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IMMUNOTHERAPY
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The most powerful cancer therapy in 130 years is concerned with immunotherapy. Some patients with the deadliest of cancers are finally, for the first time, being declared cancer free. This does not involve pills, diets, surgery, radiation or chemotherapy. It is a living cure, found in every living body. When activated, it is capable of ridding the body of cancer. This is **immunotherapy.**

Every year, 1.7 million Americans get the diagnosis of cancer. For them, this is life changing. **Cancer kills one out of every four** Americans and after heart disease, is the most common cause of death in the United States. **There are 500,000 deaths every year** from cancer. In 2021, 6.3 billion dollars was spent in the United States on cancer research. 209 billion dollars for the care of cancer patients. This is estimated to increase to 245 billion dollars by 2030. **Finally,** progress is being made in this area of medicine.

The death rates for common cancers (breast, prostate, colorectal, liver and pancreatic) has been unchanged since the 1930's. On the other hand, the death rates for heart disease has fallen 64% and for stroke, 74% between 1950 and 2006.

Change is a'Coming

The most important change ever in the treatment of cancer is immunotherapy. It is clear from research in the last decade that within our bodies is the power to defeat cancer. The trick is to unleash the body's immune system against this disease.

The Secret Weapon Inside of You

There have been documented cures of **end-stage disease** in the cases of lymphoblastic leukemia, metastatic Stage 3 cervical cancer **with mets to the lungs** and malignant melanoma **with diffuse systemic spread.** A revolution is taking place and for the most part, the public has been shut out from the results and completely unaware.

For years, scientists have wondered what if we could turn on our immune system against cancer cells? This actually goes back 130 years. In 1891, Dr. William Coley, was on a mission. Find Fred Stein. Fred was a German immigrant house painter who lived on the lower East side of Manhattan. He was normal in every way except he had a fast-growing tumor in his neck. After four separate surgeries, his case was deemed hopeless. But he sustained a bacterial infection in his face. He had no antibiotics, so he had to let his body fight it out. Miraculously he not only survived the bacterial infection, but the cancer disappeared. Dr. Coley believed the body's immune system was far more powerful than imagined. His mindset was that "if we could make people sick with other infections, possibly, we could awaken the immune response against cancer". He developed a vaccine based on the bacteria that infected Fred Stein. Thereafter two other vaccines were developed from deactivated (killed) bacteria. Most of today's vaccines still work in the same way. They are either derived from deactivated (killed) or "live attenuated" (weakened strain of bacteria). Measles, mumps, tetanus, and polio were all created with this very same technology.

Dr. Coley's therapy resulted in cures, but the results were at best spotty and the side effects resulted in death at times. His therapy was therefore banned by the medical community, despite the evidence of occasional success.

Today, we know Dr. Coley was on to something, even though cancer is not caused by infection but rather by DNA run amok. We have learned that cancer is very complex and how it starts, the way it grows, the different types of cancer, and how cancer cells function differently from normal cells all needs to be explored.

There are over 100 different types of cancers, with five main groups.

- Carcinomas: The most common form of cancer. It involves the organs (lungs, pancreas, colon, bladder, breast and skin).
- Sarcomas: These are less common and involve bone, soft tissues like muscle, nerves, cartilage and fat.
- Lymphomas: These are from the cells of the lymphatic system.
- Leukemias: These are from blood cells.
- Melanomas: From pigment cells in the skin

History of Immunotherapy

We trace the origins of immunotherapy to the Egyptians. In 1550 BC, a prominent Egyptian physician, Imhotep, wrapped tumors with moist salves coupled with an incision resulting in infections at the site with the hope that positive results would occur. There have been cases through the ages of tumors disappearing after infection.

In the 1700's and 1800's, areas affected with cancer were wrapped with septic bandages to introduce infection. This was the "laudable pus theory".

All of this seemed ludicrous to the medical community that was enlightened by Dr. Joseph Lister's work with infections in surgery. After all, if bacteria caused infections and death, why in heaven's name would we want to promote it?

By the 1930's, **radiation therapy** became the standard of care in addition to **surgery.** The breakthrough came in the 1960's and 1970's at Memorial Sloan Kettering Cancer Center in New York City through the research of Dr. Lloyd Old.

It was noted that cancer cells have **unique surface proteins** which could be targeted by the immune system.

At the University of California in Berkeley, Dr. James Allison began research on specific **switches** to turn on the immune system. He had lost his mother to lymphoma, two uncles to melanoma and lung cancer, a brother to prostate cancer, and he himself had prostate cancer, which was successfully resected in 2005.

Up until then, immunotherapy was considered "quackery". He was even advised to seek a different career course so his reputation would not be tainted.

Some non-specific immunotherapy drugs, like Interferon, had failed to be efficacious, so drug companies looked elsewhere in their research. The immunotherapy field was considered dead.

Allison persisted and in 1990 the FDA approved the first immunotherapy drug, BCG, made from live attenuated bacteria (mycobacterium bovis), that caused tuberculosis in cattle. It had previously been used for the therapy of tuberculosis in humans. In the 1990's, I personally was involved with a patient, R.S., who had 14 proven metastatic melanoma sites which I had personally excisionally biopsied. He was treated at Sloan Kettering with BCG and had a full recovery with no evidence of disease.

Today, BCG is used to treat bladder cancer. It is injected directly into the bladder wall and taken up by macrophages that trigger a full immune response. It also enters cancer cells and marks them for elimination. Today, in BCG unresponsive patients, BCG plus targeted immunotherapy has been found to be effective in treatment of some of these tumors.

In 2011, after Allison collaborated with the drug company Medarex, **Ipilimumab** received FDA approval for the treatment of melanoma. **This has resulted in over 20 percent long-term survival** of patients **with diffuse disease.** This is the first in a class of drugs known as **"checkpoint inhibitors".** There are over 200 open clinical trials that are presently ongoing for this drug. Survival in advance Stage 4 melanomas has been noted.

Second and third generation drugs targeting other parts of the immune system **("Immune checkpoints")** have been discovered. Several have been approved. Today, more than 50% of all patients with metastatic melanoma can be expected to live more than five years, with many cured.

Immunotherapy has now been approved for many types of cancer, including melanoma, prostate and bladder. Experimental studies have also shown benefit from cancers of the kidneys, pancreas, and in some cases lung cancers. Some forms of immunotherapy reprogram the patient's immune cells, others create tags that mark cancer cells for destruction.

How Immunotherapy Works

The aim is to stimulate different parts of the body to fight its own cells that have become cancerous or malignant. There are different types of cancer targeted immunotherapy.

1. Non-specific immunotherapy
    a. This treatment activates the entire immune system
    b. This includes Interleukin and Interferon drugs
    c. The results are mixed at best

2. Monoclonal Antibodies (mABS)
    a. Antibodies can be made in the lab and tailored to fight any kind of protein marker, just like the antibodies that the body makes in response to the flu vaccine.
    b. These antibodies have a protein coating in the "Y" Branch of their structure that allows them to latch on to the unique proteins on the surface of cancer cells or immune cells, thus in the former, shutting down the cancer cell or in the latter, signaling the body's immune cells to kill the cancer cells.

Since cancer cells are so similar to normal cells, they can easily camouflage themselves but they do have a few completely unique proteins that are peculiar to themselves and that makes them different, and thus targetable.

Cancer cells can also express proteins that trick the immune system into mistaking them for normal cells.

Dr. Allison's research focused on a specific white blood cells, T cells, that could attack the cancer cells. These cells need "switches" to be activated" and this is what Dr. Allison's research discovered. He discovered the first three switches.

First switch

- This is an antigen receptor the T cell uses to recognize the surface antigens (proteins) of tumor cells. This is the "ignition switch" needed to activate the T Cells.

Second Switch

- Another surface molecule (CD28), called the "co-stimulatory" receptor.
- Even if the T cell is turned on, if CD28 is not activated, the T cell doesn't work. (This is the gas pedal).

The third discovery by Allison in 2005 changed immunotherapy forever. He was studying another T cell surface marker called "Cytotoxic T-Lymphocyte Antigen 4" or CTLA-4.

- This molecule stops the T cell killing spree preventing the T cells from destroying normal cells. Both normal cells **and** cancer cells have this molecule which can shut down the T cells. Allison found that **blocking this protein** caused the T cells to attack cancers. But he also discovered how to switch CTLA- 4 back on!

He used the same method other researchers used to create antibodies and created Ipilimumab, which shut off CTLA-4, the first drug of its kind.

An even more important protein that cancer cells use to block the immune response is "PD-1" (a programmed cell death receptor that is activated by healthy cells to ensure that the immune system doesn't harm healthy tissue).

Cancer cells use PD-1 to turn off any T cells that might destroy them.

PD-1 is also a receptor on B cells, so that antibodies that shut off PD-1 result in a strong widespread attack on cancer cells.

Merck developed MK-3475, (Keytruda) PD-1 signal blocking antibody which in combination with Ipilimumab (Yervoy ®) in a study of 400 patients who had failed therapy with Yervoy resulted in 85% one year survival and 79% two year survival.

- Only 8% of the patients experienced side effects.

The third type of immunotherapy is **cancer vaccines.**

There are two types of vaccines

- **"Preventive Vaccines"**
    - For example HPV vaccine or Hepatitis B&C vaccines

- **Cancer Fighting Vaccines**
    - For SIPULEUCEL-T for the treatment of prostate cancer.

These cancer fighting vaccines work by taking the T cells (the immune cells) out of the body, exposing them to chemicals or modified viruses, and then injecting them back into the patient. These T cells are programmed to destroy specific proteins on the cancer cells.

- An example would be SIPULEUCEL-T to fight prostate cancer
- This is the only cancer fighting vaccine that has been approved thus far
- These T cells respond to a **prostate-cancer-specific protein** and an immune response occurs called **"adoptive T cell transfer".**

Using this method twelve patients with **advanced leukemia** were treated at the University of Pennsylvania in 2012. There were three complete remissions, four patients improved, two had no response, one child had a full remission, one child relapsed, and one patient was lost to follow up.

Problems with Immunotherapy

- T cells can also target normal cells leading to multiple side effects and on occasion, death.
- Cancer cells can mutate so that the "tag" that is targeted by the T cell disappears.
- Combination therapy with both chemotherapy and immunotherapy have at times resulted in a powerful effect in treating cancer.

The chemotherapy bursts the cancer cells which release the tumor specific antigens which then stimulate the immune system to target and kill the remaining cells.

Questions Which Are Still Unanswered

- Will full remissions of one type of cancer be permanent?
- Will remission as a result of immunotherapy in one cancer result in protection against other cancers?

We still don't know the answers to these questions.

There are specialized T cells called memory T cells and their durability in recognizing and fighting cancer cells in the future is being studied. Long term remission has yet to be proven.

Dr. Steven Rosenberg, the Chief of the surgery branch at the National Cancer Institute noted the main concern with immunotherapy "the immune system is so exquisitely sensitive and specific that even tiny amounts of a molecule on the cancer that is also present on normal cells, can result in the destruction not only of the cancer cells, but also of normal tissue as well."

This then is the dilemma…..finding the "targets" that are unique to, and stay unique to, the cancer cells. Every cancer mutates. The more mutations, the more easily the cancer can be recognized by the immune system. So that cancers like melanoma, lung cancer and leukemia, are prime candidates for immunotherapy. Epithelial tumors such as breast, prostate, ovary and esophagus have fewer mutations and are less likely to benefit from immunotherapy. Unfortunately, these make up 90% of the cancer deaths in the United States.

The final problem has to do with these mutations. Because of every individual's unique genetic makeup, each cancer is unique to that individual. Future research is directed toward genetic research to personalize and therefore, better target cancer therapy.

Summary and Clinical Application

Our generation is witnessing the birth of the "cure" for cancer. Total success is right around the corner.

Each of us has within our bodies, the building blocks for the prevention of and eradication of all cancers and this "cure" has been proven to lie within the T cell (the killer cell) in the immune system.

These T cells are activated (switched on) when a protein on the surface of a cancer cell is recognized. This "primes" the T cell for action, but the killing spree doesn't occur until the T cell is stimulated to action by another protein, CD-28, a co-stimulatory receptor.

The killing spree would go on unabated if there were no controls, which are checkpoint proteins found in both normal **and** cancer cells.

The morphology of these surface proteins is like the spike on the Covid virus surface; only they are in the shape of a "Y". These can unite with a mirror image of a protein on the surface of the cancer cell (PD-L1) and result in removing its camouflage, thus allowing the T cell to obliterate the cancer cell. There are three prominent checkpoint proteins

- PD-1: **(Programmed Death One)**
- CTLA-4 **(Cytoplasmic T lymphocyte antigen**) on both normal and cancer cells.
- PD-L1: On the surface of cancer cells

Inhibiting or blocking the effects of these proteins results in the enablement of T cells to go on a rampage. These proteins that have this effect are **CHECKPOINT INHIBITORS**.

Thus far, nine checkpoint inhibitors have been approved by the FDA.

Six of the most commonly used checkpoint inhibitors are as follows:

I. Checkpoint inhibitors that block PD-1

   A. Keytruda ® (PEMBROLIZUMAB)
      1. This is MK- 3475 by Merck
      2. Used to treat cancers of the urinary tract, advanced melanoma and non-small lung cancer (nslc).
   B. Opdivo ® (Nivolumab) used to treat some kidney cancers.

II. Checkpoint inhibitors that block CTLA-4

   A. Yervoy ® (Ipilimumab) used for advanced melanoma and advanced renal cell carcinoma.
   B. It is also used in combination with Keytruda with remarkable success because both the PD-1 and the CTLA-4 are blocked.

III. Checkpoint Inhibitors that block PD-L1.

   A. Tecentriq ® (Atezolizumab)
      a. For cancer of the lung, some liver cancers, some breast cancers, and cancer of the urinary tract.
   B. Bavencio ® (Avelumab)
      a. Treats merkel cell cancer (skin), and urinary tract cancer (urothelial cancers).
   C. Imfinzi ® (Durvalumab)
      a. Non-small cell cancer of the lung (nsclc)

The key to this research lies in the identification of those proteins that are unique to cancer cells. Since every individual has a unique DNA, and since cancer cells are derived from that individual's DNA, it seems reasonable to assume that therein lies the answer. Present research combines immunotherapy and genomic studies of each individual’s DNA. When these data points are combined with artificial intelligence and quantum computing, the ultimate cure for cancer has to be imminent.

The first baby steps in this process have already been taken. The full blossoming of its potential is close at hand, as the unmasking of the mysteries the Lord has placed within us is revealed.