8-8-2023

Cancer: The Burden of Treatments Eased by Recent Developments in the Field: a Review of the Literature

Zachary J. Seim

Cancer: The Burden of Treatments Eased by Recent Developments in the Field: a Review of the Literature

Zachary Seim

A Project Submitted to

GRAND VALLEY STATE UNIVERSITY

In

Partial Fulfillment of the Requirements

For the Degree of

Masters of Health Science

Biomedical Science

August 2023

GRAND VALLEY STATE UNIVERSITY

The signatures of the individuals below indicate that they have read and approved the project of Zachary Seim in partial fulfillment of the requirements for the degree of Masters of Health Science in Biomedical Science.

Kristin Renkema, PhD Project Advisor Date: 8/8/23

Chris Pearl

Christopher Pearl, PhD Graduate Program Director Date: 8/8/23

Daniel A Bergman

Daniel Bergman, PhD Unit head Date: 8/8/23

Abstract

Cancer is a very prevalent disease that has affected most of the population. Treatment options that have been used for decades are beginning to be outcompeted by newer developments in the field. Newer developments allow a more specific response to cancers that have proven to be very difficult for traditional treatment. Immune specific treatments also give the ability to specifically target areas affected by the cancer, to reduce potential risk of systemic damage and autoimmunity. Developing cancer treatments that are highly specific brings forth a new age of medicine, hoping to prolong the life expectancy of those affected with cancers, particularly those that are highly aggressive or immune related.

Table of Contents

Introduction……5

Cancer……5

B cell Development……6

T cell development……7

B and T cell Memory Development……10

Molecular Targets for Cancer……11

Treatments……13

Car-T Therapy……13

Oncolytic Viruses……20

Neoantigen Vaccines……22

Conclusion……25

Works Cited……26

INTRODUCTION

CANCER

Cancer is a disease society is too familiar with. If someone we are close to has not been diagnosed, we have at least known someone who has. Cancer, can grow, unchecked by the immune system because it is difficult for the body to detect. Cancerous tumors are comprised of human cells, making it difficult for the immune system to differentiate the difference between healthy cell and cancer. With that in mind, cancer will find ways to avoid being detected by the body in order to continue unchecked growth. Cancer has also developed many complex mechanisms in either silencing immune regulation or even diverting the course of an immune reaction away from a tumor, sometimes to help it infiltrate further. The American Cancer Association estimates 1.9 million cases of cancer were diagnosed this year alone, and over 600,000 people have died because of it (Cancer Facts & Figures 2022). Cancer has many targets and can infect various tissue types. Because cancer develops from mutation, the tissue that could develop into cancer is not necessarily predictable. Determining at risk tissues becomes potentially more predictable based upon habits and personality aspects such as smoking, drinking, genetics and various other activities (Sasco, A J et al.). While we may be able to somewhat identify what tissues within your body are at risk, there is no way to know the mechanism of immune evasion that a cancer could use (Sasco, A J et al.).

Having a disease that has the complexity to evade its own immune system can be a very difficult task to help to find an effective treatment. Cancer is not only complex enough to evade the immediate, non-selective aspects of immunity, but the adaptive, highly specific branch of

our immune system. The adaptive immune system is tailored to recognize and attack invasion from external foreign pathogens, but more importantly for cancer, it is tailored to kill pre-cancerous and cancerous cells as well ("*The Immune System*."). However, cancer has developed numerous ways of evading these mechanisms. The cells classified within the adaptive immune system are the B and T cells which contain these capabilities of attacking and kill pathogens directly, or activating inflammatory/regulatory pathways that will kill the pathogens indirectly ("*The Immune System*."). The major reason for the selectivity of B and T cells is the ability for them to create immune memory, to help fight subsequent infections.

B CELL DEVELOPMENT

During development, B and T cells all form from a common progenitor cell in the bone marrow that arises from hematopoiesis, or blood cell formation ("*The Immune System*."). These cells, dependent upon their new designation will then travel to their respective locations to develop. B cells will stay in the bone marrow, developing and then released to travel within lymph fluid throughout the body, stopping at lymph nodes and waiting to be activated (Vandana Kalia 1, et al.). Once these B cells are mature, they will then monitor lymph, which is fluid that is contained within the lymph system and monitor as it passes through. While these B cells are contained within the lymph system, they can be activated two ways: either pathogens will arrive in the lymph system directly, or the B cells will be in circulation in the blood stream and bind to an antigen to become activated ("*The Immune System*."). T cells on the other hand will travel to the thymus for the remainder of their development, and are released afterwards into the body, travelling typically in the lymph and blood stream (Vandana Kalia 1, et al.). While these cells are similar in development, they are different in overall function. B cell development begins in the

bone marrow. B cells, unlike T cells will stay in the bone marrow for the extent of their development ("*The Immune System*."). While developing, these cells undergo "checkpoints" to ensure that they do not become self-reactive or cause potentially threats to the systemic body such as autoimmune conditions ("*The Immune System*.").

T CELL DEVELOPMENT

T cell development requires these checkpoints during development as well. The checkpoints are present for a few reasons. One, the checkpoints help to ensure that the receptor on T cells that reach the surface do in fact recognize antigen that is given to them by a specific Major Histocompatibility Complex (MHC) molecule that comes via an antigen presenting cell (APC), (Kumar, Brahma V, et al.). After this first checkpoint, the cells will then be differentiated into CD4 or CD8 T cells based upon which MHC they recognize (Kumar, Brahma V, et al.). After a T cell differentiates enough to be sent to the thymus for development, it will begin the steps to become a mature T cell (Kumar, Brahma V, et al.). As the T cell progenitors are transferred into the thymus, they are considered "double negative," meaning that they do not express CD4 or CD8 yet (Yui et al.). These cells will then encounter NOTCH1 which will cause downregulation of any pathways other than T cell development (Yui et al.). NOTCH1 is a protein created by a gene pathway, that can be regulated by certain transcription factors (Yui et al.). As the process continues, they will interact with immune cells secreting cytokines allowing signals to be communicated for the completion of various molecular processes (Yui et al.). As the developing T cell continues, it will undergo two types of selection: positive and negative (Yui et al.). Positive selection occurs when the T cell receptor (TCR) is expressed and is tested against antigen (Kumar, Brahma V, et al.). The purpose for this is to ensure that the TCR can recognize

and bind to MHC and self-antigen (Kumar, Brahma V, et al.). If the cell cannot, or binds too tightly it will become anergic and eventually undergo apoptosis (Kumar, Brahma V, et al.). Finally, T cells will undergo negative selection in order to ensure that it does not react strongly to self-antigen (Kumar, Brahma V, et al.). If an antigen from the body causes reactivity, this cell will undergo the same fate as positive selection. The remaining cells that pass these checkpoints will be deemed suitable for circulation (Yui et al.). MHC is a very important receptor in T cell function. T cells, unlike B cells cannot recognize an antigen that has not been broken down and presented to it (Yui et al.). The MHC receptor is the portion that presents an antigen to a T cell (Yui et al.). The Antigen Presenting cell (APC) is what typically expresses MHC, at least in the case of the function of MHC for T cell activation (Kumar, Brahma V, et al.). An APC will envelop and break down a pathogen to get this small form of antigen needed for recognition by T cells (Kumar, Brahma V, et al.). MHC I recognition leads to differentiation into CD8 and MHC II recognition leads to differentiation into CD4 T cells (Kumar, Brahma V, et al.). CD8 or Cytotoxic T cells are helpful in recognizing and killing pathogens and host infected cells. CD8 T cells can kill infected cells through granzymes released upon binding (Kumar, Brahma V, et al.). Granzymes, which are packaged particles of digestive enzymes, will invade the pathogen and destroy it via apoptosis (Kumar, Brahma V, et al.). This is a major component that made T cells a focused target of immunotherapy with cancer (Kumar, Brahma V, et al.). CD4 or Helper T cells are important for activating other components of the immune system. CD4 T cells will differentiate again based upon which signals they get from activating cells, like dendritic cells (Kumar, Brahma V, et al.). Once in circulation, T cells require three signals to become activated. T cells are activated by three signals, antigen presentation, costimulation and cytokine interaction

(Sylvie Guerder 1, et al.). The cytokine interaction is what will cause there to be differentiation into the CD4 T cell subclasses (Sylvie Guerder 1, et al.). There are various subclasses of Helper T cells but T regulatory (Treg) cells will be the focus. One of the most important aspects of T reg cell response is the ability to inhibit the immune response once the threat has been neutralized to avoid chronic inflammation or development of autoimmune disorders. Tregs are important in modulating the immune response and turning it off once the job is done. There are two proteins expressed on Treg cells that are responsible for their activation: programmed cell death 1 (PD-1) and Cytotoxic T Lymphocyte Antigen 4 (CTLA-4). CTLA-4 indirectly shuts off the immune response by binding to the co-stimulatory receptor CD28 expressed on T cells. (Seidel, Judith A et al.). CD28 is a critical surface protein that serves a role in costimulation, transmitting important signals required for the activation of a T cell (Esensten, Jonathan H et al.). Therefore, CTLA-4 will outcompete the binding to CD-80/86, not allowing for these to bind CD28 and inhibits the signaling and in turn, T cell activation. (Seidel, Judith A et al.). PD-1, while similar in function has a different activation mechanism than CTLA-4. PD-1 is activated by either PDL-1 or PDL-2 which is found on APCs and can be seen more frequently expressed during an immune response, or more specifically when interferon gamma levels are increased (Seidel, Judith A et al.). PDL-1 and PDL-2 are PD ligands and will bind to PD-1, which will begin mechanisms to begin shutting off the immune response. (Seidel, Judith A et al.). As it is seen, CD4 and CD8 T cells express either CTLA-4 or PD-1, and most importantly, Treg cells express PD-1 (Seidel, Judith A et al.). When these Tregs are activated and begin releasing inhibitory cytokines to stop the immune response (Ronin, Emilie, et al.). When these processes work correctly, as designed, immune suppression continues accordingly. However, these processes provide targets for

cancer to shut off immune response or control aspects of inactivation that allows rapid unmonitored growth of cancer cells.

B AND T CELL MEMORY DEVELOPMENT

Immune activation and inactivation processes are a potential target of cancer, but another aspect of evasion cancer employs is the ability to evade memory creation. The ability to form memory to help treat subsequent infections is very useful in the adaptive immunity's capabilities (Sylvie Guerder 1, et al.). This poses a challenge in the scope of cancer, as cancer develops from human cells, it is difficult to create memory against. Lack of memory can potentially lead to relapse, which is when cancer can develop again after treatment. In general, when T and B cells are circulating in the body, they will be considered naïve as they are mature but have not been exposed to antigen (Sylvie Guerder 1, et al.). Once exposed to antigen, considered the primary infection, these cells will activate and carry out their functions respective to their cell type (Vandana Kalia 1, et al). Once the infection has been handled, the B cells will form memory B cells, which are capable of recognizing antigen that it has seen before and inducing the response that was done previously, such as releasing antibodies etc. T cells similarly will also create memory T cells to remember an antigen and induce an immune response the next time this is seen in the body (Sylvie Guerder 1, et al.). What is most important about this type of function is that a primary infection takes time to be contained and handled because it is an infection that has not been seen yet (Sylvie Guerder 1, et al.). Once these memory cells are created and the antigen is present again, a secondary response will occur, and having recognition and specificity, the response will be much faster and much stronger than that of previous response (Sylvie Guerder 1, et al.). Not all cells will stay as memory cells once a

response occurs and a process called, contraction, which will mean some cells die as they are no longer needed. This is important because it would not be beneficial to have all T or B cells dedicated to memory of one or many antigens because then it would not be able to recognize new infections. This is an important aspect for all adaptive immunity and is an integral aspect into the immune system's ability to respond adequately to infections. Cancer unfortunately is very complex and can evade the immune system well, but recent developments in immune tailored treatments work to stop these mechanisms and stimulate the immune system in specific ways for a higher specificity when treating cancer.

MOLECULAR TARGETS FOR CANCER

Cancer, as discussed previously, is very complex and can manipulate the immune response to be advantageous for the protection of its own growth. As cancer grows, it may attempt to silence certain cytokine pathways that are necessary for signaling the immune system that a threat is present. A signaling pathway for T cells, the NFkB pathway, is one that is characterized by a molecular chain reaction that begins with the binding of a molecule to a receptor on the cell surface, that will then lead to downstream translocation of the NFkB molecule (Barnes SE;Wang et. al). NFkB is a transcription factor and the translocation of NFkB into the nucleus will cause transcription of certain genes dependent upon what cytokine/receptor pairing activates this pathway, such as the NOTCH1 pathway for instance (Barnes SE;Wang et. al). This is a direct target seen in cancer progression, as tumors can shut down this pathway, leading to decreased T cell function (Barnes SE;Wang et. al). It has been shown that the NFkB pathway is integral in T cell destruction of tumors and that the NFkB pathway plays a key part in tumor containment and that if this process is impaired tumor

progression will continue without proper response. (Barnes SE;Wang et. al). The NFkB pathway is activated by a molecule called p65 (Oh, Hyunju, and Sankar Ghosh.). When antigen binding occurs to the receptor, the translocation cascade occurs and without p65 it cannot begin (Oh, Hyunju, and Sankar Ghosh.). This provides another potential target for cancerous tumors to shut off the immune system activation (Oh, Hyunju, and Sankar Ghosh.). Another issue with a compromised NFkB pathway is CD4 T cell differentiation inadequacies. Without NFkB, there are instances where CD4 T cells will not differentiate into the TH17 subtype (Oh, Hyunju, and Sankar Ghosh.). TH17 cells are responsible for bacterial infections, however for cancer issues, TH17 cells secrete pro-inflammatory cytokines and without could compromise the immune response (Oh, Hyunju, and Sankar Ghosh.). The adaptive immune system relies heavily on activation by antigen presenting cells and will tailor its response as such. Not having a core aspect of activation is very damaging to the response that the immune system can have against a cancerous threat.

While specific pathways of genetics can be affected, entire cell types can also be upregulated or downregulated to complete a task needed by cancer cells. This can be seen in Treg cells. Having a cell type specific for shutting down the immune system is an incredibly damaging target for cancer cells to prioritize. The binding of PD-1 causes cells to become non-responsive to certain signals and become inactivated (Ronin, Emilie, et al.). Inactivation during this pathway is caused by the binding of a ligand to PD-1 which will in turn shut off the T cell. This avoids autoimmunity so that an immune response can be turned off once the pathogen has been handled. This pathway is advantageous to the human body in terms of immunity, but a disadvantage for immunity in terms of cancer which can use this mechanism to impact the body

negatively. As cancer grows and releases certain chemicals and ligands to activate/deactivate certain immune pathways, suppression of the immune system is a top priority. Using the PD-1/PDL-1 pathway, cancer cells can express PDL-1 and activate Treg cells to deactivate T cells and the immune response (A, Gianchecchi et al.). It can be seen with CD8 T cells that having higher expression of PDL-1 by a tumor can make destruction via CD8 apoptosis very difficult (A, Gianchecchi et al.). Without CD8 cells being active, apoptosis mechanisms cannot proceed (A, Gianchecchi et al.). CD8 T cells are highly skilled at identifying and killing cancer cells by way of granzyme release and apoptosis pathways. It has also been shown that having an altered immune response leading to chronic immunity can cause negative interactions between immunity and cancer. Cancer can suppress the immune system but can also cause low levels of chronic inflammation to cause damage to the body. T cell exhaustion, seen with long lasting immune responses, is a mechanism that occurs with cancers that do cause chronic inflammation and can pose a large threat to the body. It has been shown that when T cells get exhausted their PD-1 pathways are being activated like how it would when Tregs do their job (Dolina JS et al.). If an immune response is being turned off, and these cells are then returning to circulation in the lymph nodes or bloodstream, inactivated as if the threat has been neutralized giving cancer another opportunity to grow without regulation.

TREATMENTS

CHEMOTHERAPY

Chemotherapy is an administration of drugs that has been linked to treating cancer for many years. While chemotherapy has been seen as a typical treatment of cancer, advancements

in immunomodulation may suggest more tailored treatments. Chemotherapy is used to kill cells that are replicating faster than a typical cell, which can be cancer cells, but can also be healthy cells within the body ("Chemotherapy to Treat Cancer"). This is can be very difficult to do without widely damaging the normal cells within the body, and may cause there to be collateral damage. There are many different chemotherapy drugs that have been developed that can target different aspects of cellular replication ("Chemotherapy to Treat Cancer"). Chemotherapy drugs, for instance Methotrexate, are used in various ways. Methotrexate is a chemotherapy that helps treat cancer cells because it inhibits DNA synthesis ("Methotrexate Sodium."). Chemotherapy has been a plausible treatment for many cancers throughout history. For instance, a retrospective study done regarding Methotrexate and Low risk Gestational Trophoblastic Tumor (GTT) treatment effectiveness shows between 1974 and 2000 the survival rate for the 272 patients in question was 100% and the remission rate was 75% (*Relapse Rate of Patients with Low-Risk gestational trophoblastic tumor initially treated with single-agent chemotherapy*). Overall, these numbers seem promising however it is important to consider type of cancer in question, and that there is individual variability in treatment effectiveness. Chemotherapies are not as specific as newer developments in the field of medicine, and can bring about differing effectiveness with immune system related cancers such as ones that affect B or T cells and the adaptive immune system. Chemotherapy may not be best suited for cancers that are cellular, like myelomas that are cancers of the plasma cells that are contained within bone tissue ("Why Chemotherapy Doesn't Work for Certain Cancer Patients."). Myelomas are not typically treated with chemotherapy, and gives opportunity for areas of immune modulation treatments as a therapy with higher specificity ("Why Chemotherapy Doesn't Work for Certain

Cancer Patients."). A new development in immune modulation therapy for cancer is CAR-T therapy that provides a more viable treatment option for myeloma ("Improving Treatment for Recurrent Multiple Myeloma with IDE-CEL Car T Therapy."). Most importantly, chemotherapy may be beneficial, but immune modulation allows for potential for a tailored response to specific to cancers that chemotherapy may not be helpful for.

CAR-T THERAPY

Development in technology through the years has allowed for new treatments to be created. Adaption in the field of science is integral to create new courses of action for diseases that otherwise may not have ideal outcomes or viable treatments. Some new developments use aspects of immunity that are used in a new way, or some may completely change molecular organization of cells. For instance, a newer development called Chimeric Antigen Receptor T cells (CAR-T) is an example of changing the molecular organization of a cell. T cells require an antigen to be broken down into pieces before being able to recognize and trigger a response. A CAR-T cell will have a new receptor instead of a T cell receptor, therefore circumventing the need to be presented antigen by an MHC complex and can recognize whole antigen like a B cell receptor. CAR-T cells can also skip travelling to the thymus for maturation, like a classical T cell would, allowing them to enter circulation faster. This provides the opportunity for an increased range of identification by said T cells. The receptor components a Car-T cells needs is a hinge region which helps in binding, the area that is specific to a particular antigen for recognition, a transmembrane domain, and a component that can perform intracellular signaling pathways (RM;, Sterner et al.). There are currently six different types of CAR-T cell therapy that the FDA approved and they differ based upon receptor expression, dictating their specific target. ("Car T

Cells: Engineering Immune Cells to Treat Cancer.”). Having multiple options for receptor exchange gives a wide range of treatment options. This brings forth potential for targets for highly aggressive cancers, as well as those with a very poor prognosis given prior to the development of this treatment.

While CAR-T cells seem somewhat simplified in mechanism, creating them is a difficult task. These cells are completely lab developed and take some time to make. The first step in creation is removing T cells from the body of the person infected and genetically modifying them to display the new receptor (Finney OC at al.). This new receptor will recognize antigen specific to the cancer that is in question after being introduced during the process of development in the lab (Finney OC at al.). After these cells are exposed to the antigen and ready for development, they must wait and undergo clonal expansion in order to grow populations of millions of antigen specific CAR-T cells (Finney OC at al.). Once millions of these cells are created, they will be put back into the patient to target the cancer cells (Finney OC at al.). CAR-T therapy helps to increase prognosis of one specific class of cancers, those that affect B cells (Finney OC at al.). B cells cancers can be very difficult to treat as they are a part of the immune system and are not a solid tumor (Finney OC at al.). B cell cancers are also especially talented at hiding and causing up/downregulation of the immune system as being one of the larger contributors to a normal immune response overall (Finney OC at al.). CAR-T cells however, with antigen exposure, can target CD19, which is normally expressed on all B cells (Finney OC at al.). With this specific type of targeting, these CAR-T cells will be able to search and find this antigen and destroy the B cells. It has been shown that CD19 specific CAR-T cells that cause a response early on in treatment phase can allude to a higher chance for staying in remission compared to

those that do not cause a response early in the treatment phase (Finney OC at al.). This not only allows for potential sight into the rate of remission for these cancers that otherwise may not give a chance for remission, but a good way to prove how important the immune response is in cancer therapy.

CAR-T therapy is taking the science world by storm, bringing excitement to a process that has taken a very long time overall to break through. CAR-T cells, being new to the science world, have only 6 types approved by the FDA. These names are Abecma, Breyanzi, Kymriah, Tecartus, Carvykti and Yescarta. What differs between all these types of cells is the type of specificity that the receptor they are programmed with has ("Car T Cells: Engineering Immune Cells to Treat Cancer."). For instance, Kymriah is specific for Acute Lymphoblastic Leukemia (ALL). Yescarta, which is a CD19 specific CAR-T cell is helpful in treating any type of cancer that involves B cells (Locke FL et al.). While there were many adverse events, some relating to immune activation like encephalopathy and others, others were shown to be a reduction in immunity like leukopenia (Locke FL et al.). While this may seem as an adverse event and something to forget, it may indicate that this treatment was working, as B cells were being targeted. With that, it was shown that those treated with Yescarta (axicabtagene ciloleucel) had no progression of cancer through the 6-month phase, and at the 2-year mark, it was shown that the durability of this drug was effective and needed no other intervention (Locke FL et al.) Kymriah (tisagenlecleucel), while similar in treatment mechanism to Yescarta due to it being a CD19 CAR-T cell, is helpful in ALL for younger adults and children. Kymriah showed in clinical trial to also be effective with an 80% relapse free rate over the course of 20 months. However, Kymriah showed a high rate of cytokine storm in 88% patients that were treated with this

(Maude, Shannon L, et al.). Therefore, while some of these new treatments are similar in mechanism, slight molecular changes could cause potentially detrimental issues. There are others that target other extracellular proteins and receptors such as an anti-CD30 CAR-T cell type that has shown to be effective for Hodgkin's Lymphoma (Ramos CA et al.). As Ramos et. al discuss, this anti-CD30 CAR-T therapy, shows an overall response in 62% of patients and a remission rate over 59% at the one-year mark (Ramos CA et al.). A clinical study done by Zhang et al. showed efficacy of another CD19 CAR-T cell, however this one worked along with a gene mutation. The researchers edited the gene that the anti-CD19 aspect was inserted into a locus and modified to have PD-1 integration (Zhang J et al.). It was shown that PD-1 integration by CD19 allowed for cancer regression compared to those with the PD-1 knockout (Zhang J et al.). This brings about another mechanism of Car-T cells, to not only be antigen specific but to have the ability to be genetically modified to create higher levels of specificities and potential activation of other anti-cancer mechanisms.

CAR-T cells and immunomodulation therapies effectively reroute the research direction in cancer treatment, from systemic chemical administration to specified immune modulation. Not only is this a more specific and potentially effective treatment option, but could be safer potentially in the long run, systemically. With that being said, there are always risks for all treatment options that are to be considered. A current issue that has been outlined for CAR-T therapy is the viability for use with solid tumors. CAR-T cells, being immune cells, need the correct environment to work. A large reason currently why CAR-T therapy does not work for solid tumors is the ability for these tumors to create an unfavorable "immune suppressive environment" (Ma S et al.) surrounding themselves. For a T cell to work, specifically those that

are cytotoxic, antigen must be recognized and the cell must bind to the tissue in question, which is a tumor in this case. As discussed by Shah et. al, it is very difficult for these T cells to perform diapedesis to infiltrate into the blood vessels that feed the tumor. Another issue, which is likely the most important issue, is that of the immune response that this cause. A cytokine storm, which is classical of CAR-T therapy is an immune response essentially throughout the entire body. What this does, leads to systemic inflammation, and can lead to death. Often, due to the nature of this therapy, CAR-T cells are administered in the intensive care unit (ICU) of a hospital. Finally, there have been instances where resistance to the CAR-T cells has occurred due to "loss of antigen" (TJ, Shah et al.). When antigen is lost, it means that the CAR-T cells do not have the ability to find the antigen for many reasons however, the most likely is due to the single antigen recognition mechanism that CAR-T cells employ. If or when an antigen is recognized by an immune cell and an immune response is developed, cancer cells can modify the antigens that they display, in order to protect themselves. Therefore, therapies that are multifactorial lead to higher potential for success. A positive to this therapy that others do not have is the possibility of memory development. With these being T cells and an arm of the adaptive immune response, memory is an option for post cancer infection. Being able to potentially bring about a memory aspect to cancer could significantly help those who are at risk for relapse, and potentially aggressive cancers that are hard to completely shut down. While there are many positive and negative aspects to all treatment options, it is valuable to weigh the cost/benefit ratio when determining which is best for the patient. Throughout the recent past to present, the new developments have given the opportunity for medical staff to weigh multiple options, rather than only have one option, like chemotherapy for instance, and hoping that it will do the

job that is needed. Developing not only new treatments, but having the ability to give a patient, options as a fail-safe in case one treatment does not work, is a luxury that has been brought about by the increasing modernization of technology.

ONCOLYTIC VIRUSES

Viruses have been present in this world since the beginning of the cell. There are numerous hypotheses of how these entered our world, but what is important is that they have been around for a long time. While they are seasoned in the world of the immunity, they typically are thought of as immune invaders. While this is factually correct, some are used in treatment options, and more recently in cancer treatments. Viruses that attack cancers are called oncolytic viruses. Oncolytic viruses have the capability of infiltrating a cancerous tumor and eliciting an immune response within this region. A major contributor that oncolytic viruses can bring to the table is that they are helpful in cases in which the tumors are inoperable, specifically in the realm of gliomas, which are cancers in the brain. The use of oncolytic viruses allows for a unique mechanism of entrance into a tumor environment, as these environments are usually heavily immunosuppressive. While most treatments, like CAR-T cells for instance, would have difficulty with this, oncolytic viruses do not. While some of these treatment options in immunomodulation are relativity new, the use of viruses has been around for many years. Viruses, for instance have been used in vaccines, that will help bring antigen to cells necessary for eliciting an immune response.

A reason viruses are used for tumor destruction is due to their natural abilities to induce specific immune responses, especially those which can induce a T cell response. A virus called

HF-10 is a HSV (Herpes Simplex Virus) that has been shown to be very effective when treating colon cancers and melanomas (D, Mondal et al.). The reason this is effective is that the virus can penetrate the tumor and proliferate inside the tumor and cause an immune response, mainly of T cells, which will cause tumor size to decrease (D, Mondal et al.). Inoperable cancers can cause many issues in the design of treatment, and it is important to weigh all options, as cancers in certain areas of the body, like gliomas, can be very difficult to treat (D, Mondal et al.). With oncolytic viruses and immune manipulation, there brings a new perspective and route of treatment, for cancers that cannot be accessed physically. For instance, it has been seen previously that the prognosis of DIPG is typically less than one year life expectancy for the children diagnosed. However, with treatment of oncolytic viruses, causing a T cell response improved this median life expectancy to 17.8 months, extending the life of some of these children (Gállego Pérez-Larraya J et al.). It is worth noting as well that a patient in the study has been alive for 38 months and has shown lack of tumor growth (Gállego Pérez-Larraya J et al.). When these cancer tumors do eventually rupture or begin to die due to the immune response, there can also be attack on metastasis as well, because of the immune recognition of a specific antigen (Cui C et al.). Another positive aspect of oncolytic viruses in direct comparison with CAR-T therapy is that these can be directly injected into the tumor (Cui C et al.). This then is helpful in avoidance of the immunosuppressive environment that the tumor creates. A promising oncolytic virus, OrienX010, has been seen as one of the first to be helpful and safe in treatment for melanoma (Cui C et al.). Treating with OrienX010 has been shown to be in a dose dependent manner requiring higher doses for further advanced melanoma cases. However, the use of this virus has proven to be safe and effective and does not increase the number of

adverse events, when increasing the dose given (Cui C et al.). When compared to other therapies, not increasing the adverse events experienced when increasing the dose of treatment is a positive accolade for OrienX010 (Cui C et al.). OreinX010 has been linked with late-stage melanomas which are historically hard to treat and tend to have a poorer prognosis than those of lower progression (Cui C et al.). A clinical trial concerning an oncolytic virus treatment called Talimogene Laherparepvec was done by injecting the viruses intratumorally to determine the response (Ribas A et al.). As predicted, there was increased recruitment of CD8 T cells to the site of the tumor, which then allowed for an attack against the tumor (Ribas A et al.). These viruses were also equipped with an anti-PDL1, which allowed them to modulate the inhibition of T cells, caused by the cancerous tumor, allowing these T cells to respond (Ribas A et al.). The CD8 T cells will then travel to the site of the tumor and kill the tumor through the granzyme pathways (Ribas A et al.). The importance of immune cell recruitment with oncolytic virus treatment is the most integral portion of their treatment mechanism. With that, this provides an alternative to CAR-T therapy, potentially providing a way to circumvent the immunosuppressive abilities of the cancerous tumor, due to the oncolytic virus's injection intratumorally.

NEOANTIGEN VACCINES

There are various ways that the immune system can be activated to fight cancerous tumors, and while oncolytic viruses do not have to specifically recognize antigen, there are many other ways that developments have allowed for specificity, through antigen recognition other than oncolytic viruses. The use of vaccines has been prevalent throughout modern day science. The creation of vaccines in the age of Louis Pasteur and Edward Jenner, has led to the

prevention of numerous diseases, that would otherwise be more prevalent within our society. Vaccines, in their development, were used to prevent one disease or a range of similar diseases, however recently these have been used to create an immune response in order to target certain tumors specifically. This has completely revolutionized possibilities for patients with inoperable tumors, especially gliomas, which are cancers of the brain (Ribas A et al.). While it is helpful to not operate in or around the brain, it is worth noting that creating an immune response in or around the brain can also be extremely dangerous. What vaccines for cancer treatment use are small antigenic material called neoantigens (Ribas A et al.). Neoantigens, as defined by the National Cancer Institute, are a protein that forms on cancer cells after tumor DNA undergoes certain mutations (NCI Dictionary of Cancer Terms."). Neoantigens provide a target for immune modulation and can be helpful in the development of treatments for solid tumor cancers such as non-small cell lung cancer" (Awad MM et al.). It is further shown within their research that the use of vaccines paired with a chemotherapy and PD-1 show higher concentrations of CD4+ T cell infiltration into a site of the tumor (Awad MM et al.). When a neoantigen is identified, it is then injected (Awad MM et al.). This process will allow the neoantigen to be presented to T cells and create an immune response (Awad MM et al.). As cancer grows, its entire existence is dependent upon the suppression of immune responses and being able to not be recognized (Awad MM et al.). Recognition is arguably one of the most difficult parts in treating cancers. Injecting a neoantigen to elicit recognition and response can help provide specificity for cancerous cells (Awad MM et al.). It also can induce an adaptive response which in turn can lead to the development of memory. An issue of concern in cancer is the potential for relapse. Relapsing means that the cancer has come back, and either treatment must continue or the

current process must be altered. Being able to create memory for certain cancer antigens (neoantigens) could be another groundbreaking aspect of vaccine treatment for cancers. A concern, or point of interest that must be acknowledged is determining which neoantigen is used (Bhattachary-Chatterjee M et al.). As neoantigens are found on cancerous tumors, and cancerous tumors are effectively human cells that are growing unregulated, there is high potential to be expressing some self-antigen (Bhattachary-Chatterjee M et al.). Therefore, it is important to use an antigen that the vaccines can use to generate the correct response, an anti-tumor response and not an autoimmune response (Bhattachary-Chatterjee M et al.). It is very important to ensure that the antigen epitope of interest is not expressed on healthy tissues, to avoid creating autoimmunity issues (Bhattachary-Chatterjee M et al.). Being able to find something to help identify cancer is a great achievement but can cause more damage that it does good (Bhattachary-Chatterjee M et al.). Inducing autoimmunity to any patient can have negative consequences, but most of all, inducing autoimmunity to patients that are already immunocompromised is extremely dangerous. This therapy proves to be a potential in treating many cancers and instilling hope into those who would normally have a very poor prognosis (Bhattachary-Chatterjee M et al.). An interesting aspect of vaccines is it allows for the prospect of prevention and prophylaxis. Using HPV as an example, a vaccine has been created using viral-like particles which do not contain any active virus, but mostly a protein coat that have antigenic ability to allow for recognition (Athanasiou A et al.). Another study characterized the ability for potential to have personalized neoantigen based upon genetic screening (Athanasiou A et al.). This study brought forth the possibility for personalization by taking the genetic sequence of the tumor and comparing that to the genetic sequence of a functional cell within the same patient

and showed that the personalized neoantigen expands the opportunities for this type of immunotherapy regarding cancer (Ott PA et al.). Vaccines pose an interesting alternative to classic therapies as these are potentially easier to administer and activate an immune response that is selective, but not as vigorous as CAR-T therapy for instance (Ott PA et al.). Having a prophylactic treatment, like the HPV vaccine as well brings an even larger component into the treatment world, opening the door for treatments before cancer even occurs.

CONCLUSION

Cancer is a devastating disease that claims hundreds of thousands of lives every year. To be able to develop new technologies to outcompete cancer in the realm of suppressing our immune system, brings about new hope for cancers that have otherwise been very deadly. As these may not be the universal treatment for cancer, it does mean the field of science and medicine is moving in the correct direction. Having the technology to inject an antigen and create antibodies prior to cancer development, all the way to modifying cells that are in the body to possess the innate ability to seek and destroy cancer cells is a large development. Developing new and more tailored options in the world of cancer can help to alleviate a large burden placed on society that is seen increase seemingly every year. Tailoring specific responses, prophylactically treating cancer and the potential for memory to cancers is a large step in the right direction for the field of medicine and science. Progress in medicine, especially in regards to cancer, is always a win.

Works Cited

A;, Gianchecchi E;Fierabracci. “Inhibitory Receptors and Pathways of Lymphocytes: The Role of PD-1 in Treg Development and Their Involvement in Autoimmunity Onset and Cancer Progression.” *Frontiers in Immunology*, pubmed.ncbi.nlm.nih.gov/30386337/. Accessed 17 July 2023.

Athanasiou A;Bowden S;Paraskevaidi M;Fotopoulou C;Martin-Hirsch P;Paraskevaidis E;Kyrgiou M; “HPV Vaccination and Cancer Prevention.” *Best Practice & Research. Clinical Obstetrics & Gynaecology*, pubmed.ncbi.nlm.nih.gov/32284298/. Accessed 17 July 2023.

Awad MM;Govindan R;Balogh KN;Spigel DR;Garon EB;Bushway ME;Poran A;Sheen JH;Kohler V;Esaulova E;Srouji J;Ramesh S;Vyasamneni R;Karki B;Sciuto TE;Sethi H;Dong JZ;Moles MA;Manson K;Rooney MS;Khondker ZS;DeMario M;Gaynor RB;Srinivasan L; “Personalized Neoantigen Vaccine NEO-PV-01 with Chemotherapy and Anti-PD-1 as First-Line Treatment for Non-Squamous Non-Small Cell Lung Cancer.” *Cancer Cell*, pubmed.ncbi.nlm.nih.gov/36027916/. Accessed 17 July 2023.

Barnes SE;Wang Y;Chen L;Molinero LL;Gajewski TF;Evaristo C;Alegre ML; “T Cell-NF-KB Activation Is Required for Tumor Control in Vivo.” *Journal for Immunotherapy of Cancer*, pubmed.ncbi.nlm.nih.gov/25648675/. Accessed 17 July 2023.

Bhattachary-Chatterjee M;Nath Baral R;Chatterjee SK;Das R;Zeytin H;Chakraborty M;Foon KA; “Counterpoint. Cancer Vaccines: Single-Epitope Anti-Idiotype Vaccine versus Multiple-Epitope Antigen Vaccine.” *Cancer Immunology, Immunotherapy : CII*, pubmed.ncbi.nlm.nih.gov/10881692/. Accessed 17 July 2023.

“Cancer Facts & Figures 2022.” *American Cancer Society*, www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html#:~:text=The%20Facts%20%26%20Figures%20annual%20report,incidence%2C%20mortality%2C%20and%20survival%20statistics. Accessed 16 July 2023.

“Car T Cells: Engineering Immune Cells to Treat Cancer.” *National Cancer Institute*, www.cancer.gov/about-cancer/treatment/research/car-t-cells. Accessed 17 July 2023.

“Chemotherapy to Treat Cancer.” *National Cancer Institute*, www.cancer.gov/about-cancer/treatment/types/chemotherapy#how-chemotherapy-works-against-cancer. Accessed 2 Aug. 2023.

Cui C;Wang X;Lian B;Ji Q;Zhou L;Chi Z;Si L;Sheng X;Kong Y;Yu J;Li S;Mao L;Tang B;Dai J;Yan X;Bai X;Andtbacka R;Guo J; “ORIENX010, an Oncolytic Virus, in Patients with Unresectable Stage IIIC-IV Melanoma: A Phase IB Study.” *Journal for Immunotherapy of Cancer*, pubmed.ncbi.nlm.nih.gov/35383116/. Accessed 17 July 2023.

D;, Mondal M;Guo J;He P;Zhou. “Recent Advances of Oncolytic Virus in Cancer Therapy.” *Human Vaccines & Immunotherapeutics*, pubmed.ncbi.nlm.nih.gov/32078405/. Accessed 17 July 2023.

Dolina JS;Van Braeckel-Budimir N;Thomas GD;Salek-Ardakani S; “Cd8+ T Cell Exhaustion in Cancer.” *Frontiers in Immunology*, pubmed.ncbi.nlm.nih.gov/34354714/. Accessed 17 July 2023.

Esensten, Jonathan H et al. “CD28 Costimulation: From Mechanism to Therapy.” *Immunity* vol. 44,5 (2016): 973-88. doi:10.1016/j.immuni.2016.04.020

Finney OC;Brakke HM;Rawlings-Rhea S;Hicks R;Doolittle D;Lopez M;Futrell RB;Orentas RJ;Li D;Gardner RA;Jensen MC; “CD19 Car T Cell Product and Disease Attributes Predict Leukemia Remission Durability.” *The Journal of Clinical Investigation*, pubmed.ncbi.nlm.nih.gov/30860496/. Accessed 17 July 2023.

Gállego Pérez-Larraya J;Garcia-Moure M;Labiano S;Patiño-García A;Dobbs J;Gonzalez-Huarriz M;Zalacain M;Marrodan L;Martinez-Velez N;Puigdelloses M;Laspidea V;Astigarraga I;Lopez-Ibor B;Cruz O;Oscoz Lizarbe M;Hervas-Stubbs S;Alkorta-Aranburu G;Tamayo I;Tavi. “Oncolytic DNX-2401 Virus for Pediatric Diffuse Intrinsic Pontine Glioma.” *The New England Journal of Medicine*, pubmed.ncbi.nlm.nih.gov/35767439/. Accessed 17 July 2023.

“Improving Treatment for Recurrent Multiple Myeloma with IDE-CEL Car T Therapy.” *Memorial Sloan Kettering Cancer Center*, 10 Feb. 2023, www.mskcc.org/news/recurrent-multiple-myeloma-ide-cel-car-t-therapy.

Kumar, Brahma V, et al. “Human T Cell Development, Localization, and Function throughout Life.” *Immunity*, 20 Feb. 2018, www.ncbi.nlm.nih.gov/pmc/articles/PMC5826622/.

Locke FL;Ghobadi A;Jacobson CA;Miklos DB;Lekakis LJ;Oluwole OO;Lin Y;Braunschweig I;Hill BT;Timmerman JM;Deol A;Reagan PM;Stiff P;Flinn IW;Farooq U;Goy A;McSweeney PA;Munoz J;Siddiqi T;Chavez JC;Herrera AF;Bartlett NL;Wiezorek JS;Navale L;Xue A;Jiang Y;Bo. “Long-Term Safety and Activity of Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma (Zuma-1): A Single-Arm, Multicentre, Phase 1-2 Trial.” *The Lancet. Oncology*, pubmed.ncbi.nlm.nih.gov/30518502/. Accessed 17 July 2023.

Ma S;Li X;Wang X;Cheng L;Li Z;Zhang C;Ye Z;Qian Q; “Current Progress in Car-T Cell Therapy for Solid Tumors.” *International Journal of Biological Sciences*, pubmed.ncbi.nlm.nih.gov/31754328/. Accessed 17 July 2023.

Maude, Shannon L, et al. “Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia.” *The New England Journal of Medicine*, 1 Feb. 2018, www.ncbi.nlm.nih.gov/pmc/articles/PMC5996391/.

"Methotrexate Sodium." *National Cancer Institute*, www.cancer.gov/about-cancer/treatment/drugs/methotrexate#:~:text=Methotrexate%20sodium%20is%20a%20type,immune%20system%20kill%20the%20cancer. Accessed 2 Aug. 2023.

N;, Fischer JW;Bhattarai. "Car-T Cell Therapy: Mechanism, Management, and Mitigation of Inflammatory Toxicities." *Frontiers in Immunology*, pubmed.ncbi.nlm.nih.gov/34220853/. Accessed 17 July 2023.

"NCI Dictionary of Cancer Terms." *National Cancer Institute*, www.cancer.gov/publications/dictionaries/cancer-terms/def/neoantigen. Accessed 17 July 2023.

Oh, Hyunju, and Sankar Ghosh. "NF-KB: Roles and Regulation in Different CD4(+) T-Cell Subsets." *Immunological Reviews*, Mar. 2013, www.ncbi.nlm.nih.gov/pmc/articles/PMC3576882/.

Ott PA;Hu Z;Keskin DB;Shukla SA;Sun J;Bozym DJ;Zhang W;Luoma A;Giobbie-Hurder A;Peter L;Chen C;Olive O;Carter TA;Li S;Lieb DJ;Eisenhaure T;Gjini E;Stevens J;Lane WJ;Javeri I;Nellaiappan K;Salazar AM;Daley H;Seaman M;Buchbinder EI;Yoon CH;Harden M;Lennon N. "An Immunogenic Personal Neoantigen Vaccine for Patients with Melanoma." *Nature*, pubmed.ncbi.nlm.nih.gov/28678778/. Accessed 17 July 2023.

Parham, Peter. *The Immune System*. Garland Science, 2014.

Ramos CA;Grover NS;Beaven AW;Lulla PD;Wu MF;Ivanova A;Wang T;Shea TC;Rooney CM;Dittus C;Park SI;Gee AP;Eldridge PW;McKay KL;Mehta B;Cheng CJ;Buchanan FB;Grilley BJ;Morrison K;Brenner MK;Serody JS;Dotti G;Heslop HE;Savoldo B; "Anti-Cd30 Car-T Cell Therapy in Relapsed and Refractory Hodgkin Lymphoma." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, pubmed.ncbi.nlm.nih.gov/32701411/. Accessed 17 July 2023.

Relapse Rate of Patients with Low-Risk ... - Gynecologic Oncology, www.gynecologiconcology-online.net/article/S0090-8258(04)00918-7/fulltext. Accessed 17 July 2023.

Ribas A;Dummer R;Puzanov I;VanderWalde A;Andtbacka RHI;Michielin O;Olszanski AJ;Malvehy J;Cebon J;Fernandez E;Kirkwood JM;Gajewski TF;Chen L;Gorski KS;Anderson AA;Diede SJ;Lassman ME;Gansert J;Hodi FS;Long GV; "Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy." *Cell*, pubmed.ncbi.nlm.nih.gov/28886381/. Accessed 17 July 2023.

RM;, Sterner RC;Sterner. "Car-T Cell Therapy: Current Limitations and Potential Strategies." *Blood Cancer Journal*, pubmed.ncbi.nlm.nih.gov/33824268/. Accessed 17 July 2023.

Ronin, Emilie, et al. “The NF-KB RELA Transcription Factor Is Critical for Regulatory T Cell Activation and Stability.” *Frontiers in Immunology*, 30 Oct. 2019, www.ncbi.nlm.nih.gov/pmc/articles/PMC6842949/.

Sasco, A J et al. “Tobacco smoking and cancer: a brief review of recent epidemiological evidence.” *Lung cancer (Amsterdam, Netherlands)* vol. 45 Suppl 2 (2004): S3-9. doi:10.1016/j.lungcan.2004.07.998

Seidel, Judith A et al. “Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations.” *Frontiers in oncology* vol. 8 86. 28 Mar. 2018, doi:10.3389/fonc.2018.00086

Sylvie Guerder 1, et al. “T-Cell Activation: Two for T.” *Current Biology*, 26 Aug. 2004, www.sciencedirect.com/science/article/pii/S0960982295001758?via%3Dihub.

TJ;, Shah NN;Fry. “Mechanisms of Resistance to Car T Cell Therapy.” *Nature Reviews. Clinical Oncology*, pubmed.ncbi.nlm.nih.gov/30837712/. Accessed 17 July 2023.

Vandana Kalia 1, et al. “Differentiation of Memory B and T Cells.” *Current Opinion in Immunology*, 2 May 2006, www.sciencedirect.com/science/article/pii/S0952791506000689.

“Why Chemotherapy Doesn’t Work for Certain Cancer Patients.” *Life Sciences*, lifesciences.byu.edu/why-chemotherapy-doesnt-work-for-certain-cancer-patients. Accessed 2 Aug. 2023.

Yui MA;Feng N;Zhang JA;Liaw CY;Rothenberg EV;Longmate JA; “Loss of T Cell Progenitor Checkpoint Control Underlies Leukemia Initiation in Rag1-Deficient Nonobese Diabetic Mice.” *Journal of Immunology (Baltimore, Md. : 1950)*, pubmed.ncbi.nlm.nih.gov/23440410/. Accessed 17 July 2023.

Zhang J;Hu Y;Yang J;Li W;Zhang M;Wang Q;Zhang L;Wei G;Tian Y;Zhao K;Chen A;Tan B;Cui J;Li D;Li Y;Qi Y;Wang D;Wu Y;Li D;Du B;Liu M;Huang H; “Non-Viral, Specifically Targeted Car-T Cells Achieve High Safety and Efficacy in B-NHL.” *Nature*, pubmed.ncbi.nlm.nih.gov/36045296/. Accessed 17 July 2023.