TO: Professors Theofrastous & Jankowski
FROM: Team RenoRegenX
DATE: December 10, 2019
SUBJECT: Final Memo – CAR T-Cell Therapy

Recommendation

Immunotherapy is a rapidly growing industry with an increasing demand and lucrative future. Dr. Sekaly and his team's discovery of a long-lived, pluripotent chimeric antigen receptor (CAR) T-cell phenotype and innovative selection method can potentially satisfy the varying degree of ineffectiveness of current CAR T-cell therapy treatments. In addition, Dr. Sekaly's 20 yearlong world renown expertise and development in human immune response to vaccines and to chronic viral infections, with a specific focus on cancer and HIV infection, boasts a track record of high performance and leadership in the industry. His passion and commitment to his work is evident. However, the absence of a strong proof-of-concept, the lack of intellectual property, and the shortage of funding for cancer specific research fails to inspire confidence in investors and stakeholders. Therefore, due to these factors, we do not recommend investing into this invention at this time.

Background

Cancer affects thousands of people worldwide. By the end of 2019, there will be an estimated 1,762,450 new cancer cases and 606,880 cancer deaths in the United States alone.[1] Although there are several types of treatments available for the treatment of cancer, recent years have added immunology as the fifth pillar to the standard conventions of cancer treatment. An immunotherapy technique called adoptive cell transfer (ACT) is rapidly emerging. There are several types of ACT therapies, but chimeric antigen receptor (CAR) T- cell therapy has become the first immunotherapy treatment to be approved by the United States Food and Drug Administration (FDA). CAR T-cell therapy equips patients with enhanced T-cells that can recognize and fight the infected cancer cells in their body. This process requires T-cells to be removed from the patient's blood. Then, in a lab setting, the gene that encodes for the specific cancerous antigen receptors are incorporated into the T-cells; thus, producing the CAR receptors on the surface of the cells. The newly modified T-cells are then further harvested and grown in the lab. After a certain time period, the engineered T-cells are infused back into the patient.

Unmet Need

For the vast majority of patients with blood cancer, and all with solid cancers, current CAR-T cell therapies have not yet proven to be effective because they are too toxic, or are not available due to expense or geography.[5] Reported data continues to support the variable efficacy and durability of responses to anti-CD19 CAR-T cell therapy. Response rates in acute lymphoblastic leukemia are reported between 68% and 93%, in chronic lymphocytic leukemia between 57% and 71%, and in B cell lymphoma between 64% and 86%.[5] This variability in effectiveness amongst patients could partly be attributed to the lack of robust long-term CAR T-cell driven responses. An effective CAR T-cell therapy for cancer patients who have adverse or short-lived positive responses to current cancer treatments is in demand. CAR T-cell therapy

has been found to be effective in many patients with non-solid tumor cancers, however, there are a few shortcomings. One of the shortcomings is that, in some cases, the CAR-T cell expression does not last long enough in a patient for it to effectively destroy the cancerous cells.

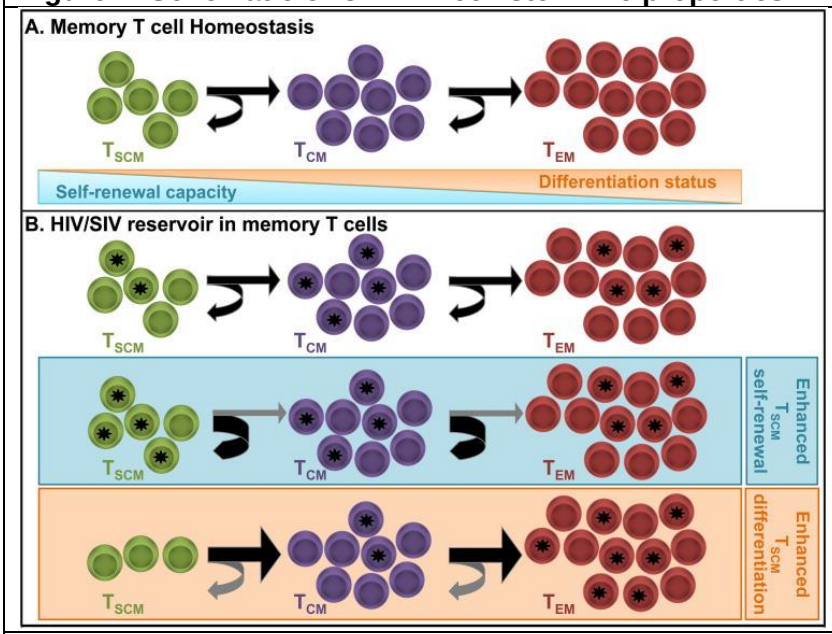
Proposed Solution

The effectiveness of CAR T- cell therapy could be improved by generating long-lived, self-renewing CAR T-cells that routinely populate the effector compartment. A method for selecting CAR T-cells that express a particular phenotype with long-lived, self-renewing properties has been developed. We believe this method will result in a more effective anti-CD19 immunotherapy.

Proof-of-Concept

The human immunodeficiency virus (HIV-1) is capable of avoiding detection by the body's immune system by hiding in memory T cells, the same cells that are meant to destroy them. Memory T cells represent the largest lymphocyte population in the adult human body, and play critical roles for maintaining life-long antimicrobial immune defense against specific pathogens.[6] Although there are several different subsets of memory T-cells, they can be divided into two main categories, central memory (T_{CM}) and effector memory (T_{EM}) T-cells. Through the research of SB-728-T, an investigational gene therapy product that is being studied to treat or possibly cure HIV, characterization and differentiation of a novel stem-like T-cell population was discovered.[7] From the experimental data, researchers learned that these memory T-cell populations evolved in a hierarchical developmental process during which more immature, long-lasting T-cells served as precursors for more differentiated, mature and short-lived memory cell subsets.[6] This was very similar to the hierarchical developmental structure of the hematological and epithelial systems, in which small populations of multipotent, tissue-specific stem cells are able to constantly repopulate large populations of differentiated effector cells, while maintaining their own life-long survival through homeostatic self-renewal.[6] Also, researches noticed that persistence of infused CCR5-modified CD4 T-cells was driven by an increase in $CD45RA^{int}CD45RO^{int}$ cell subsets. Collectively, these observations led scientists to believe that this small population, that expressed this specific phenotype, of highly undifferentiated and long-lived memory T-cells with stem cell like properties could be the basis for the continual generation of central memory, effector memory and effector t-cells (see **Figure 1**). Dr. Sekaly and his team hypothesized that this unique cell type could be amplified into an effective CAR T-cell therapy with a long-lasting immune response against the immunosuppressive microenvironment of cancerous tumors. As a result, they have devised a platform for the development and selection of a long-lived and pluripotent CAR T-cell population, with a capacity of effector differentiation.

Figure 1. Schematic of CD4+ T-cell stem like properties



Schematic of CD4+ memory T cell homeostasis (A) and proposed relative contribution of CD4+ memory subsets to the persistent reservoir of HIV/SIV (B, top panel). In (B) the potential effects of drugs promoting enhanced self-renewal (middle panel) or enhanced differentiation (bottom panel) of TSCM on the overall CD4+ memory T cell reservoir are shown. Stars represent cells latently infected with HIV/SIV.

Source: Chahroudi, Ann et al. "T memory stem cells and HIV: a long-term relationship." *Current HIV/AIDS reports* vol. 12,1 (2015): 33-40. doi:10.1007/s11904-014-0246-4

Intellectual Property Analysis

After analyzing the current invention disclosure, the potentially protectable intellectual property interests have been identified as the method for generating long-lived CAR T-cells for effective anti-CD19 immunotherapy. It may be difficult to pursue patent protection for the created product itself because it is resembling a stem-like cell that naturally exists in the body, therefore the protection fall under unpatentable subject matter under 35 USC § 101. However, if the product is thought to involve enough human intervention to deem this product more than just a product of nature, and therefore patentable.

There are three major types of intellectual property rights protectable within Intellectual Property Law. These rights are patent rights, trademark rights, and copyright rights. Trademark Law can protect logos and other branding elements of a company or product. However, Patent Law will be the most useful and valuable form of protection for the identified invention. While patent protection is limited in duration, obtaining a patent would provide the patentee with the right to exclude all others from making or using the protected invention for twenty years from the date of filing. Obtaining patent rights would also significantly increase the possibility of investors and the value of the invention in general.

Currently, a provisional patent was filed in the United States Patent and Trademark Office (USPTO). This application describes the method of generating long-lived CAR T-cells. However, the provisional patent only protects the invention for 12 months, and utility patent must be filed within the 12-month limit or else protection expires. The provisional patent does not include any claims, so in order to submit the utility patent within the 12-month period to

continue protection of the invention, the inventor must do more research to finalize what points of novelty should be claimed.

A prior art search shows a multitude of patents specifically focusing on increasing the therapeutic efficacy and longevity of CAR T Cells. As exemplified by WIPO, W02017049166A1, issued to Novartis, the biggest player in the field of CAR T Cell therapy, demonstrates different methods and amino acid compositions have been invented to increase efficacy of CAR T Cell therapy. This patent shows specifically Novartis is heavily investing in R&D of amino acid sequences in three different levels of extracellular, transmembrane and intracellular levels. Through engineering of these sequences, different cell signaling machineries could be blocked as well as triggered thus enabling a higher efficacy of CAR T Cell therapy. Also, multiple methods of exposure of CAR T Cells to different inhibitors such as Tet1 and Tet2 have been invented. These methods might narrow down the scope of what is potentially patentable, making it more difficult to protect the identified invention described above. The patent confirms that Novartis is working very closely on similar subject matter, RA and RO CD45 cells, which may create a race to the Patent Office.

Market Analysis

Presently, CAR T-cell therapy is only FDA approved as standard of care for some forms of aggressive, refractory non-Hodgkin lymphoma and for patients with relapsed or refractory acute lymphoblastic leukemia.[8] This means that the total addressable market is very small. According to the American Cancer Society (ACS), approximately 74,200 people (41,090 males and 33,110 females) will be diagnosed with Non-Hodgkin Lymphoma (NHL) by the end of 2019.[9] This number includes both adults and children. Also, sixty percent of all NHL cases in the United States are aggressive, with the most common subtype being DLCL (diffuse large B cell lymphoma).[10] Furthermore, 35% of NHL patients relapse or do not respond to traditional cancer treatments.[11] Combining these three pieces of information, we were able to estimate the addressable NHL market for CAR T-cell therapy in the U.S. to be about 15,582 patients. Acute lymphoblastic leukemia (ALL) is the second most common acute leukemia in adults, with an incidence of over 6,500 cases per year in the United States alone.[12] While 80% of ALL occurs in children, it represents a devastating disease when it occurs in adults.[12] From this information, it was estimated that the addressable ALL market for CAR T-cell therapy in the U.S to be approximately 5,200 patients. In sum, the total addressable market for FDA approved CAR T-cell therapy was about 20,782 patients (see **Figure 2**).

Figure 2. Total Addressable Market for FDA Approved CAR T-Cell Therapy

Title	Data	Unit
Estimated number of NHL diagnosis in US	74,200	patients
Aggressive NHL out of total NHL population	60%	percent
NHL patients that DO NOT respond / relapse	35%	percent
Addressable NHL Market, USA	15,582	patients
Acute lymphoblastic leukemia (ALL), incidence US	6,500	patients
Acute lymphoblastic leukemia (ALL) in children, incidence US	80%	percent
Addressable ALL Market, USA	5,200	patients
Total Addressable Market, USA	20,782	patients

Due to the strict regulations on FDA approved CAR T-cell therapy treatments, the total addressable market in the US was estimated to be about 20,782 patients.

Sources: ACS, City of Hope, PubMed

As of today, there are only two CAR-T cell therapies currently approved by the U.S FDA, Kymriah and Yescarta (see **Figure 3**). Therefore, the entire U.S Car-T cell therapeutic market, and global market, consists of just two companies; Novartis and Gilead (see **Figure 4**).

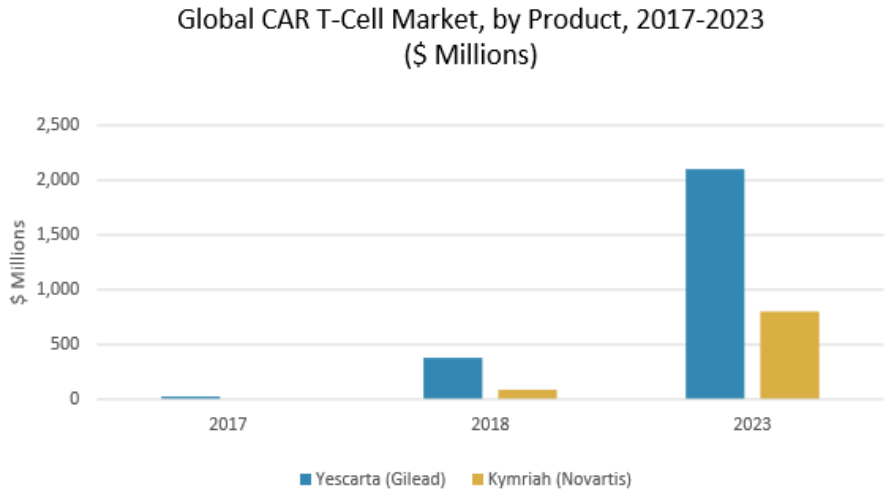
Figure 3. US CAR-T Cell Market

Kymriah	Yescarta
Drug: Tisagenlecleucel	**Drug:** Axicabtagene ciloleucel
Expedited Review: Priority Review, Breakthrough Drug.	**Expedited Review**:Priority Review, Breakthrough Drug, Orphan Drug Status.
IND Submission: 9/23/2014.	**IND Submission**: 12/2014.
FDA BLA Approval: August 30, 2017	**FDA BLA Approval:** Oct 18, 2017
Company: Novartis	**Company:** Gilead
Price: $475,000 per treatment	**Price:** $373,00 per treatment

Kymriah has been FDA approved for the treatment of patients, up to 25 years of age, with Acute Lymphoblastic Leukemia (ALL) or aggressive Non-Hodgkin Lymphoma (NHL) that relapse and/or do not respond to any other treatments. Yescarta, on the other hand, has been FDA approved for the treatment of patients,18 years of age or older, with aggressive Non-Hodgkin Lymphoma (NHL) that relapse and/or do not respond to any other treatments. According to BCC Research, Yescarta (Gilead) accounted for 75% of the global CAR T-cell market shares and Kymriah (Novartis) accounted for the remaining 25% in 2018. This is reflected in the calculated

total addressable market in **Figure 2**. Out of the total 20,782 patients, about 75% of patients have NHL and the remaining 25% have ALL. Since the majority cancer patients with NHL are adults, as only 7.1% or children with cancer are diagnosed with NHL, it is logical that Yescarta is approved for adults and Kymriah is approve for patients 25 years old and younger. Interestingly, although both Yescarta and Kymriah dominate the market, they are not competitors as their addressable markets do not see to overlap.

Figure 4. Global CAR-T Cell Market Shares



Source: BCC Research

In 2018, Yescarta (Gilead) accounted for 75% of the global CAR T-cell market shares and Kymriah (Novartis) accounted for the remaining 25% of the global CAR-T cell market shares.

Figure 5. Global CAR T-Cell Market Share Projections

Global CAR T-Cell Market, by Product, Through 2023
($ Millions)

Product	2017	2018	2023	CAGR% 2018-2023
Yescarta (Gilead)	25	380	2,100	40.8
Kymriah (Novartis)	--	87	800	55.9
Total	25	467	2,900	44.1

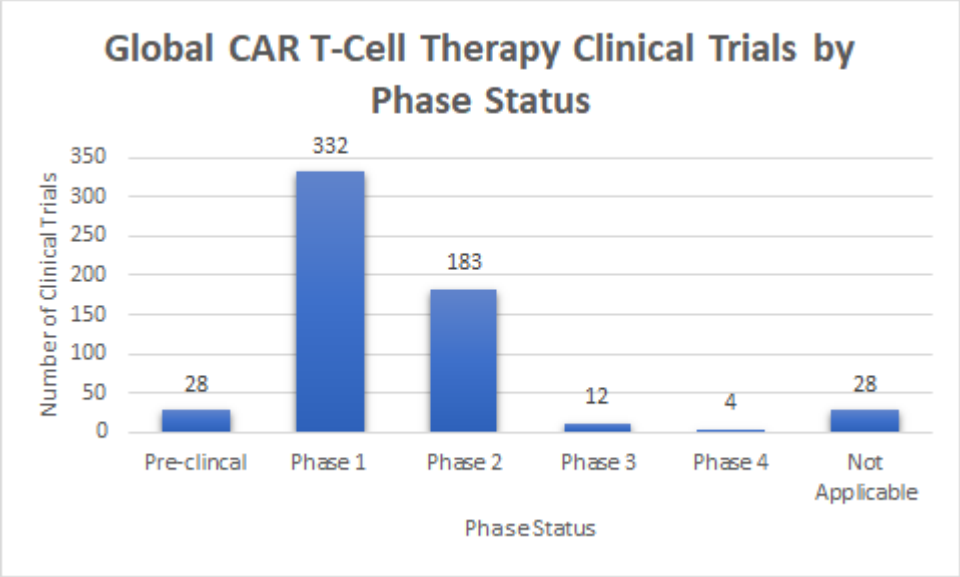
Source: BCC Research

According to BCC Research, the global market for CAR T cell therapies was valued at $25.0 million in 2017 and $467 million in 2018. By the end of the forecast period in 2023, it is predicted that the global market will have increased in value to $2.9 billion, representing a compound annual growth rate of 44.1%.

Competitive Analysis

In addition to the current market players, Novartis and Gilead, there are several unknown laboratories and companies that have are conducting CAR T-cell therapies (see **Figure 6**). On December 10, 2019, over 500 publicly and privately funded clinical trials related to CAR T-cell therapies have been registered.[3]

Figure 6. Global CAR T-cell Therapy Clinical Trials by Phase Status as of December 10,2019



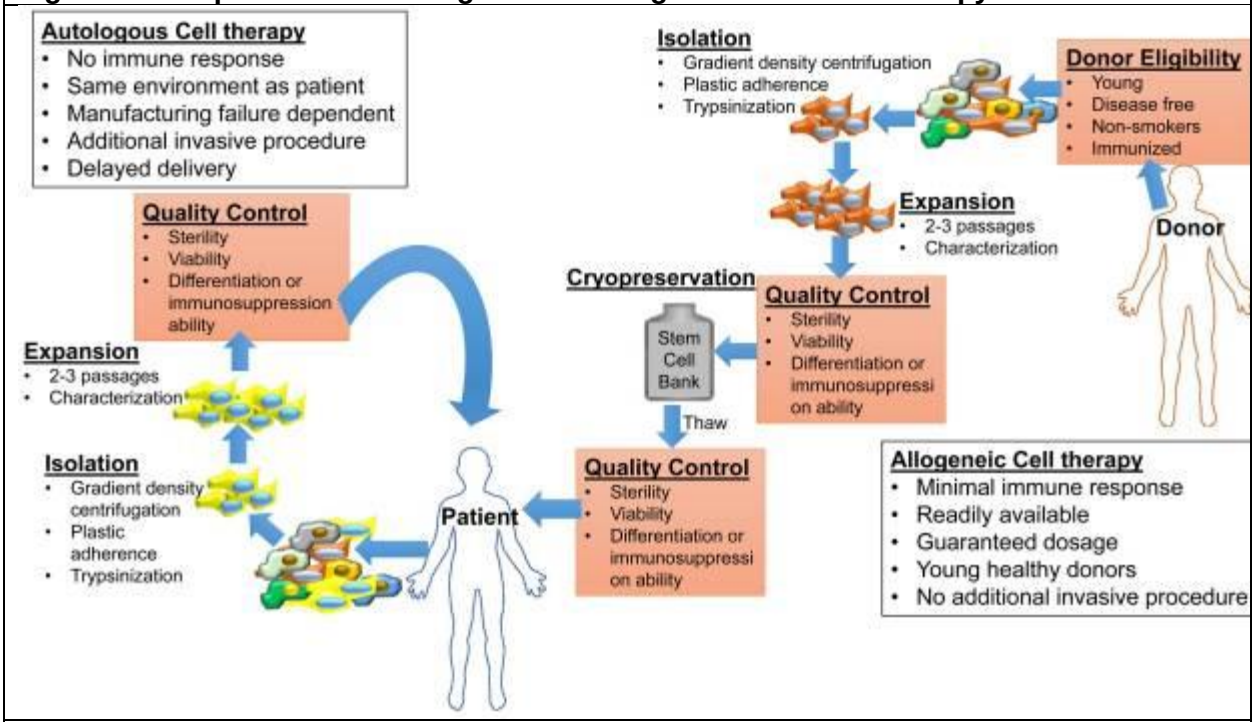
Pre-clinical: A phase of research used to describe exploratory trials conducted before traditional phase 1 trials to investigate how or whether a drug affects the body. They involve very limited human exposure to the drug and have no therapeutic or diagnostic goals (for example, screening studies, microdose studies).	Phase 3: A phase of research to describe clinical trials that gather more information about a drug's safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs. These studies typically involve more participants.
Phase 1: A phase of research to describe clinical trials that focus on the safety of a drug. They are usually conducted with healthy volunteers, and the goal is to determine the drug's most frequent and serious adverse events and, often, how the drug is broken down and excreted by the body. These trials usually involve a small number of participants.	Phase 4: A phase of research to describe clinical trials occurring after FDA has approved a drug for marketing. They include postmarket requirement and commitment studies that are required of or agreed to by the study sponsor. These trials gather additional information about a drug's safety, efficacy, or optimal use.
Phase 2: A phase of research to describe clinical trials that gather preliminary data on whether a drug works in people who have a certain condition/disease (that is, the drug's effectiveness). For example, participants receiving the drug may be compared to similar participants receiving a different treatment, usually an inactive substance (called a placebo) or a different drug. Safety continues to be evaluated, and short-term adverse events are studied.	Not Applicable: Describes trials without FDA-defined phases, including trials of devices or behavioral interventions.

Pipeline Products

CAR -T cell therapy cannot help patients with tumorous cancers at this time, and so further research and development is currently being conducted to determine a way to treat solid tumors. The strong immunosuppressive tumor microenvironment makes it difficult for current CAR-T cell therapies to retain their effectiveness. In the future, we are looking into partnering with other labs that are presently working on a solution to this problem. We believe our CAR T-cell longevity expression method could be applied in tumorous cancers.

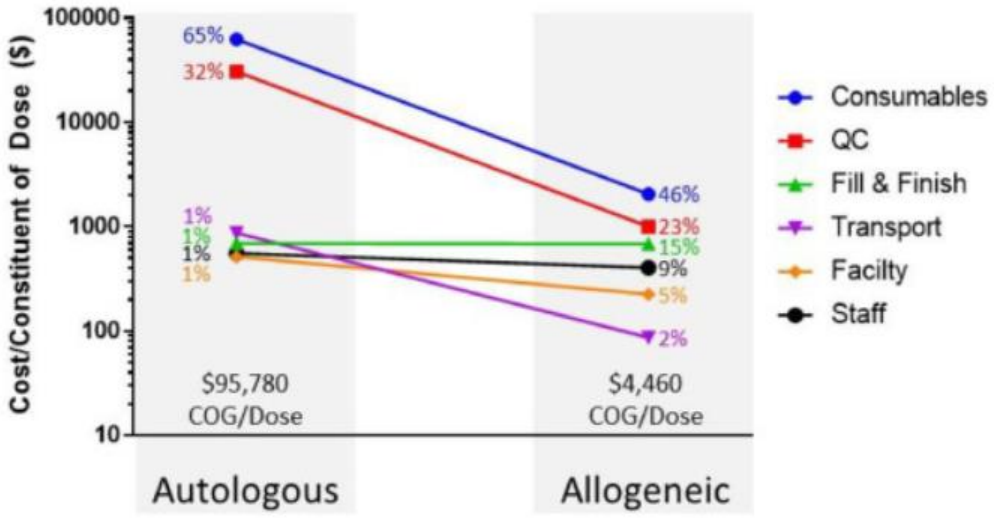
In the future, we are looking to apply our CAR T-cell longevity expression method to universal allogeneic therapeutic treatments (see **Figure 7**). Right now, our CAR T-cell method is used in autologous therapies, which uses each individual patients' T-cells. In order to use allogeneic CAR T-cell therapies, we would need to find a way to remove any kind of allogeneic activity. Allogeneic stem cell therapy offers advantages over the autologous counterpart, in that the stem cells are derived from young healthy donors, eliminates any co-morbidities associated with disease states.[14] Allogeneic cells from healthy donors are grown and kept in stem cell banks so that they are available for immediate delivery. An allogeneic model could significantly reduce aggregate cost of goods (COGs), potentially improving market penetration of these life-saving treatments (see **Figure 8**).[13] This COG reduction stems chiefly from the ability to spread the high initial cost of the donor materials and subsequent selection and enrichment, as well as the associated batch QC across a larger number of doses.[13] This would save time and money for both hospitals and patients.

Figure 7. Comparison of Autologous and Allogeneic stem cell therapy



Source: Karantalis, Vasileios et al. "Allogeneic cell therapy: a new paradigm in therapeutics." *Circulation research* vol. 116,1 (2015): 12-5. doi:10.1161/CIRCRESAHA.114.305495

Figure 8. Comparison of COGs between Autologous and Allogeneic Treatments



Source: Chimeric antigen receptor–T cell therapy manufacturing: modelling the effect of offshore production on aggregate cost of goods. Harrison, Richard P. et al. Cytotherapy, Volume 21, Issue 2, 224 – 233

Economic Profile

The first key milestone is obtaining a patent or a portfolio of patents which could be challenging more technically than financially. On average the cost of a patent in the field of biomedicine/biomedical engineering falls in a range of $25-$50K which is absolutely minuscule compared to the cost of R&D that culminates in a patent. Technical challenges regarding the issuance of a patent with a strong position becomes more of a challenge when mammoth players race against each other. As mentioned before, Novartis has secured a very comprehensive patent which might render many feature endeavors unpatentable or at least hard to protect. Recently Juno has challenged Gilead Sciences patent on Yescarta which will be heard soon December 2019. The patent was acquired through the acquisition of Kite Pharma, the original developer of Yescarta. 10k filings of Kite Pharma shows that over $200 million was spent on R&D of this therapy. However, it is not known what portion of it was due to original work that led to IP protection of Yescarta. But it is known that a $16 million investment by U of Penn resulted in the development of Kymriah, the closest and the only competitor of Yescarta available in the market. This is the closest estimation we can imagine for a potential future therapy. This amount could be obtained by a multiple grant strategy similar to that of Professor Carl June, the PI of the project that led to the invention of Kymriah.

In the light of the above, it can be realized that while a bad patenting strategy might cost a huge amount of money and time, it can also lay a strong foundation for future steps including but not limited to manufacturing, acquiring, merging and licensing.

The next milestone will be clinical trials and FDA applications. The timeframe of FDA regulation can be summarized in the following manner: 1) Pre - Investigational New Drug ("IND") preparation; 2) IND Application 3) Institutional Review Board ("IRB") Compliance; 4) Phase I and II trials; 5) Biologics License Application ("BLA"); 6) Risk Evaluation and Mitigation Strategies (" REMS"). For the fiscal year 2020, the user fee under the Prescription Drug Fee User Act ("PDUFA") is $ 2,942,965 for biologic products requiring clinical trials. Each stage of the FDA regulation timeframe is time-consuming and expensive. Generally, FDA's standard review for drugs without an accelerating process will take more than 10 years. There is, however, expedited reviews available for our products. Based on experiences of other CAR T cell therapies regarding FDA regulation, like Yescarta and Kymirah, expedited reviews like "Breakthrough Therapy," "Orphan Drug Designation" can greatly shorten the amount of time our application pending with the FDA.

Novartis claims it has invested more than $1 billion in R&D of Kymriah after it purchased the entire technology from U of Penn. Kite Pharma's 10(k) fillings show an amount of more than $200 million. No legitimate data released either by Kite Pharma or Novartis suggests how much was spent in each phase of clinical trials. However, in a profit analysis report by patients for affordable drugs, it was revealed that close to $1 million per patient was spent in clinical trials of Kymriah. Knowing that the patient population was 456, we can say the cost of clinical trials for Kymriah was $456 million. We can estimate an expenditure of $10 million for phase I, $20-$100 for phase II and $100-$300 for phase III of clinical trials, based on conventional size of patient population for each phase.

Juno also mentioned the cost of its CAR-T research in its 10k of the year 2014. For its JCAR015, which was in ongoing Phase I trial, in total $ 2,618k for R&D was spent specifically for it for nine months ended on Sep. 30, 2014; for its JCAR014 which was in ongoing Phase I and II trials, $ 4,103 k was spent for its R&D development for nine months ended on Sept. 30, 2014. And for the nine months, there was a $ 3,069 k expenditure for a so-called "platform development" and a $ 2,916k for "early development".

What should also be noted is that the FDA process is time-consuming, uncertain and expensive. Costs projection of trials of each Phase reside on the presumption that first an IND can be issued by the FDA. As Juno Therapeutics mentioned in its 10k of the year 2014, in which year it went to public, it asserted that because of the uncertainty of FDA regulation, it cannot ensure that an IND can be filed within next five years and that FDA would grant an accelerated review to its multiple CAR T cell candidates.

Conclusion

The logistics of CAR T-Cell therapy is very challenging. The supply chain requires a rigorous system of different players that each must provide timely and diligently to make the therapy happen. There are few facilities worldwide that engineer, expand and preserve CAR T-cells. It could be understood that even though manufacturing is enticing, a competition against giant players seems daunting, therefore, licensing, merger/acquisition exit strategies would be strategically better.

Appendix A: References

1) National Cancer Institute. (2015). Cancer Statistics. [online] Available at: https://www.cancer.gov/about-cancer/understanding/statistics.
2) LaRussaA (2015). Chimeric Antigen Receptor (CAR) T-Cell Therapy | Leukemia and Lymphoma Society. [online] Lls.org. Available at: https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy#Results,%20Limitations,%20and%20the%20Future%20of%20CAR%20T-Cell%20Therapy [Accessed 10 Dec. 2019].
3) Clinicaltrials.gov. (2019). Home - ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/home.
4) Karantalis, Vasileios et al. “Allogeneic cell therapy: a new paradigm in therapeutics.” *Circulation research* vol. 116,1 (2015): 12-5. doi:10.1161/CIRCRESAHA.114.305495
5) Charrot, Sarah, and Simon Hallam. “CAR-T Cells: Future Perspectives.” *HemaSphere* vol. 3,2 e188. 19 Mar. 2019, doi:10.1097/HS9.0000000000000188
6) Chahroudi, Ann et al. “T memory stem cells and HIV: a long-term relationship.” *Current HIV/AIDS reports* vol. 12,1 (2015): 33-40. doi:10.1007/s11904-014-0246-4
7) Treatment Action Group website. Research toward a cure trials. http://www.treatmentactiongroup.org/cure/trials. Accessed December 09, 2019
8) Cancer Institute, D. (2019). Frequently Asked Questions About CAR T-Cell Therapy - Dana-Farber Cancer Institute | Boston, MA. [online] Dana-farber.org. Available at: https://www.dana-farber.org/cellular-therapies-program/car-t-cell-therapy/faq-about-car-t-cell-therapy/ [Accessed 9 Dec. 2019].
9) Society, A.C., Information and Resources about for Cancer: Breast, Colon, Lung, Prostate, Skin. American Cancer Society. Available at: http://www.cancer.org/ [Accessed December 9, 2019].
10) Hope, C.O., FDA-approved CAR T cell therapy for non-Hodgkin lymphoma: City of Hope. *City of Hope Comprehensive Cancer Center*. Available at: https://www.cityofhope.org/research/car-t-cell-therapy/nhl-car-t [Accessed December 8, 2019].
11) Anon, Comprehensive Cancer Information. National Cancer Institute. Available at: https://www.cancer.gov/ [Accessed December 7, 2019].

12) Terwilliger, T, and M Abdul-Hay. “Acute lymphoblastic leukemia: a comprehensive review and 2017 update.” Blood cancer journal vol. 7,6 e577. 30 Jun. 2017, doi:10.1038/bcj.2017.53
13) Chimeric antigen receptor–T cell therapy manufacturing: modelling the effect of offshore production on aggregate cost of goods. Harrison, Richard P. et al. Cytotherapy, Volume 21, Issue 2, 224 – 233
14) Karantalis, Vasileios et al. “Allogeneic cell therapy: a new paradigm in therapeutics.” *Circulation research* vol. 116,1 (2015): 12-5. doi:10.1161/CIRCRESAHA.114.305495