Cancer, Immune System, Immunotherapy

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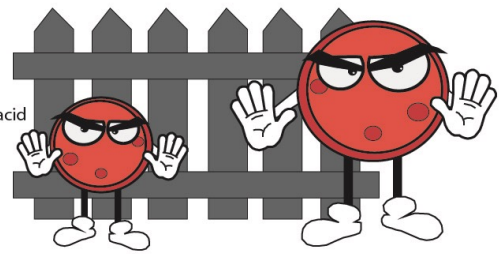
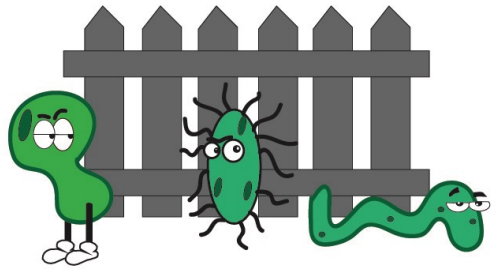
The Innate Immune System: The first line of defense

Physical and chemical barriers that try to keep foreign invaders from getting into the body.

Physical barriers like ...
- Skin
- Tears
- Earwax
- Mucus
- Urine
- Stomach acid



Bacteria, viruses and fungi are constantly invading.

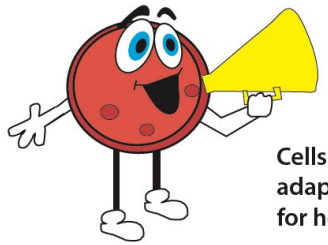


Sometimes some get around the barriers

Innate immune cells try to do what they can.

They are like the garbage man and target anything foreign.

Sometimes backup is needed.



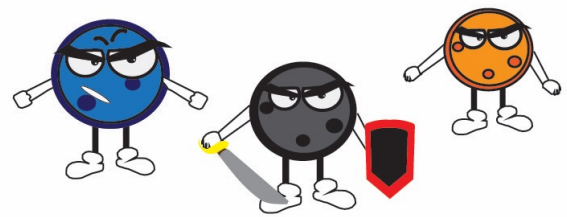
Cells signal to the adaptive immune system for help!

The Adaptive Immune Response:

Cells that are called in to fight the infection. This response is specific to the type of invader.

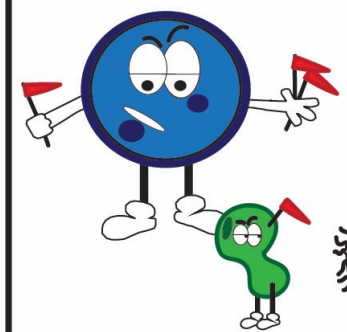
Meet the team:

The Special Defense Unit: T cells and B cells



The Helper

Uses chemical signals to call on the B cells and other T cells to help fight the invader.

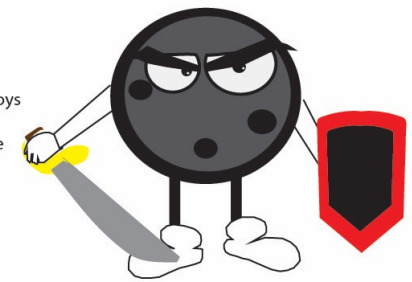


The B Cell

Creates anitbodies that identify foreign invaders that need to be killed.

The Killer

Indentifies infected host cells and employs chemical signals to cause them to die and be eliminated from the body.

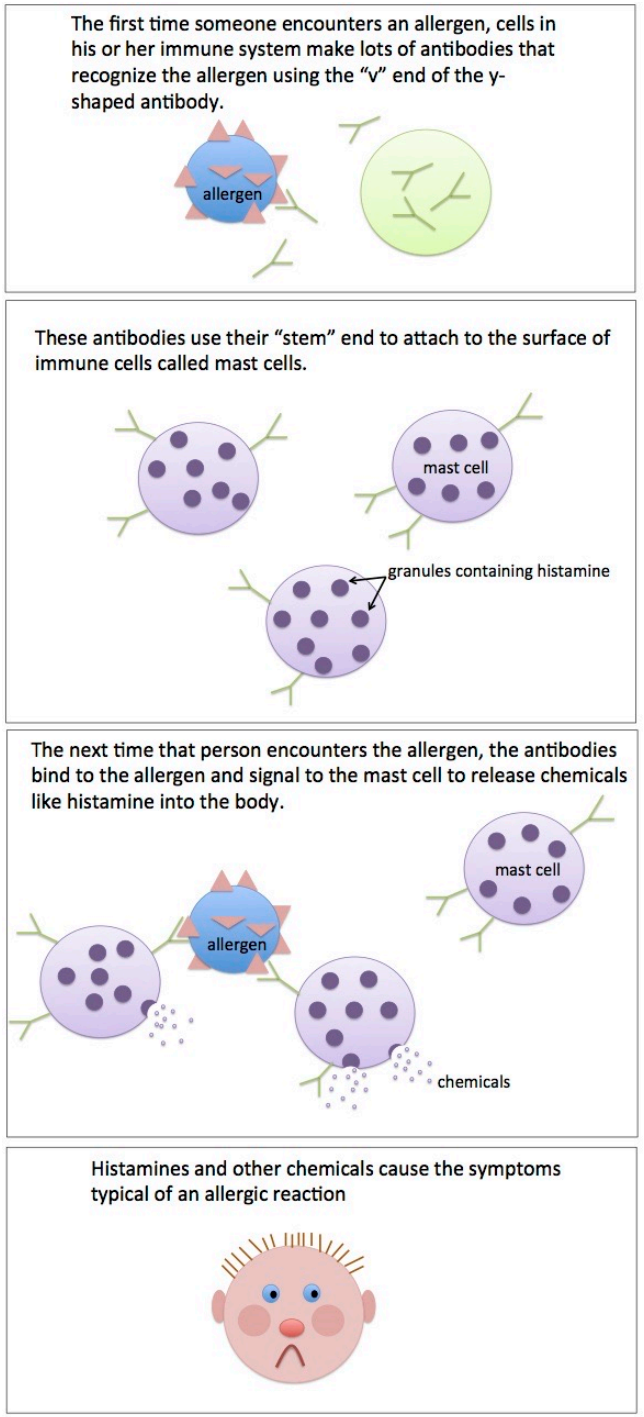


Immune System malfunctions
Immune System gone rogue

Allergies and the Immune System

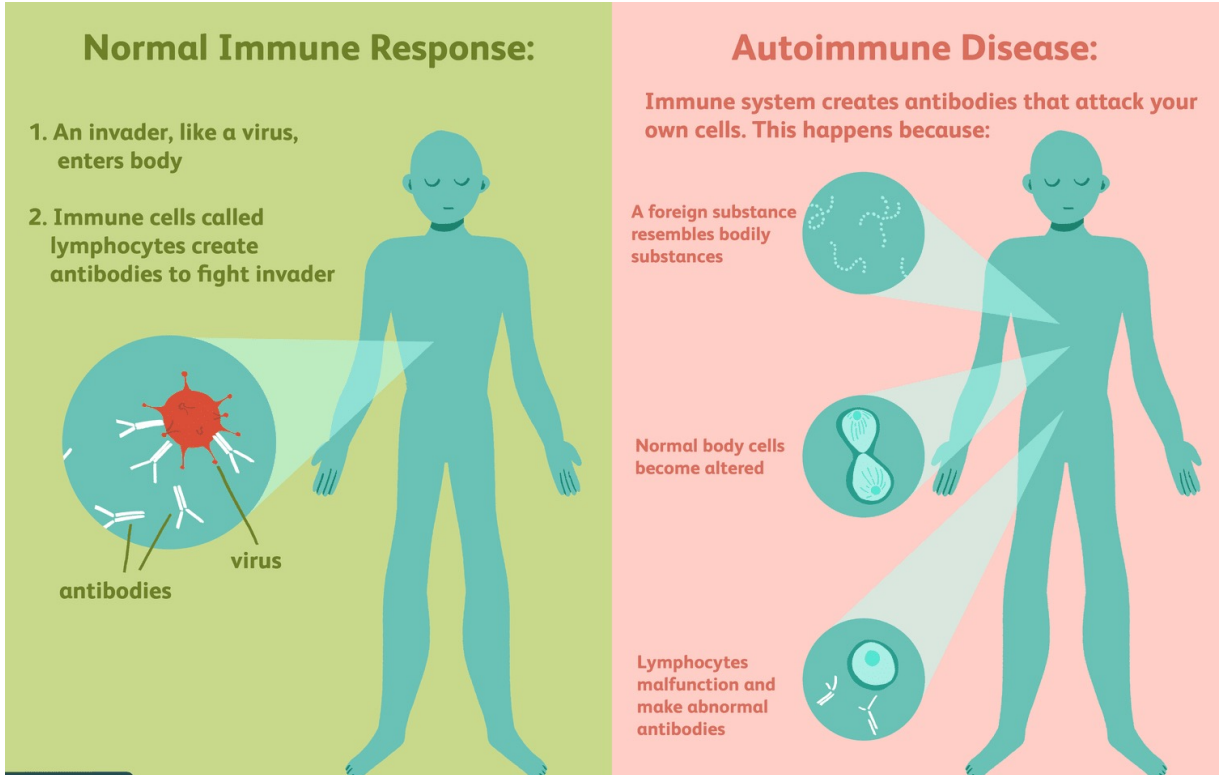
- Allergies are often described as “the immune system overreacting”
- An allergic response is when the body’s defense system has identified some substance, usually a harmless one, as a threat to be removed
- Treatments-Antihistamines, Epi pen etc
- All proteins have the potential to be allergens, but in reality, only a small percentage of proteins cause allergic reactions- scientists are still trying to understand which ones and why
- Researchers are also trying to determine why some people differ in their susceptibility to allergies and why allergic reactions vary in their severity.

https://www.youtube.com/watch?v=hBO2oEk_hOs



Autoimmune Diseases

- Autoimmune diseases are a case of mistaken identity in which the body's immune system attacks itself
- Autoimmune diseases can affect a single organ or multiple organs. Each disease is characterized by unique antibodies/cells that detect and target specific self-antigens
- **Type 1 Diabetes Mellitus**-occurs when autoantibodies destroy the beta cells in the pancreas that are responsible for making insulin
- **Multiple Sclerosis**- autoantibodies attack the fatty sheath (myelin) that covers the nerves and is necessary for nerves to work properly
- **Rheumatoid Arthritis-** is characterized by pain, swelling, and joint damage
- **Inflammatory Bowel Disease-** chronic inflammation of the digestive tract

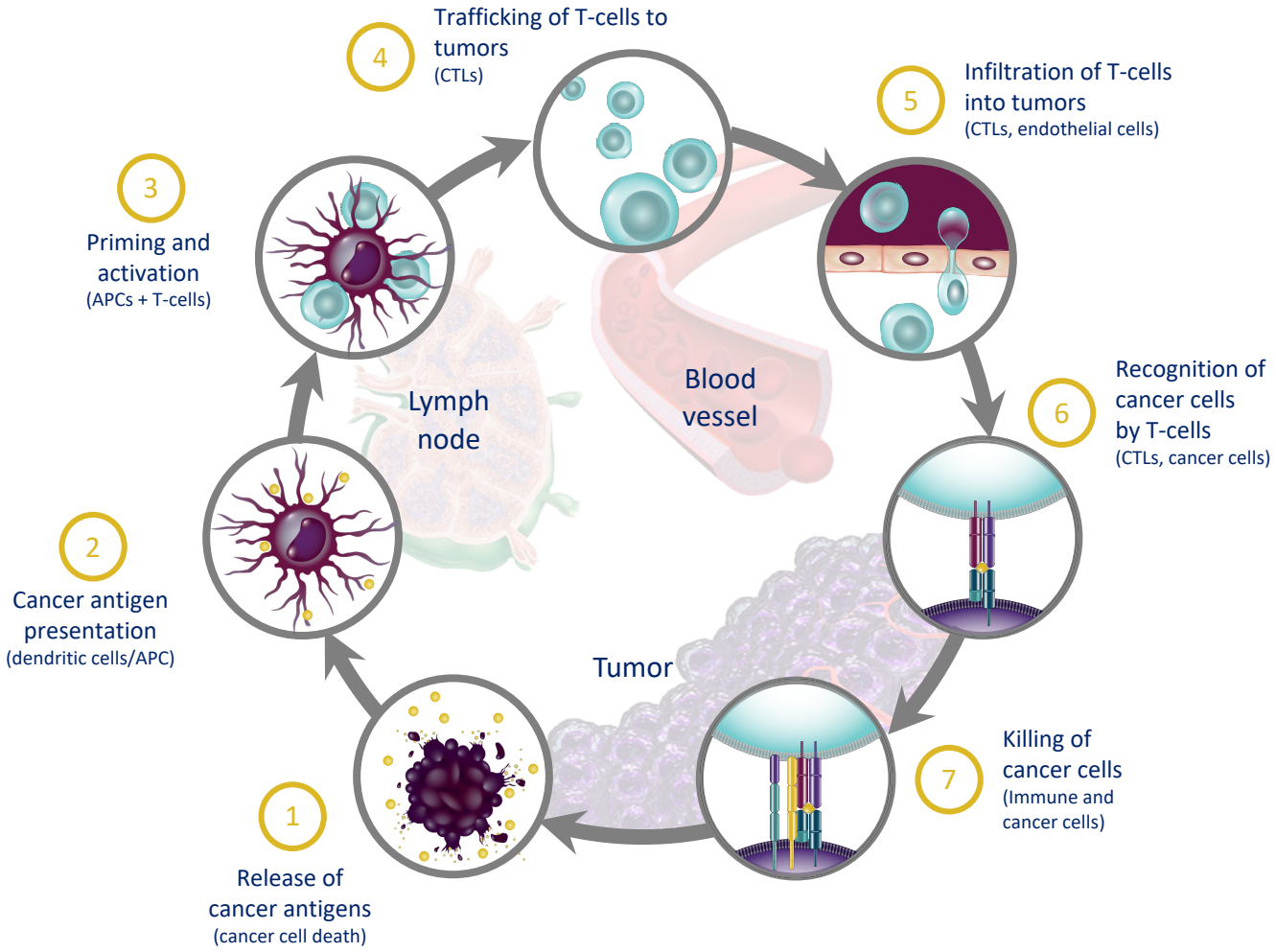


Cancer and the Immune System

- "Cancer" is an umbrella term used to describe diseases that result from abnormal cell division
- Cancer Immunology is an interdisciplinary branch of biology concerned with the role of the immune system in the progression and development of cancer
- Cancer immunosurveillance is an important host protection process that decreases cancer rates through inhibition of carcinogenesis and maintaining cellular homeostasis
- **Cancer immunotherapy** (also called **immuno-oncology**) is the artificial stimulation of the immune system to treat cancer, improving the immune system's natural ability to fight the disease

Cancer Immunity Cycle- Immunosurveillance Hypothesis (Paul Ehrlich)

- Cancer can occur at “overwhelming frequency” if it was not for host immune responses preventing the outgrowth of continuously arising cancer cells
- Cellular immune mechanisms can recognize unique antigens expressed by cancer cells and eliminate them before they present clinically as tumors.
- Tumor antigens can be viral proteins found in tumors caused by viruses, neo-antigens from mutated proteins or overexpressed self antigens.
- Similar to when the body encounters a pathogen, **T cells act as sentinels in recognizing and eliminating continuously arising, nascent transformed cells**



Chen and Mellman, Immunity 2013

Cancer immunosurveillance hypothesis evolved into the "Cancer Immunoediting" model

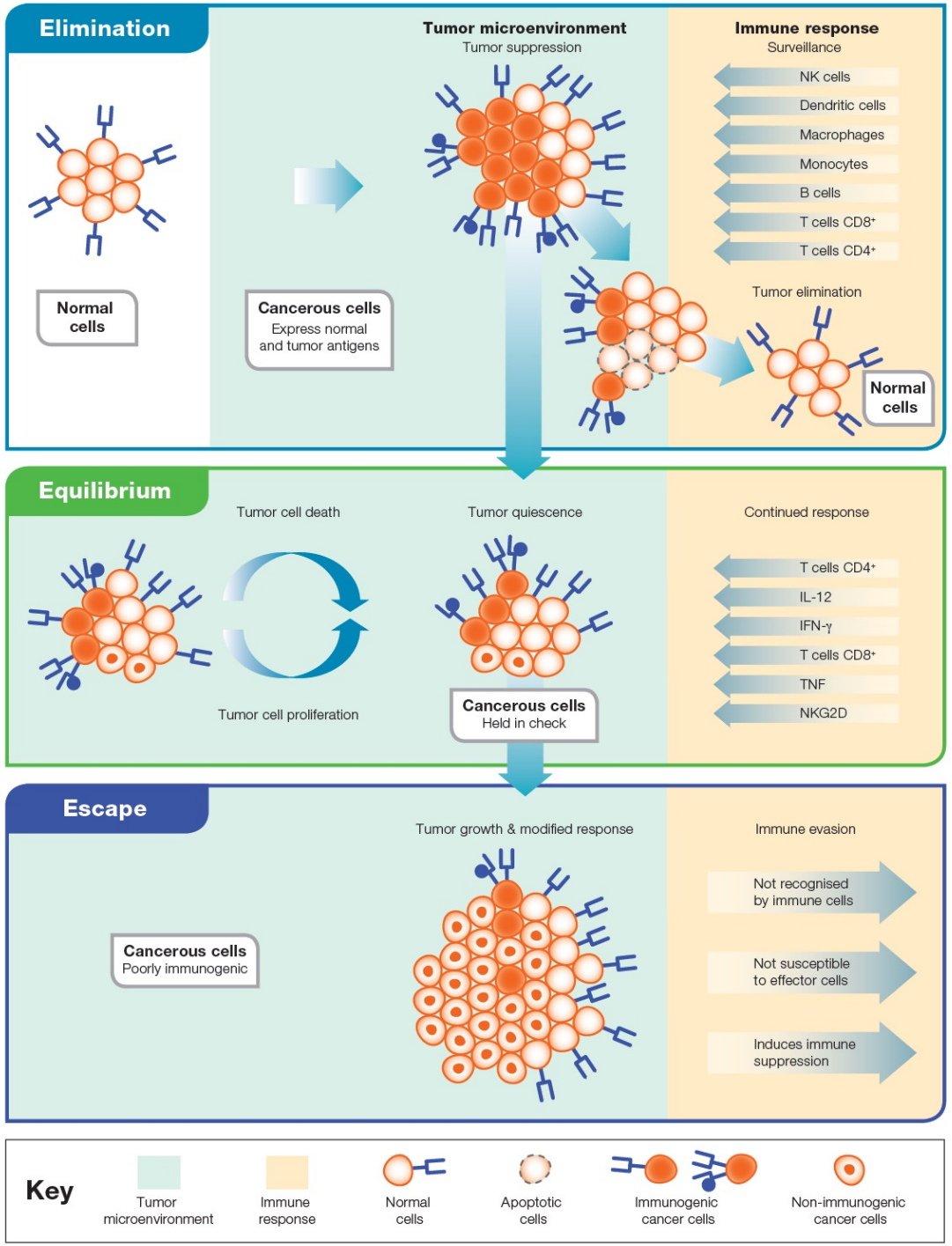
The 3Es of Cancer Immunoediting

Elimination = Immune cells recognize and destroy transformed cells to prevent the development of malignancy

Equilibrium = In this phase, the surviving cancer cells and the immune system are in a dynamic balance where anti-tumor immunity controls tumor growth, but does not completely eliminate the tumor, and tumor cells appear to be clinically dormant

Escape = Cancer cells that escape elimination and evolve during the equilibrium phase adopt multiple immunosuppressive mechanisms allowing tumor cells to escape from control by the immune system and grow in an unrestricted manner

Scientists are targeting these known mechanisms of evasion to develop effective cancer immunotherapy approaches- with the ultimate goal to skew towards tumor elimination rather than tumor progression



Immunotherapy

Stimulating, or boosting, the natural defenses of the immune system so it works harder and smarter to find, attack and get rid of cancer cells

Unleashing the power of the immune system is a smart way to fight cancer

✓The immune system is precise, so it is possible to target cancer cells exclusively while sparing healthy cells

✓The immune system can adapt continuously and dynamically, just like cancer does, so if a tumor manages to escape detection, the immune system can re-evaluate and launch a new attack

✓The immune system's "memory" allows it to remember what cancer cells look like, so it can target and eliminate the cancer if it returns

Immunotherapy- the first steps

- Immunotherapy predates the more commonly known chemotherapy and radiation as the first non-surgical treatment of cancer
- In the early 1890s, William B. Coley, M.D., a New York-based surgeon, stumbled upon a surprising finding in case files : a patient's cancer had regressed after he came down with an acute bacterial infection
- In 1891 Coley injected his first patient with streptococcal organisms and noticed the shrinkage of a malignant tumor
- Coley continued to pursue his approach and ultimately developed a mixture of killed bacteria that became known as Coley's mixed bacterial toxins, or simply "Coley's toxins."
- Treated over 1,000 cancer patients with these toxins, with varied success. Though the treatment clearly worked in some cases, the results were unpredictable
- As other cancer treatments—first radiation, then chemotherapy—became popular, Coley's method faded from view and was virtually forgotten for years

Immunotherapy

- The first modern immunotherapies took their cue directly from Coley's toxins and were essentially extensions of his work- using bacterial products to generate an intensified non-specific immune response against cancer
- In the late 1950s, researchers began experimenting with BCG (Bacillus Calmette-Guérin- weakened form of the TB bacterium) in cancer
- In 1990 BCG was approved by the FDA as first-line treatment for early forms of bladder cancer, for which it is still used as a mainstay of therapy

How the Immune System Fights Cancer?

Non-Specific Immunotherapies

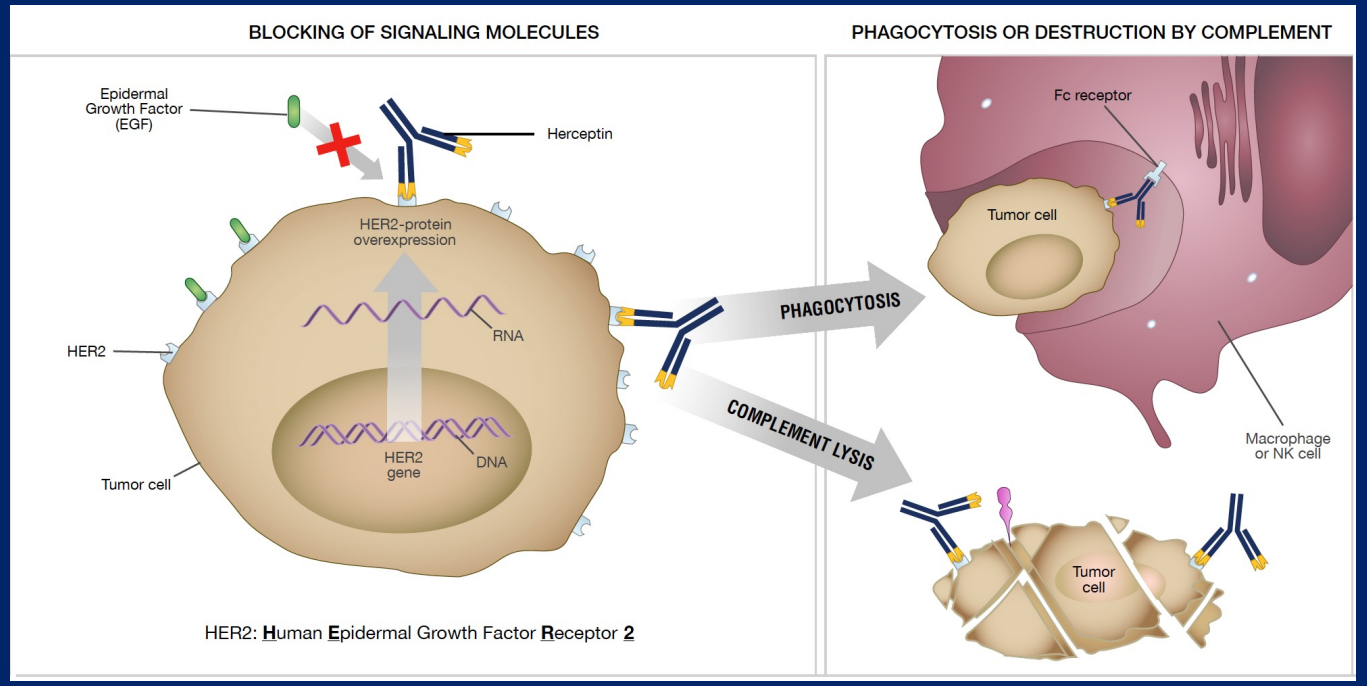
- **Cytokines- molecules that immune cells secrete to communicate with each other- are often used as a form of non-specific immunotherapy**
- Some cytokines, such as tumor necrosis factor alpha and interferon alpha, interact directly with tumor cells, inducing them to either commit suicide or stop growing
- Cytokines, such as IL-2 and GM-CSF, activate important immune cells such as natural killer cells, T cells, and dendritic cells
- **Cytokine therapy is approved for clinical use in several cancers**
- Because they stimulate the immune system in a general way, cytokines are often combined with other immunotherapies

NAME	FUNCTION	TESTING STATUS
Interleukin (IL)-2	Enhances cytotoxic ("killer") T cell and NK cell function	FDA approved for melanoma and renal cell carcinoma
IL-7	Enhances T cell function	Phase II testing
IL-10	Inhibits tumor antigen presentation	Phase I testing
IL-12	Enhances cell-mediated immune response; inhibits angiogenesis	Phase II testing
IL-15	Enhances cytotoxicity	Phase II testing
IL-18	Enhance tumor antigen presentation and cytotoxicity	Phase I testing
IL-21	Enhances T cell and NK cell function	Phase I/II testing
GM-CSF	Enhances tumor antigen presentation	FDA approved for use with bone marrow transplants; phase III testing with cancer vaccines
Interferon (IFN)-alpha	Enhances tumor antigen presentation and cytotoxicity	FDA approved for melanoma, chronic myelogenous leukemia, hairy cell leukemia, follicular non-Hodgkin lymphoma, and Kaposi's sarcoma
IFN-gamma	Enhances tumor antigen presentation and cytotoxicity	Phase I testing
Tumor necrosis factor-alpha	Induces tumor-cell death	Phase III testing

Antibody Immunotherapies

- Antibodies are proteins made by B-cells that circulate in the blood and protect us from free-floating pathogens and cancer cells
- Since the mid-1970s, it has been possible to generate abundant quantities of specific antibodies in the laboratory for use as medicines
- Monoclonal Antibodies can:
  - physically interfere with important signaling molecules on cancer cells and halt their growth
  - promote destruction by macrophages or NK cells
  - activate complement that causes tumor cells to burst
- Monoclonal antibodies can also be fitted with poisons or radioactive isotopes

https://www.youtube.com/watch?v=dxnjAc-rqz8



- *Herceptin is an FDA-approved antibody, specific for the human epidermal growth factor receptor 2 (HER2)*
- *HER2 is overexpressed in 25-30 percent of primary breast cancers*
- *Herceptin blocks the activity of this important growth receptor and leads to cancer cell death. Herceptin was approved by the FDA in 1998 for the treatment of HER2-overexpressing breast cancer*

Antibody Therapies

- The plus side of monoclonal antibodies is that they are usually well tolerated, with minimal side effects, and often lead to significant cancer reductions
- The downside is that they are rarely curative; even when remissions are achieved, many cancers can develop resistance to the drug and come back
- Another limitation is that they do not work well on bulky tumors, which tend to be inaccessible to antibodies

SELECTED FDA-APPROVED MONOCLONAL ANTIBODIES FOR CANCER

TRADE NAME (GENERIC NAME)	TARGETS	INDICATIONS	FDA APPROVED
Rituxan (rituximab)	CD20	B cell non-Hodgkin lymphoma, chronic lymphocytic leukemia	1997
Herceptin (trastuzumab)	HER2	HER2+ breast cancer, HER2+ gastric cancer	1998
Erbitux (cetuximab)	EGFR	Colorectal cancer, head and neck cancer	2004
Avastin (bevacizumab)	VEGF	Colorectal, lung, brain, kidney, cervical, and ovarian cancers	2004
Vectibix (panitumumab)	EGFR	Colorectal cancer	2006
Arzerra (ofatumumab)	CD20	Chronic lymphocytic leukemia	2009
Adcetris (brentuximab vedotin)	CD30	Hodgkin lymphoma	2011
Perjeta (pertuzumab)	HER2	HER2+ breast cancer	2012
Kadcyla (ado-trastuzumab emtansine)	HER2	HER2+ breast cancer	2013
Gazyva (obinutuzumab)	CD20	Chronic lymphocytic leukemia	2013
Cyramza (ramucirumab)	VEGF2	Gastric, lung, and colorectal cancers	2014
Unituxin (dinutuximab)	GD2	Neuroblastoma	2015
Darzalex (daratumumab)	CD38	Multiple myeloma	2015
Empliciti (elotuzumab)	SLAMF7	Multiple myeloma	2015
Portrazza (necitumumab)	EGFR	Lung cancer	2015

CD, cluster of differentiation; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor

To date, nearly 20 monoclonal antibodies have been approved by the FDA for use in cancer treatment

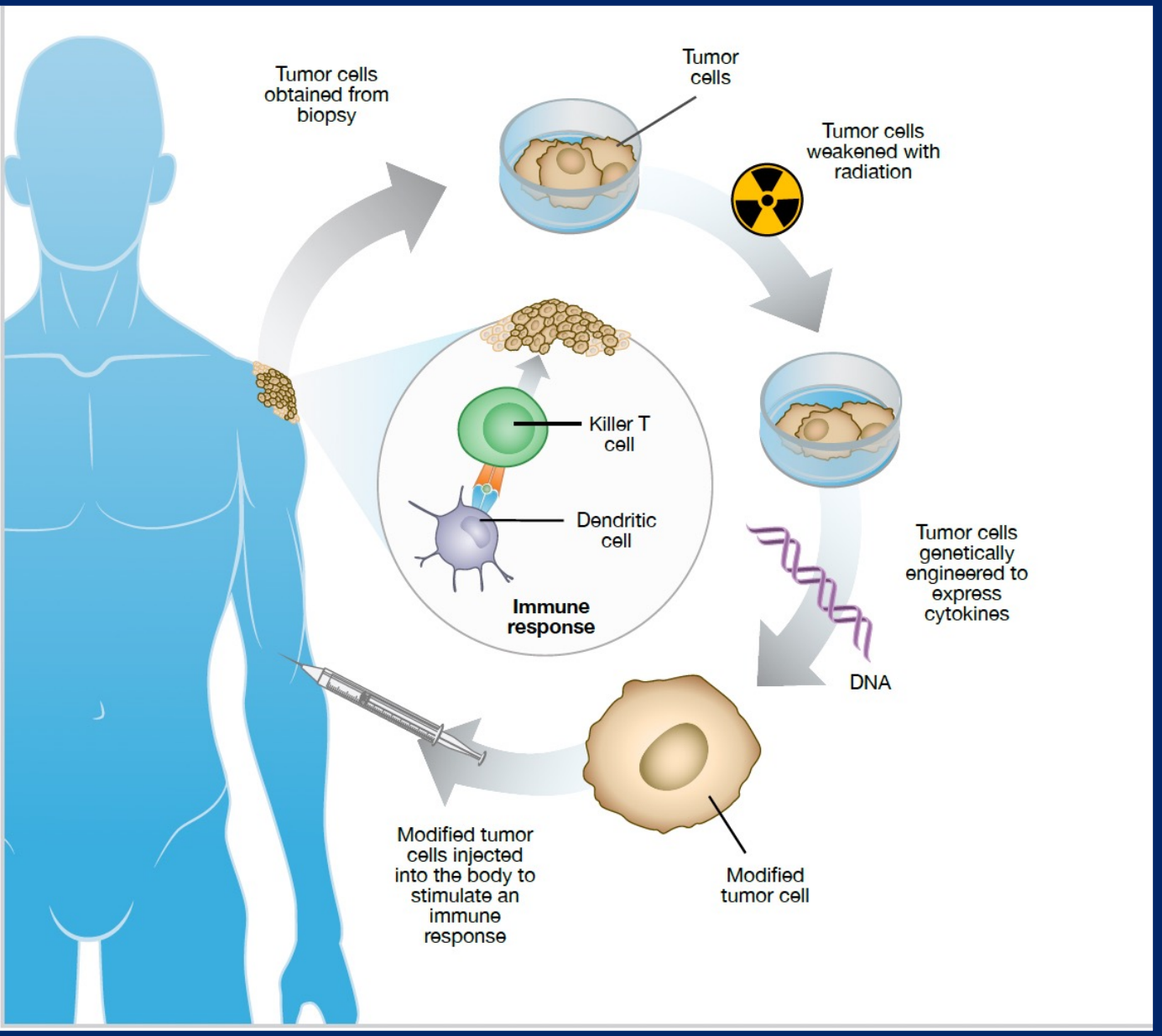
CANCER VACCINES

- Goal of Cancer Vaccines is to present cancer antigens to the immune system to trigger an immune response against cancer.
- Two broad classes of cancer vaccines:
  - Preventive vaccines- like vaccines against infectious diseases in that the aim is to prevent cancer from forming in the first place
  - Therapeutic vaccines- are designed to stimulate an immune response against an existing cancer, in the hope of destroying it.

Preventive Vaccines- Several cancers are known to be caused by viral infections. In these cases, it is possible to prevent the cancer by vaccinating against the virus

- FDA approved Preventive Cancer Vaccines
  - Liver cancer can be caused by infection with the hepatitis B and C viruses. Vaccinating against the hepatitis B virus is an effective way to prevent liver cancer.
  - Cervical cancer is caused by infection with human papillomavirus (HPV). Cervical cancer vaccine Gardasil protects against nine types of HPV that cause approximately 90 percent of all cases of cervical cancer worldwide

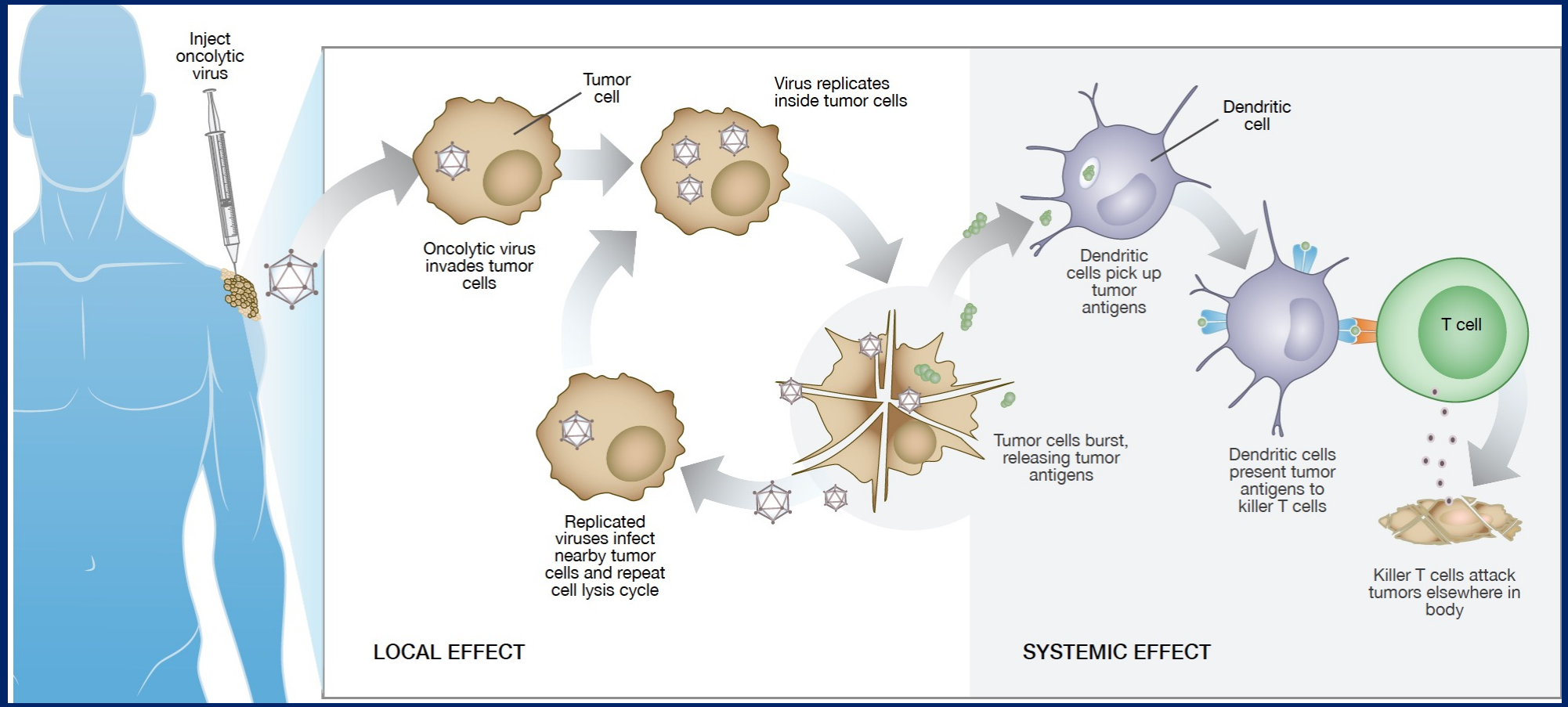
Therapeutic Cancer Vaccines- Whole Tumor Cell Vaccines



- Involves extracting whole tumor cells from the patient, blasting the cells with radiation to weaken them, genetically modifying them with important cytokines and then transferring them back into the patient
- Advantage of whole tumor cell vaccines is that scientists do not have to isolate a specific antigen from tumor cells and many tumor antigens are presented to the immune system at one time, generating a broader response.

https://www.mskcc.org/videos/therapeutic-cancer-vaccines-how-they-work

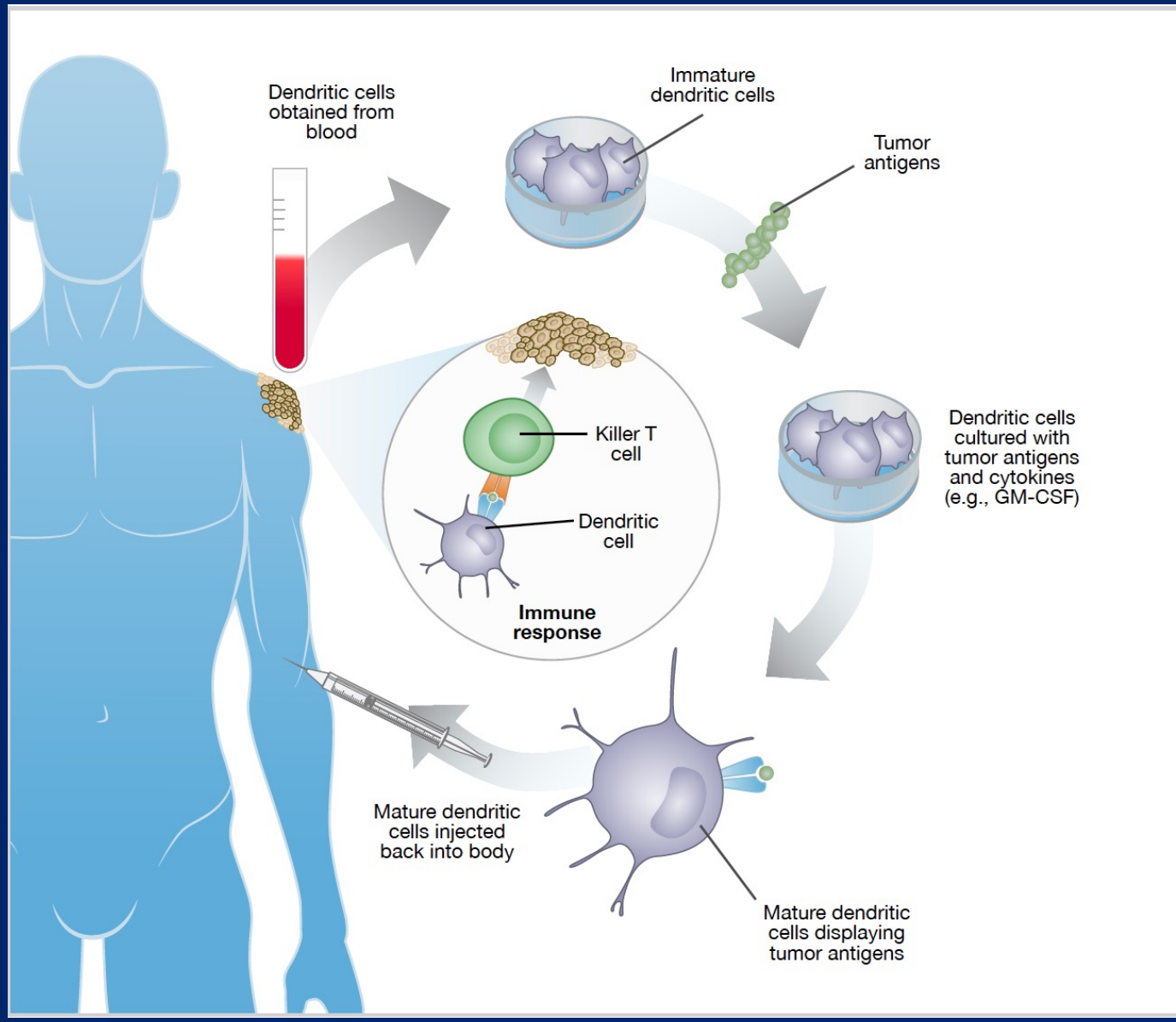
Virus Based Vaccines-Oncolytic Viruses



- Oncolytic viruses genetically engineered to preferentially reproduce inside tumor cells and kill them by causing them to burst
- Both a direct and an indirect effect on cancer: Killing a cancer cell directly and/or triggering an immune response
- Imlygic- FDA approved for treatment of advanced non-resectable melanoma
- Consists of a modified herpes virus that has been genetically engineered to replicate in cancer cells Imlygic is injected into accessible tumor sites, where the virus kills cancer cells and releases tumor antigens that can stimulate an immune response

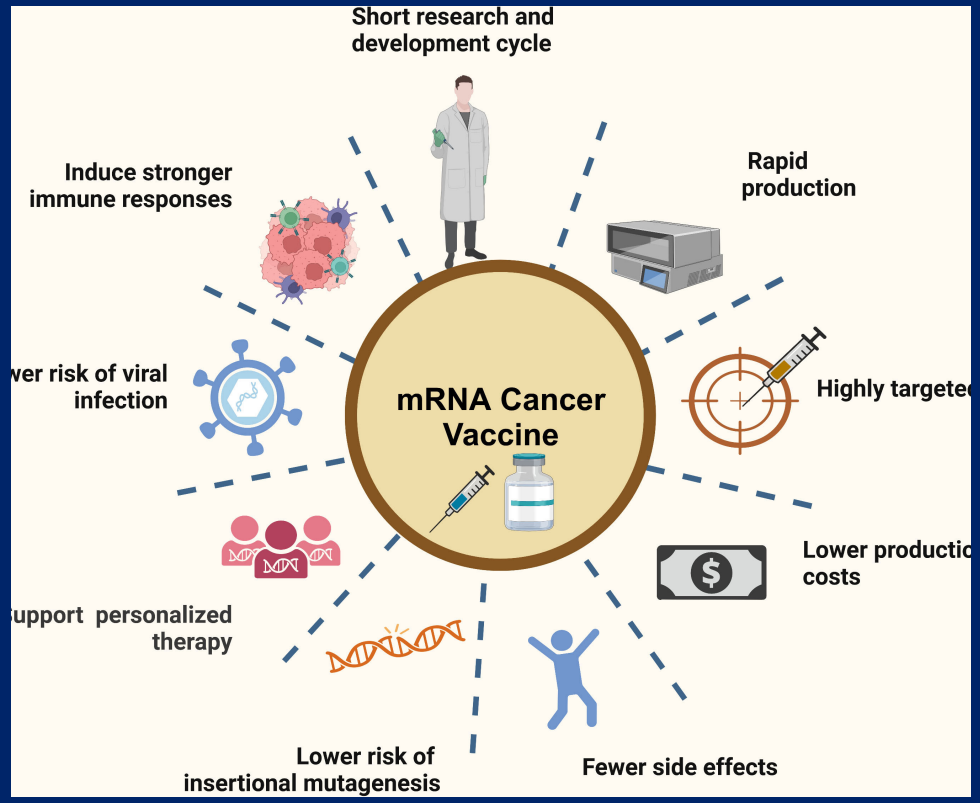
Dendritic Cell Based Vaccines

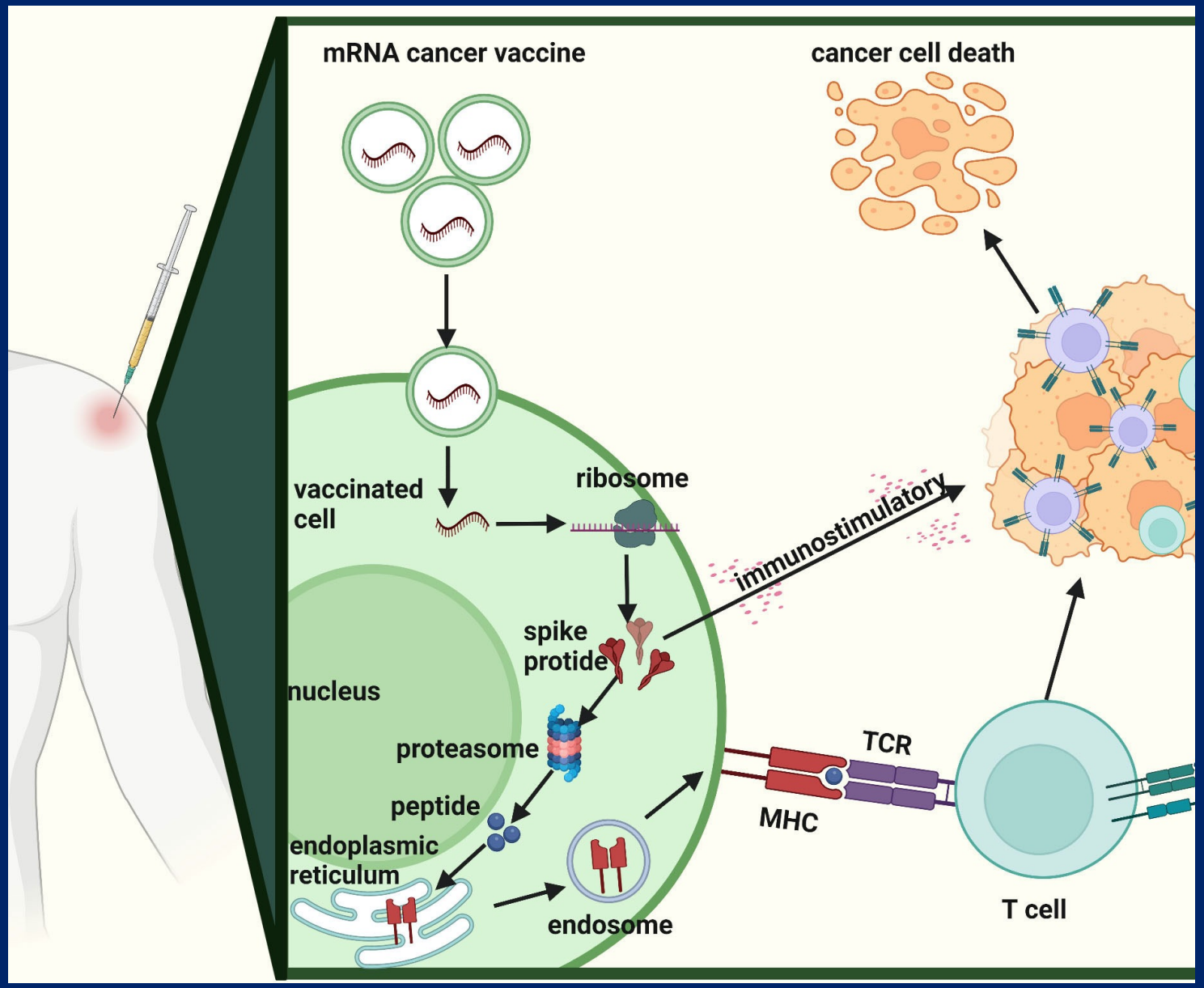
- Dendritic cells are obtained from the patient's blood, treated in the lab with cancer antigens and cytokines; cells are then returned to the patient where they stimulate an immune response
- Advantage of DC-based vaccination is that they can produce all the molecules required for eliciting an immune response
- Provenge- approved by the FDA in 2010 for the treatment of prostate cancer
- Made by removing immature cells including DC from patients, culturing with cancer-associated antigen prostatic acid phosphatase (PAP), and then returning them to the patient
- Provenge has been shown to extend, the lives of patients with metastatic prostate cancer



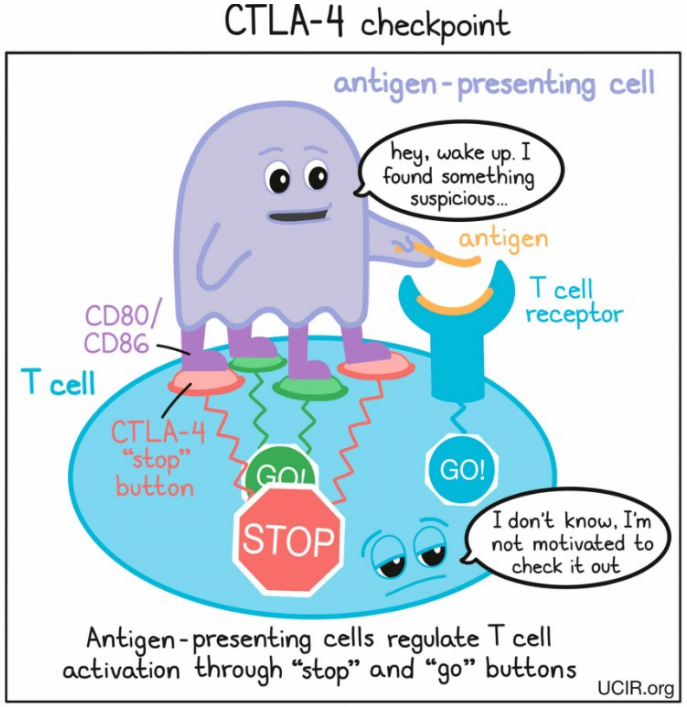
https://www.youtube.com/watch?v=zL1l8PpAJJg

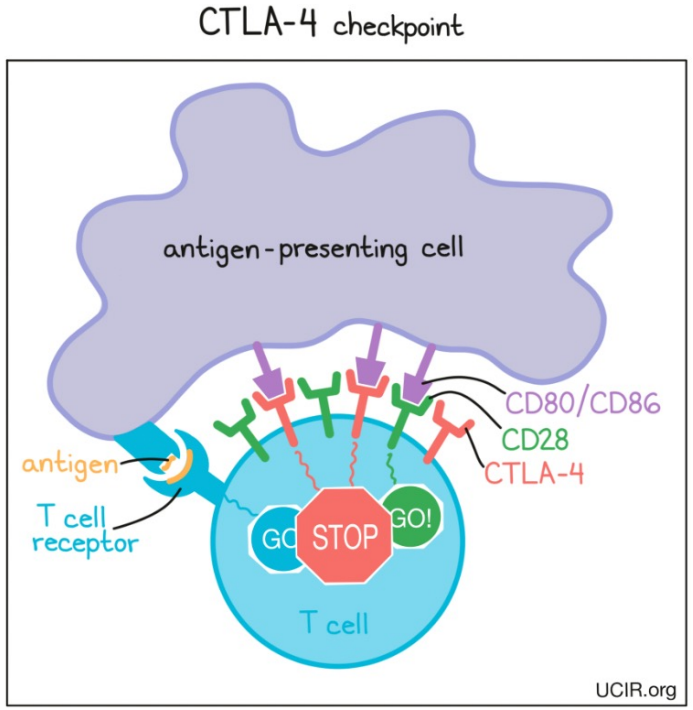
mRNA Vaccines for Cancer





Checkpoint Blockade



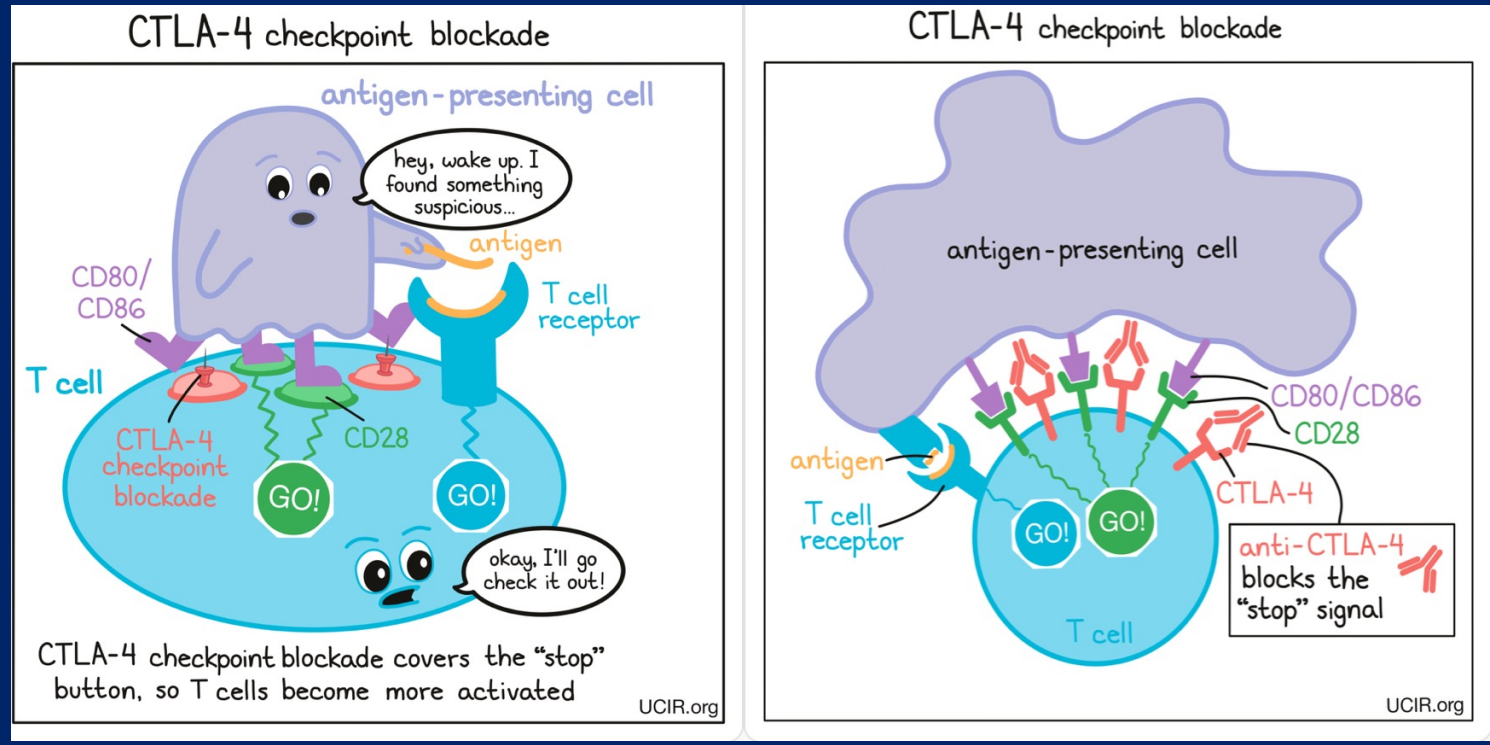


https://www.youtube.com/watch?v=GIUu239FWMg

- Immune checkpoints are a normal part of the immune system, they prevent an immune response from being so strong that it destroys healthy cells in the body
- T cells come equipped with a T cell receptor to recognize specific antigens on cancer cells. In addition, several distinct "co-stimulatory" receptors provide signals for the T cell to attack (CD28); other receptors (CTLA4), provide signals to stand down
- *Using the analogy of a car- If the T cell receptor is the ignition switch, then the CD28 molecule is the gas pedal, telling the T cell to go. The CTLA-4 molecule, on the other hand, is the brake, helping to keep the immune system in check so it doesn't speed out of control*
- If a T cell receives enough "go" signals, it will be convinced that the threat is real, and will prepare to patrol the body and hunt for any dangerous cells.
- CTLA-4 acts as a checkpoint for T cells to not overreact

Checkpoint Blockade/ Checkpoint Inhibitors

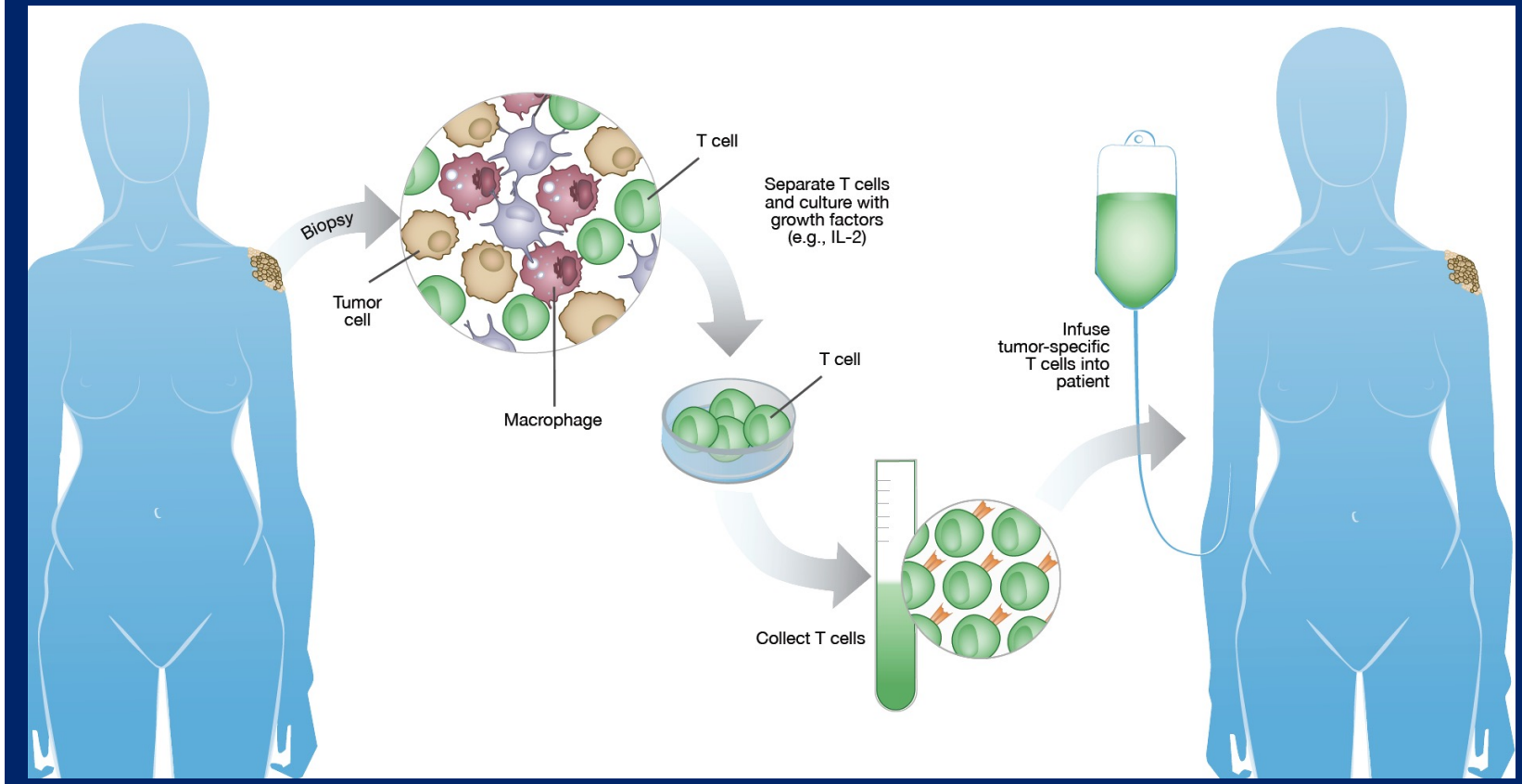
- T cells have checkpoint proteins that act like brakes. Checkpoint inhibitors bind to these proteins and “take the brakes off” the immune response, enabling a stronger attack against cancer
- In the 1990s, James Allison showed that an antibody directed against CTLA-4 in mice could quickly and permanently cure them of their tumors.
- This dramatic laboratory finding led to the drug Ipilimumab the first drug of any kind to show improved survival in a phase III trial in melanoma patients.
- Approved by the FDA in 2011 for the treatment of advanced melanoma
- Checkpoint inhibitors can be used alone or as combination therapies
- Currently approved treatments for Lung, Kidney, Bladder, Head and Neck cancers and many more trials ongoing



Two of the researchers who pioneered the study of these checkpoint blockades received the Nobel Prize in Physiology or Medicine in 2018

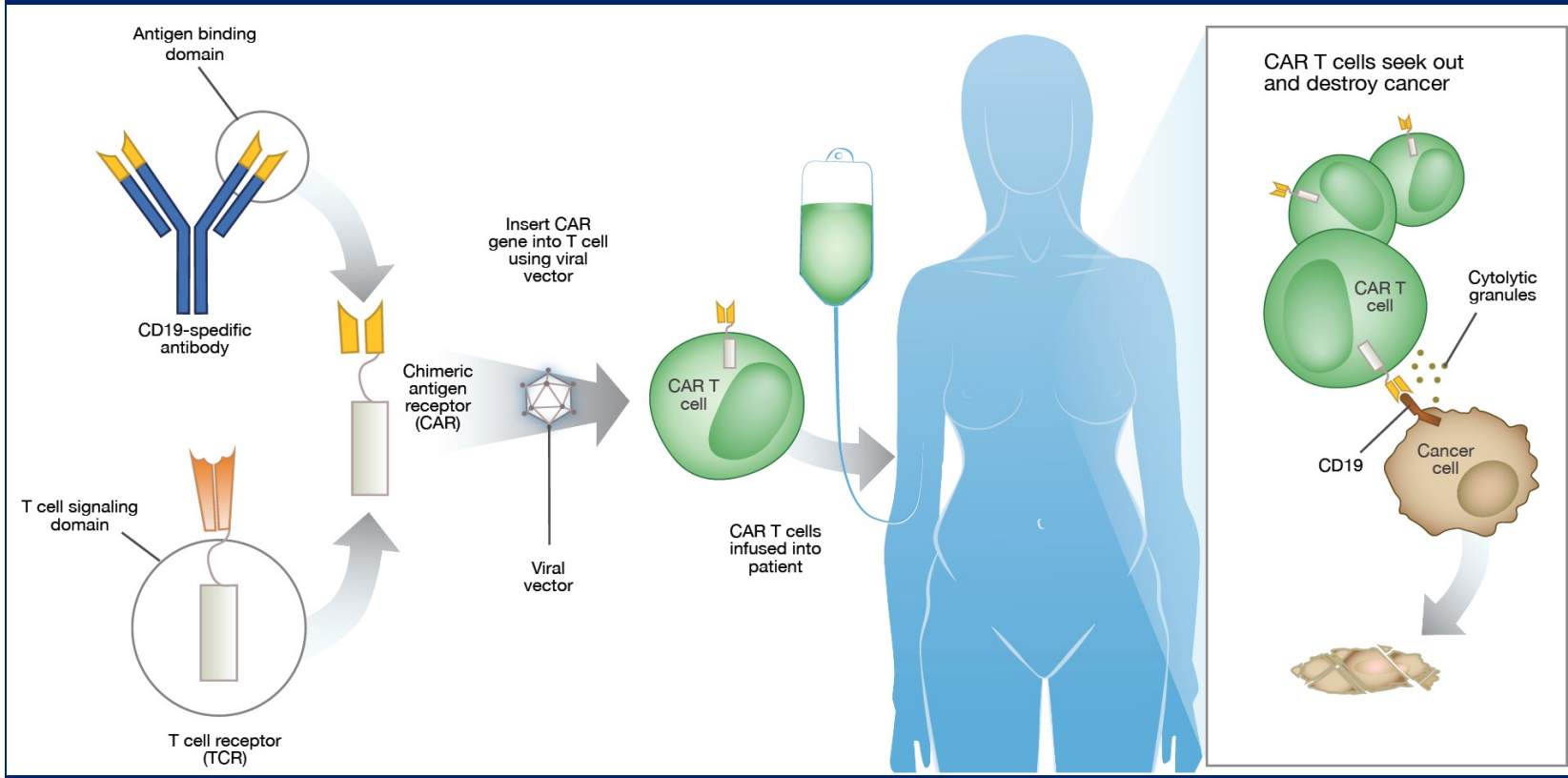
Cell Therapies

- Adoptive cell therapy is a way to enrich and expand cancer-specific T cells from a person's own body and then give them back to the patient in vastly increased numbers
- Immune cells are often found associated with the tumor-**Tumor Infiltrating Lymphocytes** (TILs) that recognize cancer
- TILs can be isolated from a tumor and expanded in the lab by treating them with the T cell growth factor IL-2 and then infused back into the patient



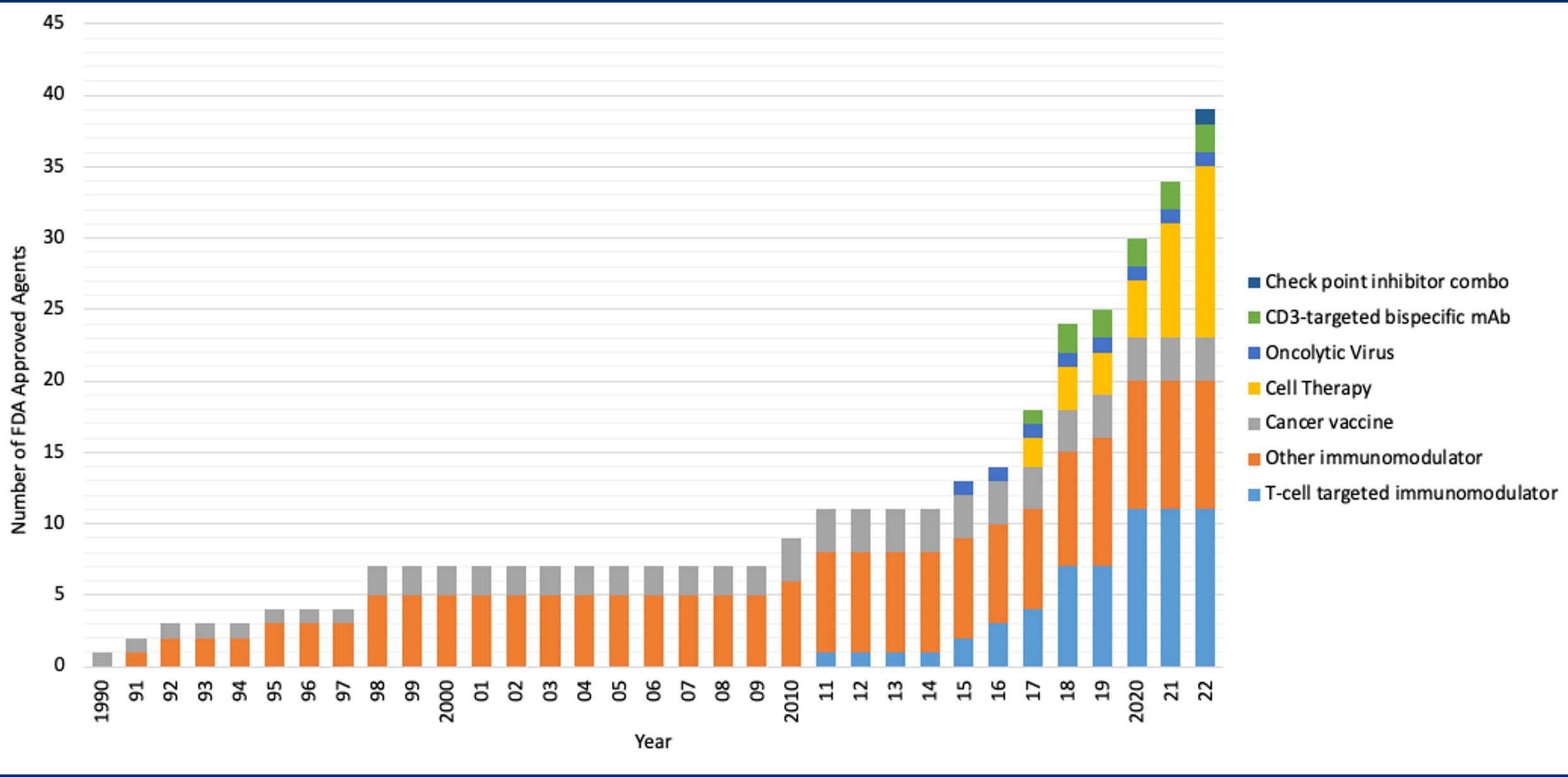
CAR T Cells

- Chimeric antigen receptors (CARs) are genetically engineered proteins made up of an antibody binding domain linked to a T cell signaling domain. They turn a person's own T cells into cancer fighting weapons
- CAR T cells have several advantages over regular T cells, mostly because they bring together the best part of an antibody with the best part of a T cell
- In October 2017, the U.S. Food and Drug Administration (FDA) approved the first CAR T cell therapy to treat adults with certain types of large B-cell lymphoma



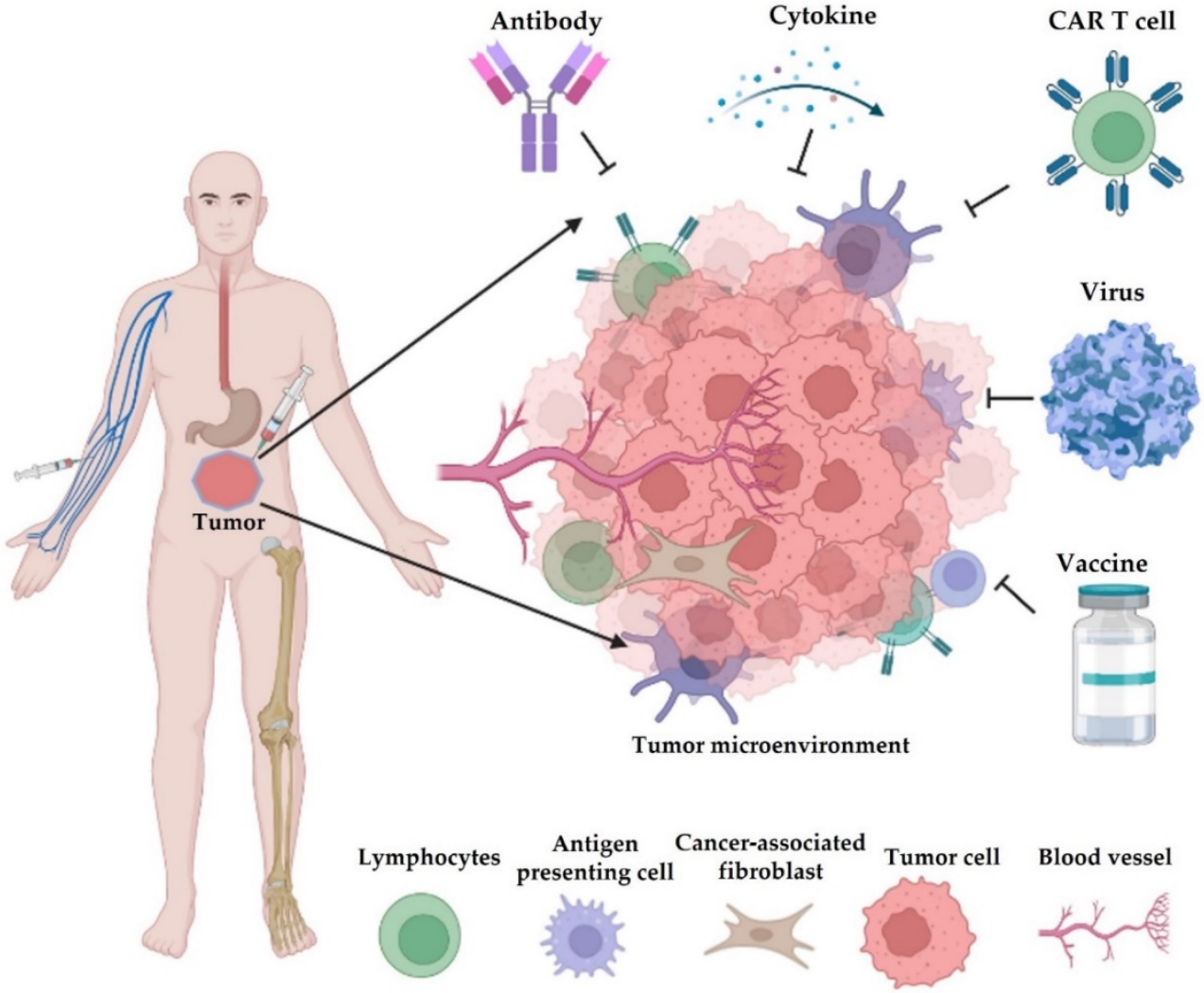
https://www.mskcc.org/videos/car-cell-therapy-how-it-works

Immunotherapy Agents Approved over the years



Immunotherapy

- Immunotherapy targets the immune system rather than the tumor itself. Because cancer cells develop new mutations quickly, they can grow resistant to conventional chemotherapies
- **Immune system, by contrast, can adapt to the changing tumor, evolving with it**
- **Even if new mutations occur, the immune system may be able to develop new cancer-specific T cells. The result is that immunotherapy has the potential to offer patients long-term, durable remissions**
- Some of the earliest melanoma patients treated with CTLA-4 checkpoint inhibitors, for example, are now more than 10 years out and still free of disease
- The FDA has approved immunotherapies as a first line of treatment for nearly 20 cancers (melanoma, lung, kidney, breast, bladder, lymphoma)
- Immunotherapy may be given alone or in combination with other cancer treatments
- At MSK alone there are over 195 Immunotherapy Clinical trials currently ongoing in multiple cancer types



Resources

https://www.cancerresearch.org/what-is-immunotherapy

https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy.html

Feel free to reach out-

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