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The Future Lies Within: Why Personalized Medicine in Immunotherapies Holds the Key to Cancer Treatment

Jared Salas
Regis University

THE FUTURE LIES WITHIN: WHY PERSONALIZED MEDICINE IN IMMUNOTHERAPIES HOLDS THE KEY TO CANCER TREATMENT

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by

Jared Salas

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Thesis written by

Jared Salas

Approved by

Thesis Advisor

Thesis Reader

Accepted by

Director, University Honors Program

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Preface

Cancer has affected family members and friends in my own life, and I have seen the harsh effects it can have on a person. I never understood how cancers disarmed our immune system until I took the upper division course "Immunology" in my third year of my undergraduate education. I was astonished by how our immune system functioned and how cancerous cells could simply become unrecognizable to our immune response. The idea that our immune systems all react differently to stimuli captured my mind and made me realize how difficult it is to treat cancer. Although most households across the nation recognize how difficult cancer is to treat, most people do not understand the significance of our immune response to the disease. I wanted to explore what type of cancer treatments there currently were, and what the future of cancer treatments looks liked. I found the most potential in immunotherapies; specifically ACT therapies and CAR-T cell therapies, because of the amount of personalized medicine that goes into them.

"It is now conceivable that our children's children will know the term cancer only as a constellation of stars"

- President Bill Clinton

"Wherever the art of medicine is loved, there is also a love for humanity"

- Hippocrates

CHAPTER I: Evolution of Immunotherapies in Cancer Treatment

The treatment of cancer has been and will continue to be one of the most difficult aspects of healthcare worldwide. Cancer is not simply one disease, but rather a large group of related diseases that influence the cells in our tissues to divide uncontrollably. Cancers arise from genetic changes in DNA that can either be inherited or derived from external pressures on the body (Podolskiy & Gladyshev, 2016; National Cancer Institute, 2015). These genetic mutations lead to the uncontrollable cell division that is difficult to treat. Although cancers are not all identical, they all produce severe consequences on tissues and organs throughout the body. One typical characteristic of cancer is that of malignancy, which is a term for describing the ability of cancerous tumors to spread throughout nearby tissues (National Cancer Institute, 2015). Uncontrollable cell division and malignant tumors create a microenvironment that is difficult to treat, in part because of the affects they have on the immune system and response.

The human immune system is primarily involved in the protection of the body against disease and infection. The immune response to disease consists of an innate response and an adaptive response, each of which are important in the recognition and eventual elimination of a disease from our body. The innate response occurs first, and sets the stage for the adaptive response through inflammation mechanisms and antigen presentation (Murphy & Weaver, 2017). Inflammation is initiated when macrophages and specific leukocytes, known as neutrophils, travel to infected areas of the body and provide the first barrier against infected cells. The transition between the innate response and the adaptive response occurs when antigen-presenting cells, such as dendritic cells,

present foreign antigens to T-lymphocytes, otherwise known as T-cells (Murphy & Weaver, 2017). There are two types of T-cells in the adaptive immune response. T-cytotoxic cells are activated through antigen presentation and can directly eliminate infected cells through induction of apoptosis or through attachment and release of specific molecules, such as perforin (Anderson et al., 2006). On the other hand, T-helper cells secrete specific cytokines that are critical in the activation of macrophages or the stimulation of B-cells to create antibodies (Alberts et al., 2002). B-cells, the other type of lymphocyte involved in the adaptive response, provide memory defense for the body by creating antibodies that will recognize disease.

T-cells are not the only cells involved in our adaptive immune response, yet these cells have been linked to cancer treatment in many different ways because of their importance in the recognition of cancerous cells. Even though T-cells have the ability to recognize and eliminate cancer cells, they also have the ability to promote tumor growth (Cancer Research UK, 2017; Anderson et al., 2006). This is one reason why cancer is such a difficult disease to treat. Tumor cell development and proliferation is promoted through mechanisms such as the disruption of T-cell functions and consequent evasion from immune recognition (Kerfelec, et al., 2016). This mechanism shows why it is important for researchers to understand the many functions of T-cells, especially in cancer treatment. T-cells have been labeled as the "soldiers of the immune system," because of the role they play in our bodies (D'Errico et al., 2017). Despite the fact that T-cells are "soldiers" and crucial in the defense against cancerous cells, they can still have their roles reversed completely by cancer. For example, it has been found that the type of

tumor infiltrating T-cells is an underlying factor in tumor progression or regression. A higher ratio of infiltrating T-regulatory cells compared to T-effector (TCD8+) cells can lead to disease progression, while the opposite can lead to disease regression in some types of cancer (Graciotti et al., 2017). Hence, a better understanding of T-cells and how they can aid tumor growth is critical moving forward, because of their importance in the immune response against cancer.

Over the last few decades, cancer treatment has been at the forefront of medical research, and yet researchers are still searching for answers. Today, there are multitudes of isolation or combinatorial treatments that try and limit the spread of cancer. One of these treatments is chemotherapy, which has been a prominent form of cancer treatment over the last few decades. Basically, chemotherapy involves drugs that are developed specifically for the prevention of uncontrollable cell division and the inhibition of the spread of cancer to numerous tissues (Southeast Radiation Oncology Center, 2017). Rather than using an individual's own immune system, chemotherapy drugs can inhibit further division of cancerous cells' by limiting the affected cells ability to make nucleic acids. In addition, chemotherapy is not solely focused on specific parts of the body, but rather it will affect dividing cancer cells throughout the entire body (Southeast Radiation Oncology Center, 2017). When examining therapies that directly target affected tissues or organs, radiation therapy has been at the forefront of cancer treatment.

Radiation therapy involves targeted radiation into a specific tissue where the cancer initially started or spread. Radiation therapy aims to stop the further spread of the cancer in that tissue by damaging the DNA in the cancerous cells and eventually killing

them (Southeast Radiation Oncology Center, 2017). There is no doubt that both chemotherapy and radiation therapy can be effective against cancer, however, a look into the effects they have on patients makes it difficult to believe that these treatments are the future of cancer treatment. Both of these cancer treatments can kill healthy cells in patients during the course of a treatment, which may lead to hair loss, muscle weakness, and other debilitating effects. Since these two regimens can be very strenuous on an individual's body and social life, researchers have been exploring other types of cancer treatment for decades that provide the patient with better efficacy and higher quality care.

Recently, there have been major advances in the industry of cancer immunotherapy. Although most immunotherapies are not as well-known as chemotherapy and radiation therapy, over the last two decades they have found a foothold in cancer treatment. Immunotherapies are treatments that modify and enlist the patient's own immune system to react to or recognize cancerous cells. Our immune system is very complex, leading to variability and unpredictability when treating cancer. Hence, immunotherapies have multiple types and ways for treating cancer. The four main types of immunotherapies are monoclonal antibodies (MAB), immunological vaccines, cytokine modification, and adoptive cell transfer (ACT) (Kerfelec, et al., 2014; Cancer Research UK, 2017). Each of these immunotherapies treats cancer in distinct ways. Monoclonal antibodies are produced in the laboratory and injected back into the patient with hopes of them attaching to cancer cells so that certain T-cells or other immune cells can recognize them and consequently eliminate the cancerous cells. Immune vaccines are injected into a patient in order to recognize proteins on specific cancerous cells, allowing

an immune response to prevent further cancer development or spread. Cytokine modification is when specific cytokines are artificially made and modified so that once injected into a cancer patient, there will be a stimulation of the immune system against the cancer or a release of specific chemicals by the cancerous cells (Cancer Research UK, 2017).

The fourth immunotherapy type, ACT, is the fastest developing form of immunotherapy. ACT therapies are similar because they modify the patients' own T-cells to recognize and remove cancerous cells from the body. Chimeric antigen receptor (CAR), T-cell receptor (TCR), and Tumor infiltrating lymphocytes (TIL) are three main types of ACT immunotherapy (Wang et al., 2014). The main differences between each of them are the methods of modifying the T-cells. For example, CAR T-cell therapy actually genetically modifies T-cell receptors so that they can target and recognize specific antigens that are secreted by tumor cells. There have been four generations of CAR T-cells, and each successive generation has become more specific. The fourth generation of CAR T-cells is used for recognizing antigen-negative, a surface antigen on tumor cells (Zhang et al., 2017). The process of CAR T-cell therapy starts with the removal of leukocytes from a patient and then the transfer of the cells to a lab. In the laboratory, effector T-cells are isolated and given a viral vector that is integrated into the genomes of these cells. The use of a viral vector is essential for transferring the proper genes and structural enzymes efficiently. After culturing and cell growth, the T-cells are administered back into the patient in order to be activated by their artificial antigen receptors (Zhang et al., 2017). The end goal is for the T-cells to recognize and target the

cancer cells easier, so that they cannot continue evading the immune response (Emens et al., 2016).

Although the process of developing CAR T-cells can be long, most patients that undergo this treatment only need one round of therapy, which is different than chemotherapy and radiation therapy. If CAR T-cell therapy can continue to be successful in fewer rounds of treatment for patients, then it may provide higher quality care and more cost-effectiveness in the future. Dana Cooper, a spokesperson for Novartis, says the goal for patients undergoing immunotherapy treatment is "to resume a normal life, including the possibility to return to work" (OncLive, 2017). Fewer hospitalizations and outpatient visits for treatment is definitely a step in that direction. There have been recent successes in CAR T-cell therapy, which has made extensive progress in the fight against childhood and adult acute lymphoblastic leukemia. The FDA approved two CAR T-cell immunotherapies in 2017 to treat acute lymphoblastic leukemia as well as another for treating adult large B-cell lymphoma (American Society of Clinical Oncology, 2018). These newly approved immunotherapies have been able to utilize fewer rounds of treatment, and if this trend continues, CAR T-cell and other immunotherapies will prove to be the most effective cancer treatment.

Similar to chemotherapy and radiation therapy, immunotherapies can have their own adverse side effects, although they are far less harsh then the other types of treatments. Shortness of breath, migraines, and nausea are possible side effects of immunotherapy treatment. The main reason that immunotherapies have less severe toxicities is because overtreatment rarely occurs when treating cancer with an

immunotherapy. In many cases of chemotherapy and radiation therapy, overtreatment leads to death of immune cells that are not cancerous (Ciardiello et al., 2014). The idea of killing our own cells is important because of the harsh consequences it produces on the human body. By targeting our immune response more effectively, immunotherapies can limit toxicities and continue developing higher quality patient care.

CAR T-cell therapy is a very promising cancer treatment, however its challenges relate directly to the same reason it has taken immunotherapies so long to gain a foothold in cancer treatment. In CAR-T cell therapy and other immunotherapies, viral vectors are the best method for integration and modification of the cells' genome. Although viral vectors, such as retroviruses and adenoviruses, have been studied extensively, there is always a chance of mutagenesis. Mutagenesis could lead to a variety of adverse effects, including the expansion of tumors (Zhang et al., 2017). This very drawback was encountered in 1999, when a gene therapy treatment with an adenovirus vector led to the death of an 18-year-old patient, due to mutagenesis. In addition, two patients receiving gene therapy for an immunodeficiency disease in 2002 acquired a form of cancer, most likely due to the viral vectors they received (Thomas et al., 2003). While these cases may not be directly from immunotherapies, the viral vector is a very important aspect in ACT and so precautions need to be made when using the vectors. While there have been mistakes in the past, research over the last decade has greatly decreased the risk of mutagenesis. Immunotherapies have overcome this initial hurdle, yet they need to continue to advance with patient care as the highest priority.

One of the aspects that make immunotherapies unique is the amount of personalized medicine that is needed for each patient. Personalized medicine is a treatment method that operates on a patient-to-patient basis, in order to shape treatment around the patient's personal needs and reactions. Many immunotherapies require personalized medicine; because of the way they engage tumors in our bodies. Personalized medicine has developed tools that can detect changes within the molecular basis of the patient's tumor as well as tools that can estimate disease risk and biomarker profiling (Agyeman & Ofori-Asenso, 2015). These tools provide oncologists with a better understanding of each individual's tumor, leading to better patient-to-patient treatment.

I remember going to the doctor when I was 13 years old, because my parents were worried about my lack of growth. I was the smallest kid in my 8th grade class, and I was well below the average height of a normal 13 year old. We were there to discuss whether I needed to take any steroids to initiate growth or whether I just needed time to grow. My doctor mentioned that some kids need more time, and he thought I was still on track based off past cases that he had monitored and overseen. Although he may have thought it was best to just give me time based off his experience with other kids, it still may not have been the best treatment for me. If I were to go back to that moment, I would ask him whether or not this is best for me personally? This question reflects the very basis of personalized medicine. In many cases, we see doctors treat patients based off general populations and guidelines. However, personalized medicine considers individual variations, the differences in adverse patient responses, and the efficacy within therapies

(Agyeman & Ofori-Asenso, 2015). Personalized medicine may be time consuming, but as it continues to progress in immunotherapies, it will provide the best patient care that cancer treatment has seen.

There are definitely challenges in ACT and CAR-T cell therapy, yet their unique ways of targeting cancer and the amount of personalized medicine that they use, show why they hold the keys to the next generation of cancer treatment. George Santayana once said, "Those who fail to learn from history are doomed to repeat it" (Emens et al., 2016). This quote is very significant to the failures that immunotherapy has encountered in the past. Although failures may seem to be insurmountable at first, they help us learn from past mistakes in order to deliver a better and more precise product. We saw the foundation of personalized medicine when gene therapies were introduced in the 1990's. The immunotherapy industry has learned from past mistakes, and seen recent success in the form of FDA approved CAR T-cell therapies. However, personalized medicine will be the major determinant of immunotherapies efficacy moving forward.

CHAPTER II: Personalized Medicine & the Growth of the Immunotherapy Industry

In all the health sciences, personalized medicine is always an idea that has to be brought to light. Is that treatment or medication right for the patient? What is the patient's past history? These are examples of questions that healthcare professionals across the country have to ask before treating a patient. Personally, my experience of working in both a retail and long term care pharmacy has shown me how important personalized medicine is to patients. Pharmacists spend huge amounts of time each day with patients, giving insight on when to take the medication and how often. If the pharmacist does not understand previous health issues, current health issues, or how specific medications work, then how can they truly help their patients? Hence, it is of utmost importance for health care providers to understand each of their patient's personal health issues, in order to provide the best care possible. Although this example exemplifies personalized medicine on a daily basis, it is more complex and specific in cancer treatment.

Personalized medicine in immunotherapy is not as simple as a pharmacist monitoring and providing medication to his patients, yet it is still based off the quality care that pharmacists provide day to day. Specifically, personalized medicine within ACT therapy begins with a cancer patient who may have a peculiar set of symptoms, genetic traits, or inherent disease patterns. Rather than placing patients in treatment groups because they display specific phenotypic biomarkers, oncologists can tailor treatments to the patient's needs and individual molecular information (Agyeman & Ofori-Asenso,

2015). For example, ACT or another immunotherapy may be the best treatment method because of the disease progression and molecular profile of the individual's tumor. Personalized medicine allows immunotherapies to offer patients a safer form of treatment because there is rarely overtreatment when oncologists can personalize treatment to the patient's immune system and tumor microenvironment (Ciardiello et al., 2014). By taking a patient's very own genetic profile, tumor heterogeneity, disease pattern, amongst other variables, oncologists can tailor cancer treatment to these specific characteristics in order to provide more efficacious healthcare.

Personalized medicine is very promising, yet there are still challenges that need to be overcome in order for it to become the most prominent form of cancer treatment. Consolidating and interpreting the massive amount of data that is collected about patients is no easy or cheap task. The large-scale cancer genome projects that provide information of biomarkers and tumor heterogeneity have difficulty translating information from the laboratory to a clinical setting (Ciardiello et al., 2014). Thus, there is a need for better analytical and translational methods that can help transform personalized medicine in the field of cancer treatment.

Preclinical trials may always have their drawbacks, but in order for more of these immunotherapy trials to make it further, there needs to be more defined targets and better strategies for personalized medicine (Neelapu & Sathyanaranyanan, 2015). One of the unique aspects of personalized medicine is that it can be used in diverse ways across all cancer treatments. Although some patients may have similar intrinsic and extrinsic tumor factors, there can always be different reactions to ACT therapy. This is why the

development of an "immunogenicity score," would be beneficial to condensing strategies and defining boundaries. Basically, an immunogenicity score would assess tumors based on specific biomarkers that relate the intrinsic and extrinsic factors of the tumor (Neelapu & Sathyanaranyanan, 2015). A strategy and baseline such as an immunogenicity score could definitely benefit personalized medicine by making data evaluation and integration much simpler. It would make this process easier, because it would provide oncologists with the ability to assess tumors both quantitatively and qualitatively through a baseline system that is based off biomarkers that tumors express. Strategies such as this one will be crucial to the advancement of personalized medicine in immunotherapies in the future.

Additionally, there are always questions about the validity of biomarkers and toxicities associated with certain immunotherapies. Biomarkers are specific molecules or patterns that an individual's tumor expresses. The main problem with biomarkers is defining "real evidence." It is difficult to decipher what is "real evidence," because of the fact that there is no set of rules for biomarkers that have been defined for each type of cancer or each type of response. Oncologists need a better idea of what each biomarker signals, so that personalized medicine can increase its efficacy. While there are multitudes of biomarkers for immunotherapy targets, there is still plenty of variability between patient responses and disease responses that make it difficult to find consistency in the industry.

One way to help validate biomarkers would include wider availability and access to multiple biological platforms, so that there can be easier interpretation of them in the laboratory (Ciardiello et al., 2014). These challenges are definitely no easy task to

overcome, however this is where cancer treatment can continue to advance. Over time, the consolidation of bio-information such as biomarkers, genetic traits, tumor intrinsic and extrinsic factors, symptoms, and adverse effects can definitely happen, and that is when cancer treatment will be at its best. With the help of this personalized medicine, doctors will be able to confidently tell patients that a specific immunotherapy will stop the development of their cancer.

Within personalized medicine, patient characterization is a difficult challenge for the immunotherapy industry. (Emens et al., 2016) For example, identifying the proper bioimmunomodulatory molecules, target moieties, and biophysical compositions of tumors is critical for beneficial disease response (Graciotti et al., 2017). However, tumor mutagenesis and variability makes it difficult to predict these characteristics. Although a new immunotherapy could look promising after testing on mice, human variability is one of the major factors contributing to the slow developments of this type of cancer treatment. Today, immunotherapies are used to harness the patient's own immune system to recognize or inhibit cancerous cells, but it is hard to predict how each patient's immune system will respond to certain cellular modifications. There are numerous considerations that must be taken into account before starting a patient on a specific immunotherapy or combinational approach. Response rates, dose assessment, systemic toxicity, and characterization of disease response are also important factors to consider for each cancer treatment (Emens et al, 2016). Patient characterization is difficult, yet researchers should be able to consolidate this task after there is more efficient translation

of data. This is why personalized medicine takes time; however, these personalized approaches are what make immunotherapy so unique and critical to cancer treatment.

Additionally, there are new combinatorial approaches that have been implemented into personalized treatments. Some patients may only react to a specific immunotherapy, while others may need a combination of immune specific drugs and chemotherapeutic agents. Some early results from combinatorial trials have shown that more people could benefit from combination therapies, in comparison to monotherapy (Neelapu & Sathyanaranyanan, 2015). However, it has been found that there were more immune-related side effects from combination treatments, even with a higher patient response (Wolchok et al., 2013). If these immune related side effects can be limited, there is definitely a place for combination therapy within immunotherapy and personalized medicine. The ability of immunotherapies to be used in combinatorial approaches shows their versatility in cancer treatment, which can help oncologists provide more effective personalized medicine.

Furthermore, another great example of the possibilities of personalized immunotherapies is their ability to be used even if they are unsuccessful in the past. For example, Thalidomide, an immunotherapeutic drug that has been used for some cancer treatments in the past, had been discovered to cause fetal deformities in some pregnant women. With the help of personalized medicine researchers were able to find that Thalidomide was effective against some myelomas (Agyeman & Ofori-Asenso, 2015). Although this is not the case for all immunotherapies, this example shows how one failed drug can be transformed into an effective treatment as a result of personalized medicine.

Whether it is the diversity or ability to be used in combination or in new trials it seems that immunotherapies, with the help of personalized medicine, have a place in cancer treatment. Patient characterization and the translation of data across all platforms are hurdles that personalized immunotherapies seek to overcome; yet the future seems bright for this cancer treatment. Increasing access across platforms can create more effective collaboration, which should produce more efficacies in this type of cancer treatment. Collaboration in this industry is a team effort that ranges across pharmaceutical companies, biotechnology companies, clinical laboratories, and political policies (Agyeman & Ofori-Asenso, 2015).

If personalized medicine wants to continue being the driving force behind immunotherapies then these players will need to find better strategies for collecting, integrating, and translating data across the many platforms. Without proper funding this industry cannot truly expand, because there will always be a need for research. This field is expensive, and so the amount of funding may dictate whether or not immunotherapies are the most efficacious cancer treatment in the near future.

CHAPTER III: The Implications of Funding on the Expansion of the Immunotherapy Industry

Lack of funding is one of the largest limitations to scientific and medical advancements. There is just never enough money to support all projects, even if these projects have valuable content and evidence behind them. The immunotherapy industry is no exception to this limitation. Over the last few decades there have been hundreds of immunotherapies in preclinical studies that have provided evidence of disease remission, yet many of them did not make it to clinical trials because of funding limitations. At times there can be minimal funding for initiating clinical trials, which illustrates one of the main hurdles for immunotherapies, economically speaking (Fox et al., 2011). Comparatively, preclinical studies can be completed with less funding, however massive amounts of money and support are needed to initiate and complete clinical trials.

So, how can this funding issue be dealt with? For starters, the 2011 Immunotherapy summit asserted that better communications between the research groups and both local and national economies were needed. Many people underestimate the impact that immunotherapies can have on their economies. For example, the Milken Institute of Health-Care Investment actually estimated that a 1% reduction in cancer mortalities in the U.S relates to around a $500 billion economic value (Fox et al., 2011). Although not all preclinical trials will turn into a major effort, it is important to support as many of these projects as possible, as long as there is real evidence behind them.

Recently, the immunotherapy industry has been making major progress in terms of financial gains. Immunotherapy was the highest invested industry in the category of

life science companies in 2015 (Bubela et al., 2017). This is very promising for immunotherapies, however there are obstacles that are preventing the industry from really exploding financially. First, is the idea of chain reactions that can cause major losses within immunotherapy pharmaceutical companies. Economically, a chain reaction is a sequence of events that occur after a specific incident initiates them. There were two major incidents in 2016 that had drastic effects across immunotherapeutic companies. Juno therapeutics, a biotechnology company, had to cease clinical trials when two patients died from clinically induced acute lymphoblastic leukemia (ALL). In a second incident, the FDA shut down another clinical trial, due to the deaths of two patients from clinically induced cerebral edema (Bubela et al., 2017). These incidents led to the decrease in investments and funding for immunotherapies during the remainder of 2016. Shut downs like these can lead to chain reactions amongst pharmaceutical and biotechnological companies, because of how fast information travels across the media. Public perception, influenced by the media, can have a significant effect on immunotherapy funding. The media can convey both the failures and successes of immunotherapies in simple terms, which can truly alter how the public views them.

"Cancer Drug Proves to Be Effective Against Multiple Tumors," was a headline by the New York Times in June of 2017. This headline is similar to many others around the U.S, in that they trumpet the promise of immunotherapies that could be the next great cancer treatment. However, over the last few decades, hundreds of new cancer immunotherapies have been created, and yet, only a few have been successful within a few types of cancer. The media can distract people from the actual reality and truth of

what immunotherapies can do and what they cannot. There are plenty of challenges when treating cancer, and the media should not dictate public perception of immunotherapies. In order to not let the media dictate funding of immunotherapies, pharmaceutical companies and clinical laboratories need to ensure that immunotherapies are more effective once they are translated into the clinical setting.

One way this can be accomplished is through more innovation centers that link platforms across the industry. Speaking of innovation centers, Patrick Gallagher, chancellor at the University of Pittsburgh says,

> "We are creating an unprecedented ecosystem—one that connects basic science discoveries from Pitt with life-changing advances from UPMC while leveraging the catalytic power of industry partners. It is a combination that will transform immunotherapy care and help us tackle some of medicine's greatest challenges" (University of Pittsburgh, 2018).

This new Immune and Transplant and Therapy Center (ITTC) at the University of Pittsburgh, is a perfect example of why the immunotherapy industry needs to overcome logistical challenges and improve the effectiveness of immunotherapies in clinical settings. Gallagher relates an "unprecedented ecosystem," that can connect industry partners. The ability to connect the developers and laboratories can produce more efficient communication that will only benefit immunotherapies moving forward. The faster creation and commercialization of immunotherapies will prove to be crucial for generating funding for this industry in the near future, because personalized medicine in immunotherapy is not a cheap investment.

Both the development of immunotherapies and the use of personalized medicine to bring forth the best treatment for a cancer patient are very expensive. The new logistical challenges of ACT immunotherapy has driven prices significantly up, because of the amount of resources and personalization that is needed for each patient. These logistical obstacles have propelled the range of immunotherapy costs to around $150,000 to $500,000 per round of treatment (Bubela et al., 2017). The FDA approved CAR-T cell therapies have a set price of $475,000, which is a lot higher than chemotherapies and radiation therapies that cost around $30,000 per round of treatment (OncLive, 2017). Even if chemotherapies need at least ten rounds of treatment, the CAR T-cell therapies are still more expensive. However, the ability for immunotherapies to treat cancer through far less rounds of treatment can be very cost-effective in the future. As more immunotherapies become FDA approved, the price ranges of these treatments will have to decrease, because of competition between pharmaceutical companies. The end goal for immunotherapies would be to create lower costs and fewer rounds of treatment. Therefore, if immunotherapies, including CAR T-cell therapies can continue with higher effectiveness and fewer rounds of treatment they will truly create a more efficacious cancer treatment.

In their annual report, the American Society of Clinical Oncology named CAR T-cell immunotherapy the advance of 2017. The progress that CAR T-cell immunotherapy made in 2017 highlights the recent success in this field and just how important funding will be in the near future. The report also claims that 73% of Americans believe that the federal government needs to increase funding in cancer research and treatment (American

Society of Clinical Oncology, 2018). This shows how important cancer treatment is throughout the U.S, and also how important federal funding will be in the advancement of immunotherapy in cancer treatment. Both the public and private sectors will impact the transformation of immunotherapies in cancer treatment.

There is a need for more public-private partnerships (PPP's) in the U.S. PPP's are collaborations or associations that share and provide interdisciplinary skills in order to achieve specific goals (Holden et al, 2015). These partnerships are critical for immunotherapy development because they can increase expertise through shared knowledge, and transform research platforms through extensive training and production (Holden et al, 2015; Bubela et al., 2017). In 2012, Novartis Pharmaceuticals along with the National Cancer Institute and the University of Pennsylvania agreed to a 5 year global PPP in order to research and create targeted CAR T-cell immunotherapies. In this scenario, Novartis and the University of Penn were the private platforms that received public funding from the National Cancer Institute in order to collaborate together. Another example is the 2013 PPP between Juno Therapeutics and Seattle Children's Research Institute that connects them for the development and commercialization of CAR T-cell immunotherapies (Bubela et al., 2017). Both of these PPP's have produced successful results in the form of the 2017 FDA approved Car T-cell therapies. If this industry is to continue making progress in cancer treatment, partnerships like these will be critical for effective immunotherapy development.

While it may seem like commercialization of this industry could be a negative force, it cannot really hurt immunotherapy. Commercialization could actually lead to

more focused collaboration and better efficacy in this industry. This is exactly what this industry needs right now. Better efficacy and logistical consolidation may be the most important progress that needs to be made, because if these problems can be fixed, the economic sector can expect more funding.

There have been some huge investments into ACT immunotherapies, especially CAR T-cell therapies. In January of 2018, Tmunity Therapeutics announced a $100 million dollar plan to support their research into T-cell based immunotherapies. Investors, the likes of The Parker Institute for Cancer Immunotherapy and Gilead Sciences, poured money into Tmunity projects because of the company's foundation in T-cell immunotherapies. In addition, the biopharmaceutical company Celgene bought the T-cell developer Juno Therapeutics, for $9 billion dollars in January of 2018. There is money being invested into T-cell development because of the potential in this industry (Vinluan, 2018). The funding of clinical projects will be crucial for immunotherapies moving forward, yet the primary concern should be the improvement of patient care. In order to improve patient care moving forward, there needs to be strong ethical considerations throughout the industry.

IV. Ethical Considerations for Immunotherapies and Personalized Medicine Moving Forward

On the front page of Celegene's website it says, "They are committed to improving the lives of patient's worldwide." This goal is quite simple, but in order to meet this goal, Celegene and other biotechnological companies need to ensure that higher quality care is developed. Monetary endeavors should not be the driving force behind these companies' research and development, and so looking ahead there must be ethical improvements. One of the most important ethical issues that needs to be addressed is the idea of informed consent or therapeutic misconception (McGowan et al., 2014). Therapeutic misconception occurs when there is a lack of communication between a physician and patient, leading to patient involvement in treatments that are not ideal for their circumstances (Wcg Oncology, 2017). Many cancer patients find themselves in situations where they think they are partaking in simple clinical care, yet they are actually partaking in an experimental research study. This is currently a major problem within cancer treatment, and so these misconceptions need to be addressed. Oncologists need to be clear when defining what type of treatment they are recommending for a patient. This is a perfect of example of where personalized medicine can refine itself. There is so much data integration in personalized medicine that oncologists should continue to improve the translation of this data to cancer patients. Recommending specific treatments to individuals is an important aspect for patient recovery and survival, and improving the communication between physician and patient will be crucial for personalized medicine moving forward (Wcg Oncology, 2017).

In order to improve, oncologists need to be straightforward with patients. Many of the new investigational immunotherapies have unknown risks and toxicities, and so the patient needs to be aware of this before accepting the treatment (National Cancer Institute, 2016). Oncologists and developers sometimes overlook informed consent because the patient may fill all the criteria for the trial. Although genetic data, disease progression, and tumor heterogeneity may associate a patient to a certain treatment because of specific characteristics, the patient should be aware of all risks associated with it. Over anticipating a response can hurt a patient in the long run, especially if the individual is not aware of the risks and toxicities. (Wcg Oncology, 2017). By taking a more ethical approach towards informed consent, personalized medicine can continue to advance cancer treatment.

The European Society for Medical Oncology (EMSO) described the future of cancer treatment as,

> "A new era of personalized cancer medicine that will touch every aspect of cancer care – from patient counseling, to cancer diagnosis, tumor classification, treatment and outcome — that demands a new level of in-depth education and collaboration between researchers, cancer specialists, patients and other stakeholder" (Ciardiello et al. 2014).

In essence, this quote summarizes what personalized medicine is and what it can be in the future. As cancer treatment begins to apply more personalized medicine, there will be a demand for higher standards of care. The path towards higher quality care will not be simple, and will require plenty of time and money. Patient counseling, cancer diagnosis,

and tumor classification are important aspects of personalized medicine, but demand more time than regular clinical care, because of how difficult it is to predict the progression of a tumor.

Not only can it be difficult for oncologists to relay all the necessary treatment information to the cancer patients, but it also can be very tedious and time consuming. There is a large amount of data that comes with genetic tests, which makes it difficult to translate information from the laboratory all the way to the patient. Hence, patient counseling puts oncologists in difficult situations, because of the sheer volume of data that needs to be integrated and explained properly (Wcg Oncology, 2017). Information overload can make decision making more difficult for patients and oncologists, and so personalized medicine needs more defined guidelines for oncologists (McGowan et al., 2014). Better guidelines and clearer communication can help lower the stress on patients, consequently producing higher quality care (National Cancer Institute, 2016). While this idea of patient counseling applies to all of health care, patient counseling in cancer treatment is more demanding because of the difficult situation that cancer patients are in.

Cancer patients are vulnerable during diagnosis and treatment, because of the unpredictability of disease progression. When diagnosis occurs late in disease progression, cancer patients may not have many options. Clinical trials that have shown promise are options in these situations, however they may not be the most ethical because of the how late the cancer was diagnosed. There are new trial designs that have allowed personalized medicine to connect clinical activity to biological activity of immunotherapies, especially CAR T-cell and vaccine therapy. For example, adaptive

trials provide oncologists the ability to adapt to incoming data, while platform-based trials utilize combinatorial treatments in order to examine the evolution of multiple immunotherapies in patients (Emens et al., 2016). On one hand, adaptive trials offer the ability to adjust to incoming data in real time, which can really help the oncologist make decisions regarding treatment. On the other hand, platform-based trials evaluate specific combinations of therapies in order to create the best treatment option. Personalized medicine will be at its best when there is optimal data integration, and the continuing development of trial design can help create less vulnerability in patients and clearer communication.

Overloading the patient with information is not the sole ethical consideration when discussing patient counseling and informed consent. New genetic tests and projects, such as whole genome sequencing (WGS), Cancer Genome Atlas (TCGA), and the International Cancer Genome Consortium (ICGS), are being used to select patients for specific immunotherapies (Ciardielo et al., 2014). These large genomic sequencing projects can have benefits and drawbacks to cancer patients. On one hand, genomic sequencing can help patients take control of their lives, as they understand what steps they have to take in their treatment after learning what mutations they have and what precautions they need to take. On the other hand, knowledge of mutations and diseases prominent in their genetic sequence can have consequences for family members and the patient. Thus, precaution needs to be used when recommending genetic testing to a patient, because there can be both positive and negative outcomes from it (McGowan et al., 2014). One step forward in this ethical aspect should be studies that examine patient

preferences and feelings towards genomic sequencing. A better understanding of what the patients expect when it comes to genetic testing could really help answer this ethical question in the future.

Furthermore, privacy issues regarding the patients' information from genetic testing brings forth another huge ethical concern. While it would be ideal to gain an understanding of how they feel towards genetic testing, patients also need to be aware of what information these tests generate and who has the ability to look at that information (McGowan et al., 2014). There are plenty of regulations and laws that limit the sharing of patient information, however how can personalized medicine advance without researchers and developers gaining access to data to produce more efficacious immunotherapies? A large-scale data disclosure agreement between the major genomic projects and pharmaceutical companies could be a solution (Ciardiello et al., 2014). If this disclosure can happen, a much larger and consolidated molecular medicine network can be created, which will provide the industry with the boost it needs to create more focused projects and more defined biomarkers. This network could be pivotal in the evolution of both personalized medicine and immunotherapy cancer treatments, as researchers would be able to gather the necessary genetic criteria for more defined and focused research. By ensuring that a patient's information is not shared if they ask for it to remain private, a global network with proper informed consent could be the solution that personalized medicine needs to advance cancer treatment.

These genomic tests not only lead to ethical issues of privacy and information sharing, but also monetary issues for patients. When examining the high costs of

personalized medicine, there is a rift between who can afford it and who cannot (McGowan et al., 2014). Hence, there is doubt that personalized medicine is realistic for everyone, which begs the question whether or not it can truly be ethical? There are multitudes of genomic technologies that are being developed, such as whole-genome sequencing, gene expression profiling, and disease-targeted paneling (Agyeman & Ofori-Asenso, 2015). These technologies, along with next generation sequencing, are providing researchers with more depth of coverage DNA sequencing, which is crucial in immunotherapy for targeting genes and mutations in the patient. Although the value of these technologies in personalized medicine is extensive, there still needs to be ethical considerations for accessibility moving forward.

The ethical issue that needs to be considered is whether or not patients who do not have sufficient funds for all personalized tests should still be granted these tests? Currently, it would be difficult to create population-wide access to all genomic testing. However, there still should be some type of access for people who cannot afford certain treatments or testing out of pocket. One possible solution down the road would include allowing access to NGS to all patients even if insurance does not allow for it (McGowan et al., 2014). Providing some type of genetic testing could benefit the patient even if they cannot afford the best. As NGS continues to be narrowed down and widely available, some form of access should be allowed, so that monetary discrepancies can be limited.

The advancement of technologies throughout history has relied on innovation, but in some instances has lacked ethics and moral ground. Ethics is not simply the idea of morality, but rather the idea of responsibility, and compassion for the people,

environment, animals, and tools that go into the research. These ethical challenges can be overcome, through pharmaceutical companies, oncologists, and developers, need to take more responsibility of the issues at hand. Responsibility will be critical in the development of a higher standard of cancer care, but so will innovation within both personalized medicine and immunotherapies. Innovation and development will play a huge role in determining whether or not immunotherapies become the most effective cancer treatment in the future.

CHAPTER V: The Current State of Molecular Biomarker Research and the Improvements Needed for Success

"Practice makes perfect" is a phrase that relates to all aspects of life. In many cases, the more work or practice you put into something, the more you get out. This context perfectly describes where many immunotherapies are currently standing. While the economic funding will be key in the success of immunotherapies, there needs to be more focused research in order to receive this funding. For starters, a better understanding of biomarkers and targets is crucial to the future success of immunotherapies.

Dr. Steven A. Rosenberg, a prominent immunologist, believes that the most glaring issue in immunotherapy development is the lack of suitable targets (Bubela et al., 2017). Although there are many biomolecules that have been studied, there are still not enough specific targets. Biomarkers are specific molecules that indicate certain disease patterns and parameters, and they include proteins, cytokines, and T-cells, among others. There is framework that helps researchers determine biomarkers in cancer treatment. Tumor mutational burden, immune status of patient, amount of T-cell infiltrates, sensitivity of tumor cells to recognition by T-cells, and tumor PD-L1 expression create this framework for oncologists and researchers to determine what molecules play a role in disease patterns (Haanen, 2017).

Each tumor has its very own intrinsic and extrinsic factors that rely on each other for tumor development. Extrinsic factors are characteristics of the tumor that allow it to escape immune recognition, while intrinsic factors include certain genetic mutations that

the tumor exhibits. One of the most important intrinsic characteristics of tumors is their mutational landscape (Podolskiy & Gladyshev, 2017). It has been recently discovered that the primary antitumor response is targeted against mutated neoantigens that are derived from the tumors themselves (Neelapu & Sathyanarayanan, 2015). Neoantigens are tumor-specific antigens that are expressed by cancer cells after mutation occurs. The mutations have allowed researchers to evaluate and analyze tumors through genomic sequencing (Schoenberger & Cohen, 2016). Although the antitumor response relies on neoantigen recognition and presentation to T-cells and NK cells, high amounts of neoantigens do not correlate with better immune responses. Tumors can also escape immune recognition through inhibition of MHC class I receptors which are vital in antigen presentation to T-cells (Neelapu & Sathyanarayanan, 2015). Intrinsic factors, such as these, are not the only tumor aspects that need to be understood.

Extrinsic factors of the tumor generate additional challenges to cancer treatment. A very important extrinsic factor is the recruitment of cells to promote tumor growth or inhibit the functions of effector T-cells. Rather than simply disrupting antigen presentation to T-cells, extrinsic factors from an individual's own immune system are produced by the tumor to promote its own growth and proliferation (Alberts et al., 2002). Both intrinsic and extrinsic factors pose obstacles to preclinical trials and biomarker research because of the high amounts of variability. This variability makes patient characterization one of the most difficult challenges for clinical trials.

Patient selection is the major key to success in immunotherapy trials (Emens et al., 2016). While patient selection may seem easy, it is definitely one of the most difficult challenges for researchers developing trials based off certain biomarker characterization. Not only does there need to be scientific rationale behind patient selection, but there also needs to be more focused biomarker research in these clinical trials. The success of clinical trials relies on patient selection, because cancer patients are recommended certain treatments based on their disease progression, tumor microenvironment, and genetic landscape (Graciotti et al., 2017). Thus, more programs and research platforms that focus on biomarker development are needed in order to create a better understanding of each biomarker. Mass cytometry, whole exome sequencing, and gene expression profiling are examples of platforms that personalized medicine can utilize to develop better biomarkers in immunotherapy (Haanan, 2017). An increase in more quality clinical trials and more eligible patients who undergo clinical trials can help these platforms develop higher efficacy in immunotherapies.

It is important for immunotherapies to improve their patient selection process, in order to produce successful clinical trials. In many cases, immunotherapy trials select patients because they have not had previous immunotherapy treatment, or in other words they are immunotherapy naïve. However, this should not be the case, because of the instances where individuals who received prior immunotherapies still reacted well to a new immunotherapy (Emens et al., 2016). Thus, patient selection needs to include both naïve individuals and individuals who have received prior treatment. This may make it

more difficult to select patients, but there must be rationale and certainty behind these decisions.

One platform that has really allowed personalized medicine to conduct more focused biomarker research is that of genomic sequencing and genetic profiling. An understanding of individual's minute genetic differences can be critical in the success of cancer treatment. As humans we all share similar DNA, however our genetic makeup varies slightly from person to person. There are genetic mutations that cancers produce and genomic sequencing allows researchers to understand these genetic mechanisms that stimulate cancer progression (Ciardiello et al., 2014). Genomic sequencing is an important player in personalized medicine, because gene profiling can provide better estimations of T-cell content, specific cytokine expression by the T-cells, and what response a patient could have to antibody therapy (Agyeman & Ofori-Asenso, 2015). The need for more genetic analysis compilation is apparent in this field, because it can produce better estimates of the number and genetic landscape of stromal and immune cells within the tumor microenvironment. This, in turn, can lead to better understanding of how the patient's tumor will react to specific immunotherapies. Gene analysis is another key component of personalized medicine, and should be a top priority for funding, because a more detailed understanding of tumor microenvironments can increase the effectiveness of immunotherapies against cancer (Ciardiello et al., 2014).

The Personal Genome Project is an example of a project that is trying to consolidate personal genomes, in order to create wider accessibility across this industry. This project, since its conception in 2005, has garnered 2806 volunteers, and is hoping to

individualize personal ancestries, biomarkers, and disease risk factors (Agyeman & Ofori-Asenso, 2015). This is a prime example of collaboration that could benefit cancer treatment like immunotherapy. A better understanding of biomarkers and risk factors associated with each disease can help oncologists provide patients with more correct treatment and preventive measures (Haanen, 2017). Collaboration across the platforms can lead to the discovery of more suitable targets, which is currently one of the most glaring issues for immunotherapies. This idea of collaboration relates directly back to PPP's, which provide more focused biomarker research, and consequently more biomarkers.

One of the time-consuming hurdles is that of ex-vivo manipulation of T-cells, especially in the ACT immunotherapies. However, researchers have been looking into ways to circumvent ex vivo isolation, by exploring the possibility of in situ manipulation of T-cells. In this in situ case, researchers can manipulate T-cells in circulation rather than having to remove T-cells from an individual, isolate them, and manipulate them in a laboratory. One way that this can be done is through injection of DNA carrying nanoparticles that are coated with anti-CD3 antibodies. These nanoparticles could consist of DNA that encodes for leukemia-specific CAR T-cell receptors (Graciotti et al., 2017). The next step would then be to translate it to humans and to other types of cancer, especially solid tumors. Even though immunotherapies have hurdles that need to be overcome, we see here how researchers are moving forward and trying to overcome these hurdles.

In addition, researchers are also looking into artificial antigen presenting cells (aAPCs) to improve the current ACT immunotherapies. These aAPCs have the ability to increase and stimulate T-cell expansion, by presenting a peptide MHC complex on their surface, which then binds to a TCR. Not only do aAPCs have the ability to stimulate T-cell expansion but they also eliminate the need to isolate and develop patient specific dendritic cells, which are cells that play a major role in antigen presentation. This new route in ACT immunotherapies may also be much more cost-effective since companies do not need to isolate these dendritic cells ex vivo (Graciotti et al., 2017). Although this is a very promising approach, there are disadvantages to artificial cell creation. Some researchers have found difficulty in the recreation of surface rigidity, especially after T-cell interaction with the antigen presenting cells. Improvements in biomaterial production can provide this approach with the efficacy that ACT immunotherapies need going forward. If these improvements can be made, the ability to use aAPCS in vitro offers a solution to the time consuming process of ex vivo manipulation. These approaches prove that companies are trying to find ways to overcome the challenges, and show us that immunotherapy has a bright future ahead.

In closing, tumor mutagenesis and malignancy pose so many challenges for researchers and oncologists when treating cancer. While this task may be difficult, the discovery of new and viable biomarkers is one way that researchers can determine why cancer is able to evade the immune response and how we can treat it better. ACT immunotherapies offer a unique way to treat cancer, and personalized medicine provides oncologists with a better understanding of how to treat cancer on a patient-to-patient

basis. Genomic sequencing is a technique that can truly revolutionize personalized immunotherapies, by creating a better understanding of the genetic profile of an individual and why mutagenesis may be occurring. The recent FDA approved CAR T-cell therapies highlight the promise of immunotherapies, however there is yet to be one FDA approved ACT immunotherapy that can treat solid tumors. Thus, the next step for these immunotherapies is the ability to triumph over solid tumor cancers.

CHAPTER VI: The Role of Immunotherapies in Head and Neck Squamous Cell Carcinoma Treatment

There are many instances throughout life when people are reminded of the consequences of smoking or chewing tobacco and consuming alcohol. Major League Baseball, an American pastime, has a culture where players chew tobacco on a daily basis, because of the brotherhood that the sport exhibits. While this may only be one example of a cultural norm within our society that promotes tobacco use, there are plenty more that are immersed throughout our world. Whether or not people understand the health consequences that come with tobacco and alcohol consumption, the ramifications on the human body can be deadly. Tobacco and alcohol consumption are not the only factors that contribute to health complications, yet they are definitely correlated with many health risks, including cancer. One area of the human body where cancer risks are very high due to the over use of these substances is the head, neck, and oral cavity (Economopoulou et al., 2016).

Head and neck squamous cell carcinomas (HNSCCs) are the sixth most prevalent form of cancer in the world (Jiang et al., 2015). Squamous cells are epithelial cells that primarily compose the exterior layer of our epithelial tissue. These cells are found throughout our body, especially surfaces like our skin and function as a protective tissue layer. They are unique because of their flat arrangement along epithelial tissue, which differentiates them from the other epithelial tissue types such as cuboidal and columnar (American Academy of Dermatology, 2018). Carcinomas are cancers that arise in epithelial tissue. Hence, HNSCCs are cancers that develop in squamous cell tissue, due to

certain external pressures that cause mutations in these cells, which make this cancer the most prevalent type of cancer in our oral cavity, neck, and head (Nalabolu et al., 2017).

The external factors that can promote HNSCCs include: heavy UV radiation, alcohol consumption, and tobacco consumption (Polanska et al., 2014). Since external pressures promote this cancer, there are definitely some preventive measures that can be taken. Additionally, genetic predisposition and infection by human papillomavirus (HPV) are internal factors that can lead to HNSCC development. HPV infections and its ability to cause pathogenesis in some subsets of HNSCCs is really dangerous because of the emergence of the cancer in the lingual and palatine tonsils, which makes it easier for the cancer to spread (Polanska et al., 2014). The lymphatic tissue that the tonsils consist of makes malignancy easier in the head region. New research into HPV infections and their progression into HNSCCs show why this cancer can be difficult to treat. Due to the difficulties of treating this cancer, prevention and early detection are important components for limiting the initiation and progression of HNSCC (Ye & Costantini, 2017).

Dentists have a huge role in early detection and diagnosis of this cancer. The first step in limiting HNSCCs is spreading awareness to patients that do consume alcohol or tobacco. For every patient visit, dentists should remind them of the consequences that come with the consumption of these substances. By taking this extra step for every patient visit, dentists could be saving lives. Whether this is a matter of knowing who consumes more tobacco and alcohol or identifying individuals who are prone to these cancers because of past family history, dentists can truly make a difference for their

patients. Another aspect in early detection could be simply taking more time when examining an individual's jawline to ensure that there are no abnormalities. It is important to stress the importance of dentists in early detection, because of the difficulty in treating HNSCCs after disease progression.

One of the reasons HNSCCs are difficult to treat is because of their ability to initiate T-cell apoptosis and inhibit antitumor immune responses in the epithelial layer. Once tumor growth is initiated in the squamous cells, the cancer can be difficult to stop, because of the high amounts of lymphatic tissue in the oral and neck areas. Lymphatic tissue serves as easy ways for the cancer to spread to other parts of the head and neck, which creates an even more difficult situation for treatment of the cancer (Polanska et al. 2014). For example, HPV infections cause the alterations of specific cell-to-cell signaling pathways in the squamous cell layer, which can cause tumor growth and development in these tissues (Ye & Costantini, 2017).

There has been poor efficacy when treating this cancer in the past. Both the ability of HNSCCs to repress immune system functions and the ability of it to spread easily has made researchers look to improve clinical efficacy. Chemotherapy, radiation therapy, and surgical resection are the primary treatments of HNSCCs, with surgical resection being the most commonly used treatment against this cancer. The problem with surgical resection is that it can cause health issues, because it removes whole tissues or organs in the head and neck, while possibly not removing all of the cancer (Ye & Costantini, 2017). Additionally, radiation therapy and chemotherapy have their own issues, because of the toxicities and side effects that can develop, especially marrow-suppressive and infectious

disorders (Jiang et al., 2015). Hence, there is massive need to create new treatments that can improve cancer patient's quality of life, while still inhibiting tumor growth. Immunotherapies may prove to be the solution in treating HNSCCs, while still maintaining quality care for cancer patients.

ACT immunotherapies are currently being researched in respect to treating HNSCCs. The majority of patients with late detection of HNSCCs have very low survival rates, because chemotherapy usually only allows for an average of a six to ten month survival rate after late detection. In HNSCCs, it has recently been found that the prevalence of CD8+ tumor infiltrating lymphocytes (TILs) has a positive correlation to survival in cancer patients after chemotherapy treatment (Jiang et al., 2015; Newman et al., 2015). This is important because ACT immunotherapies isolate TILs from the patient in order to modify them in the laboratory. Thus, ACT immunotherapy in combination with chemotherapy treatment has seen positive results in some patients with solid tumor HNSCCs. The ability to utilize immunotherapies in monotherapy or in combinatorial treatments shows the potential of these treatments in HNSCCs (Ye & Costantini, 2017). However, can ACT immunotherapies treat solid cancers in HNSCCs by themselves?

The real issue that ACT immunotherapy has with solid tumors is their ability to disrupt antigen presentation to T-cells and ability to cause apoptosis within these T-cells. Additionally, tumor heterogeneity of HNSCCs demonstrates the ability of the cancer to disrupt effector T-cell functions, which leads to evasion and the inability to recognize the tumor cells (Newman et al., 2015; Economopoulou et al., 2017). CAR-T cell therapy has worked well against leukemias that are not solid but rather circulating throughout your

body. Most HNSCC's are solid tumors and so ACT immunotherapies must produce better clinical trials in order to overcome the challenge of solid tumors in HNSCC's. More platform-based trials that allow oncologists to use combinatorial approaches and adjust to incoming data may be a starting point for developing more effective ACT immunotherapy clinical trials. As more of these platform-based trials find where and when ACT immunotherapies work best, then there will be a better understanding of how they can use them in monotherapy to treat HNSCCs.

Furthermore, personalized medicine is critical in the development of biomarkers for HNSCCs and the translation of data from the laboratory into clinical efficacy. Personalized medicine can help immunotherapies advance cancer treatment against HNSCC's through the emergence of successful clinical trials, where there has been some positive developments. Currently, there is a phase II clinical trial that is using ACT therapy to deplete patients' lymphocytes and also using ACT therapy to modify TILs in order to initiate an immune response against HPV (+) solid tumors (Economopoulou at al., 2017). In another phase I clinical trial with ACT immunotherapy, 6 of 17 patients witnessed disease control against a solid tumor when treated with effector T-cells from their inguinal lymph nodes (Economopoulou et al., 2017). Clinical trials like the ones above prove that researchers are looking for ways to successfully treat solid tumors with ACT immunotherapy. While these clinical trials may not be completely successful, they show improvements for ACT immunotherapies in treating solid tumors. As more clinical trials like these one conducted, along with the aforementioned platform-based trial

design, personalized immunotherapies are moving in the right direction in the treatment of HNSCCs.

In essence, personalized medicine is needed for individuals with this cancer, because of how difficult it is to treat solid tumors in the head region. A better understanding of the biomarkers in HNSCCs can be valuable for immunotherapy and personalized medicine efficacy down the road. There has been research on HNSCCs that uncovered certain biomarkers, such as specific cytokines that are over expressed in certain populations within the tumor. In addition, there have been studies that found that metallothionein protein levels are high in HNSCCs solid tumors (Ioachim et al., 1999). Further research into biomarkers can truly help ACT immunotherapies treat HNSCC with higher efficacy and with quality care that does not include the side effects that are derived from chemotherapy and radiation therapy.

Although ACT immunotherapy and personalized medicine do have challenges, they are showing plenty of promise in the treatment of HNSCC's. Within HNSCC research, there is a need for more condensed strategies for combatting each subset, especially the new HPV+/- pathogenesis with HNSCC's (Ye & Costantini, 2017; Nalabolu et al., 2017). Dentists and physicians need to increase their role by spreading more preventive awareness and understanding patients' personal needs and issues. The role of dentists and physicians in early detection is a crucial aspect in personalized medicine. Personalized medicine will need the help of these healthcare providers to provide higher quality care to patients with HNSCCs. While healthcare providers will play an important role in the treatment and prevention of this cancer, I truly think that the

discovery of more viable biomarkers in HNSCCs will be the most impactful. If you consider the importance of biomarkers in providing platform-based and combinatorial clinical trials the evidence to treat HNSCCs more effectively, then you see why there is a need for it not only in HNSCCs but also in all types of cancer.

VII. The Future Direction of the Immunotherapy Industry in Cancer Treatment

Our bodies are complex and always undergoing processes at the cellular level. These cellular processes are so critical to our health, yet they represent a crucial role in the development and growth of cancer. Whether cellular functions are disrupted or simply evaded, cancer is a force that is difficult to stop once it develops. The idea of our own immune system being evaded is difficult to understand, but it is what interested me in the idea of immunotherapy cancer treatment. There is no doubt that no individual wants to hear the term "cancer" come from a doctor's mouth during a routine check-up. However, maybe there can be a day, when people hear that word, and do not see it as a death sentence. Maybe there is a day when there is a cure for all cancers. Maybe there is a day when chemotherapy is not an option for cancer treatment. There are plenty of these "maybes" but the most important aspect for immunotherapy going forward is the development of biomarkers so that personalized medicine can allow immunotherapies to become more effective against all types of cancer. The ability to personalize a cancer treatment around an individual's specific genetic profile and tumor microenvironment is definitely important, because of how unpredictable cancer can be.

Cancer has been and will continue to be one of the most difficult diseases to treat. For this reason, cancer treatment needs to improve its care to patients, because of how debilitating most current treatments can be on the human body. Immunotherapies have the potential to limit side effects during treatment, since they target the human immune response. As a result, ACT immunotherapies, with the help of personalized medicine can

set a new standard of quality care in cancer treatment. A cancer treatment that allows cancer patients to continue living their normal life, and one that does not put cancer patients in such vulnerable situations. There are still challenges that immunotherapies and personalized medicine must overcome to create this standard of care. Clinical funding and support represents one of the factors that will impact how immunotherapy transforms over the next decade. The need for better translation and integration of laboratory data into preclinical and clinical trials is apparent, however there are already major investments being made into immunotherapy research in the U.S that shows the bright future ahead.

In 2017, the University of Pittsburgh Medical Center (UPMC) along with University of Pittsburgh announced the new plans for a brand new $200 million immunotherapy center that could pave the way for new innovation in cancer treatment (Mamula, 2017; The University of Pittsburgh Medical Center, 2018). The UPMC Immune Transplant and Therapy Center will look to transform immunotherapy research and is a great example of why immunotherapies may be the most prominent form of cancer treatment in the future. Centers like the one at UPMC are exactly what this industry needs, because they will create more focused research along with higher quality care for cancer patients. More centers and platforms that revolve around immunotherapies and the use of personalized medicine are essential for cancer treatment moving forward.

Another challenge that immunotherapies and personalized medicine will need to solve is the high price that comes with both them. Personalized medicine comes at a high

price because of the amount of time and data integration that is needed on a patient-patient basis. Immunotherapies are expensive because of how new and unique they are in regards to treating cancer. Nevertheless, as efficacy in this industry continues to increase with time, the opposite will be true for prices. Wider availability of immunotherapies and personalized medicine will allow for more clinical trials to be successful. Prices will be driven down with higher success rates and consequentially competition and demand should increase, as more immunotherapies become FDA approved. When more personalized immunotherapies become FDA approved, ethical questions will always arise.

Ethics is always an important aspect of science, because it provides science with a reminder that we are all human. There are ethical issues in personalized medicine that revolve around informed consent, patient privacy, and monetary discrepancies. In order to ensure proper handling of genetic information there needs to be better regulation methods of approval and transfer of information. The U.S has the Genetic Information Nondisclosure Act that is supposed to create ethical use of all genetic information. Even though this act is supposed to provide assurance to the patient, there is still a need for better communication between developers, healthcare providers, and the laboratory so that informed consent is better and privacy issues can be resolved. If communication gaps can be limited, personalized medicine should continue being the driving force behind effective immunotherapies and cancer treatment.

Moreover, treatments of solid tumors constitute another obstacle in immunotherapy. ACT therapy, including CAR T-cell therapy cannot breakdown solid

tumors, yet there is potential in ACT immunotherapy treatment of HNSCCs solid tumors, as seen in the clinical trials that were aforementioned. The utilization of ex vivo manipulation of TILs may be found to produce better treatment of this cancer, as biomarkers are developed. The ongoing clinical trials of ACT therapy are indicating that there is a future of these immunotherapies in the treatment of this type of cancer. Immunotherapies will require higher quality personalized medicine to treat HNSCCs because of how fast the cancer can spread throughout lymphatic tissue. Additionally, dentists and physicians will play a huge role in early detection and prevention. They can improve the effectiveness of treatment for HNSCCs by detecting the cancer in the early stages of progression. By taking a few additional measures on a patient-to-patient basis, they can truly influence the outcome of cancer treatment. This can be accomplished through people taking responsibility for their decisions. This includes everyone who is involved in the process of cancer treatment, including the patients, developers, oncologists, dentists, and researchers.

Both my family and the Jesuit values that I have implemented in my own life have fueled my belief in ethical and responsible science. Regis has allowed me to refine what "Magis" looks like in my own life. I have found that responsibility is one of key the aspects of Magis. Not only is it the responsibility of my own actions but responsibility of the environment and society that I live in. Responsibility is a huge aspect of ethical science and of innovative science. The idea of responsibility fueled my interest in Immunology and on into Immunotherapy. I wanted to research a branch of biology that really interested me, and Immunology was definitely my first choice. The unique way of

targeting our immune response, rather than targeting cancerous cells themselves made me interested in why immunotherapy was truly different than other cancer treatments. I had no idea what this thesis would evolve into, but I think that personalized medicine allowed me to see where immunotherapy fits into the future picture of cancer treatment. Specifically, I wanted to look into a type of cancer that means something to me, and HNSCC was that cancer. I recently was admitted into dental school, and felt an obligation to understanding what role a dentist could have in detection and prevention of cancer. Dentists play a huge role in early detection of HNSCCs, and so this research has provided me with a better understanding of what type of dentist I want to be in the future. A mindfulness of patients and their lifestyle is required for providing both the best service possible and the proper mentorship that can impact their own health care.

Cancer treatment is currently in an era of transition because of the amount of personalized data and information that can be brought into the decisions on treatment. Both immunotherapies and personalized medicine are revolutionizing cancer treatment and are moving in the right direction regarding the development of higher quality patient care and more efficacious treatment. In the end, the discovery of more viable biomarkers in cancers, including HNSCCs, will determine if immunotherapy clinical trials find more success against solid tumors. The end goal is to change the view on cancer from something that is "helpless" to that of something that is "hopeful." The fight against cancer will never end until there is a cure for every single type, and until then personalized medicine will be the driving force behind immunotherapies and the transformation of cancer care in our world.

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