What is immunotherapy, and more specifically, cancer immunotherapy? How does immunotherapy treatment work?

Immunotherapy is a form of treatment in which we harness the immune system, which is meant to keep us healthy and fight infections and diseases. Cancer immunotherapy works similarly. The immune system is designed to recognize germs and viruses as invaders and get rid of these invaders so we remain healthy. Cancerous cells are invaders and can evade our immune system. Sometimes there are so many that the immune system becomes overwhelmed, and sometimes cancerous cells give off substances that stop the immune system from doing its job.

The goal of cancer immunotherapy is to help the immune system fight these cancerous cells. One way the immune system fights these cells is through the use of monoclonal antibodies, which are man-made antibodies or proteins that will target and destroy a specific part of a cancer cell. We can also use drugs like checkpoint inhibitors to give a boost to the immune system by “taking off the immune system brakes.” Once those brakes are off, the immune system can better recognize and then attack cancerous cells.

Another immunotherapy option involves the use of therapeutic vaccines, meaning they are designed to treat a disease, such as cancer, that’s already present. Doctors are also using patients’ own immune cells to treat their cancer, through a process called adoptive T-cell transfer. This approach has been tested in several clinical trials, resulting in significant responses for patients with advanced blood cancers. Trials are underway for solid tumors like pancreatic cancer.

ABOUT DR. ELIZABETH JAFFEE

Dr. Jaffee is an internationally recognized expert in pancreatic cancer and immunotherapy research. She has been working on developing immunotherapies for the treatment of pancreatic cancer for over 20 years. Dr. Jaffee is the Dana and Albert “Cubby” Broccoli Professor and Deputy Director at the Sidney Kimmel Cancer Center at Johns Hopkins. She is also an Associate Director of the Bloomberg-Kimmel Institute for Immunotherapy. She currently serves as the Chairperson of the National Cancer Advisory Board at the National Cancer Institute and as the President of the American Association for Cancer Research. Dr. Jaffee has been involved with the Lustgarten Foundation since its founding.

ABOUT THE LUSTGARTEN FOUNDATION

The Lustgarten Foundation is America’s largest private foundation dedicated to funding pancreatic cancer research. Based in Woodbury, N.Y., the Foundation supports research to find a cure for pancreatic cancer, facilitates dialogue within the medical and scientific community, and educates the public about the disease through awareness campaigns and fundraising events. Thanks to separate funding to support administrative expenses, 100% of your donation goes directly to pancreatic cancer research. For more information, please visit lustgarten.org.
How has our understanding of the immune system’s response to cancer changed?

There have been incredible strides made over the last 30 years in our understanding of cancer and the immune response. Today, through ongoing scientific research, we better understand the genetic drivers behind potentially life-threatening cancers.

Technology has changed dramatically, especially molecular technology. We now have faster and less expensive genetic sequencing, and that means we can use treatments targeting the mutation that’s driving the cancer. We now know that pancreatic cancer has a minimal natural immune response. However, I am confident that we will see progress in pancreatic cancer and other cancers that don’t naturally respond well to immunotherapy, and that’s due to a better understanding of the immune system. Mouse models are also helping to show inhibitory pathways within the pancreatic tumor microenvironment that prevent immunotherapy from working. We hope these models will provide valuable information that will lead to new immunotherapeutic opportunities.

How would it be determined that pembrolizumab could work for a specific patient? Where could a patient get this test?

It is so important for every cancer patient to be tested to help determine his/her tumor’s molecular profile. Tests are commercially available. Generally, a test to determine mismatch repair or microsatellite instability, which means that a tumor is prone to mutations, is done through a biopsy. If results are positive, patients should speak with their doctors to determine if treatment with pembrolizumab is right for them. The Lustgarten Foundation played a critical role in bringing pembrolizumab to patients by funding the research, encouraging patients to get tested, and paying for patients’ testing to determine if their tumors are mismatch repair deficient.

Where is immunotherapy treatment given? Do patients need to travel to a specific center to receive treatment?

The FDA has approved immunotherapy for a number of cancers, but often it is given in conjunction with other treatments, such as chemotherapy or radiation. Patients who are receiving an immunotherapy that has been FDA approved would most likely receive it in an outpatient cancer treatment center. How often you receive the treatment is really dependent on the stage and type of cancer. It can be administered by pill, IV or injection.

For pancreatic cancer, immunotherapy is still under investigation in research studies. Patients would receive some type of immunotherapy, along with standard of care treatment, at the site where the trial is taking place. The timing of those treatments would follow the research protocol. Teaching hospitals, academic centers, and other large medical practices are all involved in clinical trials, so location is dependent on the trial site. Sometimes a large academic center is affiliated with a smaller hospital that may be closer to a patient, so the patient will receive treatment there.

Is immunotherapy treatment covered by insurance?

When a treatment is FDA-approved, it is usually covered by insurance, though some insurers have far less paperwork for their approval process than others. Patients should contact their insurance companies to thoroughly understand their health insurance policy. It is incredibly important to know what services are covered and what the out-of-pocket obligation will be per calendar year. Patients should request a case manager to help optimize benefits and navigate the intricacies of their policies.

What are the side effects of immunotherapy treatment? How can patients minimize/manage these side effects?

People usually associate side effects with chemotherapy, but immunotherapy is not without its own set of side effects. How you feel during treatment depends on the type of immunotherapy and how healthy you are overall when you start treatment. Generally, most side effects are tolerable and treated with over-the-counter medications. Fatigue is common, and doctors recommend trying light exercise for more energy rather than sleeping throughout the day. Fevers, headache, nausea, muscle aches, and chills are also common and treated with over-the-counter medications. Your doctor and cancer treatment team can help you manage these symptoms.
The most potentially serious side effects are autoimmune problems, as immunotherapy is reviving up the immune system. As a result of immunotherapy treatment, the immune system may sometimes work too hard, attacking healthy tissue and organs. If that happens, patients can develop inflamed lungs, bowels, eyes, or livers. Some patients may develop endocrine disorders and experience hair loss or rapid heartbeat and sweating. Some might develop immune-related arthritis. These conditions could be mild or quite severe. If patients experience any of these symptoms, their doctors would need to be notified immediately. Sometimes corticosteroids to calm the immune system will be given. Other times, some patients might have to stop treatment.

**Can immunotherapy be used as first line treatment for pancreatic cancer, or is it used in conjunction with chemotherapy? How long can a patient stay on immunotherapy treatment?**

Immunotherapy is not approved for pancreatic cancer, with the exception of those with the disease who have a DNA mismatch repair tumor type. In that case, they would be eligible for pembrolizumab. In most research trials, some form of immunotherapy is generally combined with another treatment. However, there are some trials looking at immunotherapy alone. More research is needed to determine how long a patient can stay on immunotherapy, and this research can vary, as every immunotherapy is different.

**How do physicians determine if immunotherapy is working?**

Immunotherapy will help your immune system recognize the cancer cells and, hopefully, attack those cells. However, there are several factors involved in getting the immune system to attack the cells when compared to a treatment like chemotherapy that kills everything in sight. Therefore, it takes longer to determine whether immunotherapy is actually working. To determine the efficacy of the immunotherapy treatment, patients would undergo scans and other tests at intervals that are dependent upon the treatment protocol.

**What new research is being done in immunotherapy?**

The answer to that question is enough to fill a book! There are numerous trials and basic research studies underway to develop newer monoclonal antibodies, checkpoint inhibitors, vaccines and CAR T-cell therapies. (See page 4 for information about these immunotherapies.) I think we first need to recognize that immunotherapy is already changing what we may consider the standard of care for some cancers. Some types of immunotherapy have proven to be better tolerated (in some patients) and have extended survival in some cancers. However, many unanswered questions remain, including why some patients respond while others don’t and which biomarkers we should be looking for. Individual immunotherapies have produced some amazing results, but ongoing work strongly suggests that combinations may be the most effective option, and researchers are actively working to identify the best combinations.

**What is chimeric antigen receptor (CAR) T-cell therapy and how is this immunotherapy being applied to pancreatic cancer treatment?**

CAR T-cell therapy is a novel form of cell therapy using altered cells to specifically target cancer cells. The cells used are T-cells, which look for and then attack invading or abnormal cells, including cancer cells. Doctors collect a sample of a cancer patient’s T-cells, and then those cells are engineered so they grow special receptors called chimeric antigen receptors on their surface. When these CAR T-cells are reintroduced into the patient, the receptors on the surface potentially help the T-cells identify and attack cancer cells throughout the body.

CAR T-cell treatment is approved for some forms of leukemia and lymphoma, both of which are blood cancers. However, it has been difficult to apply CAR T-cell therapy to solid tumors, like pancreatic cancer tumors. The Pancreatic Cancer Collective (pancreaticcancercollective.org), a partnership between the Lustgarten Foundation and Stand Up To Cancer to accelerate research for pancreatic cancer patients who desperately need better treatments, is currently investigating new ways that CAR T-cell therapy can be applied to pancreatic cancer patients. This research is focusing on epigenetics – those gene changes that are heritable, without changing the DNA – that may be occurring in pancreatic cancer and that influence the way genes are expressed. Early trials will be looking at CAR T-cell therapy along with those epigenetic changes that are common to pancreatic cancer patients who don’t respond to immunotherapy and will be comparing patients who respond to immunotherapy to those who do not. Analyzing those epigenetic changes is a huge undertaking, so these early trials are vital if we are going to reach an end goal of trying to improve the immunotherapy response rate for pancreatic cancer.

**Vaccines are another type of immunotherapy. Cancer vaccines are meant to stimulate the immune system and help the body recognize cancer cells as foreign and fight them. What research is being conducted to develop a pancreatic cancer vaccine?**

Vaccines can prevent a disease (like those approved for liver cancer and HPV infections), or treat a disease that is already present, such as cancer. My team and I are studying a vaccine treatment for pancreatic cancer, although it’s clear that prevention would be the Holy Grail.

Vaccine treatment, like other forms of immunotherapy for this disease, has some significant challenges. One reason is that pancreatic tumors develop deep within the body and surround themselves with a tough, fibrous capsule called a stroma that’s difficult for drugs to pierce. The stroma also wards off the immune system’s T-cells. Moreover, pancreatic cancer cells are immunosuppressive and create a barrier to effective immune surveillance by T-cells. Adding to the challenge is that T-cells are somewhat tolerant of cancer cells.

We need to discover how to reprogram the tumor microenvironment to better mount a more robust anti-cancer immune response. We have trials underway focusing on identifying and overcoming these immune pathways unique to pancreatic cancer, and we are also using a T-cell activating vaccine to try to prime the immune system to fight back. One vaccine we are looking at is called GVAX, which I co-developed. It boosts the immune system, resulting in immune cells seeking out pancreatic cancer cells throughout the body and then, hopefully, destroying those cells.

In one of our studies, GVAX was combined with the chemotherapy drug cyclophosphamide and a special bacterium that boosts the immune response. The result: those participants with metastatic pancreatic cancer who received the combination treatment had an overall improved survival with only limited side effects. Several other trials using GVAX, combined with other therapies, are ongoing.

We’re also working on other vaccine approaches, both given as a prevention measure to people at high risk for the disease (due to a family history) and those administered once a patient has been diagnosed. Approaches include one that directs the immune system toward the KRAS mutation, which contributes to approximately 90 percent of pancreatic cancer tumors. This could be a possible pancreatic cancer prevention strategy for people at high risk, such as those with a significant family history of the disease.
Additionally, we are studying a neoadjuvant vaccine that is administered prior to surgery with additional injections later to further boost the immune response.

What resources would you recommend for pancreatic cancer patients and their families who want to learn more about cancer immunotherapy?

At Johns Hopkins, we have an entire site devoted to cancer immunotherapy, including videos and easy-to-understand information. Some of our offerings on this site are reviewed by patients who have undergone cancer immunotherapy. View our site at: https://www.hopkinsmedicine.org/kimmel_cancer_center/centers/bloomberg_kimmel_institute_for_cancer_immunotherapy/

Most academic or teaching hospitals sites, as well as organizations like the American Cancer Society, the National Institutes of Health, and the Lustgarten Foundation, also have important information on immunotherapy that is continually updated. In addition to thoroughly researching the disease and treatment options, it is extremely important that patients and their loved ones consult their cancer care team. Information by itself can be overwhelming, and the cancer care team can help put things in perspective.

In your opinion, how is immunotherapy changing the pancreatic cancer landscape?

Immunotherapy isn’t changing the landscape yet, but we’re working on it. We are seeing responses in approximately four percent of patients, not the big boost of longer-time survival that we want to see, let alone the ability to say the word cure. I think the next set of studies that we’re working on with the Lustgarten Foundation and through the Pancreatic Cancer Collective, as well as the significant work being conducted by researchers worldwide, will give us some answers to our questions. We now have mechanisms in place in which data are shared, and that’s a substantial achievement. Through additional research, we will continue to expand the community of pancreatic cancer survivors.

IMMUNOTHERAPY AT-A-GLANCE

Immunotherapy is a form of treatment in which we harness the immune system to keep us healthy and fight infections and diseases. Immunotherapy works on the principle that a patient’s immune system will recognize cancer cells as foreign and then mount an attack to destroy them. Many therapies are currently being studied, and patients should discuss with their physicians if immunotherapy is right for them. Types of immunotherapy include:

- **Pembrolizumab** is the first FDA-approved immunotherapy treatment for advanced pancreatic cancer patients whose tumors have a unique genetic mutation called mismatch repair deficiency, found in approximately 1 in 50 advanced pancreatic cancer patients.

- **Monoclonal antibodies** are man-made molecules whose job is to act as substitute antibodies to mimic the immune system’s attack on cancer cells by binding to the multiple antigens on the cancer cells’ surface.

- **Checkpoint inhibitors** are drugs that are designed to “release the brakes” on the immune system, as cancer cells sometimes turn these brakes on or off; once these brakes are released, the immune system can better do its job of making sure that healthy cells aren’t being attacked.

- **Chimeric antigen receptor (CAR) T-cell treatment** uses altered T-cells that, when reintroduced into a patient’s body, potentially help to identify and attack cancer cells.

- **Cytokines**, including interferons and interleukins, are signaling proteins that normally help regulate immune system activity by enhancing the body’s immune response to cancer.

- **Vaccines** can prevent a disease or treat a disease that is already present, such as cancer; Dr. Jaffe’s GVAX, currently under investigation, works by boosting the immune system, resulting in immune cells seeking out pancreatic cancer cells throughout the body, and then, hopefully, destroying those cells.

LEADING IMMUNOLOGY EXPERTS WIN NOBEL PRIZE

James P. Allison, Ph.D., MD Anderson Cancer Center, and Tasuku Honjo, M.D., Ph.D., Kyoto University, were jointly awarded the 2018 Nobel Prize in Physiology or Medicine for demonstrating how different strategies for inhibiting the brakes on the immune system can be used to treat cancer. Dr. Allison studied the T-cell protein CTLA-4, and Dr. Honjo discovered PD-1, another protein expressed on the surface of T-cells. These discoveries represent a pivotal step forward in the fight against cancer.