A Look at the Promise of Immunotherapy

One of the most advanced therapies for fighting and even curing cancer is enhancing and boosting the patient's own immune system to fight the disease. The human immune system is very complex and able to successfully ward of diseases and infections during one's lifetime. When it does not, white blood cells (B and T cells) can be stimulated by specially designed drugs that allow them to recognize and kill cancer cells.

One of the first immunotherapies was monoclonal antibodies (mABs) [6]. Once researchers knew what distinguishes specific cancer cells from healthy cells, they attached the engineered antibodies to drugs or other substances and delivered them to the patient. The early therapies with monoclonal antibodies had big risks associated with them because antibodies are proteins and their presence leads the immune system to destroy them. There could be other side effects like allergies. The newer monoclonal antibodies are less likely to have such side effects. There are several types of mABs. Naked mABs are antibodies that don't need radioactive material or other substances to work. For example alemtuzumab is a medication used for patients with chronic lymphocytic leukemia. It attaches to cells with the ad52 antigen, which are the lymphocytes. Then the immune system finds the diseased cells easier and destroys them. Another naked mABs treatment is trastuzumab which attaches itself to the antigen on the cancer cells and stops them from multiplying. Other naked mABs work on the checkpoints that the immune system uses.

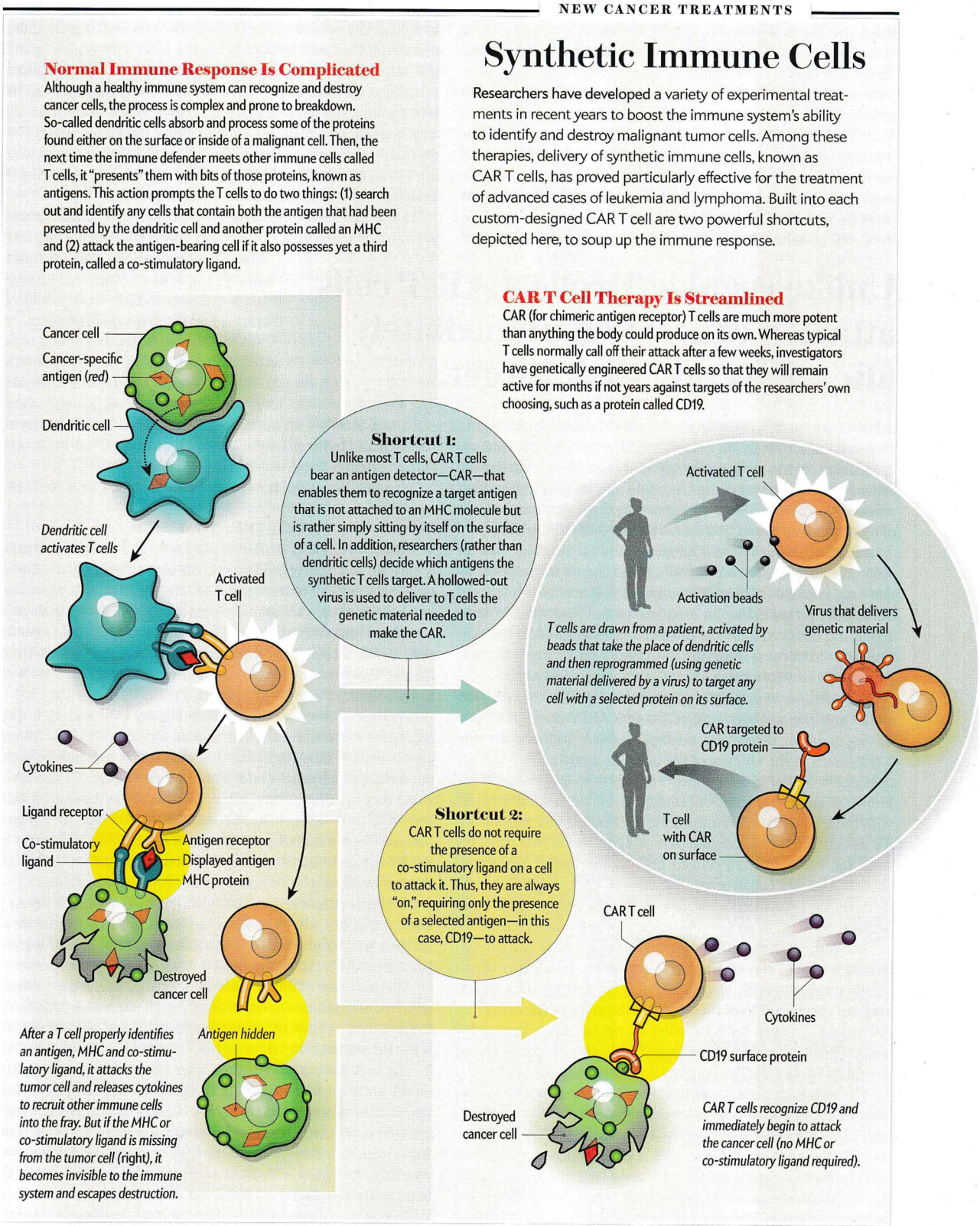
Immune checkpoints inhibitors work by switching on a checkpoint in immune cells [2]. Normally, immune cells have an on/off switch (a checkpoint) that prevent the immune cells from attacking healthy cells. This switch is called PD-1, a protein on immune T cells. It attaches to PD-L1 that is present on healthy and some cancerous cells. When PD-1 attaches to PD-L1 then the T cell won't attack the other cell.

The immune checkpoints inhibitors will act either on PD-1 or PD-L1 and inhibit this binding [2]. These medications are effective but have also the side effect that healthy tissue is attacked. Examples of PD-1 inhibitors are medications like Pembrolizumab and Nivolumab. PD-L1 inhibitors are Atezolizumab and Avelumab. Researchers are now looking into having two antibodies, one attaching to the cancer cell, the other attaching to the immune cells so that the immune cells attack only diseased cells. This type of monoclonal antibody therapy is also called bispecific.

One very promising immunotherapy is chimeric antigen receptor (CAR) T-cell therapy [1]. In the March issue of Scientific American, researchers describe how they created synthetic immune cells because the immune response is prone to breakdown. Dendritic cells absorb proteins that are on the surface of a malignant cell. When it meets other immune cells, like T-cells, it presents them with bits of those proteins, called antigens. The T-cell then searches any cells that contain the antigen in conjunction with a protein called MHC. Major histocompatibility complex (MHC) are cell surface proteins used by the immune system to recognize foreign molecules. The T-cell then attacks the antigen bearing cell only if it also possesses a protein called a co-stimulatory ligand. The problem is that if the MHC or the co-stimulatory ligand is missing from the tumor cell, it becomes invisible to the immune system and escapes destruction. The synthetic immune cell however is designed not to require the MHC protein or the co-stimulatory ligand to attack cancer cells.

Synthetic immune cells, or CAR T cells (chimeric antigen receptor), are used for advanced cases of leukemia and lymphoma. They are more potent than the body can produce and they are genetically engineered so they will remain active for months at a time, not only just a few weeks as is the case with natural antibodies. Researchers engineered these cells so that they don't require the tumor cells to have the MHC protein or the co-stimulatory ligand. These synthetic cells are engineered to

attack the target that the researchers choose. The antigens that the T-cell target can be customized for each patient. The next diagram shows how this engineered cell finds its targets, in this case cells that have the antigen CD19. [1]



Billions of such T-cells can be created and injected in the patient. In a few days, the immune system is revving up and attacking the cells that have the targeted antigen. No MHC protein or co-stimulatory ligand has to be present, which is a plus because some cancers avoid detection by not producing such proteins. This immunotherapy has great success as patients with advanced leukemia or lymphomas were free of cancer after a few weeks. In some cases the patient's immune system mounted an attack that almost killed the patient. That is why at first the researchers didn't receive more funding. But bio-technology companies and other institutions were interested in licensing the technology from the University of Pennsylvania where this research took place. The media also was interested in the articles published by the authors in The New England of Medicine and started covering the results extensively. This in turn led to more funding and grants. This year, Novartis is asking the FDA to approve this treatment for pediatric acute lymphoid leukemia, and Kite wants approval to treat a type of lymphoma.

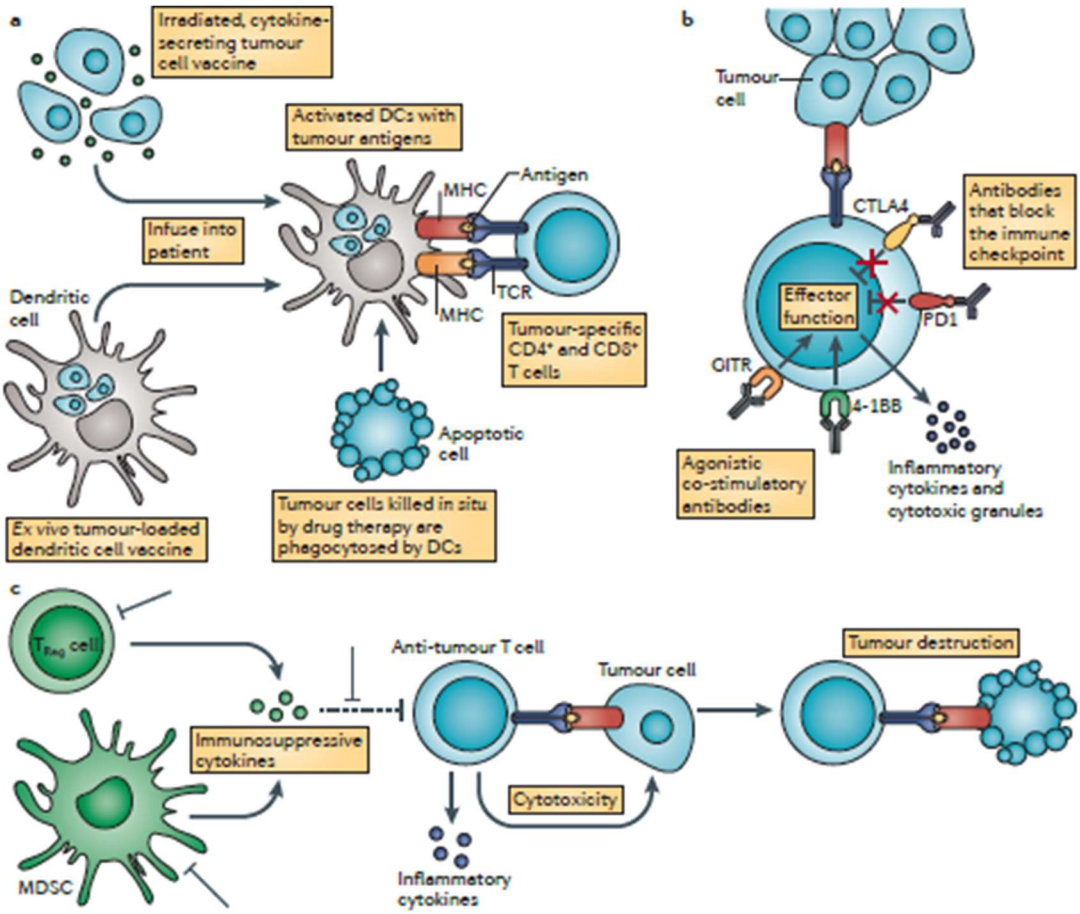
The process of creating the synthetic immune cells involves using the HIV virus that is stripped of the genes that make HIV a deadly disease. The HIV virus is very effective at infecting T cells removed from the patients. This engineered HIV virus contains genes that help build the antibody activated chimera. This HIV virus then transfers these new genes into the T cell. This treatment can be used for any type of cancer in which the tumor cells has an antigen that is distinct from the patient's healthy cells. One of the researchers of this study is looking to develop an immune based treatment for breast and pancreatic cancers. Such cancers are good at hiding from the immune system and will need a combination of antigens rather than one antigen to target the diseased cells.[1] It is interesting to note that knowledge and work that was produced to fight off the AIDS epidemic is now used to cure cancer.

Another class of immunotherapy is the cancer vaccine. The cause of many cancers may be viral infections. HPV is thought to raise the incidence of cervical and anal cancers. But other cancers like breast cancer and lung cancer are not known to be caused by viral infections. Some cancer treatment vaccines are made from inactivated cancer cells, parts of cells, or pure antigens. Sometimes a patient’s own immune cells are removed and exposed to these substances in the lab to create the vaccine. Once the vaccine is ready, it’s injected into the body to increase the immune response against cancer cells. Cancer vaccines use also adjuvants as another way to boost the immune response.

Sipuleucel-T is the only vaccine approved in the US to treat cancer, specifically prostate cancer. It's being used when hormone therapy is no longer effective. The patient's own immune cells are manipulated into dendritic cells, made to recognize and attack the cancer cells. Then they are injected back into the patient.

These new therapies are available not only for humans, but also for pets. My uncle's dog developed a tumor in his mouth, under his tongue. He was operated a couple of times but the tumor kept growing back and he was given two months to live. Then his vet gave him a new vaccine that uses human DNA for the enzyme tyrosinase. Tyrosinase is the rate limiting enzyme in melatonin synthesis, to stimulate an immune response against cells that contain the enzyme. Melanin synthesis is generally limited to melanocytes, the cells which oral melanoma uses, thus the vaccine is very specific for melanoma. Human DNA is used because it was found that using a foreign species' DNA is more effective in stimulating an immune response as compared to using the same species' DNA. The vaccine is safe, with minimal side effects and was found to be effective in prolonging survival time in dogs with oral melanoma. The melanoma vaccine is considered to be most effective when the local tumor has been controlled with surgery and/or radiation. Samson is still well two years later after given only two months to live.

Dendritic cells are at the center of the immune system. They are also called “nature's adjuvants” and are used as a way to deliver antigen and vaccination against cancer. When compared with other antigen presenting cells such as macrophages, dendritic cells are more efficient at inducing T cell immunity. Dendritic cells can be immature and then they can induce tolerance either by deleting T



cells or by the expansion of regulatory and suppressor T cells. The mature denditric cells can start efficient immune responses. The adjuvant in vaccines acts by maturing dendritic cells [3].

Early clinical studies show that one can improve treatment efficacy using combination approaches like immunotherapy+ immunotherapy, immunotherapy+small molecule, or immunotherapy+chemotherapy. However, there remains the danger of these treatments causing bad synergistic effect when combined. Recently, studies are trying to find ways to raise the tail of the survival curve for cancer [5].

Combining targeted therapies and immunotherapy increases survival rate [4]. Targeted therapies help dendritic cell maturation which suggests that combining it with cancer vaccines would lead a better vaccine response. Targeted therapies alone might lead to the emergence of drug-resistant variants of the disease, because of either secondary mutations, or compensatory changes in the targeted pathway that bypasses the drug mediated inhibition. Targeted therapies against tumors affect pathways that are used also by immune development which might help by optimizing the immune responses of immunotherapies. So combining targeted therapies and immunotherapies might lead to better results than using each in part. To generate anti-tumor responses of the immune system all the following 3 steps are combined and these drug-resistant responses are usually avoided [4].

The advances made in the past several years in immunotherapy are exciting and this new research shows amazing results. For some patients who were dying, it completely changed their outlook and offered them another opportunity to live life to the fullest because their cancer was not detectable anymore. It is the future of cancer treatment because it works together with the body's immune system, undoing the mechanism by which the cancer hid in the first place from the immune system and gives the immune system a necessary boost. The researchers and doctors who work on these treatments are at the forefront of science and their work will alleviate tremendous suffering.

Works Cited

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