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Immunotherapy:
Therapy vs. Enhancement

The Ethics of Immunotherapy

Honors Interdisciplinary Thesis

Mariah Daly

April 21, 2020

"On my honor, I have not given, nor received, nor witnessed any unauthorized assistance on this work."

Signed: *Mariah Daly*

Introduction

Every day we strive to create new medical technologies, and these consistent advances are saving and improving the lives of millions. As with all new medical advancements, we must consider the practicality of the technology, as well as the ethical implications. When discussing the valid usage of new biotechnologies, an important distinction to make lies between therapy and enhancement. We can examine this issue by considering immunotherapy in the field of cancer, which is one of the fastest growing areas of research and development of technology in the medical sphere.

The battle against cancer is a long-standing struggle that has resulted in new information and the development of novel medical technologies and treatments, including the development of cellular-based therapies for the treatment of cancer (Morgan et al., 2006). Cancer is the uninhibited growth of abnormal cells in the body. Hallmark traits of cancer include the ability of cancer cells to sustain chronic and proliferative signaling, evade growth receptors, avoid immune destruction and detection, enable replicative immortality, facilitate tumor-promoting inflammation, activate invasion and metastasis, induce angiogenesis, allow for genome instability and mutation, resist cell death, and deregulate cellular energetics (Hanahan and Weinberg, 2011).

Medical advancements have taken the form of new procedures, drugs, vaccines, screening techniques, and other therapies. The ongoing battle with cancer has been a force that has ignited innovation and development of therapies. Current cancer treatments include chemotherapy, radiation, and surgical procedures to remove tumors. Chemotherapy kills cancer through cytotoxic properties (Sadozai et al., 2017). While effective, there is the risk of normal cells being impacted by cytotoxic agents. This can elicit adverse effects, and the toxicity of the symptoms have the potential to decrease patient quality of life. One key hallmark of cancer is the cells' capabilities to

avoid immune destruction and detection (Hanahan and Weinberg, 2011). A novel treatment is needed to overcome this key hurdle and contribute to the ultimate goal of curing cancer.

A popular area for medical research is in the field of immunology. Much effort is going into investigating how we can use the body's own defense mechanism, the immune system, to fight off cancer in what has been called immunotherapy. Immunotherapy is treating disease by activating or suppressing the immune system. The immune system identifies numerous threats and eliminates them to continue homeostasis, but now, directed activation/suppression allows for immune system machinery to be used in the eradication of cancer (Abbott and Ustoyev, 2019). The difficulty of such treatment arises in the fact that cancer cells are the body's own mutated cells, so the immune system often does not recognize these harmful cells as invaders.

Cancer cells differ from normal cells in the body in that they are able to fend off and override the response of the immune system if one were to be activated. Cancer cells can avoid immune detection and destruction by inactivating machineries of the immune system that have been sent out to eliminate them or by having different surface proteins compared to normal cells (Hanahan and Weinberg, 2011). The surfaces of cancer cells have tumor-associated glycopeptide antigens, exogenous substances that can provoke an immune response, that arise due to the expression of various glycan processing enzymes. This expression leads to the development of membrane structures not seen in normal cell phenotypes (Brinãs et al., 2012).

Current research aims to figure out a way to reprogram cells and bodily mechanisms to eliminate those cells that are harmful and cancerous without destroying healthy cells in the process. Methods which use the body's own mechanisms, such as immunotherapy, have shown and continue to show potential. Immunotherapy in this case is being used to specifically target cancer cells. The option to genetically modify T cells stands, but there is the question of whether or not

we *should*. As the development of this novel treatment is taking place, it is important to think of the bioethical aspects of this usage. Just because we *can* does not always mean we *should*. If we consider a healthy individual to be "normal," or use them as the baseline, then it can be agreed that cancer puts an individual below the norm of health. The end goal of immunotherapy is to selectively eradicate cancer cells without impacting normal cells. The bioethics of immunotherapy will be discussed further.

The research question to be answered is: to what extent does the modification of the body's own naturally occurring immune system mechanisms cross the line from therapy to enhancement? My position is that immunotherapy does not have the potential to do more than therapy or remedying a patient back to the norm but rather enhances the ability of the therapy to be effective. Immunotherapy cannot enhance an individual beyond the norm. Immunotherapy does not work beyond disease, even with considering the mechanisms by which CAR T cell modification occurs. The treatment cannot be abused or used beyond its intended purpose because it only accomplishes what a normal immune system response is intended to do- eradicate abnormal cells from the body. Immunotherapy is an enhancement of a therapy**. In this thesis, I will demonstrate how the mechanisms by which immunotherapy is accomplished are not solely enhancement, but rather *enhancement of a therapy*.**

This thesis will first discuss the mechanisms of the immune system, as well as the biology behind immunotherapy. An understanding about the biology of immunotherapy and CAR T Cell modification is essential for the discussion of the bioethics involved. After the interaction between the immune system and cancer is defined, I will then cover the distinction between therapy and enhancement. There is much controversy as to where the line between the two can be drawn, so I will define where this line falls in reference to immunotherapy.

Immune system

The key role of the human immune system is to protect the body from diseases that have exogenous origins. Other important functions of the immune system are to protect the body from self-attack, cancer, and faulty cells. This can be done by a set of orchestrated mechanisms that can ultimately distinguish between materials from the self as opposed to non-self. The immune system is comprised of white blood cells, as well as lymph system organs and tissues. These organs and tissues include the thymus, lymph nodes, lymph vessels, tonsils, spleen, and bone marrow (Abbott and Ustoyev, 2019). The immune system is able to protect the host from the harmful effects of foreign materials by eradicating or suppressing expression or harmful infection of the body (Swann and Smyth, 2007).

Immune responses can be divided into innate immunity and adaptive immunity. The innate immune system uses leucocytes or white blood cells called neutrophils, macrophages, and dendritic cells, which are the first to act (Janeway and Medzhitov, 2002). Phagocytes are able to bind to the pathogens, such as bacteria, proteins, viruses, fungi, and parasites, and engulf the pathogen via endocytosis. Once inside the cell, the pathogen is encased in a membrane called a phagozome. Within this phagozome, the pathogen is broken down into pieces of polypeptides. The polypeptides are then moved to the membrane surface by type two major histone compatibility proteins (MHC-II) (Cossart et al., 2000). MHC types one and two become membrane-bound proteins and essentially present a piece of polypeptide from the pathogen. Simply put, phagocytes kill a pathogen by engulfing and digesting it, breaking it into smaller pieces, and then presenting one of pieces like a medal of honor as if to say, “look what I killed.” As effective killer cells, they consume and digest invaders through phagocytosis and present the antigen to the rest of the immune system. Macrophages, dendritic cells, mast cells, neutrophils, eosinophils, and natural

killer (NK) cells have innate immune recognition and act rapidly to develop into short-term effector cells to clear the infection. These cells present polypeptides of the antigen on their MHC-II proteins, which makes them antigen presenting cells (APCs). This is a nonspecific response, as any pathogen can be bounded, engulfed, and presented (fig. 1). Even after phagocytes engulf a pathogen, some pathogens can survive inside the phagocytic cell, which makes them intracellular pathogens that can avoid immune detection and persist by hiding from the immune cells involved in the specific response. Specific immune responses are carried out by other cells in the immune system. Through adaptation and memory, these innate immunity components allow the immune system to make more specific responses and remember specific types of infection. (Nicholson, 2016).

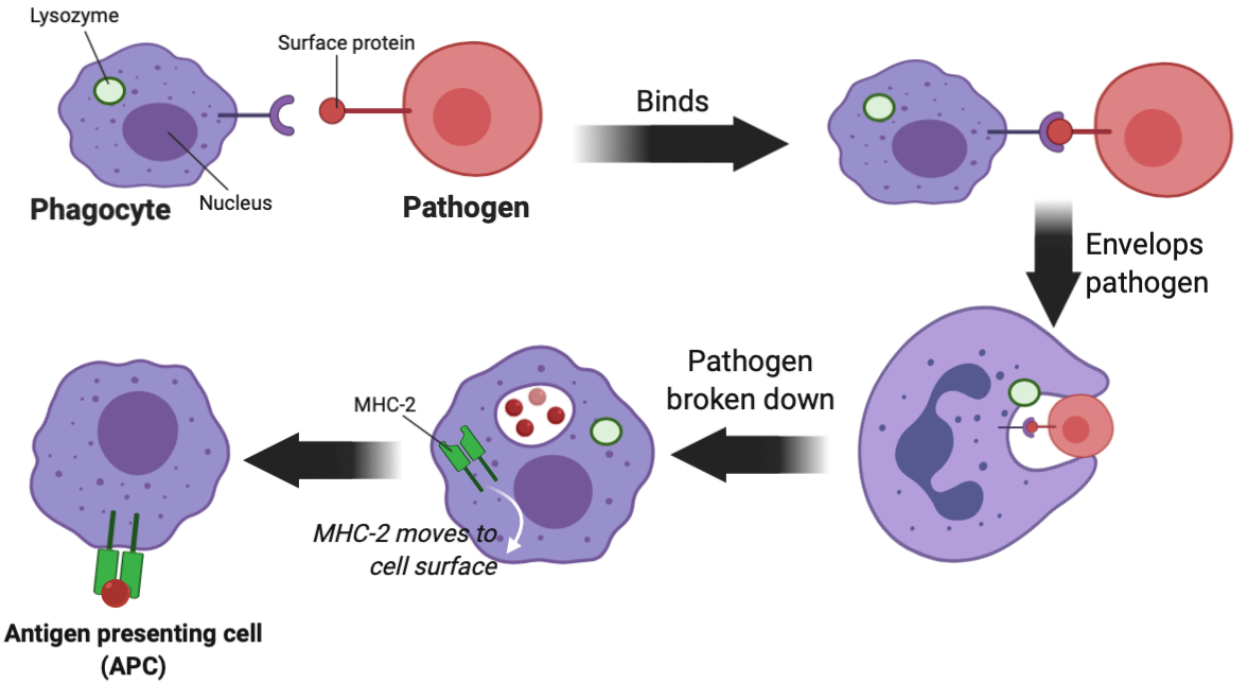


Figure 1. Phagocytes can become antigen presenting cells after ingesting pathogens. Phagocytes engulf pathogens through endocytosis and intracellularly digest the pathogens. The cell then takes a polypeptide or piece of the broken-down pathogen and presents it on its surface MHC-II receptors. This presents the antigen to the rest of the immune system.

The specific response by the adaptive immune system is characterized by the production of various immune receptors for expected confrontation with pathogens. Pathogens are rapidly evolving, so this poses challenges to the host's defense mechanisms (Josefowicz et al., 2012). Pathogens have antigens as part of their makeup, and the immune system constantly surveys for these antigens, which does not always enflame a response. There are millions of different antibodies circulating throughout our system that specifically bind when the antibody sees the corresponding antigen. There is an element of chance that occurs, because the right antibody must come in contact with the antigen to incite the immune response. Antibodies bind to a target antigen and then send signals to immune cells to elicit a response. Specific antibodies are made when the antigen is seen, and the message is relayed to activate the adaptive immune system.

Antibodies, also called immunoglobulins, are Y-shaped proteins that bind to antigens. Antigens are found on the surface of pathogens. When antibodies bind to antigens, the location where the antibody binds is called the epitope (Cossart et al., 2000) (fig. 2). Immunoglobulins have two identical heavy and light chains, which are linked by disulfide bonds. At the end of the heavy and light chains in the arm of the Y-shape lies a variable region, which is composed of approximately one hundred amino acids (fig. 3). This region enables the antibody to be specific for the antigen it binds (Roghanian and Newman, 2014). The production of antibodies depends on the APC that presents antigens from the environment and T cells or T lymphocytes that recognize the target antigen on the APC.

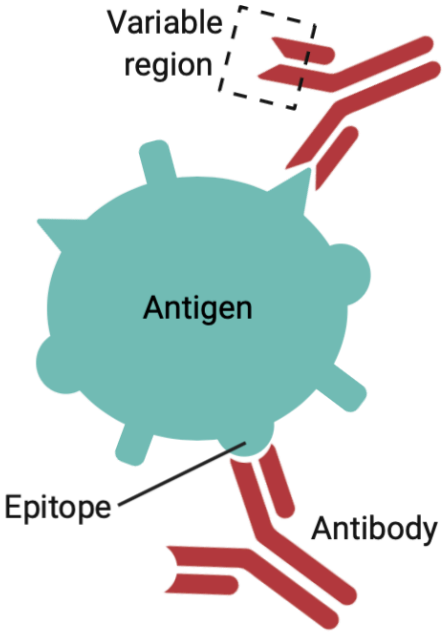


Figure 2. Variable regions on antibodies bind to antigens at a region called the epitope. Antibodies have unique variable regions that allow them to specifically bind to certain epitopes.

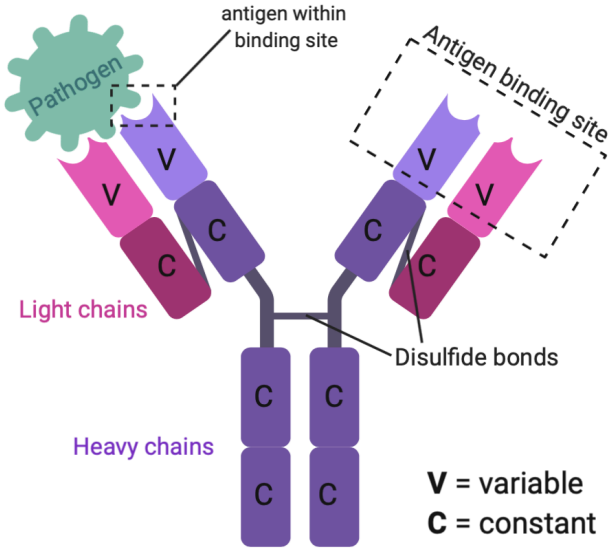


Figure 3. The structures of antibodies allow for specificity and stability. Antibodies have two identical heavy and light chains linked by disulfide bonds. The tops of the arms of the Y-shape of antibodies have variable regions, which are composed of approximately one hundred amino acids, and the order and composition of these amino acids allow for uniqueness.

The adaptive immune system can be divided into two types of lymphocytes or white blood cells: B lymphocytes and T lymphocytes. These lymphocytes interact with one another regularly to coordinate immune responses (fig. 4). B lymphocytes, or B cells, are produced in the bone marrow and are involved in humoral response (Shen et al., 2016). Humoral responses take place when pathogens are floating through the blood in the body, as opposed to being present in body cells. T lymphocytes, or T cells, are involved in cell-mediated response, meaning that there is a pathogen infecting a body cell, and the infected cell must be eliminated.

B cells have membrane bound antibodies that differ from B cell to B cell. These lymphocytes are responsible for facilitating the manufacture of antigen-specific immunoglobulin. Again, specific antibodies are not made until the antigen is seen and the message is transmitted to activate B cells, which mature to become plasma cells. Plasma cells can be thought of as specific antibody producing factories. The antibodies available at first are weak, so the antibodies that are produced by B cells mature and select in such a way as to increase the strength with which they bind the target antigen. Antibodies developed from B cells start as cell-surface receptors, called B cell receptors (BCRs), and are later released. In the humoral response, the plasma cells' specific antibodies float through the blood, which increases the chances of binding to the target pathogen. One difference from T cells is that these BCR antibodies can function in numerous places that T cells cannot (Nicholson, 2016). Antibodies circulate through the blood, within the mucus that lines organs, and within interstitial tissue fluids. This makes them available in many places, enabling a fast-immune response (Cossart et al., 2000). This humoral response is effective, but the cell-mediated response adds another layer of protection.

T cells are involved in cell-mediated response. The choice to respond to an antigen or not is made by innate immune recognition receptors when confronting pathogen-associated molecular

patterns (PAMPs) (Janeway and Medzhitov, 2002). T cells orchestrate the immune response and kill cells infected by pathogens. There are two subdivisions of T cells that can either direct the manufacture of antibodies or kill the cell presenting the antigen. Helper T cells (T_h cells) are involved in production of antibodies, and cytotoxic T cells (T_c cells) are involved in killing infected cells (fig. 4).

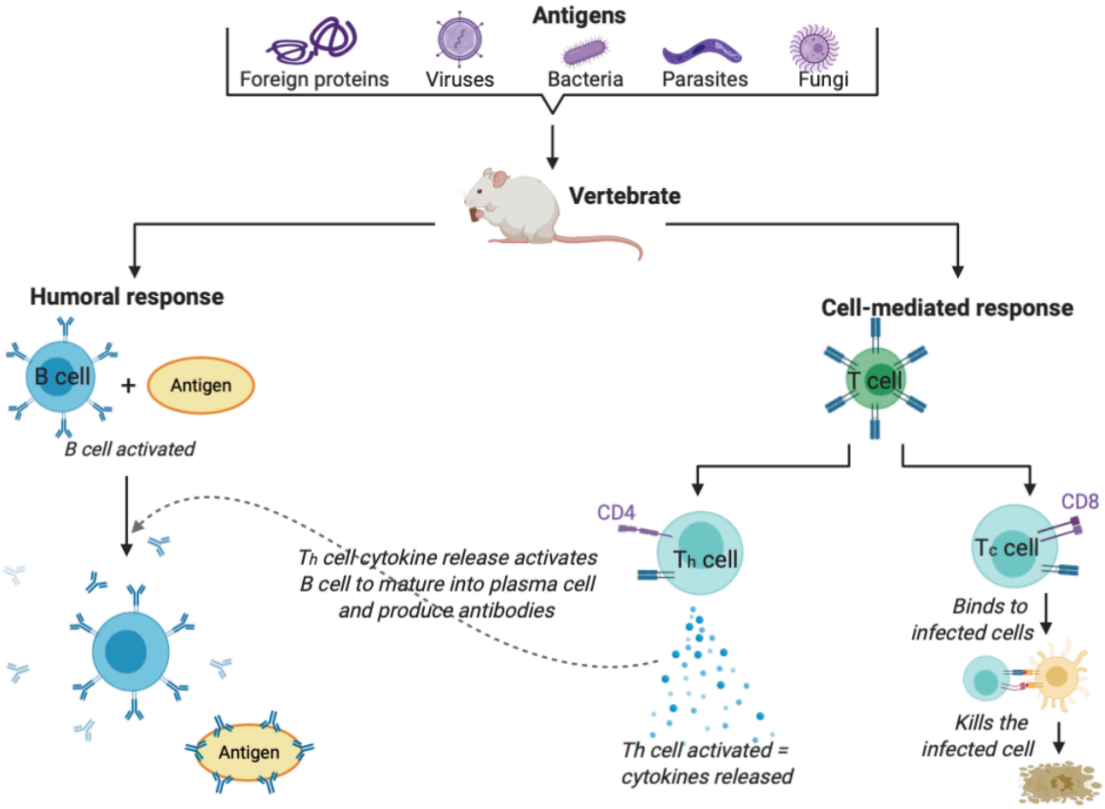


Figure 4. The adaptive immune system can be divided into a humoral response and a cell mediated response involving two types of lymphocytes or white blood cells: B lymphocytes and T lymphocytes, respectively. The interplay between these two cell types allow for a specific immune response.

T_h cells act as an alarm for the immune system. T_h cells specifically bind the presenting MCH-II of APCs, which causes activation. When activated, T_h cells differentiate into memory T_h cells and effector T_h cells. If reinfection occurs, faster and more effective counterattack takes place via recognition by memory T_h cells of certain foreign antigens, immunological remembrance of

infection, and pathogen-specific adaptor proteins (Janeway and Medzhitov, 2002). Effector T_h cells release cytokines- small signaling proteins- which stimulate B cells to differentiate into memory B cells or effector B cells.

Antigen presenting is a very specific process that is limited to immune cells. T_c cells bind to major histone compatibility type one protein (MCH-I) antigen presenting proteins (fig. 4). MHC-I are found in every nucleated cell in the body. The role of these surface proteins is to indicate if and when there is an issue occurring intracellularly. For example, an infected cell will present polypeptide segments from intracellular proteins on the MHC-I to tell the immune system that there is an issue and that cell must be eliminated. MHC-Is attract T_c cells. T_c cells bind and release perforins that make incisions in the infected cell membrane or release granzymes that trigger apoptosis from the inside out. T_h cells are also called CD4+ cells. Located on the surface of T_h cells, CD4 glycoproteins bind to MHC-II molecules. T_h cells are attracted to APCs, while T_c cells are attracted to intracellularly infected cells. T_c cells are also called CD8+ cells. Located on the surface of T_c cells, CD8 glycoproteins bind to MHC-I molecules (Cossart et al., 2000) (fig. 5).

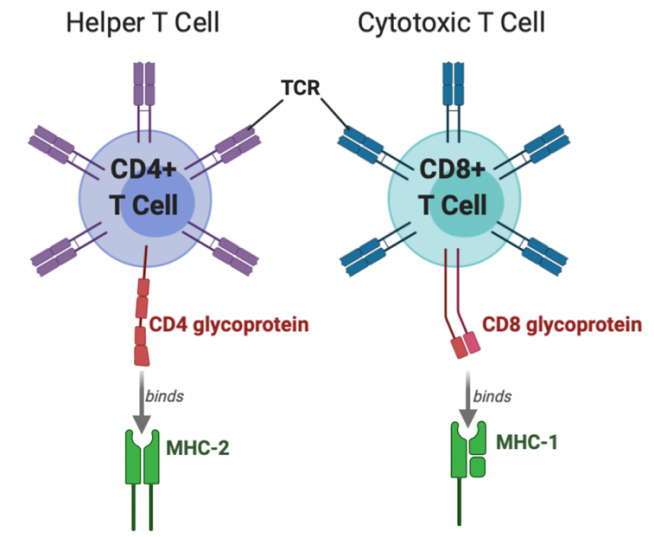


Figure 5. A comparison of CD4+ and CD8+ cells shows that CD4+ helper T cells bind to MHC-II proteins and CD8+ cytotoxic T cells bind to MHC-I proteins.

Once B cells are stimulated by binding to a specific antigen or by being stimulated by cytokines released from T_h cells, they can divide into memory B cells or effector B cells. Memory B cells express the specific antibody and remain in the body system in case of future infection due to the reappearance of the specific antigen. Effector B cells, known more commonly as plasma cells, generate thousands copies of the specific antibody (Alberts et al., 2005). These released antibodies are able to circulate, bind pathogens, group pathogens, and, by signaling, allow macrophages to find the pathogens (Cossart et al., 2000). B cells also can promote anti-tumor immunity through providing antibodies to CD4+ and CD8+ T cells (Roghanian and Newman, 2014).

The key players in the immune system have been outlined, and it appears to be a solid system. However, cancer is still able to escape all these mechanisms of immune protection. Researchers are continually attempting to find the answer as to why the body cannot locate and eradicate cancer before it proliferates into tumors.

Immunology

Immunology is the study of how the immune system physiologically functions. A brief history about major milestones in immunology helps in highlighting the developments that laid the foundation for today's immunological advancements. Edward Jenner is credited with developing the smallpox vaccine in 1796. This was seen as the first successful vaccine, and this development is now considered to have set the groundwork of immunology (Abbott and Ustoyev, 2019). It is important to note that Jenner did not come to this innovative finding on his own. As early as 430 B.C, those who survived smallpox were called upon to take care of the afflicted because it was observed that they did not contract the disease a second time. Later in the 10th century, the Chinese took this observation one step further. They proactively exposed susceptible

individuals to smallpox in order to transfer the infection with the goal of making them immune in the case of future exposure. The theme of pre-exposure to smallpox was put to the test once again between the 17th and 18th centuries. During outbreaks, blankets used by those with smallpox were gathered and used to wrap children. This was done with the intention of transmitting a milder disease form (Gross and Sepkowitz, 1998). Methods were aimed at achieving immunity through patient exposure to a mild form of smallpox as close to the real thing as possible.

Inoculation was developed soon thereafter. Inoculation is the instillation of smallpox virus into nonimmune individuals. The terms inoculation and variolation are used interchangeably. Inoculation was done by lancing a ripe pustule of someone who has had a smallpox, taking the infectious material from the infected person, and transferring it to another person through an incision in the forearm. In 1706, Reverend Cotton Mather learned about inoculation from Onesimus, a slave who had been inoculated in Africa as a child. 50 years later, in 1757, a 7-year-old boy was inoculated in Gloucester. The boy was one of thousands inoculated that year, a practice that saved thousands of lives. In fact, he developed a slight case of smallpox but was later immune to the disease. The boy's name was Edward Jenner. On May 14, 1796, Edward Jenner vaccinated a boy named James Phipps using material from a cowpox vesicle on milkmaid Sarah Nelmem. These therapies take advantage of the immune system to treat disease (Gross and Sepkowitz, 1998).

Immunotherapies use the host immune system to kill tumor cells (Abbott and Ustoyev, 2019). With the development of medical technologies and further oncological study, the immune system was found to have the ability to suppress cancer. There is a recognized interaction between cancer and the immune system. Cancer can be targeted and intentionally suppressed or treated through immunotherapies. However, many cancers are able to escape immune detection. Some

tumors have an ability to suppress immune response, which can result in tumor escape from the immune system (Sharpe and Mount, 2015). Cancer cells avoid immune detection by deactivating components of the immune system sent out to eliminate them. Cancer cells also have different surface proteins in comparison to normal cells (Hanahan and Weinberg, 2011).

The immune system protects the host from virus-induced tumors by eliminating or suppressing viral infections. DNA composition and glycoprotein structure on cells allow for a distinction between self and non-self, which happens at a biochemical level (Abbott and Ustoyev, 2019). Again, an antigen is a toxin or exogenous substance which provokes an immune response in the body. This immune response typically results in the production of antibodies. The immune system can purposely identify and eliminate tumor cells based on their expression of tumor-specific antigens or molecules (Swann and Smyth, 2007). Immunotherapy takes advantage of this aspect.

One major issue with treating cancer through immunotherapy is that cancer has origins of the self, which allows many cancer lines to escape or avoid immune suppression or eradication. Once the tumor cell is deemed as "non-self" or is seen as harmful, the immune system can respond through innate and adaptive immunity. Innate immunity includes leukocytes, mast cells, dendritic cells, and macrophages (Olszanski, 2015). When cytokines are released in response to the presence of non-self materials, innate immunity is the body's first line of defense (Abbott and Ustoyev, 2019). It exists from birth and stimulates a non-specific immune response. On the other hand, adaptive immunity is a specific immune response. The response is adapted to the stimuli or specific antigen detected. This type of immunity includes B cells, T cells, and the construction of antibodies (Olszanski, 2015). The response is developed over time through exposure to non-self materials. B cell antibody production and action of antigen-presenting cells, along with T_h cells,

stimulate cytotoxic T_c cells and the formation of immune memory (Abbott and Ustoyev, 2019). One limitation of using T cells in treatment is that the antigen needs to be a peptide. While antigens commonly have peptide components, this is not always the case (Nicholson, 2016).

The mechanisms by which immune cells use surface protein recognition to determine whether or not to elicit a response have been discussed. One way cancer cells can avoid immune response is by what they have displayed on their surface. The cell surface plasma membrane has a significant role interacting with other cells, coordinating cell movements, clinging to other cells, and being regulated by the immune system (Ruddon, 2003). Biochemical changes on malignant cell surfaces include the emergence of new surface antigens, proteoglycans, glycolipids, and mucins. Also, different interactions between cells, and between cells and their environment, can occur. In human adenocarcinoma, some tumor cells have a high buildup of fuctose-containing glycolipids. Glycoproteins may have chemical changes, as well. Surface carbohydrate antigens on cancer cells can be classified into three different groups, including epitopes only on glycolipids, epitopes only on glycoproteins, and then epitopes on both glycolipids and glycoproteins. Monoclonal antibodies have been developed to identify these carbohydrate or peptide epitopes on tumor cells. The monoclonal antibodies recognize the antigens by their altered glycosylation- the regulated secondary protein processing within cells (Ruddon, 2003).

The adaptive immune system can recognize foreign antigens, has immunological memory, and produces pathogen-specific adaptor proteins. It is also responsible for allergy, autoimmunity, and the rejection of tissue grafts (Janeway and Medzhitov, 2002). This shows that the adaptive immune system is not completely accurate 100% the time. Sometimes it functions well but is unable to recognize when it must work. Cancer cells have different surface proteins compared to normal cells, so the immune system does not have the antibodies available to flag the cancer cell(s)

for elimination. In order to enable the immune system to fulfill its role of ridding the body of nonhealthy cells, extra measures must be taken to assist the immune system's already existing abilities.

Immunotherapy

Immunotherapy is used to enhance and/or restore the immune system's ability to fight off disease. The overall goal of this treatment is to eliminate cancer cells without producing autoimmune inflammatory responses, which typically result in therapeutic limitations (Abbott and Ustoyev, 2019). Immunotherapy treatments approach cancer cell in hopes of triggering tumor cell death, modifying the tumor microenvironment, decreasing tolerogenic mechanisms, and stimulating immune responses against the cancer (Swann and Smyth, 2007).

Dr. William Coley, considered the "Father of Immunotherapy," was a surgeon in New York who began to work on finding methods other than surgery to treat sarcoma because he witnessed the painful passing of an 18-year-old patient in 1891. He published findings in 1893 stating that patients treated with cultures of the bacterium *Streptococcus pyogenes* experienced tumor regression (Sadozai et al., 2017). This treatment was coined as the injection "Coley's mixed toxin." We now know that the bacterial infection helped fight cancer by inducing a nonspecific immune response. The immune system was activated to fight off the bacterial infection, but the extra-active immune system was then able to detect other cells that were not healthy (i.e. cancer cells). In 1957, Macfarlane Burnet and Lewis Thomas proposed the theory of cancer immunosurveillance. Under this theory, lymphocytes were responsible for recognizing and eradicating cells that have experienced mutations and vary from normal host cells (Abbott and Ustoyev, 2019). Thomas and Burnet's theory stated that lymphocytes played a protective role, like a guard, by continuous identification of malignant cells. Under this theory, bacterial infection

helped reduce tumor growth by ramping up the immune system. Again, as the immune system works to combat the bacterial infection, the vamped immune system now has more mechanisms out detecting and searching for abnormal and unhealthy cells. This increases the chances of deviant cells being found and eradicated.

More sophisticated and focused methods of immunotherapy are being developed today. Past immunotherapy methods included the following: toxins and tumor necrosis factors (1930s-1940s), oncolytic vaccines that attempted to train body to protect itself against its own abnormal/damaged cells (1920s), and interleukin 2 treatments (1990s). Some of those therapies are still being looked at, but more current treatments include antibody therapies (1970-today), checkpoint inhibitors that release a natural brake on your immune system to allow T cells to attack tumors (1980s-today), oncolytic viruses (today), and chimeric antigen receptor (CAR) T cell therapy (2000s-today) (Abbott and Ustoyev, 2019). One especially interesting therapy gaining traction is adoptive cell therapy (ACT). In ACT,T cells are isolated from a blood sample, and *ex vivo* manipulated cells are transferred directly back to patients to mediate antitumor immunity (fig. 6) (Sadozai et al., 2017).

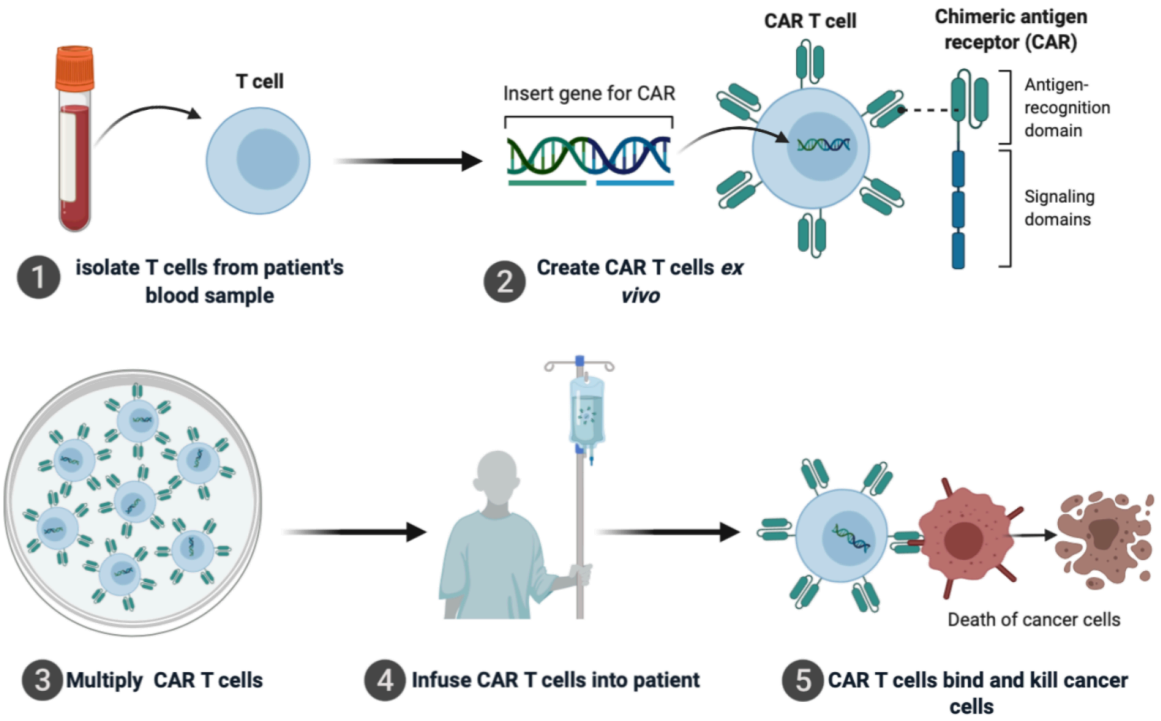


Figure 6. The process of adoptive T cell therapy involves the extraction of T cells from blood samples, *ex vivo* manipulation, amplification, and an autologous transfusion back into the patient. The *ex vivo* manipulation is the addition of CAR to T cells.

T cells can be genetically engineered to express T cell receptors (TCRs) that recognize tumor antigens or chimeric antigen receptors (CARs) built of antibody domains. These cells then express antibody binding domains on their surface that present antigen specificities that are major histocompatibility complex (MHC)–independent (Kalos et al., 2011). A TCR complex is formed from the arrangement of six different protein chains in four pairs (Nicholson, 2016). CAR T cell binding is usually done by the inclusion of a single chain antibody variable fragment (scFv) (Maus et al., 2013). These receptors are fused to T cell signaling domains (fig. 7) (Muenst et al., 2016). TCRs specific to tumor antigens can be exploited in therapeutic methods for cancer (Li et al., 2019). Unlike TCRs, CARs recognize surface antigens on target cells through the scFv. CAR T cells can then provoke cytotoxicity on target cells in an MHC-independent manner, which extends the use of genetically engineered T cells (Li et al., 2019). A CAR can be developed to be specific

to a type of cancer. For a particular cancer, the surface proteins of malignant cells must be discovered, and the CAR must be developed to be specific for those epitopes. Once the CAR can successfully target the malignant cells, it must then be able to initiate strong enough cytotoxic abilities to eliminate the cell. Also, CAR T cells have the potential to have long-term persistence by replicating *in vivo*, and this could result in continued tumor control and remove the necessity of repeated infusions of antibodies (Kalos et al., 2011). Examples of cancers that are successfully being treated include melanoma, lung cancer, kidney cancer, bladder cancer, and lymphoma. This new procedure has great potential in the war against cancer.

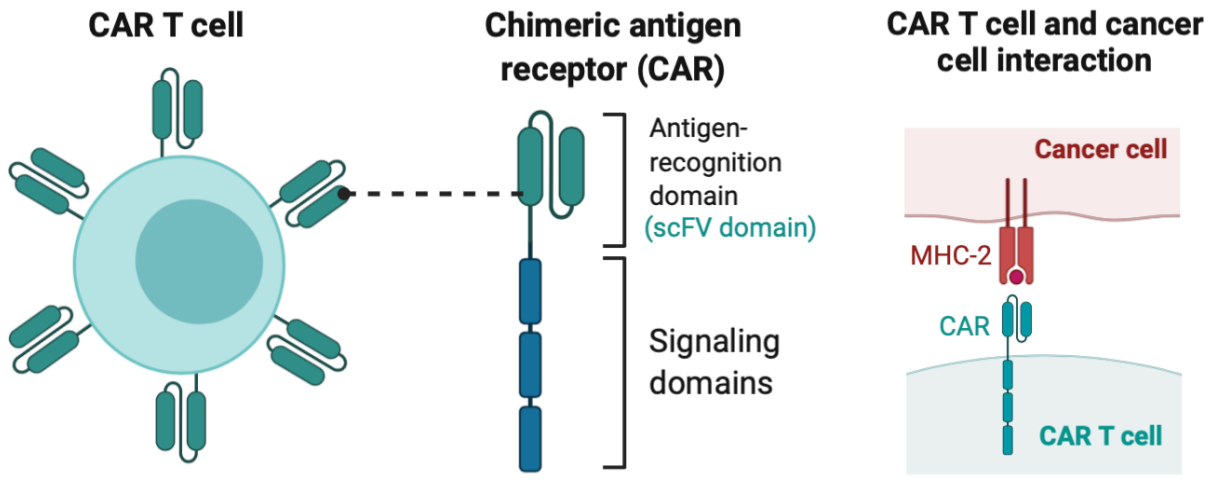


Figure 7. CAR T cells have an antigen recognition domain that is fused to T cell signaling domains (center). CAR recognizes surface antigens on target cells through the scFv domain (right).

The Role of Ethics in Immunotherapy

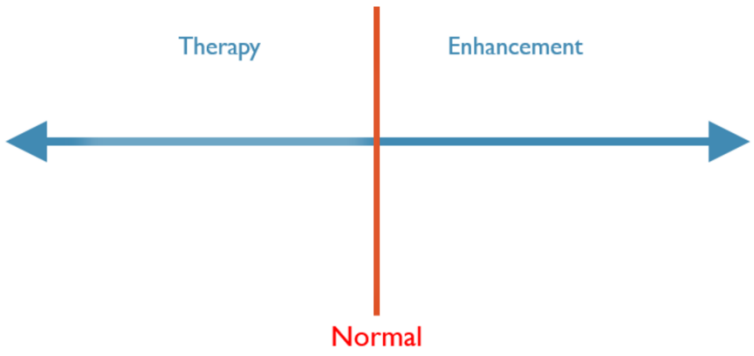
As with all new medical advancements, we must consider the practicality of the technology, as well as the ethical implications. An important distinction to make when discussing the valid usage of new biotechnologies is between therapy and enhancement. Therapy and enhancement fall on a spectrum that lacks a fine line that separates what falls under the two terms

(fig. 8A). Where the line between therapy and enhancement is drawn is an important distinction. This difference is important when it comes to insurance, government, and medical obligation.

This argument focuses on how this broad spectrum applies to the field of immunotherapy. Immunotherapy improves the previously existing abilities of the human immune system, and it is for antigen-producing diseases. The key ethical implication of concern is if this treatment has the potential to increase the human immune system and make humans invincible to disease, and consequently, creates a new "species" of humans- those who get sick and those who do not. This fear comes with the risk of increasing the anxiety of discrimination and potential eugenics. I argue that while enhancement is not inherently bad, the means by which immunotherapy is achieved are not merely enhancement, but rather, *enhancement of a therapy*.

While therapy involves remedying a problem back to the normal state, enhancement involves improving something that is not a problem to a level above the normal state (fig. 8B). This state can be considered better than well (Elliott, 2003). First and foremost, enhancement is not a bad thing. Enhancement means to give a person ability beyond the current normal. Immunotherapy is the strengthening or enhancement of the immune system's already existing abilities, but it makes these abilities better. Therefore, immunotherapy is not solely enhancement, but rather enhancement *of* a therapy.

A)



B)

Figure 8. The separation between therapy and enhancement is not as simple as a dividing line. A) Therapy and enhancement are found along a spectrum without clear boundaries. B) Therapy and enhancement are ideally separated by a line that represents what the normal state is considered.

Immunotherapy is used for antigen producing diseases. This treatment does not have the potential to create "super humans," a fear of many of those opposed to biomedical enhancements. By enhancing the therapeutic abilities of the immune system, immunotherapy increases health in the ill, but cannot move a well or healthy person to be *better than well* (Elliott, 2003). Definitions must be put in place to discuss such distinctions successfully, but it is important to note that there are even disagreements on definitions alone. It is so difficult to establish boundaries for some of these grey terms, but definitions must be set in order to effectively argue. In this argument, the following definitions will be upheld.

Definitions

Immunotherapy can be viewed either as a treatment to restore a patient to the norm, or as an enhancement beyond the natural norm. In the effort to make this distinction, the following questions arise: What is considered healthy? What is considered the norm of human health? What is the end we are striving for? If there is an end to where humans finally reach the perfected final form, does that require that the environment be constant? How do we know what traits are needed

for a final constant environment that we know nothing about? For the argument to stand, a series of definitions need to be established.

This paper will follow certain definitions. The Compact Oxford English Dictionary defines health as the state of being free of illness or injury and a person's mental or physical condition. Also, the Compact Oxford English Dictionary defines normal as "the usual, average, or typical state or condition." The term "normal," as in normal health, will be defined as the average human condition. The average human condition was chosen as the norm, and normal health can be assumed as the human state of being free of illness or injury. In this claim, there is the assumption that we can identify the healthy people in order to find out what is "typical or normal" for them. It may be possible that the true statistical norm may reveal that most people are rather unhealthy, which brings the average down to an unhealthier state. Even though the statistical norm is being taken as normative, actually obtaining the data proves to be problematic. The average in this case is more theoretical in the sense that "normal" can be thought of as the ideal middle ground. Normal falls in the middle of two extremes: one extreme being invincible individuals who never get sick and the other extreme being those who get sick and have zero ability to recover and fend off illness. Normal health looks like an individual that can get sick but is able to effectively fight sickness through naturally given immune system mechanisms.

The norm or normal state cannot be defined as one's individual level of normal, because individuals have varying levels. One person may have a naturally strong immune system while another person may have a naturally weak immune system. If we say normal is what is natural, then we allow the person to keep their relatively weak immune system instead of helping them get stronger. It is challenging to establish boundaries for this term, but normal must be defined as the

average human existence- average health. The normal human level in reference to health is the human body in a cancer free state and includes a functioning immune system.

Disorders and diseases for the sake of this paper are considered the conditions and/or illnesses by which the patient's ability to function is well below that of a typical person. The terms "treatment" and "therapy" can be used interchangeably from here on out to mean any substance, procedure, or other intervention required to correct a disorder or restore a patient to health. An enhancement is a procedure or intervention that aims to improve a person's physical or mental health beyond the level of functioning that is typical or normal of a healthy person, where a healthy person has the absence of injury, dysfunction, disease, or disorder.

Therapies and enhancements have the common goal of making a person well or better, but the endpoints of these two distinctions vary. Therapies improve conditions up to the norm, whereas enhancements improve conditions beyond what is normal. In regard to immunotherapy, the end we are striving for is a cancer free human. In order to achieve a cancer free human species, the environment is required to be constant. The environment in this case is the human body. As evolution takes its course, the human body too will adapt. If the species adapts to have a better immune system that can detect and eradicate cancer cells, then immunotherapy may become irrelevant. The present argument will be placed in the realm of the current human condition where the immune system cannot yet detect proliferating-cancer cells on its own. If the environment changes, meaning if the human body evolves to be less cancer-prone overall, the argument that immunotherapy is an *enhancement of a therapy* may not hold. The future definition of enhancement and therapy in regard to immunotherapy is dependent upon future details that cannot be obtained or determined. The argument will need to be reevaluated when there is a shift in the

environment. However, just because this argument is contingent on the current environment alone and has the potential to be altered is not enough reason to disregard the argument at hand.

Therapy and enhancement fall on a spectrum where there is not a fine line that separates what corresponds to each term (fig. 8A). Where the mark between therapy and enhancement is drawn is an important distinction when it comes to insurance, government, and medical obligation. Insurance companies may not cover procedures that are deemed as enhancements, and thus not medically necessary. Medical necessity is another term that must be defined, yet a precise definition cannot be pinpointed. I have found that medical necessity is a loosely defined and generally misunderstood concept that is very often applied to insurance and medical policy. It is open to interpretation. For this argument, assume medically necessary to mean a procedure or treatment conducted to diagnose, prevent, avoid the worsening of, or cure the conditions in the individual that endanger life, cause pain, suffering, physical deformity or malfunction, threaten to cause handicap, or result in illness (Rosenbaum et al., 2003).

This set of terms is reliant on the establishment of the other terms within the group. There is an intricate interplay of all of these concepts. For example, the definitions of therapy and enhancement require that a normal level be established to which we can refer. “Medically necessary” requires therapy to be defined. Therapy and enhancement in the realm of health fall on a spectrum that relies on a line to be established. That line must be established in reference to the current state of the environment or human body, resources available, general level of the human normal state, and individual ability.

Again, enhancement and therapy fall on a spectrum. There truly is not a natural stopping point when navigating through hypotheticals. For example, it can be agreed that replacing a baseball pitcher’s arm with a stronger, futuristic, robotic, prosthetic arm that allows them to pitch

115 miles per hour would be seen as an enhancement, pushing human capability beyond the norm. However, for a person who lost the arm to an accident, it can be agreed that replacing the limb with a non-bionic prosthetic is therapeutic as it attempts to return their normal ability. Continuing with the arm strength example, can lifting weights count as an enhancement? Lifting weights and working out increases the individual's level of "normal strength." That being said, can we go so far as to say that providing your children with a healthy nutritious diet over junk food is an enhancement as it increases the children's health? Our society and we as individuals strive every day to improve, become better, and be the best versions of ourselves. The therapy versus enhancement debate has been around for some time yet still has no definitive answer. As the spectrum has no distinct separations, one can get lost in the broad range that hypotheticals can lead such thoughts.

Some consider enhancements as interventions that will affect future generations. Enhancement is introducing favorable characteristics that affect the genetics of a life form in the future. Within this same perspective, therapeutics or treatments are interventions that only affect the individual, so the adjustment dies with the individual and has no effect on future generations. However, not all enhancements can be inherited. Even if this were the hallmark of an enhancement, this is not the case as germline cell manipulation, a mutation that can be passed on to parents and offspring, is not a possibility in immunotherapy.

My argument focuses on this wide spectrum as it applies to the specific field of immunotherapy. Immunotherapy increases the already existing abilities of the human immune system, and it is for antigen-producing diseases. Some fear that treatment could have the potential to increase the human immune system and make humans invincible to disease, creating new "species" of humans- those who contract diseases and those who do not. This fear comes with the

concerns of inequity and impending eugenics. This should not be a worry as immunotherapy is currently done in response to an already existing, antigen-producing illness.

Immunotherapy improves health in the ill by bringing already existing abilities of the immune system back to normal, effective levels. The immune system itself can be considered therapy. It acts to rid the body of illness and foreign invaders. Immunotherapy allows the immune system to recognize harmful cancer cells. Enhancement occurs outside the body when T cells are reprogrammed to be CAR T cells. The enhancement occurring externally is the manipulation of the autologous T cells. This allogenic improvement, meaning "derived from a different source," has caused concern about the ethical implications of the procedure. The concern is that that which enacts via autologous routes can be considered therapy, but an allogeneic mechanism, such as the synthetic CAR, might be considered enhancement. This is enhancing the T cells beyond what is naturally humanly possible.

However, allogenic enhancement mechanisms cannot be considered bad. Mothers transfer antibodies to their newborn babies via breastfeeding. The antibodies in the breastmilk are allogenic to the baby but protect the baby by increasing the ability of its immune system to fight off these like-antibody-producing diseases. The antibodies are good because they protect the baby from disease. Epidemiological data indicates that the risk of dying from diarrhea could be reduced about 14–24 times in breast-fed children compared to those who are not (Brandtzaeg, 2003). There are a multitude of other pathogens these breastmilk antibodies defend against. The same argument can be applied using vaccines as an example. It can be agreed by many that vaccines are "good." Vaccines supply the immune system a safe amount of virus or bacteria from which it can begin to create antibodies. Vaccines essentially teach the immune system how to defend against a specific pathogen. Both breastmilk and vaccines make the immune system better at fulfilling existent

functions. Therefore, immunotherapy is in the same moral class as vaccinations and breastmilk-transferred antibodies. In immunotherapy, CAR T cells improve the immune system. In other words, this enhancement increases the ability of the body's own internal therapeutic mechanisms. Thus, immunotherapy is an *enhancement of a therapy.*

Basic Ethics in Cancer Immunotherapy

Before diving further into the medical ethics of immunotherapy, the basis of an ethical theory must be established. An ethical theory provides a moral set of standards to be used when considering what is morally right and what is morally wrong (Mappes and Zembaty, 1991). There are different lenses of theory through which immunotherapy can be processed. Before medical ethics can be discussed, I want to look at immunotherapy through deontological and utilitarian perspectives.

Teleological ethical theories claim the rightness and wrongness of human action are solely a function of the goodness and the badness of the consequences that result directly or indirectly from that action. Utilitarianism is a teleological theory. Teleological theory is often compared with deontological theory, which is when the rightness or wrongness of human action is <u>not</u> wholly a function of the goodness or badness of consequences that result directly or indirectly from that action (Mappes and Zembaty, 1991).

Two of the most notable utilitarians are Jeremy Bentham (1748-1832) and John Stuart Mill (1806-1873). Under the umbrella term "utilitarianism" are act-utilitarianism and rule-utilitarianism. Act-utilitarianism states that a person ought to act so as to produce the greatest amount of good over evil for everyone concerned. Actions should be done in the interest of everyone involved and everyone affected. When compared to the alternatives, an act is morally right if its' likely consequences generate the greatest balance of good over evil. The net balance of

good over evil is called utility. Act-utilitarianism focuses on maximizing utility (Mappes and Zembaty, 1991). By administering immunotherapy treatments, the physician is increasing the patient's wellness, which tilts the balance towards good over evil. Good health is a consequence that holds intrinsic value- it is good in and of itself.

Hedonistic theory is interpreted by Bentham and Mill in different ways. Bentham claims that only pleasure has intrinsic value, and pain has intrinsic disvalue, whereas Mill states that only happiness has intrinsic value, and unhappiness has intrinsic disvalue (Mappes and Zembaty, 1991). Immunotherapy is intrinsically good under both of these hedonistic definitions as it allows for the individual to achieve more pleasure and happiness when their health is no longer the root of pain or suffering.

While act-utilitarians perform actions to maximize utility through individual actions, rule-utilitarians perform actions as long as they follow the rule that if generally followed, would produce the greatest amount of good over evil for everyone considered (Mappes and Zembaty, 1991). This is essentially an indirect application of the principle of utility. In rule utilitarianism, a moral code is established in reference to the principle of utility. Once the moral code is established, a set of valid moral rules is created by determining which rules would produce the greatest balance of good over evil if generally followed. All possible alternatives are weighed, but the actions are decided to be morally right if they are in accord with those rules that generally produce the most good.

Criticisms of utilitarian ethics include the following questions: how can one possibly predict all the consequences of one's actions? How do I assign weights to various kinds of human satisfaction? Utilitarians act in a way to achieve the most favorable outcome, but the reality is that not all possibilities can be known (Mappes and Zembaty, 1991). For example, we may expect for

immunotherapy to heal a patient with cancer, but the outcome may unintentionally trigger fever, weakness, nausea, vomiting, dizziness, body aches, and blood pressure issues as side effects. Another criticism of utilitarianism is that there is a lack of respect for individual rights. It is commonly held that patients have a right to treatment, but utilitarians would support that a patient may not have the right to treatment if not giving them treatment would benefit others. If not giving the patient with cancer the immunotherapy treatments would free up medications and resources for others, utilitarians would subscribe to the decision to withhold the treatment.

Through rule-utilitarianism, morally significant relationships can be established. A morally significant relationship essentially involves one party having authority over another, such as patient-physician, teacher-student, and parent-child relationships. The relationship of interest here is that between the physician and the patient. Physicians have a special responsibility to act in the interest of their patients. This is a rule that when generally followed produces the greatest amount of good or maximizes utility. Doing what is best for the patient may be immunotherapy. The decision to administer the treatment to a patient with cancer seems to be rationally in agreement with our ordinary moral thinking (Mappes and Zembaty, 1991). Act-utilitarians and rule-utilitarians may see the same situation yet view the decision to administer immunotherapy as morally wrong or morally right depending on their subscription to utilitarianism. Multiple perspectives must be utilized when evaluating such complex issues.

The contrasting philosophical framework through which immunotherapy will be evaluated is Kantian Deontology. Immanuel Kant (1724-1804) refers to the Principle of Utility as wavering and uncertain (Mappes and Zembaty, 1991). Kant argues that there is a single, fundamental principle that is the basis of all moral obligation. Kant argues that the basis is not the Principle of Utility, but rather, the Categorical Imperative. The Categorical Imperative has two formulations.

The first formulation states, “act only on that maxim through which you can at the same time will that it should become universal law” (Mappes and Zembaty, 1991). This shares *some* connection to rule-utilitarianism in so far that the rule must be universally applicable. Where the categorical imperative diverges is that the motivation for the action is the moral guide (the moral authority based on fundamental truths that drives decisions), as opposed to the consequences of the action. Immunotherapy under the first formulation of the categorical imperative can be deemed as *good*. The motivation behind administering immunotherapy is to remedy a sick patient back to good health. The second formulation: “act in such a way that you always treat humanity, whether in your own person in person of any other, never simply as a means, but always at the same time as an end” essentially requires that there be respect for persons when acting (Mappes and Zembaty, 1991). Every person has an inherent dignity. By virtue of their humanity, we must treat individuals with the utmost respect.

Kantian deontology holds that every person has a duty to self and a duty to others. There are two types of duties, perfect duties and imperfect duties. These two types of duties can be applied to the self and to others. Of interest for this argument are the perfect duties to self, imperfect duties to self, and perfect duties to others. Perfect duties to the self are unwavering duties, like avoiding drunkenness, respecting one’s self, and not committing suicide. The imperfect duties to self require that we pursue certain goals, like the welfare of others. Perfect duties to others include rules like do not lie, do not kill, keep promises made, etc. In reference to immunotherapy, the perfect duty to the self is to avoid self-destructive harm, like disease-causing agents. The imperfect duty to the self is to pursue wellness, and the perfect duty to others includes the obligation to do no harm to others. These duties are much more complex than these terms let on. Kantian deontology is not the only ethical lens through which to examine immunotherapy. There are pieces

to the complex topic of immunotherapy that follow utilitarian frameworks and other aspects that follow deontological frameworks.

A third way of looking at this procedure is by examining the situation through the lens of prima facie duties. Maximizing utility conflicts with our belief that we have clear ties of obligation to certain people. W. D. Ross's theory of prima facie duties reveals that neither the Kantian nor the utilitarian can provide an explanation of conflict-of-duty circumstances that corresponds with what he calls "ordinary moral consciousness" (Mappes and Zembaty, 1991). Prima facie in Latin translates to mean "at first glance." These duties are conditional duties, meaning that the duty at one moment in a certain situation depends and may vary with the circumstances. Prima facie duties are conditional duties. The actual duty in the moment is the one takes precedence among the duties present.

Consider the following hypothetical situation. You are on a walk, and you witness an elderly person collapse with what appears to be a heart attack. You do not have a phone and must travel a few blocks to get/call help. However, there is a bicycle nearby, and no one but you and the collapsed elderly person is around. The bicycle does not belong to you or the elderly person, and no one will see you take it. Many duties seem to push, "take the bicycle and go call for help," but other duties equally scream "taking the bike is wrong." The duties to not lie and to not harm appear within the same setting. The *actual* duty in this case is to take the bike and get help. This sense of morality is closest to what many of us act under, ordinary moral consciousness. Most would agree that you did the *right* thing.

The fundamental principle of morality is neither the Principle of Utility nor the Categorical Imperative. There are many frameworks that can come into play when trying to make sense of as

complex and intricate a situation as immunotherapy. Prima facie duties have no unitary basis and emerge from relationships and situations that are morally significant (Mappes and Zembaty, 1991).

Medical Ethics in Cancer Immunotherapy

The ethical theories mentioned thus far have been used to construct more specific and easily applicable ethical theories like that of Beauchamp and Childress's four pillars of medical ethics. The four pillars are: beneficence, nonmaleficence, respect of autonomy, and justice. In simple terms, beneficence means to do good, and nonmaleficence means to do no harm. The respect of autonomy means that the patient is aware of all the risks and benefits of the procedure, and their decision-making process is free of coercion. Justice means that there must be equitable distribution treatments among all groups in society (Beauchamp and Childress, 2001). The medical ethics principles of beneficence and nonmaleficence, to do good and do no harm, fall under utilitarianism. The third and fourth principles of medical ethics, respecting autonomy and justice, would align under the Kantian deontological theory. The respect for individual life and equal access to all are rules or maxims that when generally upheld are what is right.

When these medical ethics principles are applied to immunology, prima facie duties take over in each case because all options, consequences, and motivations must be kept in mind when making decisions. In accordance with the circumstances of each case, the prima facie duties of nonmaleficence, beneficence, respect for patient autonomy, and justice hold great weight (Mappes and Zembaty, 1991). There are touches of utilitarianism and deontological theory wrapped into each of the four medical ethics principles. Immunology will be evaluated under each of the four medical ethics principles to show why immunotherapy, an *enhancement of a therapy*, is inherently good.

1. **Beneficence**

It can be agreed that the principle of beneficence, to do good, ought to be an essential requirement when evaluating if a biotechnology should be developed and used in treatment. Under the principle of beneficence, one ought to prevent evil or harm, remove that which causes evil or harm, and do and promote that which is good (Beauchamp and Childress, 2001). This principle states that the duty of an individual is to help others further their important and legitimate interests (Iserson, 1999). Therefore, physicians *ought* to administer immunotherapy. By administering immunotherapy, the doctor is helping the patient achieve more happiness or pleasure. Under utilitarianism, maximizing utility is accomplished when the treatment is given and is successful. Immunotherapy increases the health of the ill and allows them to further their important and legitimate interests.

Immunotherapy can be considered an ethically good treatment. This is a worthwhile work and worth the resources. Physicians are scientists, and scientists have a moral obligation to conduct experiments that have beneficial results (Flynn, 1997). Because this treatment involves only remedying the patient back to normal, baseline levels and not enhancing beyond normal human capabilities, it can be accepted that allowing an ill individual to have what others naturally have access to – health – is a beneficial result. Again, immunotherapy is only trying to remedy back to normal baseline levels, not enhance beyond normal human capabilities, where the baseline is the pre-cancer human body.

The motivation behind the research and trials of immunotherapy is to develop a treatment that can eradicate cancer cells while not interfering with normal body cells. According to John Stuart Mill, actions are right in proportion as they tend to promote happiness and wrong as they tend to produce the reverse of happiness. According to Immanuel Kant, moral force must be driven by obligation in a deontological categorical imperative. Simply put, immunotherapy is done for

the greater good *and* is being done for the right reasons. Beneficence holds weight in both utilitarian and deontological theory.

According to Beauchamp and Childress, the principle of beneficence also supports a number of more specific rules. These specific rules include protecting and defending the rights of others, preventing harm from occurring to others, removing conditions that will cause harm to others, helping persons with disabilities, and rescuing persons in danger (Beauchamp and Childress, 2001). Immunotherapy prevents persons from getting more ill due to cancer, removes the cancer, helps persons with lower levels of health, and essentially rescues cancer patients and saves their lives.

The term beneficence is often understood in reference to acts of kindness or generosity that go beyond obligation. However, beneficence in medical ethics is assumed in a stronger sense as an obligation. The Belmont Report, a leading work concerning ethics in healthcare research, has defined beneficent actions to mean two things: do not harm and do maximize possible benefits and minimize possible harms (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978).

The principle of beneficence finds its place in all realms of medical ethics. At the root of medical ethics, prima facie duty appears to be the main way of making decisions involved in patients' medical care. In fact, the Hippocratic Oath requires physicians to best benefit their patients according to their best judgment (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978). The prima facie duties that exert priority over others always have the principal of beneficence at their core.

2. Nonmaleficence

The second pillar of medical ethics according to Beauchamp and Childress is the principle of nonmaleficence. This principle essentially means do no harm. The Hippocratic maxim "do no harm" has long been a fundamental value of medical ethics (Iserson, 1999). The charge "bring benefit and do no harm" expresses the principles of nonmaleficence and beneficence (Beauchamp and Childress, 2001). This principle is agreeable and palatable, meaning that is easily accepted. We ought to avoid bringing harm to others where possible. Utilitarian theory holds that one should maximize utility. In order to maximize utility, one must do that which produces the most good or pleasure and produces the least evil or displeasure. The intention of immunotherapy is to do good and reduce harm. Even though immunotherapy is intended to do good, there are risks involved with the treatment. The motivation behind the therapy is good, but a favorable outcome cannot be guaranteed quite yet. Some consequences of administering immunotherapy are possible severe allergic reaction, fever, nausea, other unfavorable symptoms, and even death. Further research is needed in order to guarantee this favorable outcome and minimize unfavorable outcomes.

Claude Bernard extended nonmaleficence to the realm of research, saying "one should not injure one person regardless of the benefits that might come to others" (Iserson, 1999). The intention of research, to bring about useful knowledge to benefit others, is good and does not intend to do harm to the one. With more research and development, immunotherapy will become safer and more efficient. The concept of immunotherapy does not violate the principle of nonmaleficence because it does not harm the person but rather increases the level of health in the individual.

It is important to discuss the risks of immunotherapy versus the rewards of successful administration. One may argue that the side effects will make the person worse than the baseline condition, with the baseline condition being currently inflicted by cancer. Severe allergic reactions

may ensue. These reactions can be life threatening. However, I hold that immunotherapy is in correspondence with the principle of nonmaleficence because the reward, achieving wellness over life threatening disease, far outweighs risks that may not even take place. One can get lost in the hypotheticals of it all, so we will remain here in the situation where immunotherapy is successful in achieving its goal of eradicating cancer and leaving healthy cells unscathed.

According Beauchamp and Childress, the principle of nonmaleficence also supports more specific rules. These specific rules include do not kill, do not cause pain or suffering, do not incapacitate, do not cause offense, and do not deprive others of the goods of life (Beauchamp and Childress, 2001). Immunotherapy follows these specific rules as it serves not to kill but rather to prevent death, not to cause pain nor suffering but rather to eliminate suffering, not to incapacitate but to rather rehabilitate, and not to deprive others of the goods of life but rather allow them another chance to strive for the goods of life.

The principles of beneficence and nonmaleficence are often tied into one principle: do good -- which is assuming that doing good also implies that you are doing no harm. The Belmont report combines beneficence and nonmaleficence into one pillar of beneficence (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978). This reiterates that these principles are fundamental in decision-making regarding the development of treatment and the administration and regulation of such treatments. The evolution of mankind can be attributed to a series of human decisions about generations to come (Mappes and Zembaty, 1991). When biotechnologies are created, it is imperative to discuss the ethical implications of what that therapy means for current human generations and those to come in the early stages of the treatment's development, such as in current immunotherapy tactics. The elimination of

suffering and disease is justification enough for the continued development and usage of those technologies that accomplish beneficence and nonmaleficence in the realm of medicine.

3. Respect autonomy

The Hippocratic Oath clearly states that a physician will benefit the ill and do no harm but actually says little about how to go about patients' rights (Mappes and Zembaty, 1991). Even though it is not explicitly stated in one of the most fundamental belief sets in current medicine, it can be agreed that there ought to be respect for life and respect for individual rights. There must be respect for persons and respect of autonomy. Respect for persons includes the ethical convictions that individuals must be treated as autonomous agents and the persons who have lessened autonomy are to be protected. An autonomous person is a person who can deliberate about personal pursuits and act under the direction of such consideration, meaning they can think and act clearly in accordance with those thoughts (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978). Personal autonomy is when one can act under self-governance, where thought and action are free of interference by others and external limitations. These limitations may be inadequate understanding or lack of information that subvert meaningful decisions (Beauchamp and Childress, 2001). Largely, patients must be respected as individuals simply due to their humanity. Individuals are treated in an ethical manner by respecting their decisions, by protecting them from harm, and by making efforts to assure their well-being (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978). They must know all risks and benefits of the treatment options, and the decision-making process must be free of coercion. Autonomy also includes the following specific rules: tell the truth, respect the privacy of others, protect confidential information, obtain

(informed) consent for interventions with patients, and when asked, help others make important decisions free of personal bias (Beauchamp and Childress, 2001).

The principle of respect for autonomy is especially important in immunotherapy because of how relatively new this treatment set is and the current status of where the procedure lies. Because immunotherapy is in clinical trials, experimentation is currently ongoing. The ethics behind informed consent and human experimentation will be discussed in the realm of immunotherapy. The industry needs a set of standards. These ethical standards must include that patients must be well informed , must voluntarily consent, their motivation must be pure, and the research units must meet technical requirements. There must be informed consent of patients in all clinical trials and treatment thereafter. There are also ethical guidelines that must be in play during the entire duration of therapy, from the development of the therapy to the implementation of the procedure itself. These guidelines include the persistent conditions of respect for life, respect for patients' rights, lack of harm, and fairness. These conditions boil down to a single principle: respect the patient's autonomy.

Informed consent has multiple components. The consenting individual must be competent, have full disclosure of all information, understand that information, have voluntariness, and ultimately consent (Beauchamp and Childress, 2001). The individual or patient must be competent, meaning they must have a decision-making capacity. They must be of sound mind. Children, people who are intellectually disabled, or those enduring major neurocognitive disorders are not considered competent in the decision-making process. These individuals have guardians assigned their durable power of attorney. This exemplifies the concept of paternalism. Stated simply, within medical paternalism lies the verdict that the principle of beneficence overrides the principle of autonomy when the patient is incapable of autonomous decision-making (Iserson, 1999). Doing

what is best for the patient must be decided by an outside authority when that individual's autonomy will be detrimental for their well-being as their competency is deficient.

A criticism of personal autonomy definitions can arise when a competent person has personal belief systems which seem to color or impact judgement. An example of this clash is when medicine and religious beliefs collide. One religion that will especially challenge immunotherapy is that of Jehovah's Witnesses. Jehovah's Witnesses refuse blood transfusions, and CAR T cell adoptive therapy involves blood extraction, manipulation, and autologous transfusion. It is not unlikely that a patient who is a Jehovah's Witness would not consent to immunotherapy. If this is a lifesaving treatment, and the person refuses treatment, their competency will likely come into question. However, a person is deemed competent if they understand the situation and the consequences of the decision, and the decision is based upon rational reasons (Iserson, 1999). The patient is asked if they understand the situation and the consequences of the decision. By refusing treatment and instead insisting that they do not need the adoptive therapy because they will be healed by Jehovah, that belief might be perceived as a religious delusion by some, but the patient is indeed competent (Iserson, 1999). For a patient to be deemed competent, they must simply understand the situation and consequences. From there, the individual is free to use their judgement and beliefs as they so please.

When making the decision, the individual must not be coerced, wrongfully persuaded or manipulated. Coercion can take the form of using a credible and severe threat of harm to force or control another. Wrongful persuasion refers to the process where a person comes into the belief of something through merit of reasons another person presents. It is wrongful when the person presenting the information frames the information in a way that can sway the decision-maker. Manipulation refers to the form of influence that is not persuasive or coercive. Manipulation is

when people are swayed to do what the manipulator wants by other means (Iserson, 1999). An example of coercion would be if a physician attempted to sway the patient's choice by threatening death as the only consequence when in fact it is not. This is the physician using the possibility of death as a consequence to get participants to join their clinical trial. Honestly predicting death as the very likely consequence of refusal of treatment is not the same as wrongfully threatening death. Persuasion would look like a physician using their place of authority to present information in such a skewed way as to sway a patient's decision-making process. Persuasion and coercion are not in play when information is presented honestly and wholly.

Informed consent also requires that the patient must have full disclosure of all information regarding immunotherapy. This includes all details of the procedure, all known benefits, all known risks, and all potential outcomes such as side effects. The patient has the right to all available information (Beauchamp and Childress, 2001). Participants should be told the purpose of the experiment, the nature of the procedure, all parts of the procedure, the pain and risks as possible side effects, and any financial costs. This information should be communicated in nontechnical language. The information must be presented in a noncoercive atmosphere, and patients must be treated with respect irrespective of whether or not they decide to partake in treatment (Flynn, 1997). In order for the decision to be an autonomous choice, a patient's choice must be voluntary (Beauchamp and Childress, 2001).

Consent is important in immunotherapy because of the treatment's current status and ongoing development. This current status can be considered experimentation. Experimentation is a process of trial and error that sometimes results in success instead of error. However, failure can be also valuable in other contexts as information is learned no matter the outcome (Flynn, 1997). Most research involving human subjects requires that subjects enter into the research voluntarily

and with sufficient information (Iserson, 1999). Some consider it morally wrong to use a human subject at all because it involves using another human as a means. The consenting individuals know that their participation will increase knowledge in one form or another, and they are accepting of that end. The moral end in medicine is the promotion of the patient's best interests, as determined by the patient's autonomous decisions. Therefore, physicians must honor the requirement of voluntary informed consent. In the duration of the experiment or clinical trial, individual rights cannot be overridden by utilitarian considerations (Mappes and Zembaty, 1991).

The primary justification for human experimentation is a utilitarian one, where the harm of one does not outweigh the benefit for the many (Mappes and Zembaty, 1991). Human experimentation increases discovery of new information. Sound medical practice requires controlled and reliable experimentation in order to bring the best possible care to patients. Many standards, regulations, and official documents have been established to protect the rights of participants in human experimentation. The Nuremberg Code outlines the criteria that must be met before human experimentation can occur and be judged morally acceptable. The Declaration of Helsinki goes beyond Nuremberg to distinguish between therapeutic and nontherapeutic practices and also mentions the conditions that must be met for the informed consent in individuals who are legally incompetent by declaring the ethical acceptability of proxy consent. In order to progress in medicine and medical practice, the use of human subjects in biomedical research is considered to be indispensable. As important as human participation is in research, both for scientists and for participants, the first priority of a civilized society is the protection of the rights and welfare of every human being (Mappes and Zembaty, 1991). The results and benefits of such experiments should be equally available to all of society.

4. Justice

The principle of justice means that there must be an equitable distribution of treatment among all groups in society. This challenges the practicality of immunotherapy. Once this treatment is made available for all, it will be those who can afford the new, likely expensive treatment who will able to receive treatment. This will make immunotherapy not seem just in the start. However, this is not a reason to not pursue this procedure. If complete, equal access from the start were enough to reject the development of a treatment, we would never progress as a society.

The pillar of justice deals with who ought to receive the benefits of the research. Justice can be talked about in the sense of fairness in distribution versus what benefits one deserves. Equitable or fair distribution can take on many meanings, including that it means each person gets an equal share, each person is given benefits according to their individual need, each person is given benefits in accordance with their individual efforts, each person is assigned benefits according to societal contribution, or each person receives benefits according to merit (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978). For utilitarians, a just distribution of benefits and burdens will be the one that produces the most overall happiness. In other words, the people who need the treatment will be given the procedure in order to maximize utility. In a perfect world, everyone who needs immunotherapy will have access to the treatment. This type of treatment does not discriminate and work for one group, just as cancer does not discriminate. Everyone has the potential to utilize this intervention.

This is where the definition of medically necessary is important. If the procedure is medically necessary, insurance must cover the cost of the procedure to allow all to have access to the treatment. This assumes all have access to insurance, which is a whole other issue in itself. The logistics and practicality of immunotherapy are still being developed. Out of Beauchamp and Childress's four pillars of medical ethics, nonmaleficence and justice are the pillars that will be

challenged most as biotechnology continues to be developed. It is known that immunotherapy is intended for good and will respect autonomy of patients, but the risks are still to be determined and the practicality of equitable access cannot yet be assured.

Conclusion

Immunotherapy aims to increase health in the ill by bringing already existing abilities of the immune system back to normal, effective levels. T cells are isolated from a blood sample in ACT and go through *ex vivo* manipulation to express CARs. The manipulated cells are transferred directly back to patients to mediate antitumor immunity (Sadozai et al., 2017). These cells then express antibody binding domains on their surface that present antigen specificities that are MHC-independent (Kalos et al., 2011). CAR can be developed specific to a particular type of cancer. The surface proteins of the malignant cell must be discovered, and the CAR must be developed to be specific to those epitopes.

The principle of beneficence is upheld. The goal is to not cause harm and uphold the principle of nonmaleficence. Patients are respected on the basis of their humanity, their decisions are informed, and immunotherapy is administered with consent, so respect of autonomy is upheld. This is a treatment that can be used in any person that qualifies for the need of immunotherapy intervention. Ideally all will have access to the procedure, thus adhering to the principle of justice.

The immune system itself can be considered therapy as it eliminates threats to individual health. Immunotherapy works to enhance the immune system of those who cannot eradicate cancer cells naturally. Immunotherapy is the enhancement of the immune system's already given ability by simply making it better at the job it aims to do. It is an area ethically worth pursuing. **The mechanisms by which immunotherapy is accomplished are not solely enhancement, but rather *enhancement of a therapy*.**

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