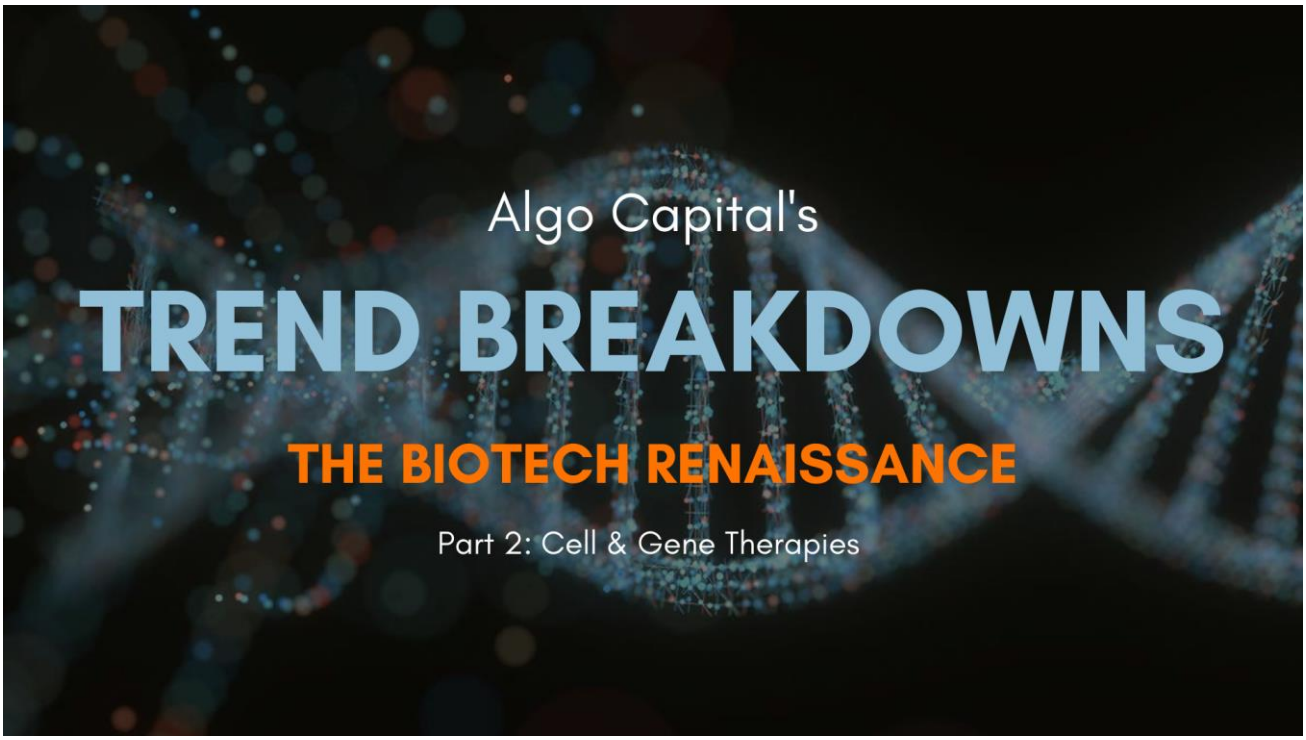


Part 2: Cell & Gene Therapies

Let us continue in our journey inside the world of cell & gene therapies started in the previous article. For those of you that missed out on the first part, you can find it here [link]. In this second section, we are going to focus specifically on *Cell Therapies*, treatments leveraging our own re-engineered cells to combat diseases in novel and exciting ways.

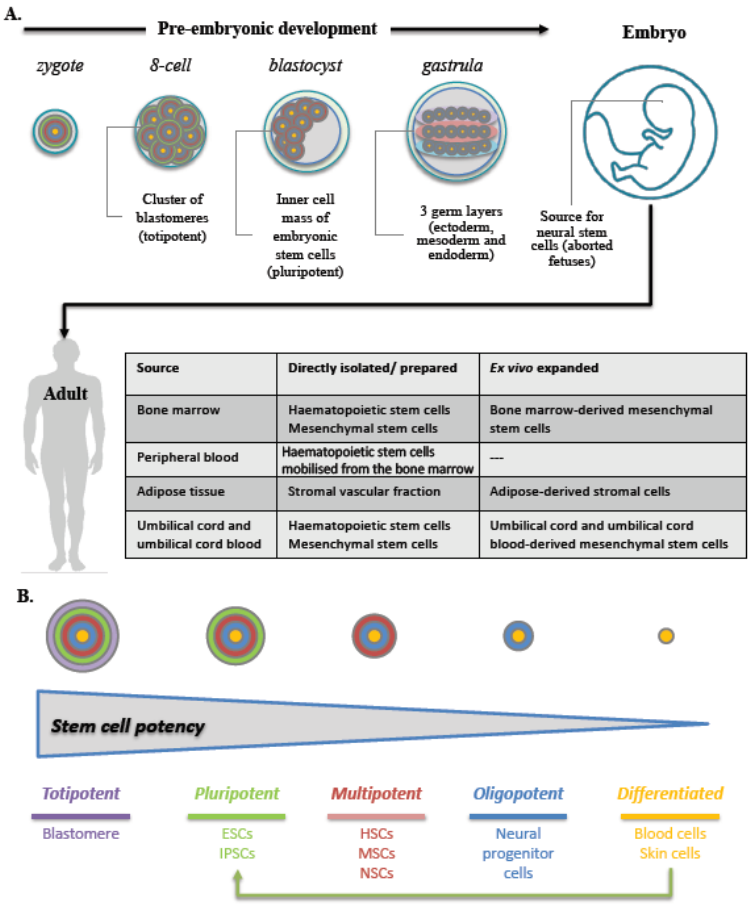
The practice of using cells for therapeutic means has been in place for more than two centuries, however, in the past decade, there has been a considerable acceleration as well as a series of breakthroughs in the cell-based therapeutics space. The most promising areas on which we are going to spend some words on are *Regenerative Medicine (RM)* – regenerating cells, tissues, or organs to restore normal function – and *Immunotherapy* – using cells to improve our immune system's ability to fight diseases, viruses, and cancers – which we briefly touched upon in our previous take on gene therapies.

Before jumping into the different use cases of *Cell Therapies*, it's important to hammer out some basic biological concepts regarding stem cells and how they work.

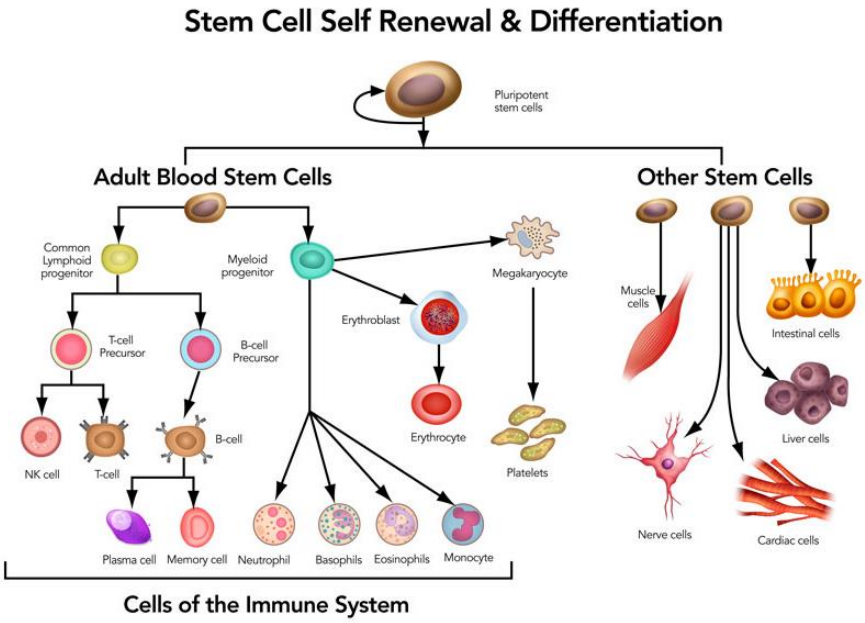
Stem Cells:

All the cells in our organism, from neurons to red blood cells, are derived from a common set of progenitors called *Stem Cells* – the building blocks of every organ in our body.

Stem cells possess distinctive properties such as the ability to self-renew, duplicate and the capacity to transform into other cell types. These precursor cells show different degrees of *potency* – ability to replicate and differentiate into different types of cells. The most "potent" a stem cell is, the more diverse the set of cells it can turn into. The graphic below [01] will help illustrating the point:



The most potent type of cells are *Blastomeres* which are *Totipotent* – meaning they can literally turn into any type of cells in the body. Blastomeres are generated by a fertilized egg during the pre-embryonic development stage. From the highest degree of potency, we can go down the ladder starting from *Pluripotent Stem Cells* that can turn into *Multipotent Stem Cells* down to lowest potency cells named *Somatic Cells* which include skin cells, neurons, blood cells and so on. The tree main branches from which all of our cells are derived from are named *Hematopoietic Stem Cells or HSC*, *Mesenchymal Stem Cells or MSC*, *Neural Stem Cells or NSC*. The following graphic [02] can help clarify the differentiation tree:

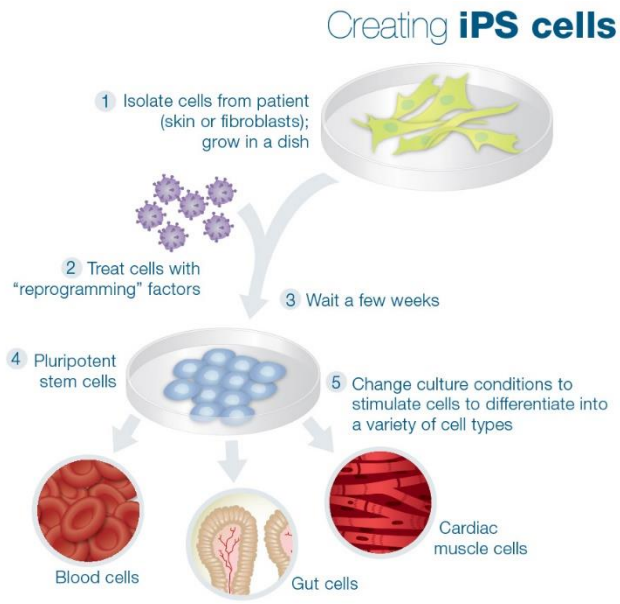


Pretty technical stuff, but the main point to bring home is that if we understand how stem cells function, we can find out a lot of things about other fundamental parts of our organism. Think about it this way, stem cells are the "grandparents" of each cell in our body. Therefore, they are a critical component providing us with the opportunity to study a very broad set of pathways like how embryos develop into full-fledged humans, how our cells are created as well as how our organs keep running. Since stem cells are at the basis of so many biological processes, our ability to leverage them as a mechanism through which we can modify our bodies' internal function is being recognized today as an extremely important field of research.

The use of cells as therapies started effectively to go mainstream with bone marrow transplants in the 1950s even though it could be dated back to blood transfusions in the 19th century. For many years transplants have been employed to save patients afflicted by bone marrow defects like *Leukemia*. The procedure is still quite delicate and finding a donor can be very challenging. There are still many patients out there that remain without an applicable treatment. For many years, bone marrow transplants have been the only game in town. Only after the 1990s the use of cells as a therapeutic mean has been expanded much more broadly to encompass a larger number of indications such as oncology and regenerative medicine.

One of the main issues that has been slowing the advance of stem cell research is the source of the cells themselves. In fact, for many years one of the most reliable sources of highly potent stem cells were embryos derived *Embryonic Stem Cells (ESC)*. It's easy to see how this has caused concern and reticence from a large part of the scientific community given the moral implications. Since ESC have historically had such a large negative externality attached to it, researchers have looked at employing *Cord Blood Stem Cells (CBSC)*, which are derived from placentas, as a better source of stem cells to be used in therapeutic environments.

In the following years, incredible breakthroughs like the invention of *Induced Pluripotent Stem Cells* (*iPSC*) by Yamanaka in 2012, completely changed the game. The Japanese researcher – who was awarded a Noble Prize for the invention – was able to identify a group of *growth factors* that almost magically enabled the re-programming of normal somatic cells back into its progenitor cell state. To make a simple anecdotal comparison, it would be equivalent to being able to turn your grandfather back into a child. The picture [03] below will help you understand how the process works:



This discovery is revolutionary because it paved the way for a new breed of cell therapies to be developed that rely on donor cells that can be infinitely produced and expanded in the lab. This promises to solve many of the ethical and logistics problems related to the sourcing of cells along with the ability to treat an ever-larger population of patients.

Cell Therapies:

Today we understand that cell biology can be leveraged in multiple ways, some of which we are just beginning to grasp and others that are still completely unknow to us. In recent times, academia and industry are principally focused on two main applications of cell therapies:

- **Regenerative Medicine:** it involves the implant of specific stem cells (HSC, MSC, …) into patients to replace, rejuvenate and regenerate damaged tissues. For example, this method has been employed to help *cardiomyocytes* (heart tissue) regenerate faster after patients had a stroke. The potential implications of the next iteration of these emerging technologies are truly extraordinary. When we'll be able to master the ability to engineer cells to renew and rejuvenate at will our damaged tissues, we'll have likely defeated a cascade of debilitating diseases and some say eventually even ageing.

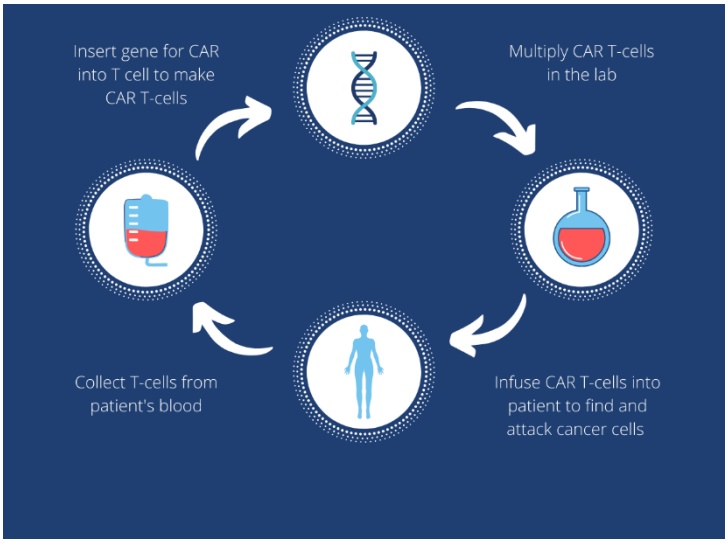
- **Immunology***:* cells can be engineered as a carrier for multiple therapeutic compounds (e.g. gene therapies, gene editing, rna vaccines, etc…) as well as being employed in fighting cancer by enhancing or re-targeting the natural capabilities of our immune system. The use of engineered *T-Cells* in *CAR-T* (*Chimeric Antigen Receptor T-Cell*) for example, has shown remarkable results compared to the standard of care in attacking horrendous diseases in the field of hematological malignancies like *Acute*

Myeloid Leukemia (*AML)*. Our immune system is in fact extremely proficient at killing cancer and pathogens, however it may need a little boost in locating and targeting the diseases which have learnt to escape its grasp.

Even though regenerative medicine is really promising, the hype around it has been quite mild as most assets are still in the clinic and a high-profile project hasn't caught the industry and public's eye yet. Cell therapy applied in cancer immunotherapy on the other hand, are a completely different story as it is probably one of the hottest segments in biotechnology right now thanks to the amazing success achieved by CAR-T therapies. Let's look briefly at how these new revolutionary approach works:

CAR-T Therapy:

This new modality entails the use of both gene and cell engineering to enable programmed T-Cells to express a specific *T-Cell Receptor* (*TCR*) that will signal to other immune cells which type of cancerous cells they should attack. Our immune system is in fact very adept at killing cancer when it can detect it. However, tumors are living organisms that strive to survive by mutating and evading the immune system's control. CAR-T is forcing this process by creating an artificial way for our immune cells to recognize and eliminate a distinct cancer that has developed ways to grow undetected. Below illustrated [04] the process through which autologous CAR-T therapy works:



CAR-T's have demonstrated incredible efficacy against tumors, especially against blood cancers like *Leukemia* reaching remission rates of up to 80-85%. These numbers have never been seen before hence the huge excitement from the scientific community. Notwithstanding, this is just first iteration of these type of engineered cells as there are still many concerns to be addressed both on the safety side as well as on the cost and manufacturing side of these therapeutic products. We'll cover these challenges in more detail in a later segment.

Another important point to make, is the difference in approach that biotech companies are taking with cell therapies. There are two main ways in which companies can choose to pursue this:

- **Autologous:** autologous cell therapies are administered utilizing the patient's own cells. They generally require a three-step procedure: first the target cells are extracted from the patient, secondly the cells are brought to the laboratory where they are reengineered or modified *in vitro*. The last step entails the re-insertion of the modified cells back into the patients' bodies.

- **Allogeneic:** allogeneic cell therapies instead rely on a healthy donors' cells. The simplest example is *HSC Transplants* (*HSCT*), which have been used extensively with patients affected by leukemia and other similar malignancies. In this case, the cells are extracted from a donor and reinserted back into the patient. More recently, allogeneic cell therapies have taken a different connotation thanks to the invention of iPSCs, which have sparked a movement to create a new "off the shelf" type of treatments that don't require a continuous sourcing of new cell from a large pool of donors or from the patient himself but can rely on an infinite supply of cells created in the lab.

Both modalities – allogeneic and autologous –are widely used in both regenerative medicine and immunotherapy approaches by upcoming biotech companies which are looking to iterate on the success achieved by their predecessors. In the later companies showcase section, we're going to illustrate both modalities in detail.

Promises

Let's now look at the future potential benefits that these new cellular therapies will likely bring about in the coming years:

- **Precision Medicine:** up until recently almost all medical treatments have been created through a one-size-fits-all approach that could be very efficacious for certain patients whereas not so much for others. With the advent of precision medicine this will shift dramatically. Precision medicine or *Personalized Medicine* is a novel way to tailor therapeutic treatment to the specific genetic makeup of different patients, environments, and lifestyles. Thanks to our ever-growing ability to understand genes, our ability to design treatments that fit perfectly to each individual will continue to grow and expand. The end goal of personalized medicine is in fact the ability to treat the right patients with the right medicine at the right time.

  We've already touched upon some examples of the first iterations of some therapies that fall under the precision medicine umbrella. As an example, autologous CAR-T therapies require the patients' cells to be extracted and genetically modified to express a precise receptor. These cells are unique to the patient and can be used only to treat this person.

  Looking ahead into the future, we can envision a world where a patient goes into the hospital for a checkup and is diagnosed with cancer. Thanks to the cutting-edge diagnostic tools that will be available to us, the exact genetic makeup of the patient's tumor will be profiled and sent to the lab where a tailor-made therapeutic compound will be designed based on the persons' unique genetic code. Through next generation manufacturing, the therapeutic will be created overnight, maybe even in the hospital, and the patients could be treated in less than 24-48 hours. This may seem like science fiction but it's not that far off from becoming reality as we'll see in a later part of this paper.

- **Infinite Supply of Cells:** as of today, sourcing cells is still a very complex and controversial endeavor. Most of the supply of cells and tissues is stemming from unsavory and inefficient sources: the main one is cadavers – not the most ethical approach with high potential for infection – followed by living donors – cause of one of the most prolific and profitable black markets in the world – or alternatively in the case of stem cells from either fetuses or a small subset of matching donors. Of course, up until now we've borne with these questionable sources because we had no other choice, however these issues are about to come to an end thanks to breakthroughs like iPSC and "off-the-shelf" cellular therapies. Our ability to reprogram cells and expand them outside of a patient's body is improving dramatically. The continuous upgrade of these technologies will enable us to spin up whatever type of

cell that each unique patient may require in a matter of days or even hours. Long gone will be the days where we needed to dissect cadavers or extract organs from people, willing or unwilling.

- **Eradicate Cancer:** cancer is the second leading cause of death after heart disease. In the USA alone, almost 600,000 people died of cancer in 2019. But this number is dropping consistently every year. According to a research done by the CDC [link], cancer deaths have dropped ~30% from 1999 till 2019, and the trend is accelerating. We believe cellular immunotherapies will have an ever-increasing contribution to this number. The next iteration of CAR-T's will improve upon the already staggering ~80% remission rates achieved today as we're already seeing new approaches coming into the clinic that have shown remarkable results also in solid tumors which have been historically almost untreatable. Looking ahead the possibility of a cancer free world is not unfathomable. Of course, people will still develop tumors, but we'll have treatments to kill every single type of cancer, especially if caught early on through even better diagnostic tools powered by more pervasive application of AI and big data analytics in healthcare settings.

- **Renewable Organs:** today, if you suffer from heart failure and you need a donor, your chances of finding a matching one in time are very limited. Stem cell and regenerative medicine approaches might be able to completely revolutionize that. Not only we're beginning to create whatever type of tissue you can think of in the lab, but scientists envision that we'll eventually be capable of growing entire organs from just a few cells. Already back in 2014, researcher Dr. Kevin Costa, director of cardiovascular cell and tissue engineering at Icahn School of Medicine at Mount Sinai in New York and his team were able to reproduce a beating heart tissue in the laboratory. You can find more information about the discovery in the following article [link]. This was just the beginning; more and more companies are looking to improve on this seminal work and are coming to the clinic with new lab grown tissues to be employed in any type of disorder from heart failure to brain damage along with helping bones heal faster in case of fractures. The possibilities are truly endless.

  Through our own work helping private companies raise capital, we've collaborated firsthand with a regenerative medicine company that was able to create an entire human bone from stem cells extracted from a tooth…from a tooth! That is just incredible. We expect this trend to continue until we'll be capable of creating any type of organ in the lab and finding a matching donor will be an issue of the past. It's easy to assume that this will contribute incredibly to people's lifespan as more and more of the things that can kill us are either eliminated or our own damaged body parts and organs can be renewed or substituted.

- **Cells as drug discovery tools:** nowadays creating a new drug is super expensive and it requires many compromises. To test the safety and efficacy of new therapeutic approaches, scientists spend years testing them in preclinical studies on animals from mice to monkeys. According to an article from Spots.com [link], in the US alone more than 22 million animals are used in a laboratory settings and over 98% of the drugs tested on them never end up being commercialized. Leaving the ethics of this aside, it seems that using animals just isn't the most efficacious mean to achieve the desired results. Advances in cell biology and engineering have the potential to solve this controversial issue too. Thanks to the ability to generate a large amount of tissue from a small sample of cells through iPSC technology or new cell expansion methodologies, relying on animal testing might end up becoming obsolete.

  As our ability to engineer and create human lab grown tissue improves, our capacity to test and iterate drugs will become more efficient and the cost of drug discovery will drop. Not only we'll have saved millions of animals, but we'll be able to test the drug directly on human tissue which is a much better predictor of how well the asset will perform in human clinical trials. In a single swoop we'll have the

opportunity to substantially boost the sheer number of drugs going into the clinic as well as reducing the time to market of these compounds exponentially.

Challenges

We've talked plenty about the incredible promise that these new therapeutic modalities have brought to patients and the even broader scope that these therapies have the potential to address in the future. However, the road ahead is still long and hazardous and there are still many problems that need to be solved with the second and third iteration of these technologies. Let's look at some of them in more detail:

- **Manufacturing Complexity:** creating a cellular therapy like CAR-T for example is extremely complex and it requires specific manufacturing capabilities that are still scarce today. Most previous and current cellular therapies are autologous, meaning they must be derived from a patient's own cells to avoid rejection by the immune system. This results in a strictly customized, one-to-one manufacturing process for each individual patient, which is costly and difficult to scale, and a complex supply chain that can delay treatment for critically ill patients. Moreover, this approach does not allow for an industrialized effort that can be leveraged to rapidly develop additional product candidates.

  Especially with the advent of the Covid-19 pandemic, the problem of biomanufacturing has been made even more acute as the new RNA based vaccines by Pfizer and Moderna rely on similar manufacturing process to cell therapies and have hence hijacked a lot of the manufacturing capacity out there. This in turn has made manufacturing capacity an even more desired skill as well as having exacerbated the need of improving upon the first iterations of these therapies by either relying on a cheaper allogeneic approach or by making the manufacturing process more efficient in other ways.

- **Serious Side Effects:** Many previous and current cellular therapies can cause serious side effects, including cytokine release syndrome, neurotoxicity and mortality. The toxicologic profile of these biologics still has ample leeway to be improved as legacy cellular therapies can extravasate in an untargeted manner into healthy tissues throughout the body, which may result in severe adverse effects. To address this issue, new modalities and improvements are emerging in the new therapeutic assets that are coming to the clinic right now. We believe this to be a temporary issue that will gradually be solved as the technology progresses and processes and compounds are made more effective and efficient.

- **Durability:** Current cellular therapies have an uncertain lifetime post-infusion. In some cases, the therapeutic benefits wane quickly. In others, the cells will continue to divide, expand and potentially transform unpredictably over an extended period of time.

Several examples of how these issues are being addressed right now can be found in a later section of the article, where we'll talk about some upcoming biotech companies that are developing the new generations of cellular therapies designed to overcome these obstacles.

Risks

We've covered promises and challenges of cellular therapies, let's now deep dive into the main risks that we see on the horizon for these new upcoming biotechnologies:

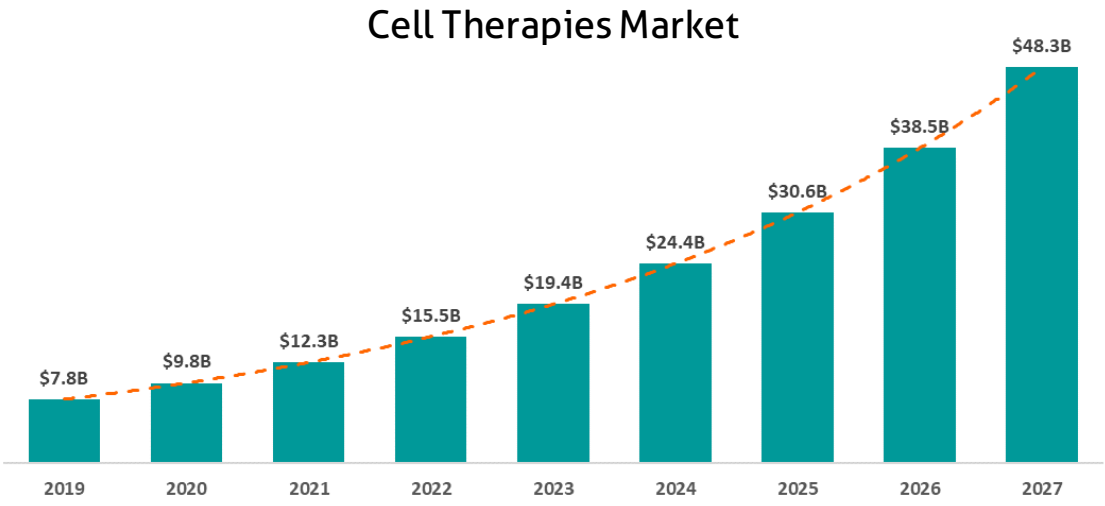
- **Regulatory Risks:** as with every innovation in biotechnology there are significant risks associated with bringing new modalities into the clinic. Recently regulators have been particularly strict with cell & gene therapies companies and have raised the bar to commercialization by a significant degree. We believe this trend will continue to perpetrate in coming years as regulators are shielding themselves from giving the green light to drugs that may cause severe side effect to patients in the short to mid term time horizon. On the other hand, taking a longer view, the integration of more precise drug discovery technologies may largely reduce this risk as companies will be able to iterate more efficiently in the preclinical stage and come into the clinic with much better assets' profiles.

- **Designer Killers:** with every new technology there is always a bright side and a dark side to it. In the end a tool is just a tool and can be used for good purposes or for evil ones. Cellular engineering in combination with gene engineering could be leveraged by malicious actors to create a new breed of weapons capable of targeting a specific subset of the population. As an example, we can imagine how in the future someone could hack into a cell production facility and modify the strains utilized to create tissues and therapeutics to induce autoimmune diseases or cancer in patients, therefore killing their victims in a highly selected and target manner without leaving a trace.

- **Social Unrest:** the current pollical and social environment is already suffering from a large divide between the haves and the have nots. We believe that this trend could be accelerated by the pace of developments of new cellular immunotherapies and regenerative medicine approaches. These new therapeutics aren't cheap to make and only the wealthiest individuals – at least initially – will be able to afford them. If we bring this thought to its logical conclusion, we could imagine an Elysium – the sci-fi film with Matt Damon – like scenario where the ultra-rich will basically have access to technologies that will cure them of every disease making them almost immortal, whereas the rest of the population will be left to suffer. This is a very dystopic scenario but not a complexly unfathomable one as we see this slowly happening already as we speak. Nevertheless, we believe that this is just a potential scenario to be wary of and we hope these therapies will eventually come down in price to a level that might be affordable by the vast majority of the population. If you haven't watched the film, we highly recommend it. You can find a trailer here [link].

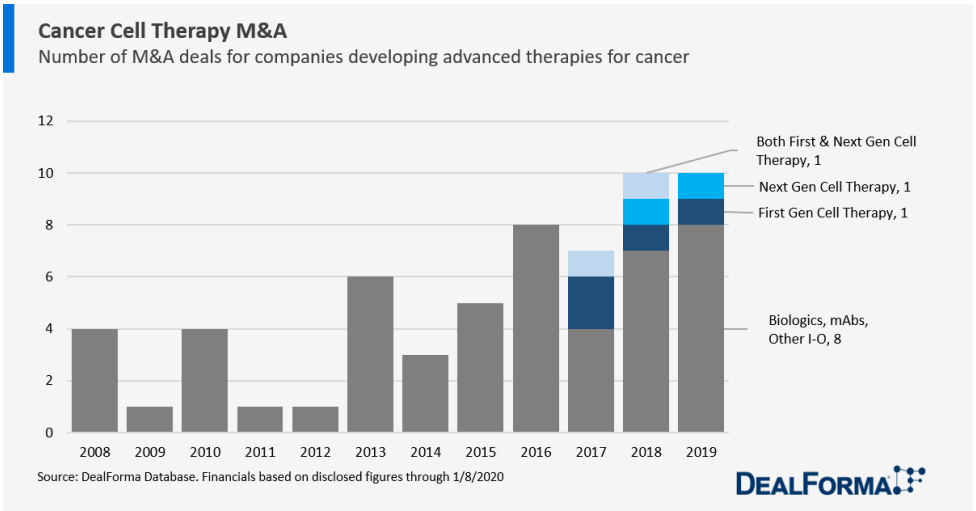
Market Landscape:

Having discussed at length the benefits and risks brought forward by new cellular technologies, let's now address the economic magnitude of these new modalities. The market opportunity for cell therapies is just gigantic. Looking at Clinicaltrials.gov, there are over 40,000 ongoing studies in cell therapies [link]. Clearly, there is a lot of interest from academia and private businesses in the space, and this is reflected both in the size and expected growth in the market. According to *Allied Market Research*'s report [link], the total market capitalization for the Cell Therapy Market was 2020 was $7.8Bn with a forecasted CAGR (2020 – 2027) of 25.6%.



The landmark cell therapy products that have been approved so far and have gained incredible attention from the scientific community are Kymirah™, a CAR-T therapy for *Acute Lymphoblastic Leukemia (ALL)* commercialized by Novartis and Yescarta™ and Tecartus™ CAR-T therapies against *B-Cell Lymphomas* created by Kite Pharma and commercialized by Gilead Sciences.

The M&A market for cell therapies has also been quite active in recent years and we're seeing a continuous increase in the number and size of deals as clearly stated by the flowing graph courtesy of Deal Forma [05]:



Below we report a table [06] of the most relevant deals up until 2019:

COMPANY	DEAL VALUE	YEAR	ACQUIRER	ASSET ACQUIRED
Kite Pharma	$11.9B	2017	Gilead Sciences	CAR-T
Cell Design Labs	$567M	2017	Gilead Sciences	CAR-T platform
Universal Cells	$102.5	2018	Astellas Pharma	Universal Donor Stem Cell Technology
Juno Therapeutics	$9B	2018	Celgene	CAR-T
Xyphos Biosciences	$665M	2019	Astellas Pharma	CAR-T
CytoSen Therapeutics	NA	2019	Kiadis	NK Therapy

We expect the acquisition trend to continue as the next iterations of cell therapy products are advancing through the clinic approaching Phase II & III, the preferred buying point for big pharma. The obstacles that could alt this trend are a tightening in regulatory requirements, a large public outrage due to unfortunate adverse events to a specific therapy or a general drying up of liquidity in the capital markets due to a recession.

Selected Companies:

In the following segment, we'll deep dive into five companies to showcase the promise of cellular therapies. Two profiles that we have selected are leveraging cells in the regenerative medicine space and three are working instead on cell-based therapies to fight different types of cancers. These companies have been chosen with the purpose of displaying the different types of approaches currently being developed in the marketplace.

Pluristem Therapeutics ($PSTI)

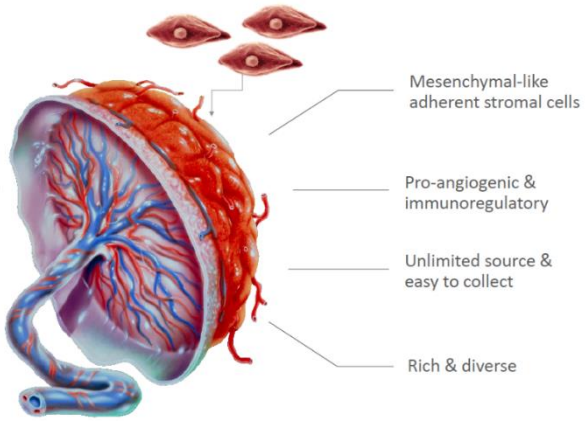
Company Profile:

- Geography: Israel
- Market Cap: $87M
- Stock Price: $2.7

Pluristem is an Israeli biotechnology firm working in the field of regenerative medicine and focusing uniquely on delivering one of a kind placenta-based cell therapies to combat a wide-ranging set of musculoskeletal, inflammatory, and hematological diseases.

The team at Pluristem has developed a platform technology based on **Placenta Expanded Cells (PLX)** extracted from donated placental cells. These cells are modified and grown employing Pluristem's proprietary

3D expansion technology and are believed to provide multiple benefits thanks to the release of specific therapeutic proteins at the site of injury. Some of those benefits are outlined in the picture [07] below:



Another fundamental advantage of PLX cells is that they can be delivered "off-the-shelf", meaning that a tissue match with the donor is not required for the cells to be safely transplanted into the patient.

Pluristem is leveraging the power of PLX cells to fight different conditions as can be observed from their pipeline represented in the following image [08]:

PRODUCT	FOCUS	INDICATION	LOCATION	FUNDING/ PARTNER	PHASE I / PHASE II / PHASE III
PLX-PAD	Muscle Injuries	Muscle Regeneration following Hip Fracture	U.S., Europe, Israel		
	Inflammatory Diseases	ARDS associated with COVID-19	U.S., Europe, Israel		
		Chronic Graft vs Host Disease (cGvHD)	Israel		
PLX-R18	Hematological Deficiencies	Acute Radiation Syndrome*	U.S.		
		Hematopoietic Recovery Following Hematopoietic Cell Transplantation (HCT)	U.S., Israel		

As we can notice from the table, Pluristem's technology is very versatile and could potentially be applied to a very diverse set of conditions, ranging from muscle injuries, *Acute Respiratory Distress Syndrome* (*ARDS*), Covid-19, *Chronic Graft vs Host Diesease* (*cGvHD*) and even in hematologic malignancies.

Selected Disease Profile:

Hip-Fracture

Population: 711,000 cases in the USA by 2023

Hip fracture is often leading to some serious collateral effects and complications such as chronic pain, decline in life conditions and disability. It has been estimated that ~20% of patients die within one year from surgery due to diseases caused by the forced lack of movement. These types of injuries are on the rise due to the lengthening of lifespans meaning a larger number of seniors that are most affected by these types of problems.

Lead Regenerative Medicine Program:

PLX-PAD

Pluristem's lead candidate is currently undergoing Phase III clinical trials. The product is designed to stimulate muscle regeneration promoting muscle volume growth and strength by introducing PLX cells near the site of injury in the same day the patients had surgery.

In Phase II, the program already demonstrated to be very effective, with a treated patients' improvement in muscle mass of 300% and an increase in strength of 500% if compared to the placebo group. These results are promising, and the company has been able to advance the program to Phase III.

Recent Updates & Outlook:

Pluristem's lead candidates in musculoskeletal injuries are currently advancing through the clinic as we've seen in previous paragraphs. Given the results achieved up until now, we expect to see positive results coming from Phase III in the coming months, which could be very positive for the company's other programs underpinned by the same underlying technology. In turn of course, this could mean a significant increase in its current market capitalization.

BioCardia ($BCDA)

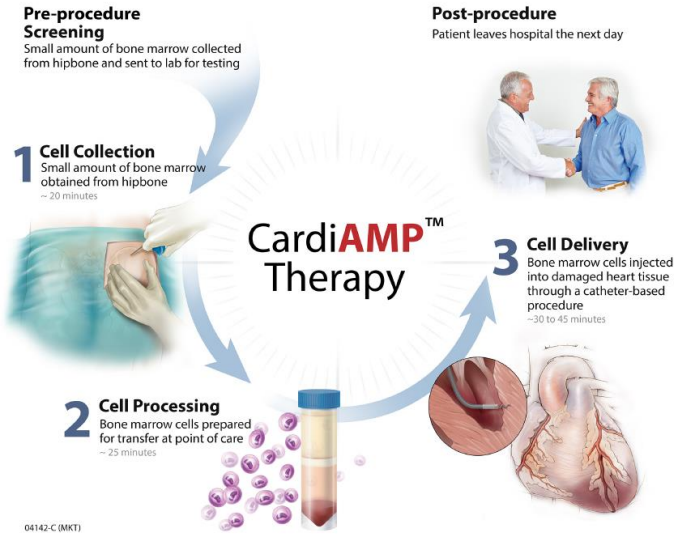
Company Profile:

- Geography: USA
- Market Cap: $48M
- Stock Price: $2.8

BioCardia is clinical-stage regenerative medicine business working on innovative autologous and allogeneic therapeutics for cardiac and pulmonary diseases. The company is leveraging the power of autologous derived bone marrow stem cells or *Mesenchymal Stem Cells (MSC)* to provide restoration and regeneration benefits to patients that have been affected by heart failure and ischemia. MSC cells could be beneficial to the heart in two ways:

- **Direct regeneration:** the transplanted cells home into the site of injury and start differentiating into new tissue to enhance the functioning of the organ. However, up until now no therapy in clinical trials has been shown to integrate directly into heart cells.
- **Indirect regeneration:** transplanted MSC release cytokines that stimulate the natural regenerative response from cells already present at the injury site.

BioCardia has developed a proprietary cellular platform named **CardiAMP**, the workings of which can be observed in the following picture [09]:



The CardiAMP system utilizes a specific assay, a delivery system and proprietary methods to differentiate MSCs from the patient's own cells to be then transplanted in the heart.

The full pipeline that BioCardia is bringing through the clinic can be observed below [10]:

Product Candidate (Pathway)	Preclinical	Phase 1	Phase 2	Phase 3
Autologous BCDA-01	CardiAMP® for Ischemic Heart Failure uses Helix			
Autologous BCDA-02	CardiAMP® for Chronic Myocardial Ischemia uses Helix			
NK1R+ Allogenic BCDA-03	CardiALLO™ for Ischemic Heart Failure uses Helix			
NK1R+ Allogenic BCDA-04	COVID-19 ARDS			
Helix Partner-01	Acute Infarction			
Helix Partner-02	Heart Failure			

Selected Disease Profile:

Heart Failure

Population: 6.5M patients in the USA

Heart failure is a critical condition that manifests when the heart can't pump enough blood into circulation to meet the needs of the metabolism. It's a progressive condition that if left unchecked and untreated can lead up to 50% mortality rate in just five years from the first diagnosis. Heart failure is becoming more and more

prevalent due to ageing population and the surge in obesity, especially across western countries. It has been estimated that in the USA alone, the healthcare burden of heart failure is ~$30B on an annual basis.

Lead RM Program:

BCDA-01

The furthest along program is currently undergoing Phase III trials. In this trial BioCardia is leveraging the CardiAMP platform to improve the regeneration of tissues previously compromised by heart failure. So far, the company has been able to demonstrate a considerable improvement in patients' conditions following the transplant, and the results look promising in light of a potential FDA approval.

Recent Updates & Outlook:

BioCardia's two lead programs are currently undergoing pivotal Phase III clinical trials and we expect a likely approval in the coming years. It will be interesting to keep an eye on this firm and the segment as the capacity to regenerate heart tissue is very compelling given the magnitude and incidence of heart related issues.

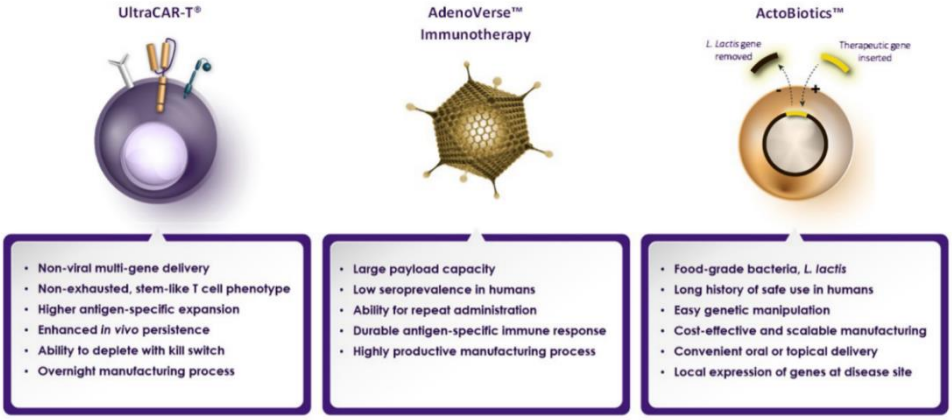
Precigen ($PGEN)

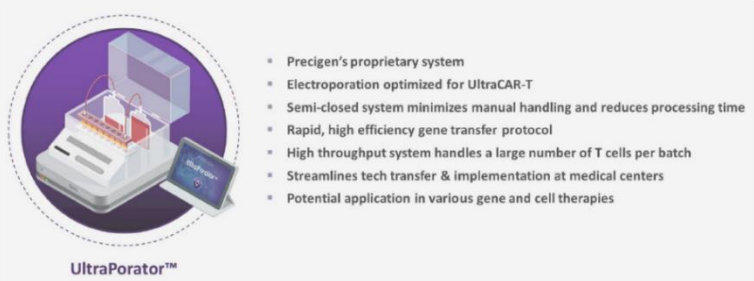
Company Profile:

- Geography: USA
- Market Cap: $948M
- Stock Price: $4.63

Precigen is a clinical stage biotechnology company advancing the next generation of gene & cell therapies for precision oncology. The company has developed proprietary therapeutic platform technologies to address several of the limitations of first-generation CAR-T therapies. These therapies, as we've seen in previous paragraphs, rely on the re-engineering of T-Cells with specific antigen receptors to supercharge these T-Cells to target a distinct antigen on the patient's tumor cells, killing or debilitating the tumor. This revolutionary approach has been extremely effective against blood cancers but not so much against more hard-to-treat tumors like solid cancers. Other limitations legacy CAR-T have been the highly complex manufacturing process due in part to the need of expanding the T-Cells ex-vivo to ensure enough cells are available before transplanting them into the patient.

Precigen is trying to address all these challenges at once, leveraging some serious IP. Let's have a look at the platforms built so far, represented in the image [11] below:





For the purpose of this analysis, we'll have a look only at two of the four platforms, if you're interested in learning more about the other two, I suggest you read through the company's 10K or S-1.

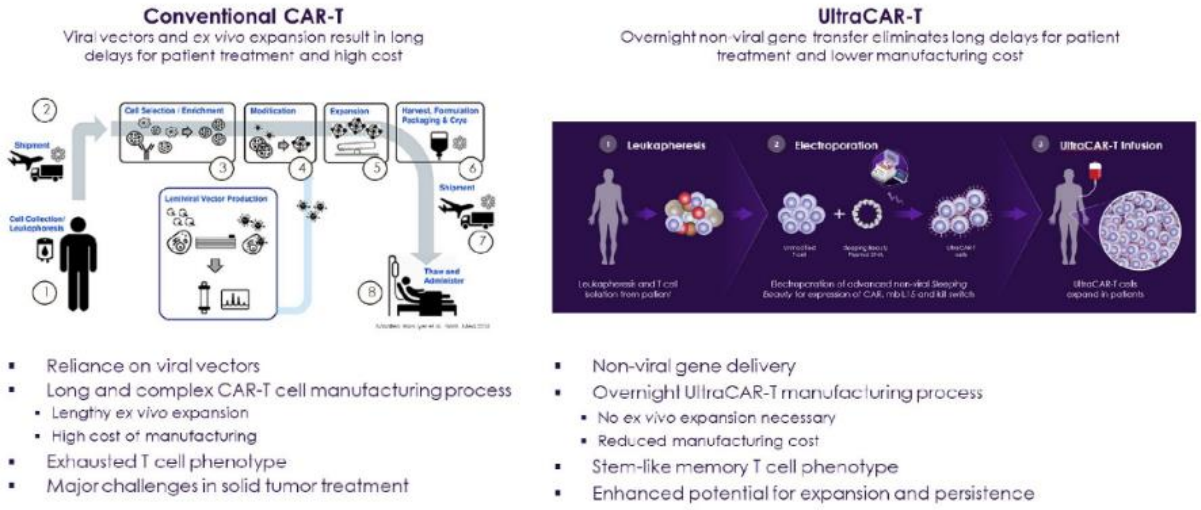
UltraCAR-T:

Unlike its competitors, UltraCAR-T has been designed to overcome the limitations of traditional CAR-T approaches by shortening the manufacturing time from weeks to days, reducing costs and improving outcomes for patients. Precigen has designed the platform with the end goal of empowering cancer centers to deliver personalized autologous CAR-T therapies with overnight manufacturing to any cancer patient out there. This scenario would be optimal for the patient and the doctors, as the treatment would be cheaper and with a much higher degree of safety and efficacy.

Let's look at what components make UltraCAR-T so promising:

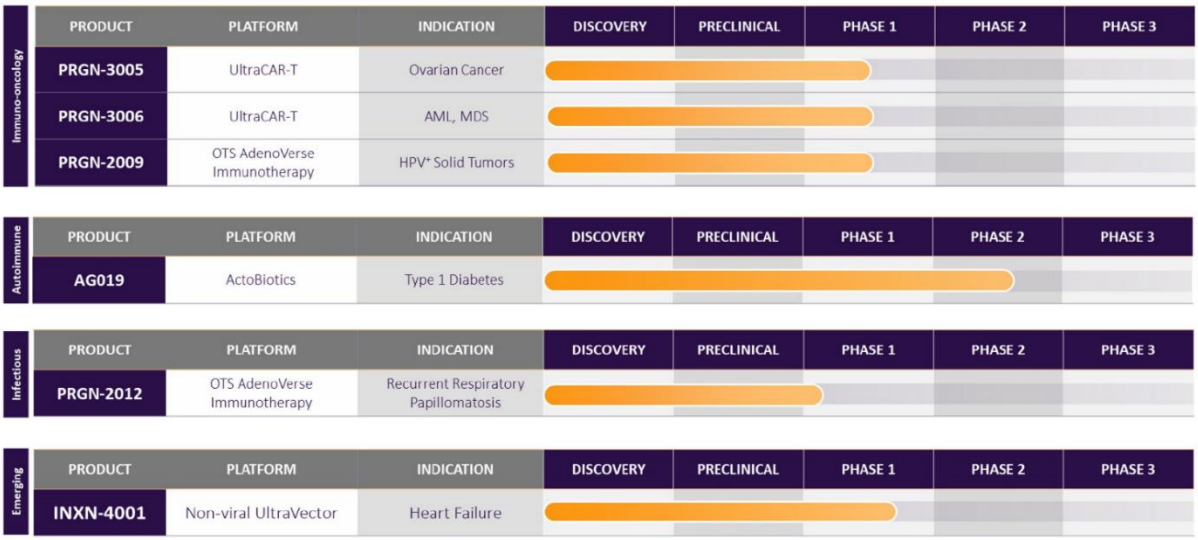
- *Advanced non-viral multigenic delivery system:* though this optimization process, Precigen can obtain CAR-T cells that co-express antigen-specific CAR, explicit genes that improve cell expansion as well as a kill switch, that can be activated to kill the UltraCAR-T modified cells in case of safety concerns.
- *Elimination of ex-vivo expansion step:* UltraCAR-T have been designed to express the gene *mbIL15* which has been shown to increase the expansion and persistence of engineered T-Cells directly in the patients' body, eliminating the need to expand the T-Cells before the transplant.
- *Rapid & decentralized manufacturing:* by leveraging another proprietary platform, the **UltraPorator**, the company can manufacture UltraCAR-T modified cells overnight and directly at the cancer center. This device has proprietary software and hardware components that enable it to streamline the process reducing times and costs significantly.

To illustrate even better the stark improvement Precigen is looking to bring to CAR-T development processes, let's look at an image [12] that directly compares the two experiences for the patient:



The company is already successfully employing this process in the clinic, while running Phase I/Ib studies for its lead programs PRCG-3005 and PRCG-3006. If the process is demonstrated further in the clinic and approved, it looks like it could be transformative for the entire CAR-T space.

In the next picture, we can see Precigen current pipeline of programs [13]:



<u>Selected Disease Profile:</u>

Ovarian Cancer

Population: 300,000 annually

Ovarian cancer ranks 5th in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system.

<u>Lead Cell Therapy Program:</u>

PRGN-3005

The firm's lead asset is PRGN-3005, a cell therapy approach leveraging the UltraCAR-T platform to deliver re-engineered T-Cells to patients. In preclinical studies, the T-Cells have shown significantly superior anti-tumor response in mouse models of ovarian cancer compared to mice treated with a saline solution or conventional CAR-T. The rodents treated with this way were all tumor free which is very promising. The asset is currently undergoing Phase I/Ib.

Recent Updates & Outlook:

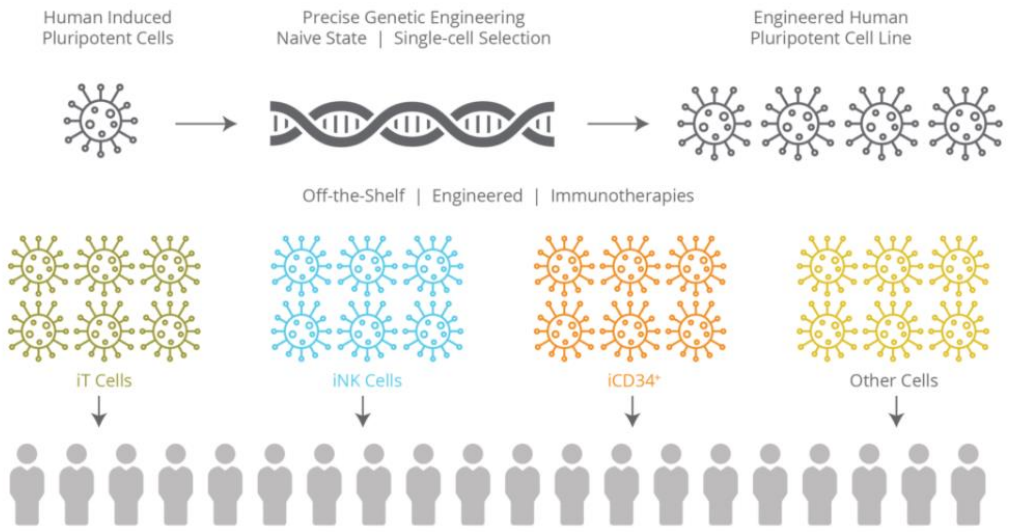
The company is currently dosing patients for its PRGN-3005 and PRGN-3006, both undergoing Phase I/Ib clinical trials. We expect to see positive interim results regarding safety in the coming months. This would potentially be very accretive to Precigen's market capitalization which is currently compressed.

Fate Therapeutics ($FATE)

Company Profile:

- Geography: USA
- Market Cap: $5.5B
- Stock Price: $57.86

Fate Therapeutics is a clinical-stage biotech firm focusing on the development of programmed cell cancer immunotherapies. The company is a specialist in cell programming, having developed a platform to create allogeneic or "off the shelf" cancer immunotherapies. Contrary to most companies working on cell therapies out there, Fate doesn't rely on the cells of the patient – autologous – but leverages *Human Induced Pluripotent Stem Cells* (*iPSCs*) to create a clonal master iPSC line that has very desirable biological properties. For a clearer understanding you can look at the illustration of Fate's platform technology below [14]:



As these master iPSC lines are programmable, the firm can decide the "biological fate" of the progenitor cells, hereby having the capability to create almost any type of cell in the body. Specifically, Fate is focusing on engineering cells of the blood and immune system to fight cancer.

The company strongly believes that its allogeneic approach will usher much needed improvements compared to legacy cellular therapies. Cell-based cancer immunotherapies approved on the market today most often rely on the use of autologous, or a patient's own cells. The need to source, engineer, expand and deliver cells patient-by-patient is very complex, resource intensive and expensive, and can result insignificant batch-to-batch variability in product purity and potency as well as in manufacturing failures. Fate sums up for us very clearly the key differentiators and improvement points on legacy technologies in the following image [15]:

Key Features	Cell Therapy 1.0 and 2.0	Cell Therapy 3.0
Cell Source	Patient and Donor Cells	Renewable Master Cell Line
Genetic Engineering	Random & Variable	Uniform & Consistent
Characterization	Imprecise	Well-defined
Product Identity	Heterogeneous	Homogeneous
Manufacturing	Low Yield-to-Cell Dose Ratio	High Yield-to-Cell Dose Ratio
Packaging	Fresh / Short Shelf Life	Cryopreserved / Long Shelf Life
Dosing	Single Dose	Multiple Doses
Delivery	Complex Logistics	Off-the-Shelf
Overall Paradigm	**Process-centric**	**Product-centric**

As we can observe from the table, Fate's process promises to solve many of the issues that plague the current iterations of cell therapies like scalability, cost-effectiveness and simpler delivery and logistics. The company therefore envisions a shift from a process-centric, complex delivery of autologous cells to a product-centric process focusing on off-the-shelf therapies.

Fate is currently working on a deep pipeline of assets as outlined in the following picture [16]:

Product	Cell Type	Engineered Functionality	Indication	R&D	Preclinical	Clinical
iPSC-derived Cell Products – Hematologic Malignancies						
FT516	iNK	hnCD16	AML			
FT516	iNK	hnCD16	BCL + mAb			
FT596	iNK	hnCD16 + IL15-RF + CAR19	BCL and CLL ± mAb			
FT596	iNK	hnCD16 + IL15-RF + CAR19	Post-HSCT + mAb (IIT)			
FT538	iNK	hnCD16 + IL15-RF + CD38-KO	AML			
FT538	iNK	hnCD16 + IL15-RF + CD38-KO	AML + mAb (IIT)			
FT538	iNK	hnCD16 + IL15-RF + CD38-KO	MM + mAb			
FT576	iNK	hnCD16 + IL15-RF + CD38-KO + CAR-BCMA	MM ± mAb			
FT819	iT	TRAC-targeted CAR19 + TCR-KO	B-cell malignancies			
iPSC-derived Cell Products – Advanced Solid Tumors						
FT500	iNK	Non-engineered	Advanced Solid Tumors + CPB			
FT516	iNK	hnCD16	Advanced Solid Tumors + mAb			
FT516	iNK	hnCD16	Recurrent Ovarian Cancer ± mAb (IIT)			
FT536	iNK	Multiplexed engineered CAR-MICA/B	Advanced Solid Tumors			
iPSC-derived Cell Products – Cancer Immunotherapy Collaborations						
Janssen	iNK and iT	Multiplexed engineered CAR-targeted	Not disclosed (hematologic / solid tumors)			
ONO	iT	Multiplexed engineered CAR-targeted	Not disclosed (solid tumors)			
Donor-derived Cell Products						
ProTmune	Hematopoietic graft	Small molecule modulated (non-engineered)	Hematologic Malignancies			

The predominant focus of the firm is producing off-the-shelf *iNK* (*Induced Natural Killer Cells*) and *iT-Cells* (*Induced T-Cells*) products to be deployed in combination with other cancer immune therapies – checkpoint

inhibitors and monoclonal antibodies – that have not proven to be particularly effective in harder to treat tumors.

Let's define briefly both cell types for those that aren't familiar with them:

- **Natural Killer Cells (NK):** NK cells are immune cells that possess the innate ability to quickly seek and kill abnormal cells, such as cancer or virally infected cells, and represent one of the body's first lines of immunological defense. They can kill cells through different and complex mechanisms that are beyond the scope of this paper.
- **T-Cells:** they are a critical component together with *B-Cells* in our adaptive immunity response and what differentiates them from other immune cells is the presence of a *T-cell receptor (TCR)* on their surface. TCR's is the mean through which a T-Cell recognizes antigens presented by other cells which enable the immune cells to react appropriately depending on the type of antigen and could potentially destroy the cell if deemed risky for the organism. The main difference between T-Cells and NK is that the former only attacks cells with a specific antigen on their surface, whereas NK don't have this restriction.

Fate is leveraging their iPSC platform to produce off the shelf NK and T-Cells that can be delivered to any patient, thanks to their unique biological properties.

Selected Disease Profile:

Advanced Solid Tumors (e.g. NSCLC)

Population (NSCLC): 200,000 annually in the US

Solid tumors are among the most lethal types of cancers which still have relatively few effective treatments on the market today. Among the ones that the company is working on we have *Non-Small Cell Lung Cancer (NSCLC)* which has a very low survivability rate of ~21%.

Lead Cell Therapy Program:

FT500

FT500 is an off-the-shelf NK cell cancer immunotherapy derived from a clonal master iPSC line that is looking to overcome resistance to checkpoint inhibitors. The program is currently undergoing Phase I trials.

Checkpoint inhibitors, as we've briefly discussed in a previous section, bind immune checkpoint proteins and block pathways that suppress T cells, and have shown very good results in multiple tumor indications. However, more than 60% of patients treated with checkpoint inhibitors will not respond or will relapse. As a result, Fate is looking to solve this unmet need by administrating allogeneic NK cells. NK cells possess the unique capability to recognize and kill cells that lack *MHC class I antigen* presentation. Furthermore, allogeneic NK cell therapy may overcome resistance to checkpoint inhibitor therapy in certain patients by directly killing tumor cells and by enhancing the adaptive immune response.

Recent Updates & Outlook:

The company is currently dosing patients in the Phase I for FT500 and we expect to see interim data coming in the next months. Fate future looks very bright as the firm is one of the few players out there that is looking to work on the future iterations of allogeneic cell therapies. If its programs are proven successful, Fate will

have much better economics if compared to a legacy cell therapy business thanks to its lower manufacturing costs and much more broad applicability and scalability of the therapeutic programs.

Rubius Therapeutics ($RUBY)

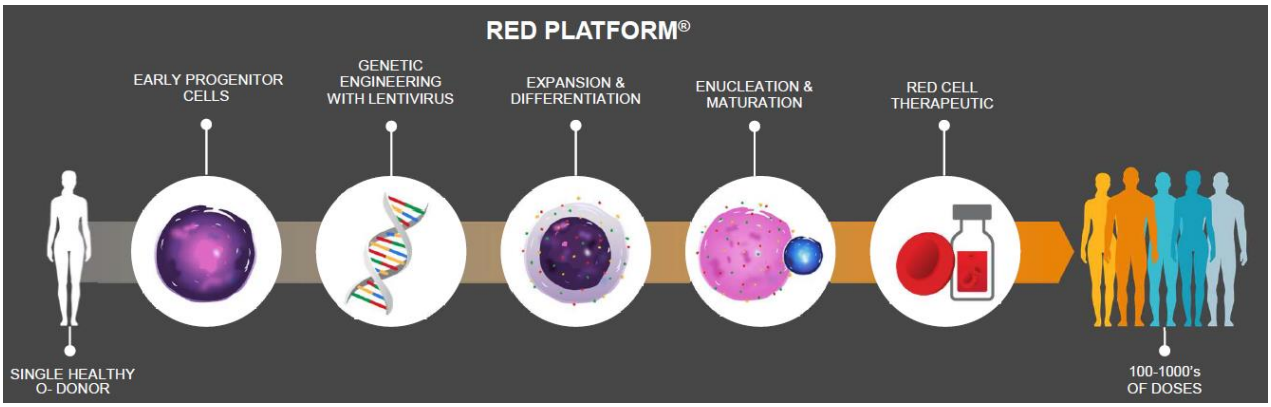
Company Profile:

- Geography: USA
- Market Cap: $1.4B
- Stock Price: $15.44

Rubius Therapeutics is a clinical-stage biotech firm that was created in a partnership between Harvey Lodish from MIT and Flagship Pioneering's Venture Lab. This cooperation between academia and a venture investor created a unique approach focused on genetically engineering *Red Blood Cells (RBC)* to create an entirely new class of cellular medicines called *Red Cell Therapeutics (RCTs)*.

Rubius is special and unique, in fact it is the only company on the market currently working on using RBCs as a mean to treat patients affected by debilitating diseases such as cancer and autoimmune diseases. Most competitors are focusing on engineering either T-Cells or NK cells, making Rubius' technology novel and interesting.

Let's now look at following picture [17] where you can observe the platform technology called **RED Platform** and what makes it so potentially appealing:



Red blood cells have been considered as mere oxygen-delivery vehicles up until now. Rubius is changing that by re-engineering the genetic makeup of RBCs using a *Lentivirus*es, which enables the cell to express particular therapeutic proteins on their surface.

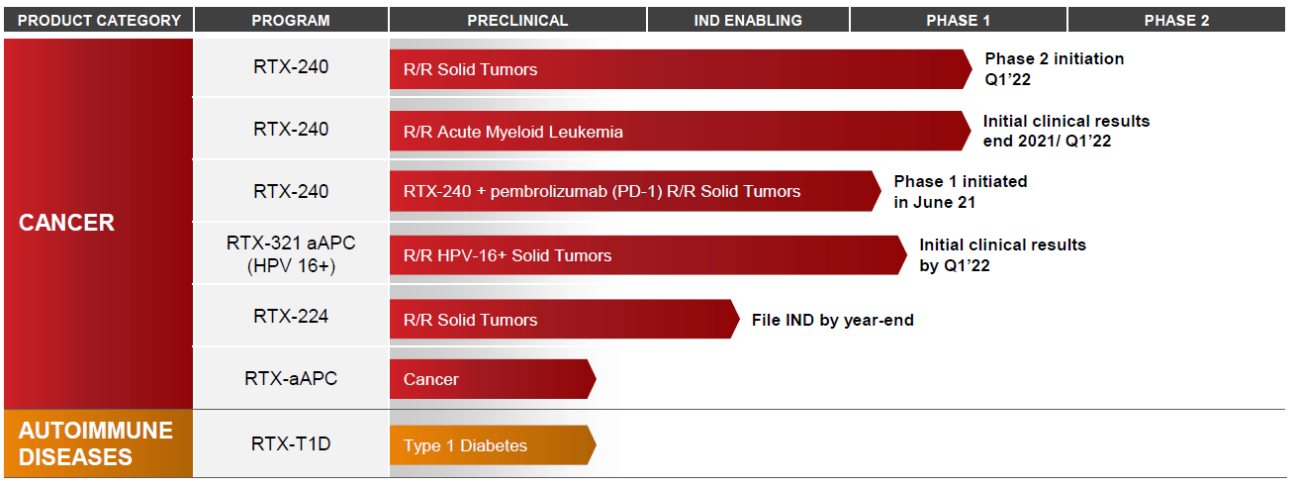
Through the following specific steps, Rubius can create a wide range of allogeneic RCTs product candidates:

1. Extract *CD34+ hematopoietic precursor cells* from the blood of O negative donors
2. Genetic engineering of the cells to express biotherapeutic proteins within the cell or on the cell surface of the RCTs
3. Expanding the number of cells and differentiating them into *reticulocytes*, which are RBC precursors that don't have a nucleus
4. Analyzing and storing the resulting RCT product for later use in patients

The resulting RCT products promise to solve many of the limitations of first generations cell therapies thanks to the following main outlined advantages:

- *Applicable in more indications*: RCTs can be leveraged in a broad range of indications such as rare diseases, cancer, autoimmune diseases, cardiovascular diseases, metabolic diseases and infectious diseases
- *Better tolerability*: RCTs don't have a nucleus, hence they don't have any genetic material and don't divide in vivo. Therefore, RCT product candidates could be less risky than legacy cellular therapies, which have shown to cause *Cytokine Release Syndrome*, neurotoxicity, as well as the possibility of causing cancer.
- *Off-the-Shelf products*: Since RBT can be synthesized from simple O negative blood stem cells, the supply is incredibly large and easy to obtain from transfusions, making the product allogeneic, easy to store and to ready to be used.
- *Predictable biodistribution*: RBCs have a very predictable biodistribution, meaning that they don't travel to off target tissues, therefore avoiding many issues related to off-target undesired effects.
- *Platform Technology*: The RED Platform is very versatile and enables Rubius to develop many new product candidates by just changing a few genes in the cells. As a result, this will allow the company to have a very effective and quick drug discovery process, bringing many new products through pre-clinical assessment.
- *Highly scalable and flexible manufacturing*: A single donor will enable the firm to manufacture up to thousands of doses. As a result, we expect the COGS for RCTs to be significantly lower than existing cellular therapies, such as legacy autologous CAR-Ts.

The benefits of this new cellular approach proposed by Rubius are very compelling as we can observe from the description of the RED platform. Let's now dive into the company's pipeline and what indications it is targeting first. The following picture [18] will be explicative:



Rubius is currently focusing their efforts mostly on cancer, specifically very hard to treat cancers like solid tumors as well as better treatable blood malignancies. In addition, the firm is also leading efforts in preclinical studies for autoimmune diseases like *Type 1 Diabetes*.

Selected Disease Profile:

Multiple Advanced Solid Tumors (e.g. PDAC)

Population (PDAC): 60,430 annually in the US

Pancreatic Cancer (PDAC) is one of the deadliest cancers out there, with a meagre survival rate of 10%. Currently, there hasn't been any real solution for this type of cancer, as chemotherapy mostly fails and other more novel approaches like legacy CAR-T therapy has not been very effective in solid tumors so far.

Lead Cell Therapy Program:

RTX-240

RTX-240 is currently undergoing Phase I clinical trials. This product has been engineered to stimulate and expand adaptive and innate immunity to generate an antitumoral response, mimicking how our immune systems normally reacts. The RBCs have been designed to express hundreds of thousands of copies of specific proteins on their surface that will activate and expand both NK cells and CD8+ memory T cells. The activation of this immune cells in return will attack the cancer and potentially reduce the tumor size.

Recent Updates & Outlook:

As clearly observable from their pipeline, Rubius has a lot of potential catalysts on the horizon. In March the stock had a major run up due to the positive results observed from interim Phase I data for RTX-240, almost quadrupling in value. We expect to see good things coming out of initial trial results from RTX-240 in AML as well as later in 2022 when we'll see initial Phase II data. Rubius is a very interesting one, being the only one using this RBCs approach, we plan to keep the company in our radar in the months to come.

Conclusion:

In this article we've covered a lot of ground on cell therapies to give you a high-level overview of the major advances in the spaces as well as the risks and challenges that we see on the horizon. We're extremely bullish on cell therapies and we believe the real potential of these new modalities is far from being fully developed and exploited. We'll keep a close watch on this market segment in the coming months and years. Hoping that you enjoyed the piece please feel free to reach out if you'd like to discuss the topic in more depth or even if you'd like to contest anything that we've written here! The whole team at Algo Capital looks forward to bringing you the next big trend topic in our next publication… stay tuned !

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