This is a *protein*. You can see the process more intuitively in the representation [4] below:



Each single protein in our body has been created from specific genes or combination of genes. Genes however, do not get translated only in proteins, but can also stay in RNA form and perform other activities. Proteins are the catalysts for most of the functions in our bodies. *Enzymes* for example, catalyze chemical reactions and are heavily involved in the transcription and translation process. These amazing conglomerates of amino acids called proteins are also responsible for switching genes on and off, by binding on to specific sites on the genes, *promoters*, and *enhancers*.

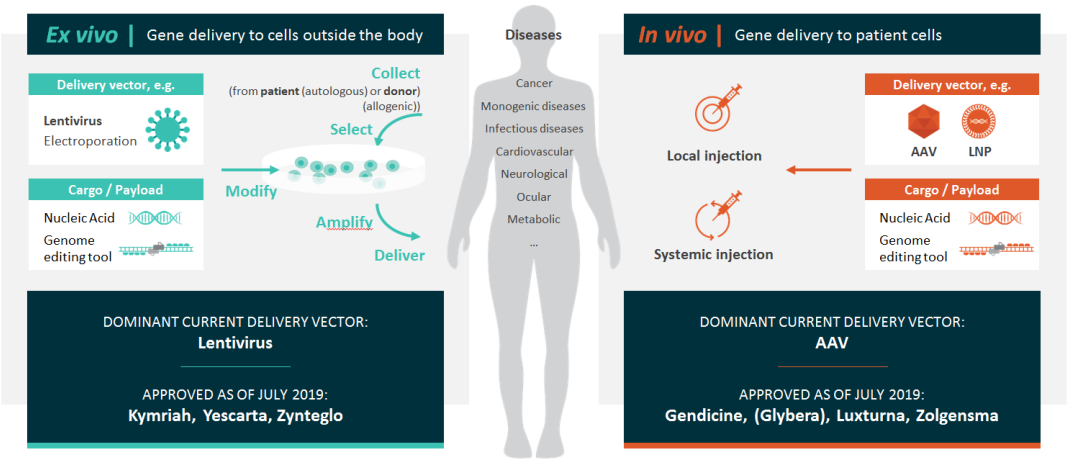
The mechanism unfortunately is not perfect, sometimes there is a mistake in the readout of a gene, or a letter might be missing. This can cause a *mutation* which can be innocuous or extremely harmful depending on the respective coding protein. Therefore, when a gene is missing, there is a mistake in the readout or the gene has been knocked off, a multitude of diseases can emerge.

All the building blocks described above will be essential to our understanding of all the innovations and therapies emerging on the biotechnological landscape today. Thank you for bearing with us for this brief biology digression. Now onto the first technology we are going to dive into, the exciting world of Cell & Gene Therapies!

Gene Therapies

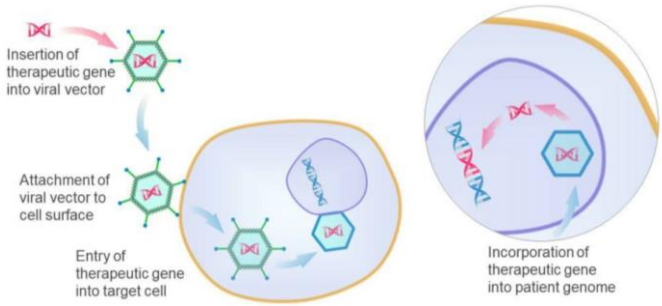
What are they?

In the general sense, gene therapy entails the introduction, removal or modification of a person's genome with the aim of alleviating or curing a specific medical condition. This definition is very broad, and there are actually several nuances and different subsections of these therapies depending on how scientists are approaching different diseases. The following picture [5] can give you a very quick breakdown of the different approaches involved.



The first separation worth highlighting is between *In-Vivo Gene Therapies*, which call for a direct delivery of the therapeutic gene through local or intravenous injections, and *Ex-Vivo Gene Therapies*, which are a form of *Cell Therapy* (use cells as delivery vehicles) where the therapeutic gene is grafted into cells that are extracted from the patient (*autologous*) or from a donor (*homologous*) and then re-administered to the patient.

The two approaches rely on different *delivery vectors*, the means through which the therapeutic gene is delivered to the nucleus of patient's cells. In-vivo therapies utilize *AAV (Adeno Associated Viruses)* or *LNP (Liquid Nano Particles)* vectors, whereas ex-vivo therapies usually employ *Lentiviruses* or *Retroviruses*. It turns out that viruses are extremely efficient at carrying their DNA through cells' nucleus membranes, and bioengineers have figured out that they can systematically modify these viruses to bring nucleic acid sequences (DNA or RNA) of their choosing to the desired tissue. Below an intuitive picture [6] of how viruses infect cells and reproduce themselves in a gene therapy setting:



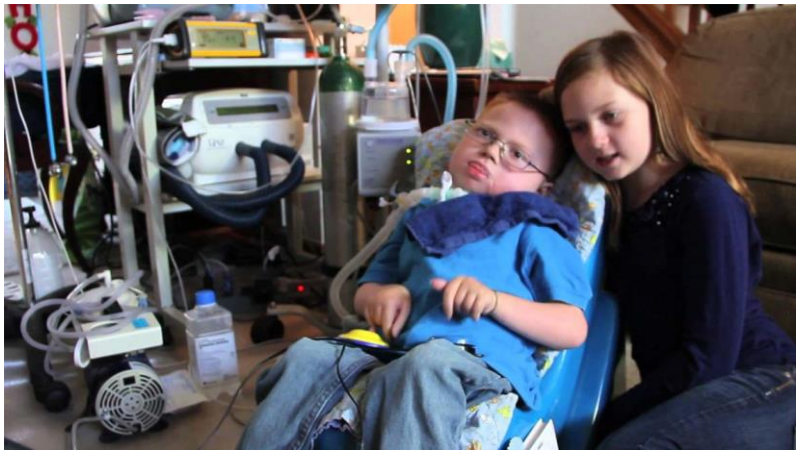
The choice among different viruses, depends principally on the type of somatic cells that need to be targeted. In fact, different strains are better at invading different types of somatic cells. Some can invade only dividing cells, some only non-dividing cells, some are more effective on liver cells, some on pancreatic cells and so forth. The size of the therapeutic gene also matters quite a lot, since different viruses have only a limited amount of room where the gene can be engineered into. As you can imagine, these are the principal drivers behind the scientists' decision of the delivery vector, and hence of the type of therapy, in or ex-vivo, they are going to pursue.

So….What's the big deal?

The revolutionary aspect of these type of therapies is that they promise to be much more effective than traditional ones. Before the advent of gene therapy, to tackle deficiencies related to lack of a specific protein for example, the only available treatments — if there were any — were to extract and produce the specific protein and give it back to the patient on a regular basis. These are known as *ERT (Enzyme Replacement Therapies)*. For the patients, this would often mean going to the hospital every month or week, constant painful injections, and no outlook of ever being cured. Certainly, this would allow them to survive, but their life would be generally adversely impacted by the disease.

Gene therapies instead, attack the problem directly at the source, by adding or modifying the defective genes, restoring their function, and hence creating the correct version of the protein. It would be analogous to getting a brand-new car, instead of salvaging it through constant repairs at the body shop. This is transformational. Patients would be effectively 100% cured of the disease.

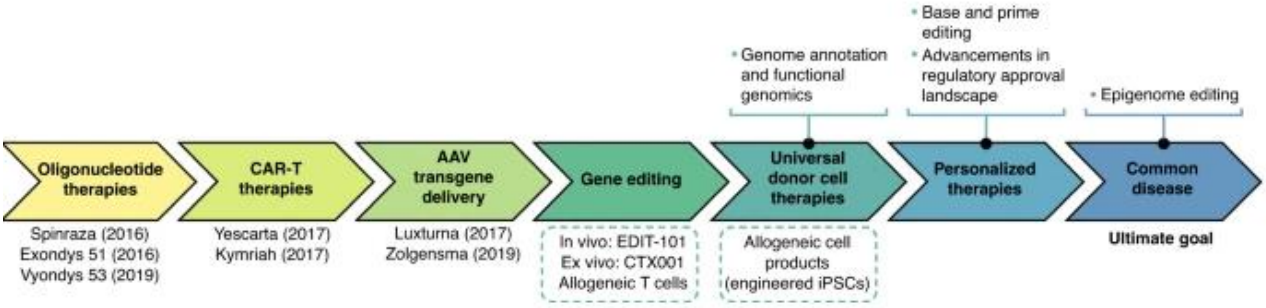
For the first time in history, we are at the precipice of commercializing drugs that will get rid of some of the nastiest genetic diseases know to men which have never been cured before. Let us look at *SMA* (*Spinal Muscular Atrophy*) for instance, an inherited devastating disorder where the *SMN1 gene* is lacking or deficient. This causes motor neuron death which translates into difficulty in breathing, swallowing, walking and even sitting unassisted. Most kids with *SMA type 1* did not even survive early childhood. Oftenly a photo **[7]** speaks louder than any words.



On May 24th2019, *AveXis* (now *Novartis Gene Therapies*) received FDA clearance for the commercialization of its in-vivo gene therapy treatment called *Zolgnsma*. This therapy encompasses the delivery of a functional SMN1 gene through an AAV delivery vector directly into the patients' motor neuron cells. With a single dose,

this has re-established the normal production of the SMN protein, completely stopping the spread of the disease in infants. This is incredible, and there are other in-vivo gene therapies that have already been approved like *Spark Therapeutics*' *Luxturna*, granted FDA clearance in 2017 for treating *LCA (Leber Congenital Amaurosis)*, a rare form of degenerative blindness. Furthermore, other treatments have been approved to date that rely on gene engineering, like *CAR-T Therapies, Yescarta* and *Kymriah*. These revolutionary therapeutic approaches have garnered incredible excitement by completely redesigning the way in which we combat cancer, creating incredible positive outcomes for patients. It was worth briefly mentioning them since they rely on gene modification, but we are not going to go into detail here since we have a whole future section dedicated to cancer immunotherapies and gene therapies applied to cancer.

Thus far, gene therapies have been developed to treat rare disease and have been deployed in cancer immunotherapies, but they are slowly but surely going down the ladder, the end goal being leveraging them for the most common diseases. The image **[8]** below can help you get a clearer picture of where the end goal is:



What are the risks ?

Well, we painted a pretty rosy picture of gene therapies and their potential so far, but when there are big rewards, there are always considerable risks to be considered. There is a reason why gene therapies took more than twenty years to come back into the spotlight. In fact, the core technological capabilities to leverage gene engineering to combat diseases were already available to us in the 90's. However, history has taught us that sometimes, having the knowledge doesn't necessarily mean that we are mature enough to use it.

In 1999, there was a major accident that halted the progress of gene therapy, the death of Jesse Gelsinger. Jesse was a 18 year old teenager affected by *OTC* (*Ornithine Transcarbamylase Deficiency*), an X-Linked genetic disorder that causes ammonia levels to build up in the body, being unable to get rid of it through urine. This accumulation is very bad for the body, and it can quickly cause severe damages to the brain, eyes, liver, and muscles. The boy was following a low protein diet and taking more than 32 pills to control his condition which was stable at the time. Scientists, looking to treat Jesses' condition permanently, administered to him a AVV vector carrying a functional copy of the OTC gene, with the intent of alleviating his symptoms. Unfortunately, Jesse died four days after the procedure due to a severe immune reaction.

This unlucky kid wasn't the only case, in the early 2000s, many children affected by *X-SCID* (*Severe Combined Immunodeficiency*) and *WAS* (*Wiskott-Aldrich Syndrome*) were treated with ex-vivo gene therapy. Even though the disease was cured after receiving the transplanted cells, they died nonetheless due to the development of Leukemia. Through later studies, researchers discovered that inserting genes

near *oncogenes* (cancer causing genes) was inducing them to get activated, causing the kids to develop cancer. This shows that we have to thread lightly when dealing with complex biological systems and especially when we are talking about modifying our own genome.

The ethical concerns that these therapies bring about is also a very relevant point of discussion. As with any experiment that alters the genome, there are people who are concerned by scientists taking the role of God. Especially when talking about *Germline Gene Therapy*, which entails a modification of the genome in embryos. It's easy to imagine really dystopic scenarios that could manifest if we don't take the necessary actions to make sure these procedures are used ethically — think designers babies and cloning. Furthermore, the multimillion dollar price tags of these therapies could engender increasing social unrest, creating a distinct gap between the "haves" and "haves-not". In fact, if we don't find a solution to create uniform access to these potentially life saving drugs, there could be real troubles brewing ahead.

Then, what are the main challenges and how are we addressing them?

Like with every breakthrough technology, the road to full application is still long and perilous. Even though these therapies are showing extremely positive signs of effectiveness, there are still several roadblocks and issues that need to be solved on the side of safety. Starting from our own immune system. Each on of us has an immensely powerful internal biological guardian which defends us fiercely against infections and pathogens. The immune system is very adept at recognizing and attacking *antigens*, or foreign entities, such as viruses for example. Clearly, this does not play along very nicely with gene therapies, that often rely on viruses to deliver therapeutic payloads to the cells. Viruses' outer shells, called *capsids*, are in fact sometimes recognized by the patients' immune system and attacked, which would consequently severely diminish the efficacy of the therapy. Furthermore, this hinders the possibility of administering a second dose, since the immune system has been trained to recognize the specific capsid used in the first treatment. Immune reactions, as we have seen before in the case of Jesse Gelsinger, can also be very dangerous for the patients. Regardless of the incredible achievements of several AAV-based therapies so far, to this date, as many as 50% of patients are excluded from treatment due to pre-existing resistance to specific viral capsids.

To broaden the spectrum of diseases we can leverage gene therapies upon, this problem will have to be solved. Many companies are already tackling this challenge, by creating specific recombinant viruses that can escape undetected from our immune system vigilant sensors, therefore avoiding immune responses. Another option is to rely on *LPN (Lipid Nano Particles)* or *Exosomes* as delivery vectors, both of which are much less likely to provoke an immune reaction. We will paint a more detailed picture of some of these solutions in later sections, when we are going to analyze some of the pioneering companies working on these exact issues.

A second challenge for the mass adoption of gene therapies, are manufacturing and pricing. Ex-vivo autologous gene therapies for example, require each treatment to be created specifically for a single patient. In fact, grafting cells derived from a donor that isn't a very close match to the patient, will cause a rejection of the cells and potentially cause what is known as *GVHD (Graft Versus Host Disease)*. Our immune system can recognize that the cells are not our own cells, and therefore attacks them as it does with pathogens. Ergo, the easiest solution is to extract the patients own cells, which will not cause any immune reaction, and engineer them with the specific gene and then graft them back into the patient. This requires the companies manufacturing the biologic compound to design each treatment separately for every patient. This necessarily drives up costs immensely for all the parties

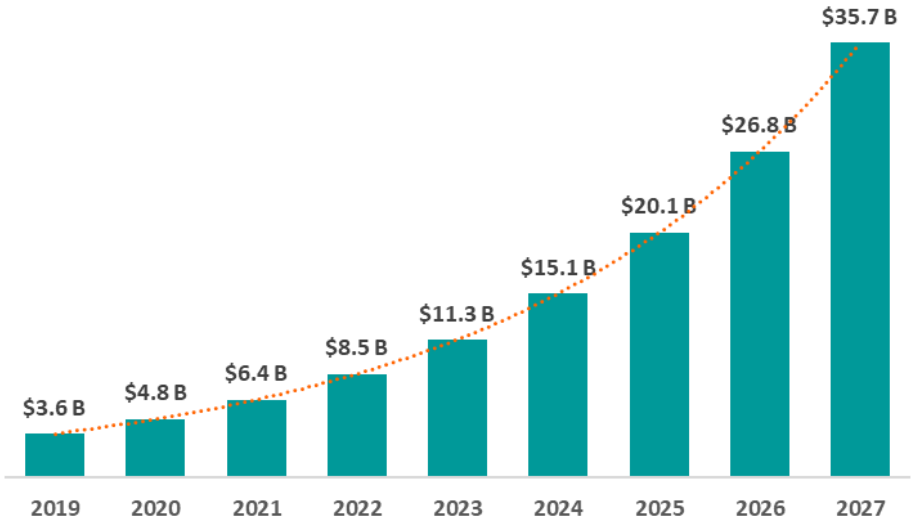
involved, mandating companies to put exorbitant price tags (up to millions of dollars) on the procedures to be able to bear the costs and generate profits at the same time. This represents an entirely different beast than what pharmaceutical companies have been used to deal with. Small molecules are standardize and easily produced in large quantities and even more traditional biologics can be generalized to be administrable to a general population.

To tackle this problem, many innovators are already working on the next generation of therapies that solve for this issue. Billions have been already invested by biotechnology firms to create "off-the-shelf" gene therapies. These are created employing donor cells, engineered to avoid immunogenic responses, and can be replicated in massive quantities and administered to patients directly without the need to worry about GVHD. Thanks to incredible advances in the fields of stem cells, cells that are able to differentiate in different somatic cells (e.g. liver cells, muscle cells, etc…), we are now able to generate a basically infinite amount of cell tissue that can be exploited to further our knowledge and improve patients outcomes. In the future, we are probably going to be able to re-create in the lab entire human organs, making donor transplants obsolete. We are still probably a decade away from that, but this is certainly a very exciting future to look forward to.

Let's now turn our attention towards a more top-down view of the market opportunity and then dive in some of the names of the pioneering businesses working in the gene therapy space.

Market Landscape:

The market opportunity is just enormous. As reported on the website **Clinicaltrials.gov**, there are currently more than 4700 ongoing studies related to gene therapies worldwide, run by industry, government, and academic institutions alike. According to *Fortune Business Insights*' **report**, the market cap for the Global Gene Therapy Market in 2019 was $3.6Bn, expected to grow at a whopping 33.6% CAGR reaching as much as $35.6Bn by 2027.



In recent years, interest in the space from major pharmaceutical companies has grown significantly. Until 2017 gene therapies have been frowned upon by big pharma as considered still too risky for their tastes. The mood changed sharply starting in April 2018 with the acquisition of *AveXis* by *Novartis* (*$NVS*) for a staggering $8.7Bn, the latter looking to incorporate the approved gene therapy for SMA into its pipeline. Following that, the hunt was open to adjudicate the most advanced gene therapy platforms on the verge of being approved by the FDA or that were further enough in their clinical trials. Among the most notable, we note the *Spark Therapeutics* acquisition by *Roche (*$*RHHBY)* in February 2019 for $4.8Bn, and the snatching of *AskBio* by *Bayer (*$*XTERA)* for $4Bn in October 2020. Even though recently the industry's focus has been in cancer immunotherapies — we are going to talk about them in a later series — the interest in rare diseases is picking up steam with more drug targets approach critical Phase III Trials and nearing approval. We foresee this trend continuing with much vigor, with more joint ventures, partnerships, and acquisitions on the horizon.

Selected Companies:

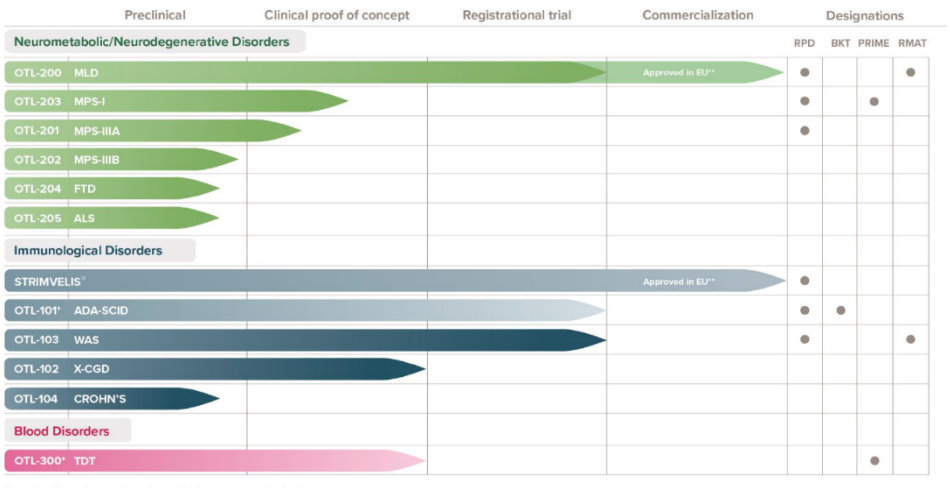
To conclude this first article on gene therapies, let us now turn our attention towards some of the most interesting companies active in the space. We have restricted our sample to public businesses specializing in gene therapy candidates for rare diseases, since we are going to discuss gene therapy approaches for cancer in the section on cancer immunotherapies. Our goal is to give you a small taste of companies at different stages of their clinical journey. We have included biotechnology firms that have drug products at the commercial stage as well as companies that are at an earlier stage but working on platforms that have the potential to revolutionize the entire gene therapy field. Since many of these firms have very deep pipelines, we have selected just one indication to describe in more depth, letting you do the rest of the digging if interested.

Orchard Therapeutics ($ORTX)

Company Profile:

- Geography: UK
- Market Cap: $832.4M
- Stock Price: $6.73
- Cash Balance: $191M
- Current Assets: $223M
- Current Liabilities: $51M

Orchard is a commercial stage gene therapy company specialized in ex-vivo autologous HSC (Hematopoietic Stem Cell) therapies leveraging LVV (Lentiviral) vectors to deliver a functional copy of a missing or faulty gene into the patient's own cells. Orchard's portfolio includes two commercial-stage products approved in Europe, seven lentiviral-based product candidates in clinical-stage development and several other product candidates in preclinical development. Their lead programs are focusing their efforts on CNS (Central Nervous System) disorders, respectively *MLD* (*Metachromatic Leukodystrophy*) and *WAS* (*Wiskott Aldrich Syndrome*). You can access their full pipeline [9] below as reported in their 2020 annual report:



Selected Disease Profile:

MLD (Metachromatic Leukodystrophy)

- Population: 1 in 40,000 people

- MLD is a rare autosomal recessive lysosomal storage disorder that hinders the growth and development of myelin, a fat coating membrane that surrounds the nerve fibers in the nervous system. The disease is caused by the lack of a specific enzyme called ARSA. It can develop at different stages, from infancy into adulthoods and progressively destroys physical and cognitive functions. In its late infantile form, mortality at five years from onset is estimated at 50% and 44% at 10 years for juvenile patients.

Standard of Care:

- Presently the disease can be mitigated with HSCT (Hematopoietic Stem Cell Transplant) which is effective only in the patient not yet showing the effects of MLD. Relying on transplant brings about several complications like finding a matching donor, undergo painful conditioning (chemotherapy) as well as being lucky enough to catch the disease in time. Furthermore, transplants can slow down the spreading of the condition but do not represent a definitive cure, which means that sooner or later the patient decease. Another option available to patients affected by MLD is to use ERT (Enzyme Replacement Therapy), which has unfortunately limited efficacy on neurological symptoms and requires chronic treatments.

Lead Gene Therapy Program:

- OTL-200 is Orchard's lead therapeutic candidate for MLD, designed as a one-time therapy that aims to correct the underlying genetic cause of the disease. It is an autologous ex-vivo gene therapy procedure. The patient's HSC (Hematopoietic Stem Cells) are extracted, and the correct version of the gene is transduced into them through a LVV (Lentiviral) vector. The stem cells are then re-administered to the patient. Having a now functional copy of the gene, patients' enzyme production is restored, stopping completely the spreading of the disease. So far Orchard has treated 39 infant patients affected by MLD and all of them have been showing durable effects with no adverse reactions over the past 11 years. This treatment has been approved for commercial distribution by EMA (European Medicine Agency) in 2020.

Recent Updates & Outlook:

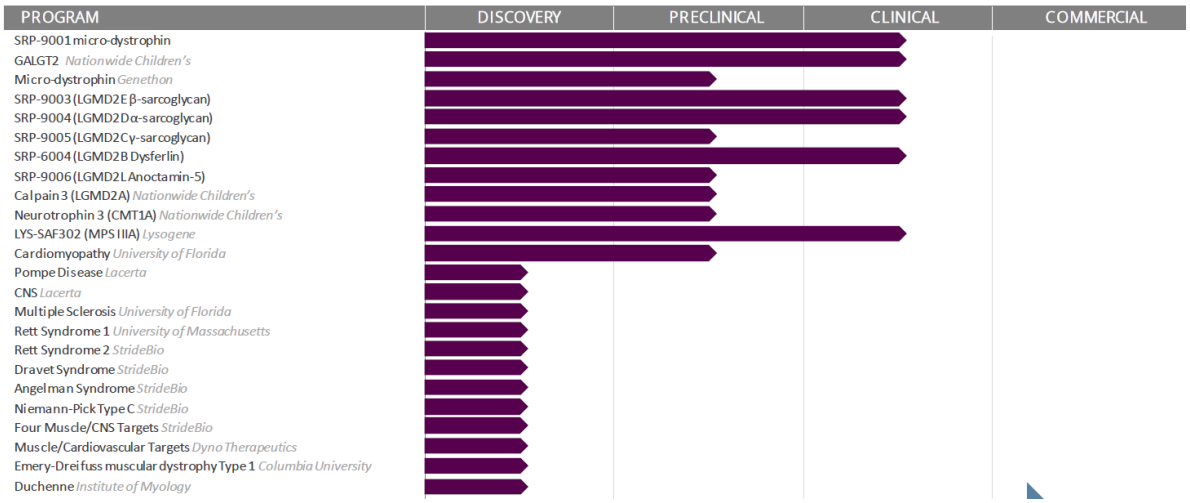
- In December 2020, the EU has approved the commercialization of OTL-200 under the label Libmeldy. Orchard expects to start launch and distribution of the therapy on the European market in the first half of 2021. The company has since joined the few companies that have managed to bring a gene therapy to market and will pursue FDA registration next to be able to market the drug in the US. Orchard plans to complete interactions with the FDA to determine the path to file a BLA (Biologics License Application by mid-2021.

Sarepta Therapeutics ($SRPT)

Company Profile:

- Geography: US
- Market Cap: $5.6Bn
- Stock Price: $70.45
- Cash Balance: $1.9Bn
- Current Assets: $2.48Bn
- Current Liabilities: $416M

Sarepta is a commercial stage biopharmaceutical company focusing on RNA and in-vivo gene therapy candidates for rare diseases, in particular *CNS* (*Central Nervous System*) diseases such as *DMD* (*Duchenne Muscular Dystrophy)* and LGMD (*Limb-girdle Muscular Dystrophies)* and other disorders. Below you can find their entire pipeline of drug candidates, as represented [10] by their 2021 presentation deck:



Selected Disease Profile:

DMD (Duchenne Muscular Dystrophy)

- Population: 1 in 3,500-5,000
- DMD is an inherited X-linked recessive disease that manifests itself very early on (3-5 years old). A malfunctioning gene causes a lack of production of the dystrophin protein, which causes increasing muscle deterioration. By age 11 children affected are usually on a wheelchair, and with the prolonging of the disease, cardiac and respiratory problem usually unfold causing potential life threatening events.

Standard of Care:

- Currently available treatment is another product from Sarepta, EXONDY51 which was granted FDA approval in 2016. It is a technology that enables to up-regulate or down-regulate the production of the dystrophin protein through pre-mRNA splice alteration. It enables to promote the production of an internally truncated but functional dystrophin protein. The treatment is applicable only to patients affected by DMD with genetic mutations amenable to exon 51 skipping. The therapy is quite effective, but it is not a definitive cure and requires more doses even though it has long lasting effects.

Lead Gene Therapy Program:

- SRP-9001 is Serepta's lead candidate, currently undergoing Phase II Clinical Trials. It is a in-vivo therapy, employing a specific AAV vector to deliver micro-dystrophin-encoding gene to muscle tissue for the targeted production of the micro-dystrophin protein. This therapy promises to be a one-time cure and to be applicable to a broader set of set of patients affected by DMD.

Recent Updates & Outlook:

- In a recent readout (Jan. 2021) of its Phase II clinical trial, Sarepta's therapy demonstrated that SRP-9001 produced large amounts of dystrophin protein. Furthermore, patients who received the treatment showed functional improvements compared to a placebo group. However, the results were a mixed bag, drawing questions on its broader efficacy in later trials. This has had a serious impact on the company's market capitalization, and doubts have been raised on its capacity to go forward with this product. We see this as potential bump in the road, and we expect the company to move along with the candidate by potentially leveraging new emerging technologies to improve the outcome of their re-do clinical trial.

Regenex Bio ($RGNX)

Company Profile:

Geography: US

Market Cap: $1.5Bn

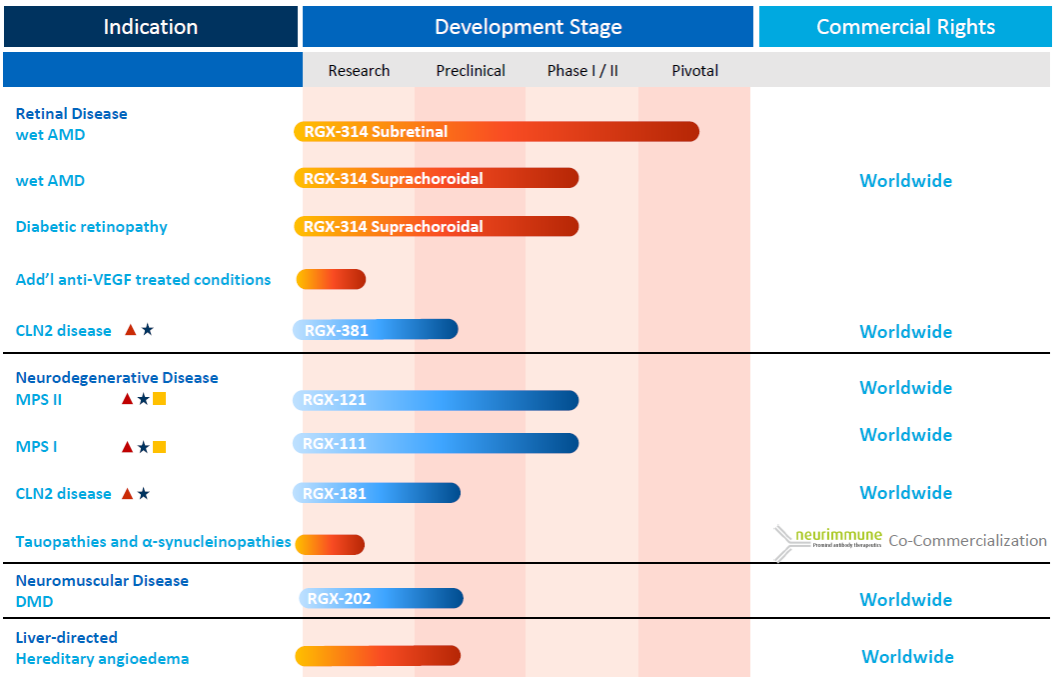
Stock Price: $35.17

Cash Balance: $475k

Current Assets: $531k

Current Liabilities: $81k

Regenex is a clinical stage biotechnology company focusing on developing in-vivo gene therapies employing their proprietary *NAV Technology Platform*. The company is focusing on treatment of *wetAMD (Wet Age-related Macular Degeneration), DR (Diabetic Retinopathy)* and other additional chronic retinal conditions which cause total or partial vision loss. Other programs include drug candidates for neurodegenerative diseases. Their *NAV Technology Platform* consists of exclusive rights to a large portfolio of viral vectors, including AAV7, AAV8, AAV9, AAVrh10 and more than 100 others novel AAV. Regenex has invested heavily in their platform and manufacturing capabilities, earning them a position among the industry leaders in AAV manufacturing. Having internal manufacturing capabilities at *GMP* (*Good Manufacturing Practices*) grade as well as patented superior viral vectors, could play very favorably for the company as it advances its pipeline through clinical trials**.** Below you can find their full pipeline of candidates, as represented by their 2021 presentation deck [11]:



Selected Disease Profile:

wet AMD (Wet Age-related Macular Degeneration)

- Population: > 2,000,000 people in US, EU and Japan
- Wet AMD is a progressive degenerative disease of the eyes that causes blurring of central vision and progressive vision loss due to formation of leaky blood vessels in the eye.

Standard of Care:

- wetAMD is treated with anti-VEGF medication through injections directly into the eye. This is a palliative measure that slows down the disease but doesn't provide a cure.

Lead Gene Therapy Program:

- Regeneron's RGX–314 therapeutic product, is an in-vivo gene therapy that aims at delivering the anti-VEGF Fab gene using an AAV8 viral vector through a direct injection in the eye. This aims at reducing leaky blood vessel formation by giving retinal cells the ability to produce an anti-VEGF fab. The promise of the treatment is to halt the disease with a single dose.

Recent Updates & Outlook:

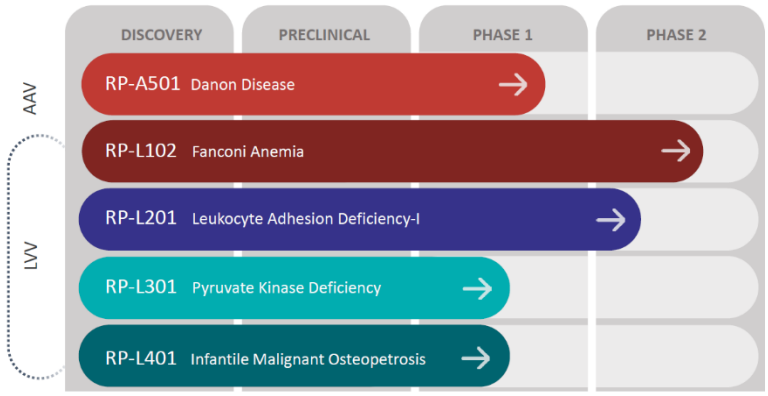
- RGX-314 has completed Phase I/IIa showing safety as well as having improved visual acuity in patients with wetAMD as well as DR. RGX-314 is now passing to Phase II, with two cohorts of patients enrolling in 2021. The company expects to see some interim data from these trials already in Q3 2021.

Rocket Pharmaceuticals ($RCKT)

Company Profile:

- Geography: US
- Market Cap: $2.43Bn
- Stock Price: $39.41
- Cash Balance: $482M
- Current Assets: $487M
- Current Liabilities: $32M

Rocket Pharmaceuticals is a multi-platform commercial stage biotechnology company developing best-in-class gene therapy candidates focusing on rare diseases with large unmet needs. They currently have four ex-vivo autologous gene therapies that have reached the clinic, employing lentiviral vectors (LVV). These include programs for *FA (Fanconi Anemia)*, *LAD-I (Leukocyte Adhesion Deficiency-I)*, *PKD (Pyruvate Kinase Deficiency)* and *IMO (Infantile Malignant Osteopetrosis)*. Furthermore, they are also developing another program for *DD* (*Danon Disease)*, this time in-vivo and relying on AAV vectors. Below you can find their full pipeline of candidates, as represented by their 2020 presentation deck [12]:



Selected Disease Profile:

FA (Fanconi Anemia)

- Population: 4,000 patients US + EU
- Fanconi Anemia is a rare and life-threatening DNA-repair disorder, which generally arises from a mutation in a single FA gene. It results in bone marrow failure, developmental abnormalities, other malignancies, often during the early years and decades of life. Bone marrow aplasia, which is bone marrow that no longer produces any or very few red and white blood cells and platelets leading to infections and bleeding, is the most frequent cause of early morbidity and mortality in FA. Leukemia is the next most common cause of mortality.

Standard of Care:

- Allogeneic *HSCT (Hematopoietic Stem Cell Transplant)* are associated with 100-day mortality, *GVHD (Graft Versus Host Disease)*, and additional increased cancer risk. Bone marrow transplant requires patients to undergo conditioning (e.g. chemotherapy) to reduce the probability immune reaction by the patient's own immune system. Since the HSC contained in the bone marrow are from a donor, the immune system needs to be weakened to ensure the cells can graft into the patient. The treatment is therefore very painful and often not very effective.

Lead Gene Therapy Program:

- Rocket's Pharmaceuticals lead candidate is RP-L102, an ex-vivo autologous gene therapy entailing the genetic modification of the patient own's *HSC (Hematopoietic Stem Cells)* to correct the FA gene defect. HSC are fundamental in generating blood cells over a patient's lifetime. RCKT extracts the cells from the patient (autologous) and infects them with a LVV vector carrying the transgene aiming at correcting defect and re-establishing a stable production of white and red blood cells. Contrary to the standard of care, this process does not require conditioning to reduce the probability of causing GVHD to the patient. Thanks to this, the treatment has the potential to significantly reduce the probability of adverse reactions after the cell transplant. RP-L102 is currently in undergoing Phase II clinical trials.

Recent Updates & Outlook:

- Rocket Pharmaceuticals recently reported positive results from several of its programs. In October 2020, the company noted high safety results as well as preliminary efficacy from its RP-L102 candidate in patients affected by FA. In March 2021, clinical data from its Phase 1 trial of RP-L301 for the treatment of PKD, showed durable normalization of hemoglobin levels up to 6 months following therapy and similar 3-month trends in the second patient treated.

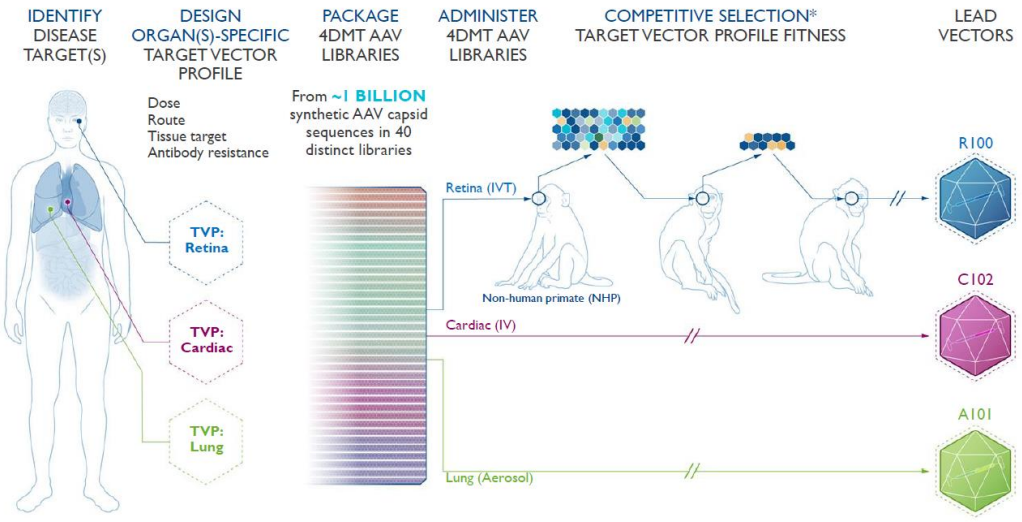
4D Molecular Therapeutics ($FDMT)

Company Profile:

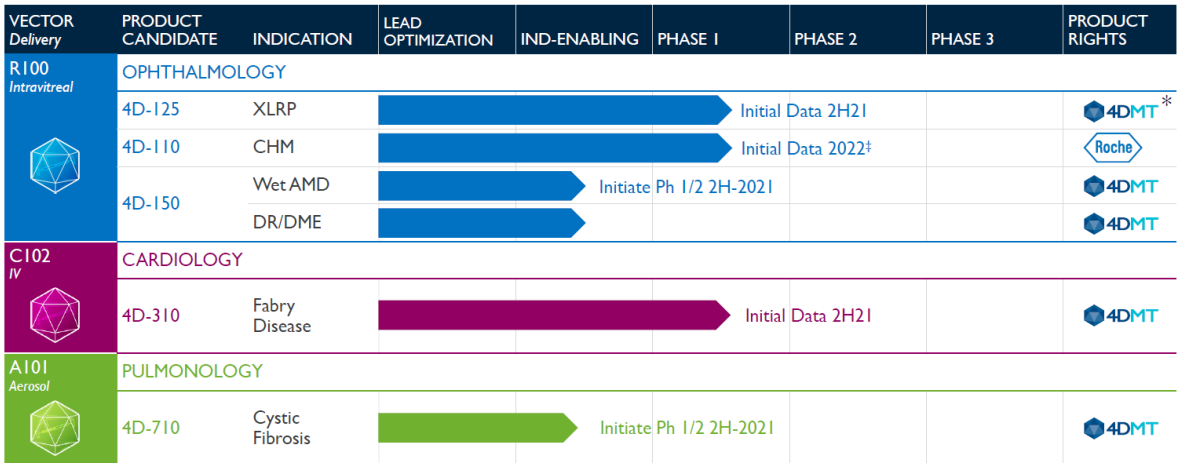
- Geography: US
- Market Cap: $1.0Bn
- Stock Price: $37.69
- Cash Balance: $276M
- Current Assets: $282M
- Current Liabilities: $16M

4D Molecular Therapeutics is a clinical stage gene therapy company dedicated to pioneering the development of therapies based on their next-generation AAV vectors. The firm has developed a proprietary *Therapeutic Vector Evolution* platform to enable what they refer as a "disease first" approach to product discovery and development, which has the potential to allow them to customize AAV vectors to target specific tissue types depending on the underlying disease.

The company is trying to address several of the challenges typical of in-vivo gene therapies that rely on natural occurring AAV viruses, such as limited delivery and transduction as well as reducing inflammation and vulnerability to attack from the patient's immune system. FDMT's Therapeutic Vector Evolution platform relies on 40 libraries comprising of more than 1 billion *synthetic capsid* sequences. According to the company's presentation, the process of selection of the specific AAV vector to utilize, follows an "evolutionary fitness" path as shown in the image [13] below:



4DMT claims that this process will ensure that their synthetic vectors are measurably superior to the ones employed in legacy in-vo therapiesAs far as their pipeline is concerned, they are targeting several therapeutic areas as shown in the picture [14] below:



Selected Disease Profile:

FD (Fabry Disease)

- Population: 19,000 patients in US + EU
- FD is a rare genetically inherited lysosomal storage disease that can affect many parts of the body, including the kidneys, heart, and skin. The mutation of the specific gene blocks an enzyme function that ensures that substances are cleared out of the cells. This in turn leads substances to store into the blood vessels and in other organs. Subsequently, patients affected by the disorder are often in constant pain, and more susceptible to kidney and heart failures.

Standard of Care:

- Currently the disease is treated with *ERT (Enzyme Replacement Therapies)* which require a lifelong treatment for the patient with bi-weekly infusion of the missing enzyme. The patient therefore will have no outlook of ever being cured and always be exposed to complications throughout his life.

Lead Gene Therapy Program:

- 4DMT's lead candidate for Fabry disease is 4D-310, an in-vivo gene therapy that relies on the company's synthetic AAV vectors to deliver the transgene to the targeted cells. Compared to ERT and traditional gene therapies, FDMT's program promises to have higher enzyme expression in all targeted cells (heart, liver and blood vessels) thanks to the synthetic capsids which will cloak the therapeutic payload from immune responses. The program is undergoing Phase I/II trials.

Recent Updates & Outlook:

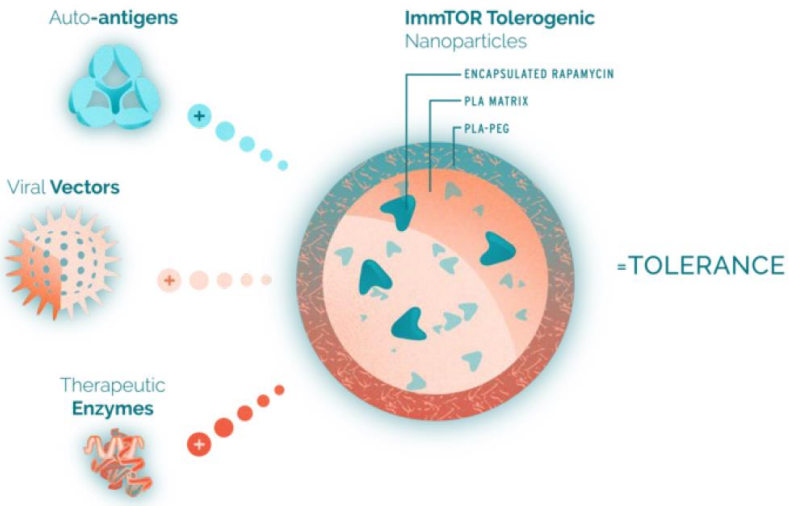
- The company expects to see first interim data on its *XLRP* (*X-Linked Retinitis Pigmentosa)* and FD *(Fabry Disease)* programs in the second half of 2021. There is a lot of excitement around the company and the results of these two Phase I clinical trials. If the readouts will be close to what the company promises, it could be a real step forward in solving several challenges related to the scaling of AAV gene therapies.

Selecta Biosciences ($SELB)

Company Profile:

- Geography: US
- Market Cap: $469.7M
- Stock Price: $4.18
- Cash Balance: $138.6M
- Current Assets: $151.3M
- Current Liabilities: $81.5M

Selecta is a clinical-stage biopharmaceutical company that has created an immune tolerance platform called *ImmTOR*™ with the goals of amplifying the efficacy of biologics, including enabling the re-dosing of life-saving gene therapies, and restoring self-tolerance in autoimmune diseases. This cutting-edge platform promises to significantly mitigate the creation of ADAs (Anti-Drug Antibodies) against specific biologics drugs. ADAs can develop to contrast the effect of a biologic drugs after the first dose, making a subsequent re-administration of the drug less effective or even dangerous. ImmTOR™ leverages a proprietary nanoparticle vector and an immunomodulatory drug as shown below [15]:



Selecta's platform promises to be a revolutionary advancement for gene therapies if proven effective. For example, it would enable AAV based in-vivo gene therapies to be administered more than once, significantly increasing their effectiveness in patients. Based on preclinical data, Selecta believes that ImmTOR combined with AAV vectors could also increase transgene expression and block immune responses to the viral capsid. The company is currently focusing their efforts on improving their ImmTOR platform, by partnering with other biotech companies that are developing gene therapy candidates as shown in their pipeline **[16]** below:

Recent Updates & Outlook:

Selecta's programs related to gene therapy are not in the clinic yet, so we must rely on preclinical data in non-human primates which so far has been very promising. The road is still long for the company to prove their technology is effective in humans, but if Selecta delivers on their promises, this will mean much safer, much more durable, and more effective gene therapies for patients.

Conclusion:

This concludes the first section related to cell & gene therapies. Hoping this article was helpful in shedding some light on the miraculous advancements that we are experiencing in biotechnology today, we look forward to continue our journey in the next series. Up next a deep dive in Cell & Gene Therapies part 2 !! Stay tuned...