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UNLOCK PROMISING KEY TO PREVENTING CANCER *ROADMAP FOR FUTURE CLINICAL TRIALS TO IMPROVE EFFICACY AND SURVIVAL AFTER TARGETED IMMUNOTHERAPIES*

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ABSTRACT

Cancer immunotherapy is a powerful, growing treatment approach to cancer that can be combined with chemotherapy, radiotherapy, and oncosurgery. Modulating the immune system to enhance anticancer response by several strategies has yielded improved cancer survival. A new approach to cancer immunotherapy has the potential to be a universal treatment for solid tumors. This approach targets immune cells that the body uses to put the brakes on an immune response. There are therapeutic antibodies that are used on some types of cancer. And many people have heard of checkpoint immunotherapies, which blocks certain parts of the immune response.

KEYWORDS: Immunotherapy, Checkpoint inhibitors, CAR T-Cell therapy, Immunomodulators, Immunostimulants, Immunosuppressant, Complement Proteins.

INTRODUCTION

Immune system: The immune system protects your child's body from outside invaders, such as bacteria, viruses, fungi, and toxins (chemicals produced by microbes). It is made up of different organs, cells, and proteins that work together. 3 main parts of the immune system: Passive immunity: This type of immunity is “borrowed” from another source, but it does not last indefinitely. Adaptive (acquired) immunity: This protect from pathogens develops as we go through life. As we are exposed to diseases or get vaccinated, we build up a library of antibodies to different pathogens. This is sometimes referred to as immunological memory because our immune system remembers previous enemies. Innate immunity: We are all born with some level of immunity to invaders. Human immune systems, similarly to those of many animals, will attack foreign invaders from day one.

How the Immune System Works?

Organs, tissues, and glands around your body coordinate the creation, education, and storage of key elements in your immune systems. Ex: Lymph Nodes, appendix, thymus Gland, spleen, bone Marrow, white blood cells.

There are two main types of leukocyte

1. Phagocytes
2. Lymphocytes

Lymphocytes help the body to remember previous invaders and recognise them if they come back to attack again.

Lymphocytes begin their life in bone marrow. Some stay in the marrow and develop into B lymphocytes (B cells), others head to the thymus and become T lymphocytes (T cells). These two cell types have different roles:

•B lymphocytes — they produce antibodies and help alert the T lymphocytes.

•T lymphocytes — they destroy compromised cells in the body and help alert other leukocytes.

Normal Anti-Bacterial Action

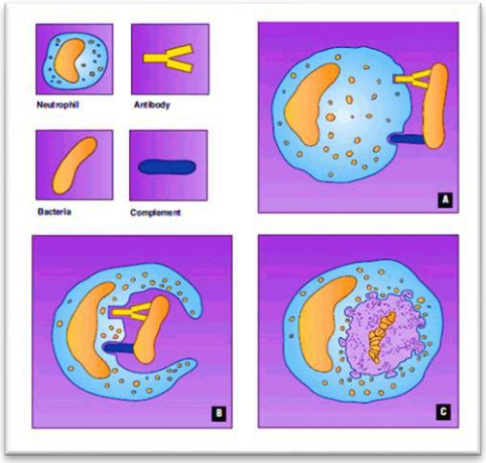


Fig 1: Normal Antibacterial Action.

In most instances, bacteria are destroyed by the cooperative efforts of phagocytic cells, antibody and complement.

A) Neutrophil (Phagocytic Cell) Engages Bacteria (Microbe):The microbe begins its attack on the microbe by attaching to the antibody and complement molecules.

B) Phagocytosis of the Microbe: After attaching to the microbe, the phagocytic cell begins to ingest the microbe by extending itself around the microbe and engulfing it.

C) Destruction of the Microbe: Once the microbe is ingested, bags of enzymes or chemicals are discharged into the vacuole where they kill the microbe.

How an immune system works

The immune system needs to be able to tell self from non-self. It does this by detecting proteins that are found on the surface of all cells.

The role of T lymphocytes

There are distinct types of T lymphocytes: Helper T cells (Th cells) — they coordinate the immune response. Some communicate with other cells, and some stimulate B cells to produce more antibodies. Others attract more T cells or cell- eating phagocytes.

Killer T cells (cytotoxic T lymphocytes) — as the name suggests, these T cells attack other cells. They are particularly useful for fighting viruses. They work by recognizing small parts of the virus on the outside of infected cells and destroy the infected cells.

The role of B lymphocytes

Once B lymphocytes spot the antigen, they begin to secrete antibodies (antigen is short for "antibody generators"). Antibodies are special proteins that lock on to specific antigens. Each B cell makes one specific antibody. For instance, one might make an antibody against the bacteria that cause pneumonia, and another might recognize the common cold virus. Antibodies are part of a large family of chemicals called immunoglobulins, which play many roles in the immune response:

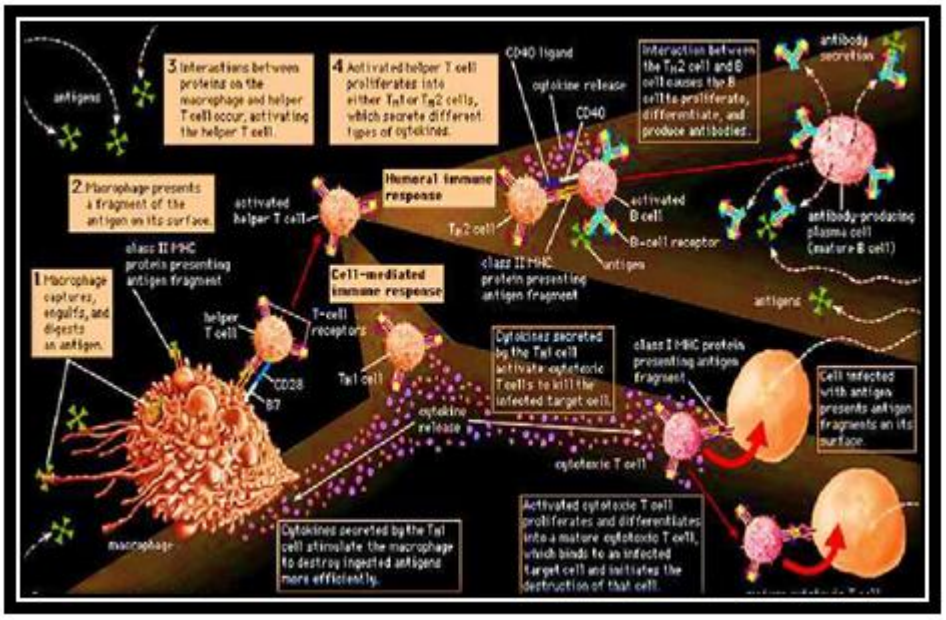


Fig 2: Immune stimulation by activated helper T cells.

Immunoglobulin G (IgG) — marks microbes so other cells can recognize and deal with them. IgM, IgA, IgE, IgD.

Stimulation of immune response by activated helper T cells. Activated by complex interaction with molecules on the surface of a macrophage or some other antigen- presenting cell, a helper T cell proliferates into two general subtypes, $T_{H}1$ and $T_{H}2$. These in turn stimulate the complex pathways of the cell-mediated immune response and the humoral immune response, respectively.

Immunity from disease is actually conferred by two cooperative defense systems, called nonspecific, innate immunity and specific, acquired immunity. Nonspecific protective mechanisms repel all microorganisms equally, while the specific immune responses are tailored to particular types of invaders. Both systems work together to thwart organisms from entering and proliferating within the body. These immune mechanisms also help eliminate abnormal cells of the body that can develop into cancer.

Mechanisms of the immune system

Nonspecific, innate immunity: Most microorganisms encountered in daily life are repelled before they cause detectable signs and symptoms of disease. These potential pathogens, which include viruses, bacteria, fungi, protozoans, and worms, are quite diverse, and therefore a nonspecific defense system that diverts all types of this varied microscopic horde

equally is quite useful to an organism.

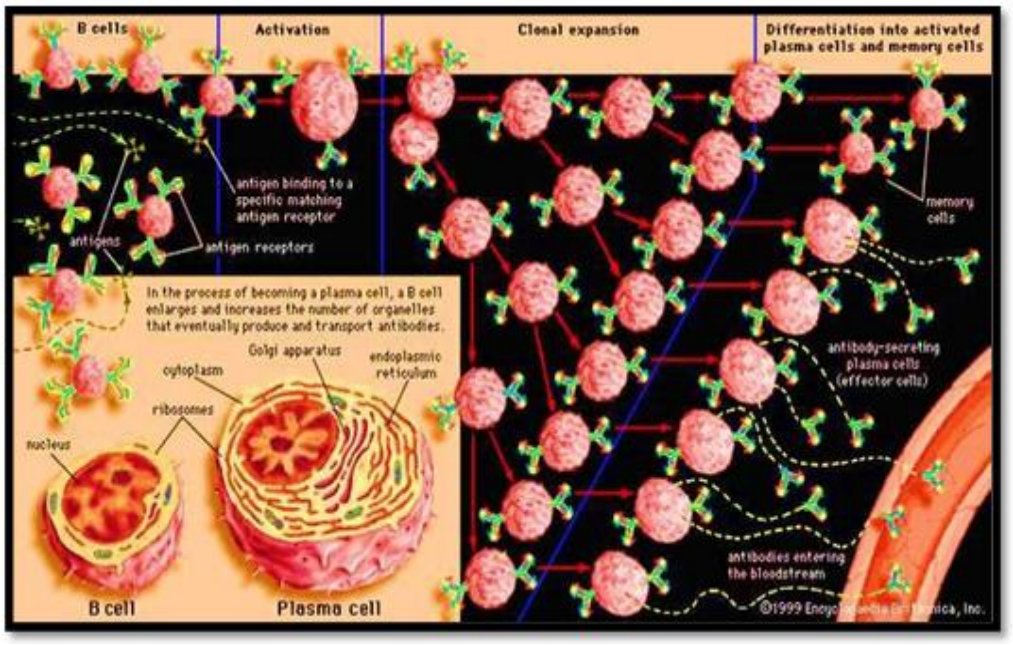


Fig 3: Clonal selection of a B cell.

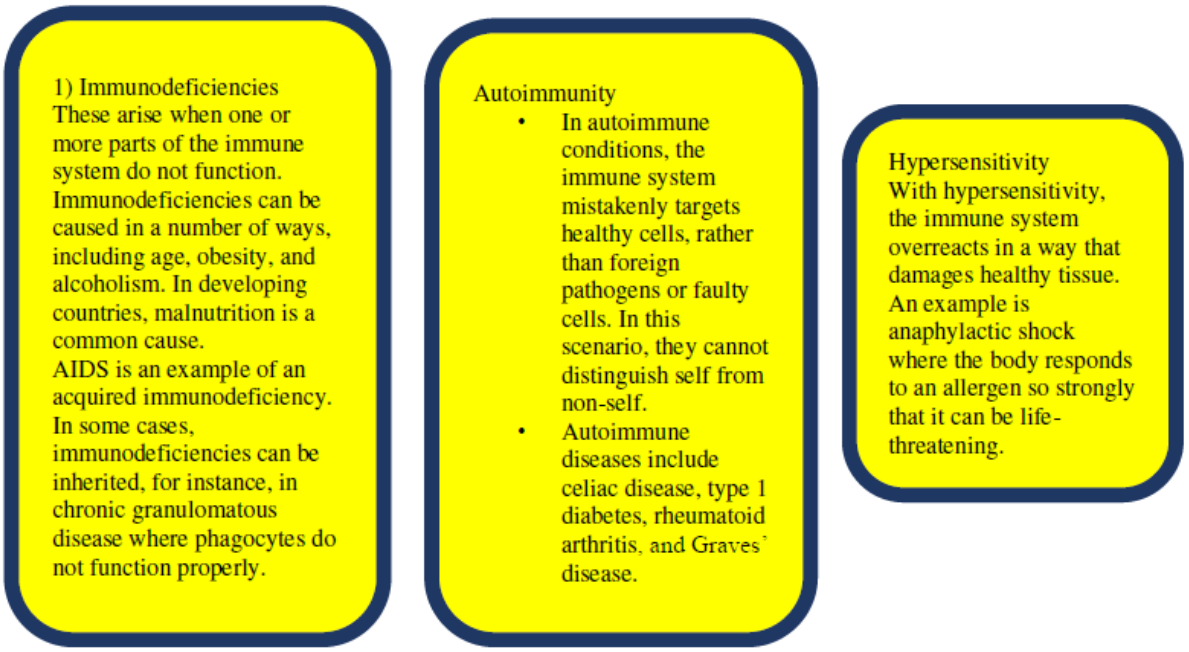
The innate immune system provides this kind of nonspecific protection through a number of defense mechanisms, which include physical barriers such as the skin, chemical barriers such as antimicrobial proteins that harm or destroy invaders, and cells that attack foreign cells and body cells harbouring infectious agents.

Clonal selection of a B cell. Activated by the binding of an antigen to a specific matching receptor on its surface, a B cell proliferates into a clone. Some clonal cells differentiate into plasma cells, which are short-lived cells that secrete antibody against the antigen. Others form memory cells, which are longer-lived and which, by proliferating rapidly, help to mount an effective defense upon a second exposure to the antigen.

Antimicrobial proteins: Complement

A number of proteins contribute directly to the body's nonspecific defense system by helping to destroy invading microorganisms. One group of such proteins is called complement because it works with other defense mechanisms of the body, complementing their efforts to eradicate invaders. Many microorganisms can activate complement in ways that do not involve specific immunity. Once activated, complement proteins work together to lyse, or break apart, harmful infectious organisms that do not have protective coats.

Immune system Disorders



Immunodeficiency

HIV is a virus that targets and alters the immune system, increasing the risk and impact of other infections and diseases. Without treatment, the infection might progress to an advanced disease stage called AIDS.

What is HIV?

Human immunodeficiency virus (HIV) is a virus that attacks immune cells called CD4 cells, which are a type of T cell. These are white blood cells that move around the body, detecting faults and anomalies in cells as well as infections.

When HIV targets and infiltrates these cells, it reduces the body's ability to combat other diseases. This increases the risk and impact of opportunistic infections and cancers. However, a person can carry HIV without experiencing symptoms for a long time.

What is AIDS?

AIDS is the most advanced stage of HIV infection. Once HIV infection develops into AIDS, infections and cancer pose a greater risk.

Without treatment, HIV infection is likely to develop into AIDS as the immune system gradually wears down. However, advances in ART mean than an ever- decreasing number of people progress to this stage.

Symptoms

Early symptoms of HIV may include: fever, chills, sweating, particularly at night, enlarged glands or swollen lymph nodes, diffuse rash, fatigue, weakness, pain, including joint painmuscle aches, sore throat, thrush, or a yeast infection, unintentional weight loss, with advancing HIV.

How HIV spreads?

To become infected with HIV, infected blood, semen or vaginal secretions must enter your body. This can happen in several ways:

- By having sex, sharing needles, from blood transfusion, during pregnancy or delivery or through breast-feeding.

Diagnosis

HIV can be diagnosed through blood or saliva testing. Available tests include:

1) Antigen/antibody tests.
2) Antibody tests.
3) Nucleic acid tests (NATs)
4) If you receive a diagnosis of HIV/AIDS, several tests can help your doctor determine the stage of your disease and the best treatment, including: CD4 T cell count. CD4 T cells are white blood cells that are specifically targeted and destroyed by HIV. Even if you have no symptoms, HIV infection progresses to AIDS when your CD4 T cell count dips below 200.
5) Drug resistance.
6) The classes of anti-HIV drugs include: (Medications)

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) turn off a protein needed by HIV to make copies of itself. Examples include efavirenz (Sustiva), rilpivirine (Edurant) and doravirine (Pifeltro).
- Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) are faulty versions of the building blocks that HIV needs to make copies of itself. Examples include abacavir (Ziagen), tenofovir (Viread), emtricitabine (Emtriva), lamivudine (Epivir) and zidovudine (Retrovir). Combination drugs also are available, such as emtricitabine/tenofovir (Truvada) and emtricitabine/tenofoviralafenamide (Descovy).
- Protease inhibitors (PIs) inactivate HIV protease, another protein that HIV needs to make copies of itself. Examples include atazanavir (Reyataz), darunavir (Prezista) and

lopinavir/ritonavir (Kaletra).

- Integrase inhibitors work by disabling a protein called integrase, which HIV uses to insert its genetic material into CD4 T cells. Examples include bictegravir sodium/emtricitabine/tenofoviralafenamidefumar (Biktarvy), raltegravir (Isentress) and dolutegravir (Tivicay).
- Entry or fusion inhibitors block HIV's entry into CD4 T cells. Examples include enfuvirtide (Fuzeon) and maraviroc (Selzentry).

Autoimmunity: (Rheumatoid arthritis)

Rheumatoid arthritis is a long-term, progressive, and disabling autoimmune disease. It causes inflammation, swelling, and pain in and around the joints and other body organs. The Rheumatoid Arthritis Support Network estimate that RA affects up to 1 percent of the world's population and over 1.3 million people in America. RA is an autoimmune disease.

Symptoms

Symptoms of RA include: pain, swelling, and stiffness in more than one joint, symmetrical joint involvement, joint deformity.

Complications

People with RA have a higher risk of some other conditions, including: heart disease, Obesity. Here is also a higher risk of developing the following conditions:

1) Carpal tunnel syndrome: This is a type of nerve damage that stems from compression and irritation of a nerve in the wrist. Symptoms include aching, numbness, and tingling in the fingers, thumb, and part of the hand.
2) Inflammation: This can affect the lungs, heart, blood vessels, eyes and other parts of the body.
3) Tendon rupture: Inflammation in the tendons can lead to rupture, especially on the backs of the fingers.
4) Cervical myelopathy: Dislocation of the joints in the neck or cervical spine can add pressure to the spinal cord. This can result in decreased mobility and pain on movement. As RA progresses, the risk of cervical myelopathy increases.
5) Vasculitis: Inflammation of the blood vessels can cause them to weaken, thicken, narrow and scar. This can affect blood flow to tissues and organ function may be affected.
6) Susceptibility to infections: There is a higher risk of developing colds, flu, pneumonia, and other diseases, especially if the person is taking immunosuppressant medications to

manage RA. People with RA should ensure their vaccinations, such as flu jabs, are up-to-date.

Diagnosis

1) Blood tests 2) Imaging scans and X-rays Medications:

- Non steroidal anti-inflammatory drugs (NSAIDs): Examples include Advil, Motrin, and Aleve.
- Corticosteroids
- Disease-modifying antirheumatic drugs (DMARDs): Examples include leflunomide (Arava), methotrexate (Rheumatrex, Trexall), sulfasalazine (Azulfidine), minocycline (Dynacin, Minocin), and hydroxychloroquine (Plaquenil).
- Types of immunosuppressants include cyclosporine (Neoral, Sandimmune, Gengraf), azathioprine (Imuran, Azasan), and cyclophosphamide (Cytoxan).
- Tumor necrosis factor-alpha inhibitors (TNF-alpha inhibitors) Examples include (Enbrel), infliximab (Remicade) and adalimumab (Humira).

Hypersensitivity: (Anaphylaxis)

Anaphylaxis is a severe allergic reaction. It can lead to a potentially fatal condition known as anaphylactic shock. Each year, there are 200,000 hospital visits due to food allergies in the United States, according to the Asthma and Allergy Foundation of America (AAFA).People also commonly have allergic reactions to medications and insect stings.

Causes and triggers

Anaphylaxis happens when the body reacts to a foreign substance as if it were a serious threat to health. The most common triggers for these reactions are medications, foods, and insect stings. Some foods that often trigger allergic reactions include: milk, eggs, fish, crustacean shellfish, wheat, soy, peanuts, tree nuts. In its reaction to an allergen, the body produces large amounts of histamine a signaling molecule that can trigger an inflammatory response.

This response can lead to: dilation of the blood vessels, a sudden drop in blood pressure, loss of consciousness, shock.

Treatment

1) Emergency treatment for a person with a severe allergic reaction involves an injection of epinephrine, or adrenaline.

2) Epinephrine helps in several ways:

- It causes the blood vessels to constrict, decreasing swelling and helping to increase blood pressure.
- It relaxes the muscles around the lungs.
- It limits the reaction by blocking the body's release of additional chemicals.

3) Most people respond well to this treatment, and symptoms usually start to subside right away. If there is no immediate improvement, the person will need another dose after 10 minutes.
4) Sometimes, symptoms of the reaction return after subsiding. The person may need to remain under observation in a hospital for 24 hours.

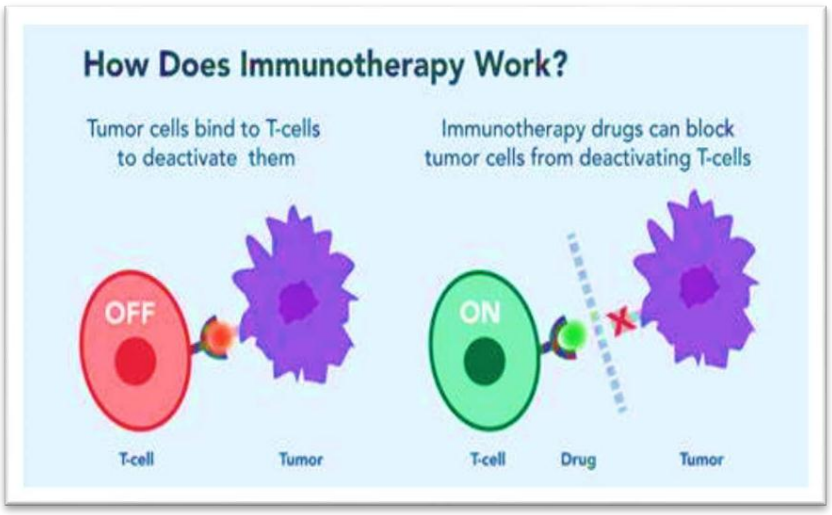
Immunotherapy

What is immunotherapy?

Immunotherapy is a type of cancer treatment that assists the body's immune system to fight cancer.

How does immunotherapy work?

There are different kinds of immunotherapy and they work in different ways. Immunotherapy can boost the immune system to work better against cancer or remove barriers to the immune system attacking the cancer.



When is immunotherapy used?

Surgery, chemotherapy and radiotherapy are still the most widely used cancer treatments but checkpoint immunotherapy is likely to benefit some people with some types of cancer. In

Australia immunotherapy has been predominantly used for the following cancers: head and neck, bladder, kidney, melanoma, Leukaemia, lymphoma.

How is immunotherapy treatment given?

- How often and how long you receive immunotherapy may depend on:
- The type of immunotherapy
- The type of cancer
- How advanced the cancer is
- How you respond to treatment
- The side effects you may experience.

Checkpoint inhibitors are usually given with an injection into a vein (intraveneously). When immunotherapy is used to treat some melanoma cases, a cream called imiquimond may be applied directly to the affected area. Sometimes more than one type of immunotherapy drug is prescribed. Immunotherapy drugs appear to keep working for varying periods of time, and in some cases, can keep working long after other treatments are no longer used.

What are the side effects of immunotherapy?

Side effects from immunotherapy can vary depending on the type of treatment you receive and how your body responds. The side effects of checkpoint immunotherapy are different from those of other cancer treatments.

Immunotherapy to TREAT cancer

Fig 4: Immunotherapy to treat cancer.

Immunotherapy is a type of cancer treatment that helps your immune system fight cancer. The immune system helps your body fight infections and other diseases. It is made up of white blood cells and organs and tissues of the lymph system. Immunotherapy is a type of biological therapy. Biological therapy is a type of treatment that uses substances made from living organisms to treat cancer.

Immunotherapy treatment harnesses the body's natural strength to fight cancer—empowering the immune system to conquer more types of cancer and save more lives.

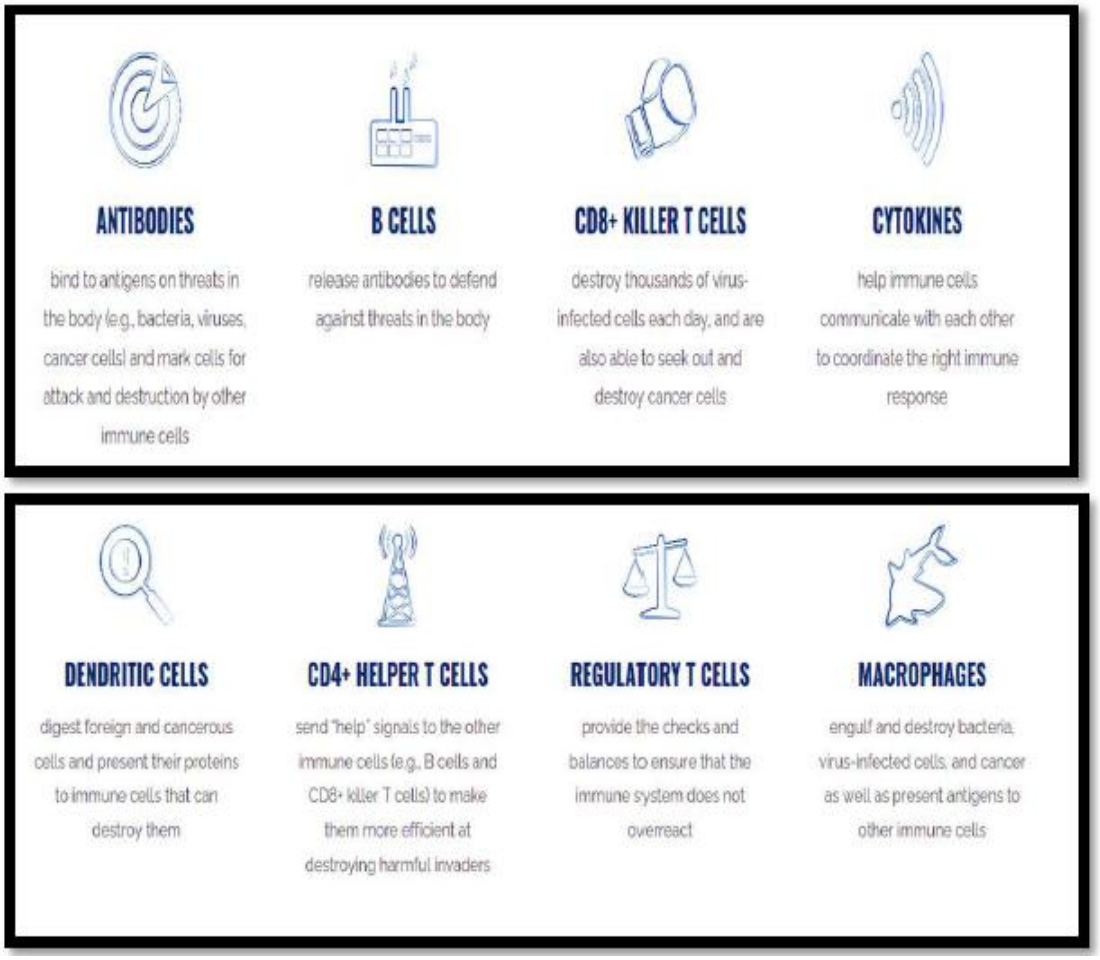


Fig 5: Boosting the Body's Immune System to Fight Cancer.

How does immunotherapy work against cancer?

As part of its normal function, the immune system detects and destroys abnormal cells and most likely prevents or curbs the growth of many cancers. For instance, immune cells are sometimes found in and around tumors. These cells, called tumor-infiltrating lymphocytes or TILs, are a sign that the immune system is responding to the tumor. People whose tumors contain TILs often do better than people whose tumors don’t contain them. Even though the

immune system can prevent or slow cancer growth, cancer cells have ways to avoid destruction by the immune system. For example, cancer cells may: Have genetic changes that make them less visible to the immune system, Have proteins on their surface that turn off immune cells, Change the normal cells around the tumor so they interfere with how the immune system responds to the cancer cells, Immunotherapy helps the immune system to better act against cancer.

How is immunotherapy given?

Different forms of immunotherapy may be given in different ways. These include:

1) Intravenous (IV)

The immunotherapy goes directly into a vein.

2) Oral

The immunotherapy comes in pills or capsules that you swallow.

3) Topical

The immunotherapy comes in a cream that you rub onto your skin. This type of immunotherapy can be used for very early skin cancer.

4) Intravesical

The immunotherapy goes directly into the bladder.

How often do you receive immunotherapy?

1) How often and how long you receive immunotherapy depends on:

- Your type of cancer and how advanced it is
- The type of immunotherapy you get
- How your body reacts to treatment

2) You may have treatment every day, week, or month. Some types of immunotherapy given in cycles. A cycle is a period of treatment followed by a period of rest. The rest period gives your body a chance to recover, respond to the immunotherapy, and build new healthy cells.

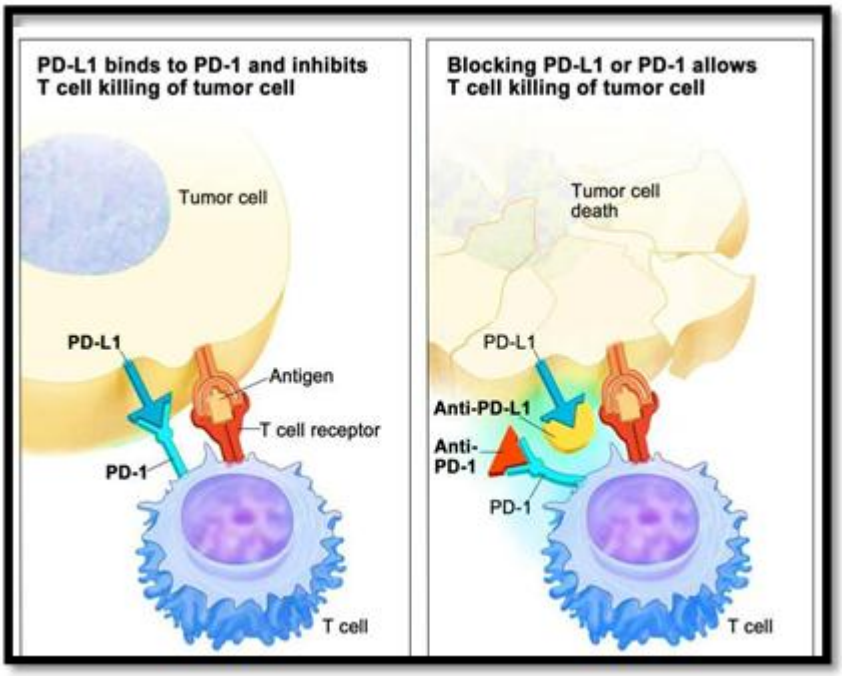


Fig 6: Imunne Checkpoint inhibitors.

Diagram Represents: Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep immune responses in check. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body (left panel). Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells (right panel).

Checkpoint inhibitors

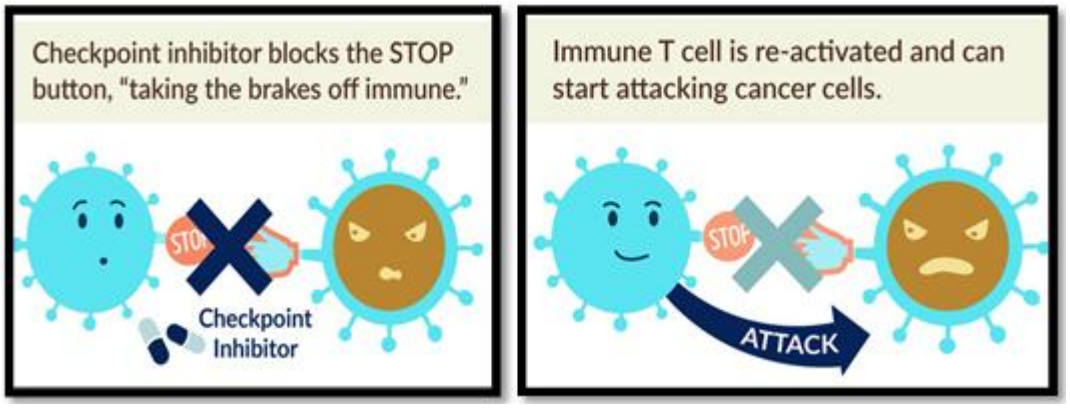


Fig 7: Check Point Inhibitor.

- Proteins called ‘checkpoints’ on the surface of T-cells can stop the immune system from attacking cancer cells.
- Checkpoint inhibitors are drugs designed to block these proteins to enable the T-cells to

recognise and destroy cancer cells.

- These types of drugs are currently the most widely used form of immunotherapy. Some are subsidised on the Pharmaceutical Benefits Scheme (PBS).

Immune stimulants

Some immunotherapy treatments aim to stimulate the immune system so it reactivates and attacks cancer cells.

How do immune checkpoint inhibitors work against cancer?

1) Immune checkpoints are a normal part of the immune system. Their role is to prevent an immune response from being so strong that it destroys healthy cells in the body.
2) Immune checkpoints engage when proteins on the surface of immune cells called T cells recognize and bind to partner proteins on other cells, such as some tumor cells. These proteins are called immune checkpoint proteins. When the checkpoint and partner proteins bind together, they send an "off" signal to the T cells. This can prevent the immune system from destroying the cancer.
3) Immunotherapy drugs called immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins. This prevents the "off" signal from being sent, allowing the T cells to kill cancer cells.
4) One such drug acts against a checkpoint protein called CTLA-4. Other immune checkpoint inhibitors act against a checkpoint protein called PD-1 or its partner protein PD-L1. Some tumors turn down the T cell response by producing lots of PD-L1.

Which cancers are treated with immune checkpoint inhibitors?\

Immune checkpoint inhibitors are approved to treat some patients with a variety of cancer types, including:

- Breast cancer
- Bladder cancer
- Cervical cancer
- Colon cancer
- Head and neck cancer
- Hodgkin lymphoma
- Liver cancer
- Lung cancer
- Renal cell cancer (a type of kidney canerr)

- Skin cancer
- Stomach cancer
- Rectal cancer
- Any solid tumor that is not able to repair errors in its DNA that occur when the DNA is copied.

What side effects are caused by immune checkpoint inhibitors?

- Immune checkpoint inhibitors can cause side effects that affect people in different ways. The side effects you may have and how they make you feel will depend on how healthy you are before treatment, your type of cancer, how advanced it is, the type of immune checkpoint inhibitor you are receiving, and the dose.
- Doctors and nurses cannot know for sure when or if side effects will occur or how serious they will be. So, it is important to know which signs to look for and what to do if they occur.
- Common side effects of immune checkpoint inhibitors include: Rash, Diarrhea, Fatigue
- Rarer side effects of immune checkpoint inhibitors can include widespread inflammation. Depending on the organ of your body that is affected, inflammation can lead to:
- Changes in skin color, rash, and feeling itchy, caused by skin inflammation
- Cough and chest pains, caused by inflammation in the lungs
- Belly pain and diarrhea, caused by inflammation in the colon
- Diabetes, caused by inflammation in the pancreas

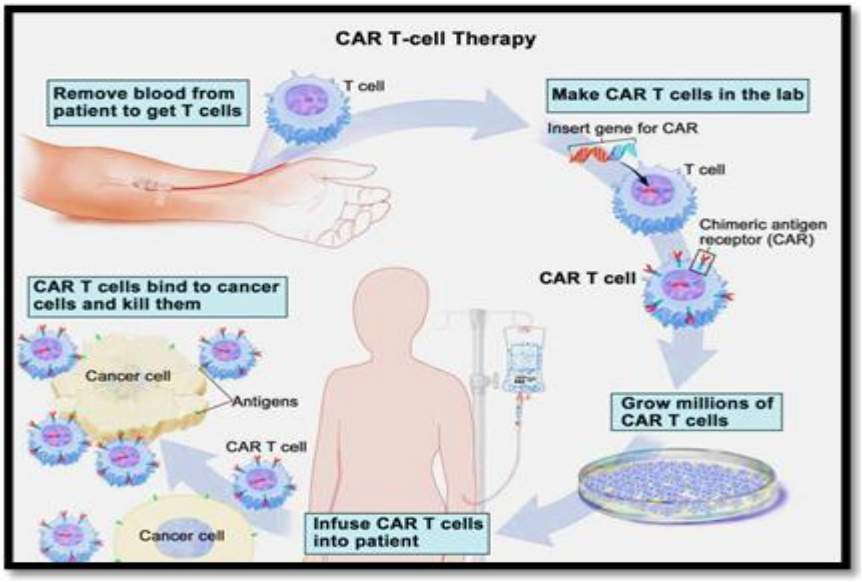


Fig 8: CAR T- cell Therapy.

Diagram Represents

CAR T-cell therapy is a type of treatment in which a patient's T cells (a type of immune cell) are changed in the laboratory so they will bind to cancer cells and kill them.

T-cell transfer therapy,

1) which is a treatment that boosts the natural ability of your T cells to fight cancer. In this treatment, immune cells are taken from your tumor.
2) Those that are most active against your cancer are selected or changed in the lab to better attack your cancer cells, grown in large batches, and put back into your body through a needle in a vein.
3) T-cell transfer therapy may also be called adoptive cell therapy, adoptive immunotherapy, or immune cell therapy.

How does T-cell transfer therapy work against cancer?

1) T-cell transfer therapy is a type of immunotherapy that makes your own immune cells better able to attack cancer.
2) There are two main types of T-cell transfer therapy: tumor-infiltrating lymphocytes (or TIL) therapy and CAR T-cell therapy. Both involve collecting your own immune cells, growing large numbers of these cells in the lab, and then giving the cells back to you through a needle in your vein. T-cell transfer therapy is also called adoptive cell therapy, adoptive immunotherapy, and immune cell therapy.
3) The process of growing your T cells in the lab can take 2 to 8 weeks. During this time, you may have treatment with chemotherapy and, maybe, radiation therapy to get rid of other immune cells. Reducing your immune cells helps the transferred T cells to be more effective. After these treatments, the T cells that were grown in the lab will be given back to you via a needle in your vein.
4) TIL therapy uses T cells called tumor-infiltrating lymphocytes that are found in your tumor. Doctors test these lymphocytes in the lab to find out which ones best recognize your tumor cells. Then, these selected lymphocytes are treated with substances that make them grow to large numbers quickly. The idea behind this approach is that the lymphocytes that are in or near the tumor have already shown the ability to recognize your tumor cells. But there may not be enough of them to kill the tumor or to overcome the signals that the tumor is releasing to suppress the immune system. Giving you large numbers of the lymphocytes that react best with the tumor can help to overcome these

barriers.

5) CAR T-cell therapy is similar to TIL therapy, but your T cells are changed in the lab so that they make a type of protein known as CAR before they are grown and given back to you. CAR stands for chimeric antigen receptor. CARs are designed to allow the T cells to attach to specific proteins on the surface of the cancer cells, improving their ability to attack the cancer cells.

What cancers are treated with T-cell transfer therapy?

1) T-cell transfer therapy was first studied for the treatment of metastatic melanoma because melanomas often cause a strong immune response and often have many TILs. The use of TIL therapy has been effective for some people with melanoma and has produced promising findings in other cancers, such as cervical squamous cell carcinoma and cholangiocarcinoma. However, this treatment is still experimental.
2) Three CAR T-cell therapies have been approved by the Food and Drug Administration for blood cancers:

- Tisagenlecleucel (Kymriah™)
- Axicabtagene ciloleucel (Yescarta™)
- Brexucabtagene autoleucel (Tecartus™)

3) CAR T-cell therapy has also been studied for the treatment of solid tumors, including breast and brain cancers, but use in such cancers is still experimental.

What are the side effects of T-cell transfer therapy?

1) T-cell transfer therapy can cause side effects, which people experience in different ways. The side effects you may have and how serious they are will depend on how healthy you are before treatment, your type of cancer, how advanced it is, the type of T-cell transfer therapy you are receiving, and the dose.
2) Doctors and nurses cannot know for sure when or if side effects will occur or how they will affect you. So, it is important to know which signs to look for and what to do if you start to have problems.
3) CAR T-cell therapy can cause a serious side effect known as cytokine release syndrome. This syndrome is caused when the transferred T cells, or other immune cells responding to the new T cells, release a large amount of cytokines into the blood.
4) Cytokines are immune substances that have many different functions in the body. A sudden increase in their levels can cause:

- Fever
- Nausea
- Headache
- Rash
- Rapid heartbeat
- Low blood pressure
- Trouble breathing

5) Most patients have a mild form of cytokine release syndrome, but in some people it may be severe or life threatening.
6) Also, although CAR T cells are designed to recognize proteins that are found only on cancer cells, they can also sometimes recognize normal cells. Depending on which normal cells are recognized, this can cause a range of side effects, including organ damage.
7) TIL therapy can cause capillary leak syndrome. This syndrome causes fluid and proteins to leak out of tiny blood vessels and flow into surrounding tissues, resulting in dangerously low blood pressure. Capillary leak syndrome may lead to multiple organ failure and shock.

Monoclonal antibodies, which are immune system proteins created in the lab that are designed to bind to specific targets on cancer cells. Some monoclonal antibodies mark cancer cells so that they will be better seen and destroyed by the immune system. Such monoclonal antibodies are a type of immunotherapy. Monoclonal antibodies may also be called therapeutic antibodies.

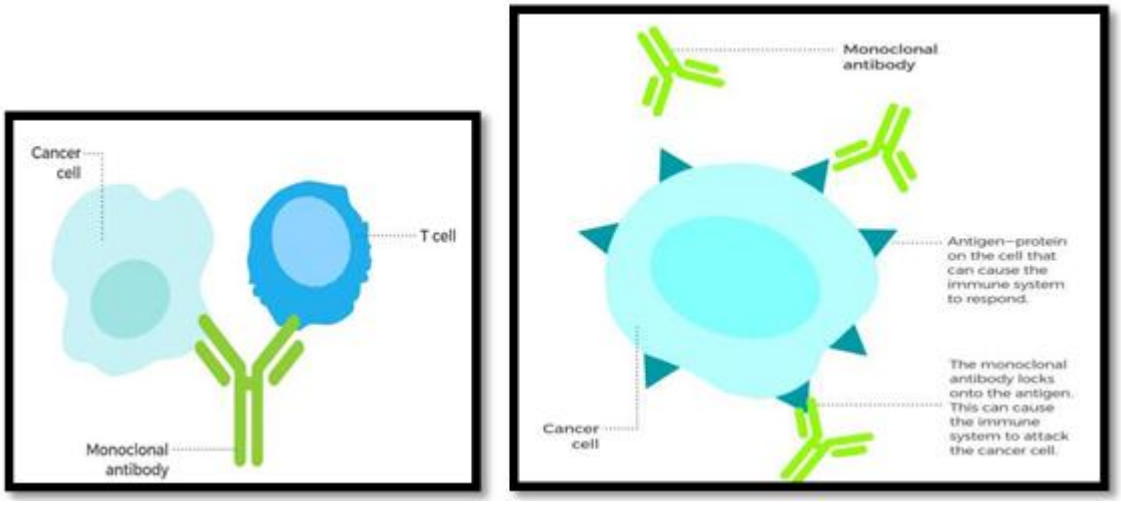


Fig 9: Monoclonal Antibody Diagram Represents.

Some monoclonal antibodies bring t cells close to cancer cells, helping them kill cancer cells. Some monoclonal antibodies mark cancer cells so that the immune system will better recognize and destroy them.

Treatment vaccines, which work against cancer by boosting your immune system's response to cancer cells. Treatment vaccines are different from the ones that help prevent disease.

How do cancer treatment vaccines work against cancer?

1) Cancer treatment vaccines are a type of immunotherapy that treats cancer by strengthening the body's natural defenses against the cancer. Unlike cancer prevention vaccines, cancer treatment vaccines are designed to be used in people who already have cancer—they work against cancer cells, not against something that causes cancer.
2) The idea behind treatment vaccines is that cancer cells contain substances, called tumor-associated antigens, that are not present in normal cells or, if present, are at lower levels. Treatment vaccines can help the immune system learn to recognize and react to these antigens and destroy cancer cells that contain them.
3) Cancer treatment vaccines may be made in three main ways.
4) They can be made from your own tumor cells. This means they are custom-made so that they cause an immune response against features that are unique to your cancer.
5) They may be made from tumor-associated antigens that are found on cancer cells of many people with a specific type of cancer. Such a vaccine can cause an immune response in any patient whose cancer produces that antigen. This type of vaccine is still experimental.
6) They may be made from your own dendritic cells, which are a type of immune cell. Dendritic cell vaccines stimulate your immune system to respond to an antigen on tumor cells. One dendritic cell vaccine has been approved, sipuleucel-T, which is used to treat some men with advanced prostate cancer.
7) A different type of cancer treatment, called oncolytic virus therapy, is sometimes described as a type of cancer treatment vaccine. It uses an oncolytic virus, which is a virus that infects and breaks down cancer cells but does not harm normal cells.
8) The first FDA-approved oncolytic virus therapy is talimogene laherparepvec (T-VEC, or Imlygic®). It is based on herpes simplex virus type 1. Although this virus can infect both cancer and normal cells, normal cells are able to kill the virus while cancer cells cannot.
9) T-VEC is injected directly into a tumor. As the virus makes more and more copies of itself, it causes cancer cells to burst and die. The dying cells release new viruses and other

substances that can cause an immune response against cancer cells throughout the body.

Which cancers are treated with cancer treatment vaccines? Sipuleucel-T is used to treat men with prostate cancer:

1) That has spread to other parts of the body
2) Who have few or no symptoms
3) Whose cancer does not respond to hormone treatment
4) T-VEC is used to treat some patients with melanoma that returns after surgery and cannot be removed with more surgery.

What are the side effects of cancer treatment vaccines?

1) Cancer treatment vaccines can cause side effects, which affect people in different ways.
2) The side effects you may have and how they make you feel will depend on how healthy you are before treatment, your type of cancer, how advanced it is, the type of treatment vaccine you are getting, and the dose.
3) Doctors and nurses cannot know for sure when or if side effects will occur or how serious they will be. So, it is important to know which signs to look for and what to do if you start to have problems.
4) Cancer treatment vaccines can cause flu-like symptoms, which include: Fever, Chills, Weakness, Dizziness, Nausea or vomiting, Muscle or joint aches, Fatigue, Low or high blood pressure.
5) Learn more about flu-like symptoms caused by cancer treatment.
6) You may have a severe allergic reaction.
7) Sipuleucel-T can cause stroke.
8) T-VEC can cause:

- Tumor lysis syndrome. As tumor cells die, they break apart and release their contents into the blood. This causes a change in certain chemicals in the blood, which may cause damage to organs, including the kidneys, heart, and liver.

How do antibiotics help fight infections?

1) Antibiotics can be used to help your child's immune system fight infections by bacteria.
2) However, antibiotics don’t work for infections caused by viruses.
3) Antibiotics were developed to kill or disable specific bacteria.
4) That means that an antibiotic that works for a skin infection may not work to cure diarrhea caused by bacteria.

5) Using antibiotics for viral infections or using the wrong antibiotic to treat a bacterial infection can help bacteria become resistant to the antibiotic so it won't work as well in the future.
6) It is important that antibiotics are taken as prescribed and for the right amount of time. If antibiotics are stopped early, the bacteria may develop a resistance to the antibiotics and the infection may come back again.

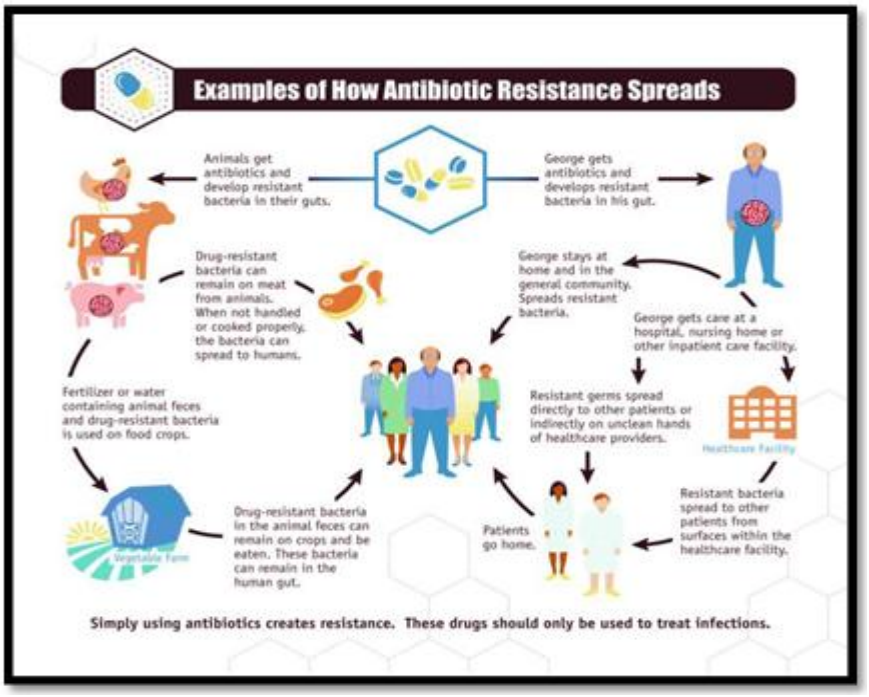


Fig 10: Antibiotic Resistance Spread.

Immune system modulators, which enhance the body's immune response against cancer. Some of these agents affect specific parts of the immune system, whereas others affect the immune system in a more general way. When inserted directly into the bladder, BCG can cause an immune response against bladder cancer cells.

How do immune system modulators work against cancer?

Immune-modulating agents are a type of immunotherapy that enhance the body's immune response against cancer.

Types of immune-modulating agents include:

- Cytokines, which are proteins made by white blood cells. They play important roles in your body's normal immune responses and in the immune system's ability to respond to cancer.

- Interferons (INFs). Researchers have found that one type of interferon, called INF-alfa, can enhance your immune response to cancer cells by causing certain white blood cells, such as natural killer cells and dendritic cells, to become active. INF-alfa may also slow the growth of cancer cells or promote their death.
- Interleukins (ILs). There are more than a dozen interleukins, including IL- 2, which is also called T-cell growth factor. IL-2 boosts the number of white blood cells in the body, including killer T cells and natural killer cells. Increasing these cells can cause an immune response against the cancer. IL-2 also helps B cells (another type of white blood cell) produce certain substances that can target cancer cells. Hematopoietic growth factors are cytokines that are used to reduce side effects from cancer treatment by promoting the growth of blood cells that are damaged by chemotherapy. They include:
- Erythropoietin, which increases the production of red blood cells

1) IL-11, which increases the production of platelets

- Granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF), which both increase the number of white blood cells. Boosting white blood cells reduces the risk of infections. G-CSF and GM-CSF can also enhance the immune system response against cancer by increasing the number of cancer-fighting T cells.

BCG is a weakened form of the bacteria that causes tuberculosis. It does not cause disease in humans. BCG is used to treat bladder cancer. When inserted directly into the bladder with a catheter, BCG causes an immune response against cancer cells. It is also being studied in other types of cancer. BCG stands for Bacillus Calmette-Guérin.

Immunomodulatory drugs (also called biological response modifiers) stimulate the immune system. They include: Thalidomide (Thalomid®), Lenalidomide (Revlimid®), Pomalidomide (Pomalyst®), Imiquimod (Aldara®, Zyclara®) Thalidomide, lenaliodomide, and pomalidomide cause cells to release IL-2. They also stop tumors from forming new blood vessels. Tumors need to form new blood vessels to grow beyond a certain size. These three drugs may also be called angiogenesis inhibitors. Imiquimod is a cream that you rub on the skin. It causes cells to release cytokines.

What are the side effects of immune system modulators?

- Fever

- Chills
- Weakness
- Nausea or vomiting
- Muscle or joint aches
- Fatigue
- Headache

BCG can also cause urinary side effects.

Thalidomide, lenalidomide, and pomalidomide can cause:

- Blood clots
- Nerve problems that lead to pain, numbness, tingling, swelling, or muscle weakness in different parts of the body.
- Birth defects, if used during pregnancy Imiquimod can cause skin reactions.

How can you tell if immunotherapy is working?

You will see your doctor often. He or she will give you physical exams and ask you how you feel. You will have medical tests, such as blood tests and different types of scans. These tests will measure the size of your tumor and look for changes in your blood work.

Immunosuppressant drugs are a class of drugs that suppress, or reduce, the strength of the body's immune system. Some of these drugs are used to make the body less likely to reject a transplanted organ, such as a liver, heart, or kidney. These drugs are called antirejection drugs. Other immunosuppressant drugs are often used to treat autoimmune disorders such as lupus, psoriasis, and rheumatoid arthritis. If your doctor has prescribed an immunosuppressant medication for you, here's what to know about what these drugs do, how they work, and how they might make you feel. The following information will tell you what to expect when taking an immunosuppressant drug and what it could do for you.

What they treat?

1) Autoimmune conditions

Immunosuppressant drugs are used to treat autoimmune diseases.

With an autoimmune disease, the immune system attacks the body's own tissue. Because immunosuppressant drugs weaken the immune system, they suppress this reaction. This helps reduce the impact of the autoimmune disease on the body.

Autoimmune diseases treated with immunosuppressant drugs include:

- psoriasis
- lupus
- rheumatoid arthritis
- Crohn's disease
- multiple sclerosis
- alopecia areata

2) Organ transplant

Almost everyone who receives an organ transplant must take immunosuppressant drugs. This is because your immune system sees a transplanted organ as a foreign object. As a result, your immune system attacks the organ as it would attack any foreign cell. This can cause severe damage and lead to needing the organ removed.

Immunosuppressant drugs weaken your immune system to reduce your body's reaction to the foreign organ. The drugs allow the transplanted organ to remain healthy and free from damage.

Treatment regimen

1) All immunosuppressant drugs are available only by a prescription from your doctor.
2) Immunosuppressant drugs come as tablets, capsules, liquids, and injections. Your doctor will decide the best drug forms and treatment regimen for you.
3) They may prescribe a combination of drugs.
4) The goal of immunosuppressant therapy is to find the treatment plan that will suppress your immune system while having the fewest, least harmful side effects.
5) If you take immunosuppressant drugs, you must take them exactly as prescribed. if you have an autoimmune disorder, a regimen change can cause a flare-up of your condition.
6) If you're an organ recipient, even the slightest change from the medication regimen can trigger an organ rejection. No matter why you're being treated, if you miss a dose, be sure to call your doctor right away.

Tests and dosage changes

1) During your treatment with immunosuppressant drugs, you'll have regular blood tests.
2) These tests help your doctor monitor how effective the drugs are and whether dosage changes are needed. The tests will also help your doctor know whether the drugs cause side effects for you.
3) If you have an autoimmune disease, your doctor may adjust your dosage based on how your condition responds to the medication.
4) If you've received an organ transplant, your doctor may eventually reduce your dosage. This is because the risk of organ rejection lessens over time, so the need for these medications may decrease.
5) However, most people who have had a transplant will need to take at least one immunosuppressant drug throughout their lifetime.

Immunomodulators are molecules that act on the pathways that regulate the immune system's activity.

Different types of immunomodulators, they can be roughly divided into four categories:

1) checkpoint inhibitors,
2) cytokines,
3) agonists,
4) adjuvants.

In 2011, the U.S. Food and Drug Administration (FDA) approved the first checkpoint inhibitor immunotherapy for the treatment of cancer—the CTLA-4- blocking ipilimumab (Yervoy®) for melanoma. Since then, the FDA has approved seven checkpoint inhibitors to treat more than a dozen different types of cancer.

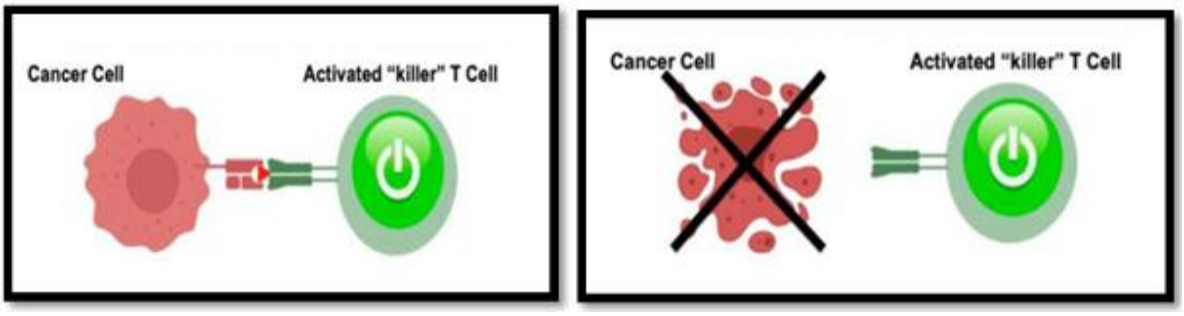
Checkpoint Inhibitors

Checkpoint inhibitors work by blocking immune checkpoints—the "brakes" of the immune system—that tumors frequently manipulate in order to shut down immune responses and protect themselves.

As a result, checkpoint inhibitors are able to unleash new immune responses against cancer as well as enhance existing responses to promote elimination of cancer cells.

For example, PD-1/PD-L1 immune checkpoint pathway can shut down cancer- targeting T cells.

However, when checkpoint inhibitors block the PD-1/PD-L1 pathway, they can enable T cells to eliminate cancer cells.



Cytokines

Cytokines are messenger molecules that regulate immune cell maturation, growth, and responsiveness. Currently, there are four FDA-approved cytokine immunotherapies—for the treatment of subsets of patients with kidney cancer, leukemia, lymphoma, melanoma, and

sarcoma. Ex: Aldesleukin (Proleukin®): a cytokine that targets the IL-2/IL-2R pathway; approved for subsets of patients with kidney cancer and melanoma.

Agonists

Agonists activate pathways that promote adaptive immune responses, either by helping to activate "killer" T cells, which directly attack cancer cells, or stimulating the activity of innate immune cells like dendritic cells, which coordinate overall immune responses against cancer by displaying cancer markers and enhancing T cell activity.

Adjuvants

Adjuvants activate pathways involved in the innate immune system that can stimulate general immune responses and ultimately promote adaptive immune responses. One FDA-approved adjuvant immunotherapy is currently available for the treatment of subsets of patients with squamous cell carcinoma, a type of skin cancer. Ex: Imiquimod: an immune adjuvant targeting the Toll-like receptor 7 (TLR7) pathway; approved for subsets of patients with basal cell carcinoma.

Side effects

associated with currently approved cytokine immunotherapies may include but are not limited to: bilirubinemia, chills, confusion, diarrhea, dyspnea, fatigue, fever, flu-like symptoms, headache, hypotension, myalgia, nausea, oliguria, rash, thrombocytopenia, and vomiting.

Immunostimulants

1) are substances that modulate the immune system by stimulating the function of one or more of the system's components.
2) There are two types. Specific immunostimulants, such as vaccines, stimulate an immune response to one or more specific antigenic types. In contrast, non-specific immunostimulants do not have any antigenic specificity but can act as general stimulants that enhance the function of certain types of immune cells.
3) In terms of immunostimulant substances used in the general human population, it is vaccines which are most commonly employed. Vaccines are used to stimulate a protective immune response to antigens from specific pathogens. The influenza vaccine, for example, uses several antigens from different strains of the flu virus. People who are vaccinated are then protected against infection from those particular strains.

4) Another type of immunostimulant called an adjuvant is often used in conjunction with vaccines. Adjuvants are a type of non-specific immunostimulant.
5) Administering an adjuvant along with a vaccine helps generate a stronger protective response to the antigens in the vaccine, providing a better degree of protection against the pathogen.
6) One example of an adjuvant is alum, which is often used in human vaccines. Alum is made from aluminum salts such as aluminum hydroxide and aluminum phosphate.
7) Many chemical substances produced by the human body function as immunostimulants. Cytokines are a type of immunostimulant which are produced by cells of the immune system, and many have a role in enhancing immune function.
8) In addition, some female sex hormones, as well as granulocyte macrophage colony-stimulating factor, prolactin, and growth hormone, are known to have immunostimulant effects.

Future Scope

What is the current research in immunotherapy?

Researchers are focusing on several major areas to improve immunotherapy, including:

- Finding ways to predict responses to immunotherapy.

Only a small portion of people who receive immunotherapy will respond to the treatment. Finding ways to predict which people will respond to treatment is a major area of research.

- Learning more about how cancer cells evade or suppress immune responses against them.

A better understanding of how cancer cells get around the immune system could lead to the development of new drugs that block those processes.

- How to reduce the side effects of treatment with immunotherapy.
- Improving Clinical trial outcomes.
- Promissing key to prevent cancer.
- *Findings lay roadmap for future clinical trials to improve efficacy and survival after targeted immunotherapies*
- The researchers discovered that cancer immunotherapies that make use of immune system cells such as T cells and CAR-T cells kill not only tumor cells that express the drugs' target, but also adjacent tumor cells that lack the targets, because of the presence of fas. This process, known as bystander killing, can be made more effective by adding therapeutics that turn off the regulation of fas proteins, the researchers said.

- Specifically, by combining immunotherapies with small molecule inhibitors that increase fas-signaling, which are already being used in the clinic, bystander tumor cell killing may be potentiated and eliminate antigen-loss variants from heterogenous tumors.

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