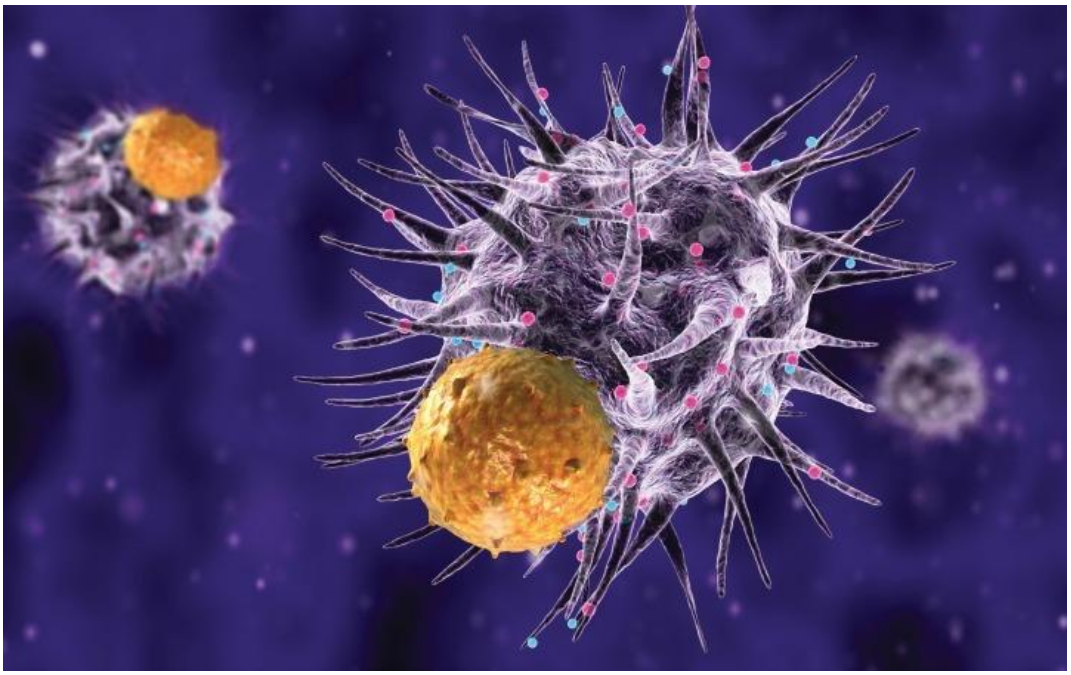
IS THE CURE OF CANCER INSIDE OF US?

ANTI-TUMOUR IMMUNOTHERAPY. TREATING CANCER WITH THE IMMUNE SYSTEM



NOM: DONA AMB PATINS

“EVERYTHING SHOULD BE MADE AS SIMPLE AS POSSIBLE, BUT NOT SIMPLER.”

ALBERT EINSTEIN

APPRECIATION

This research project would not have been possible without the support of a lot of people who have directly or indirectly participated in it. Therefore, before starting right away with my project, I would like to thank all people who have made it possible to carry it out.

In the first place my tutor, **X**, for his orientation and because he has offered me all his advice, which was great help. Also for the trust that he placed in me since the first day, which encouraged me to do my best.

Also, **X**, teacher of Catalan literature of my school, to all the unconditional help and all the guidance she offered me while writing the article.

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All those specialists that offered themselves to answer my surveys, in order to give me a general overview about their opinion on this therapy.

My parents who have been continually on my side and willing to offer their help.

To all the friends that have advised me in everything that I needed.

To everyone who have made this research project real.

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1 INTRODUCTION

Choosing the topic of my research study hasn't been an easy task, and I barely can't believe that I'm in the process of delivering it. I still remember when I had to choose the subject I would cover, and how uneasy it made me feel.. I had a thousand ideas in my mind. All different. All interesting. However, none of them were "perfect". None of them stood out, nor motivated me enough to enjoy a year-long job. In the end I knew what direction I wanted to give it, as, after all, I want to engage myself into the world of health and science; which is what I like and I am more excited about.

And that's the reason why, I tried to achieve an exciting and different subject, which people can be surprised with by the results. However, we must be able to recognize the limits we face, such as time, material and knowledge

I went through many subjects, and in any of them I could envision the research itself, and it was a little desperate at first. I like medicine very much, both because of the biological part of knowing our own body, how it works, how it is designed, and because of the human side, to understand the patient, to get into his skin, to feel the sympathy. So I chose a job in which I could immerse myself into the world of human biology, but I could also see the effects of this medicine at a clinical level. And there it was already, I already had it. A rough draft on my mind, which had many loose ends left to tie. But as my work tutor Xavier Calvó, says, 'a bit of Patchwork never hurts.'

My work revolves around the world of immunology, and about immunotherapy, which started developing a few years ago. It seemed to me the perfect subject. This one had everything, I was looking for, indeed. I could thoroughly study our immune system and see how these new techniques are being put in place to fight and overcome one of today's most serious illnesses: cancer

When we read newspapers today and we find a piece of news about cancer, it is not new to us, in fact, we do not give importance to it; it's like one more among too many others. This one new, however, is different. People do not know about their existence, and they should. Almost everyone has a relative, a

friend, or an acquaintance, who have suffered from this illness and knows its dimensions. Immunotherapy has real data, cured patients, who can enjoy a life without cancer. That's why I thought it was an important information to reveal and let the audience know, and much more interesting than current cancer treatment therapies.

Reading up on this subject, I found an article in an American newspaper whose title cover (rarely a cover of a newspaper is dedicated to science) was: is the cure of cancer inside of you? It seemed to me a question that perfectly reflected the content of my work, and that's why I decided, that it would be its title.

During these months I have read a lot, because my goal was not to limit myself to pouring a series of bibliographic concepts, but to deepen into the knowledge of techniques that save human lives day by day, and in the effort that by part of all the professionals there lies behind those techniques.

Knowledge and emotions, effort and restlessness of researchers, scientists, staff of various fields who professionally dedicate so many hours of their lives to help others and make their lives better.
This work also aims to express, from the essence of a second-year baccalaureate student, gratitude to all of them for their constant and inexhaustible dedication.

And that’s it. It's already finished and ready to try to surprise those who read it. It's been worth it, it's been a summer of hard work but I've had a great time, and I wish I have been able to reflect on this work all this effort and enthusiasm.

2 OBJECTIVES

From the outset, what was very clear was that work should not be felt as an obligation at any time, but rather a kind of hobby, a little different than usual, but that it did not represent an effort for me to do it. That's why I took a topic that appeases me and would help me get my hands on the work

The main objective of my work was to give it a focus from a very new therapy, knowing how relevant cancer is in our society, and how many resources are destined for a disease so complex.

A therapy in which I could focus on the biological field but also in the medical field, and to show how this therapy already gives real and visible results in our today's society. On the other hand, it seemed very interesting to give my work an informative approach, since no one outside would know what immunotherapy is, and that is why I decided to do an informative article that could made this interesting world be better known.

3 ABRIDGINGS INDEX

MHC: Major histocompatibility molecule

DNA: Deoxyribonucleic acid

BCR: B cell receptor

TCR: T cell receptor

APC: Antigen presenting cell

DC: Dendritic cell

NK: Natural killer

VEGF: vascular endothelial growth factor

TIL: Tumor infiltrating lymphocytes

CAR: Chimeric antigen receptor

4 THEORETICAL PART

5 IMMUNOLOGY TREATISE

We live in a potentially hostile world full of a bewildering number of infectious agents, that would use us happily as rich sanctuaries for the propagation of their 'concerned genes' if we did not develop a series of defense mechanisms, as minimum as effective and resourceful as theirs. These defense mechanisms are the ones that can establish a state of immunity against infection.
The easiest way of avoiding this infection is not letting the pathogen inside your body. That is why we have natural barriers that defend us from those thoughtless microorganisms.

Every day, humans encounter potentially harmful disease causing organisms, or “pathogens”, like bacteria or viruses. Yet most of us are still able to function properly and to be alive without constantly being sick. That’s because the human body requires a multilayered immune system to keep it running smoothly. The two main classes of the immune system are the innate immune system and the adaptive immune system, or “acquired immunity”.

5.1 Self vs non self: how does the body know?

The main question is, how does the body know which molecules are ours or which are molecules or microorganisms that are harmful for our body. It is important to know the difference between self and non-self.

- *Self* refers to particles, such as proteins and other molecules that are a part of, or made by, your body. They can be found circulating in your blood or attached to different tissues. Something that is self should not be targeted or destroyed by the immune system. The non-reactivity of the immune system to self-particles is called tolerance.

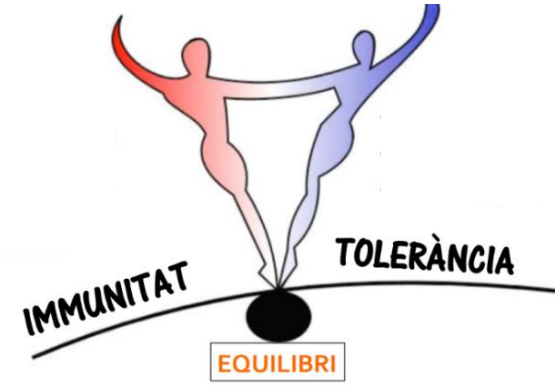


Image 1 Immunity and tolerance

- *Non- self* refers to particles that are not made by your body, and are recognized as potentially harmful. Non-self-particles or bodies can be bacteria, viruses, parasites, pollen, dust, or toxic chemicals. The non-self-particles and foreign bodies that are infectious or pathogenic, like bacteria, viruses, and parasites, make proteins called antigens that allow the human body to know that they intend to cause damage.
- *Antigens* cause an immune response. They can be entire pathogens or tiny molecules that those ones express, even cancer cells. Antigens are like a name tag for each pathogen that announce its' presence to the immune system. A general antigen would say "I am dangerous", whereas a specific antigen would announce "I am a bacteria that will cause an infection in your gastrointestinal tract" or "I am the influenza virus".

So, back to the question of how the body recognizes self and non-self-particles, those antigens described before are present in all our cells. Healthy human cells express peptides in their surface to let our immune system know that they are not a target. Those antigens vary widely according to what kind of cell is expressing them. Antigens can be peptides, polysaccharides, or lipids, among others. They are unique molecular patterns expressed by different types of cells, and allow the immune system to distinguish between different cell type, and self vs. non-self.

Two of the most important factors in allowing the immune system to distinguish between self and non-self are the major histocompatibility complexes I and II (MCH).

- **MHC class I molecules** are found on all healthy cells in the body. Those molecules are designed to present on their cells surface, peptide antigens that are found within the cytoplasm of cells. So, for example, if a virus invaded a cell in your liver, the MHC I molecules on the surface of that liver cell would display peptide pieces of that virus on the cell surface.
- **MHC class II molecules** are not found everywhere. They are restricted to specialized types of cells, basically antigen presenting cells such as dendritic cells, macrophages and B cells. Unlike MHC I molecules, which

present antigens from the cytosol, MHC II molecules display antigens from microbes that are found in cells vesicles.

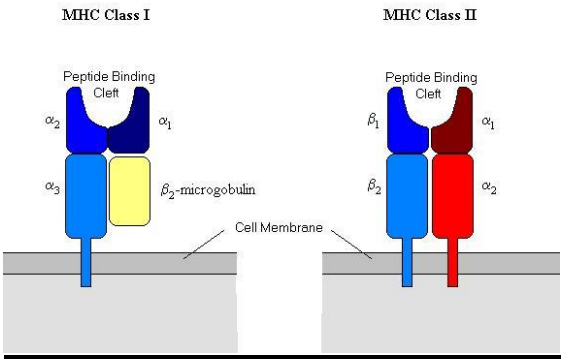


Image 2 MHC type I and type II.

When talking about the immune system there are two types: the innate immune system and the adaptive immune system.

5.2 Innate immune system

- The innate immune system is made of defenses against infection that can be activated immediately once a pathogen attacks. The innate immune system is essentially made up of barriers that aim to keep viruses, bacteria, parasites, and other foreign particles out of the body or limit their ability to spread and move throughout the body. So, it is non-specific,(because it does not attack specific antigens) short term, (it lasts few hours) and quick (it is an immediate response) and it includes:

5.2.1Physical Barriers

5.2.1.1 SKIN

The first one, and the most important is the skin. In general, the skin prevents the entry of microorganisms unless there is some physical alteration (wounds, cuts…).

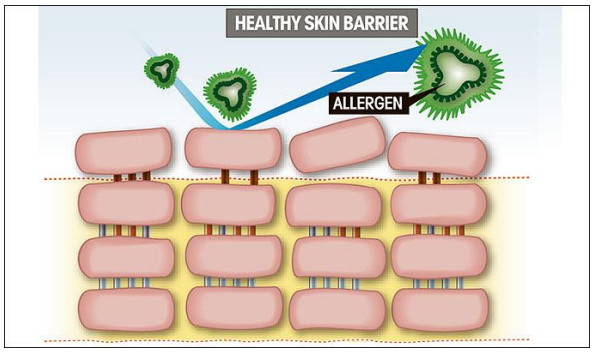


Image 3 It protects us against microorganisms, temperature and PH changes.

5.2.1.2 MUCOUS MEMBRANES

Such as the lining of the mouth, nose, and eyelids, are also effective barriers. Typically, mucous membranes are coated with secretions that fight microorganisms. For example, the mucous membranes of the eyes are bathed in tears, which contain an enzyme called lysozyme that attacks bacteria and helps protect the eyes from infection.

Many mucous membranes are covered by secretions that have antimicrobial properties. The mucus blocks the adherence of bacterial cells to the skin. Most of the secreted body fluids contain bactericidal components such as acid in the gastric juice, saliva…

5.2.1.3 DIGESTIVE TRACT

The **digestive tract** has a series of effective barriers, including stomach acid, pancreatic enzymes, bile, and intestinal secretions. These substances can kill bacteria or prevent them from multiplying. The contractions of the intestine (peristalsis) and the normal shedding of cells lining the intestine help remove harmful microorganisms.

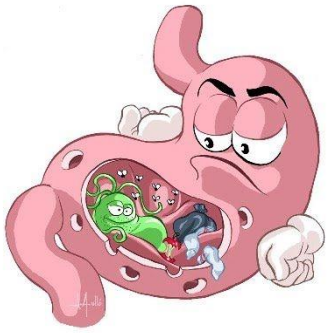


Image 4 The gastric juice helps us defend against ingested pathogens.

5.2.1.4 RESPIRATORY TRACT

The airways filter out particles that are present in the air that is inhaled. The walls of the passages in the nose and airways are coated with mucus. If the invading microorganisms reach the tracheobronchial tree, the mucociliary epithelium transports them away from the lung. Coughing also helps eliminate microorganisms. If they reach the alveoli, alveolar macrophages and tissue histiocytes engulf them. However, these defenses can be overcome by a large number of microorganisms or by an alteration due to atmospheric pollutants (egg, cigarette smoke).

5.2.1.5 UROGENITAL TRACT

The urinary tract also has several effective barriers. The bladder is protected by the urethra, the tube that drains urine from the body. In males older than 6 months, the urethra is long enough that bacteria are seldom able to pass through it to reach the bladder. In females, the urethra is shorter, occasionally allowing external bacteria to pass into the bladder. In both sexes, when the bladder empties, it flushes out any bacteria that reach it.

The vagina is normally acidic. The acidity of the vagina prevents harmful bacteria from growing and helps maintain the number of protective bacteria

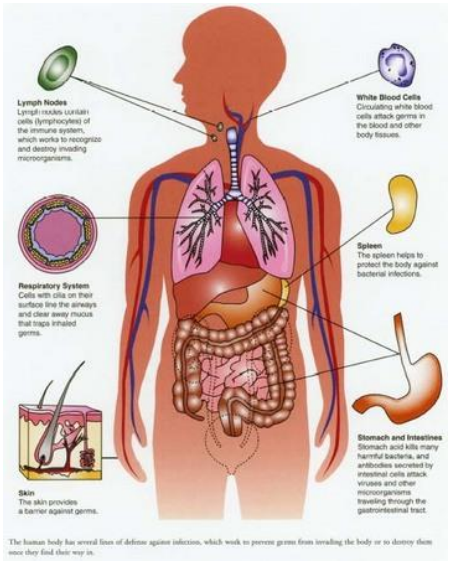


Image 5 Natural human barriers against infections.

The innate immune system is always general, or *nonspecific*, meaning anything that is identified as foreign or *non-self* is a target for the innate immune response. The innate immune system is activated by the presence of antigens and their chemical properties.

5.2.2CELLS OF THE INNATE IMMUNE SYSTEM

There are many types of white blood cells, or *leukocytes*, both innate and adaptive, which work to defend and protect the human body. In order to patrol the entire body, leukocytes travel by way of the circulatory system.

The following cells are leukocytes of the innate immune system:

- *Phagocytes*, or *Phagocytic cells*: Phagocyte means “eating cell”, which describes what role phagocytes play in the immune response. Phagocytes circulate throughout the body, looking for potential threats, like bacteria and viruses, to engulf and destroy them. They are like security guards on patrol.

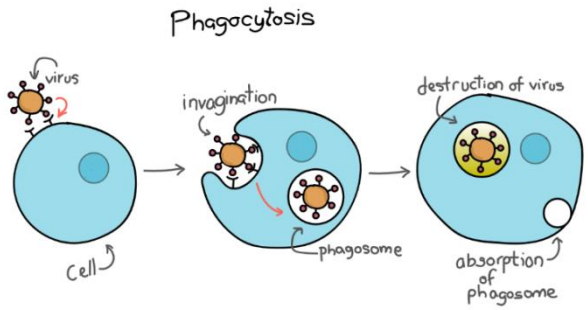


Image 6 Phogocytosis

5.2.2.1 What is phagocytosis?

Phagocytosis is a process wherein a cell binds to the item it wants to engulf on the cell surface and draws the item inward while engulfing around it. The process of phagocytosis often happens when the cell is trying to destroy something, like a virus or an infected cell, which are big and cannot be transported through the plasma membrane and is often used by immune system cells.

Phagocytosis differs from other methods of endocytosis because it is very specific and depends on the cell being able to bind to the item it wants to engulf by way of cell surface receptors. Phagocytosis won't happen unless the cell is in physical contact with the particle it wants to engulf.

5.2.2.2 How does phagocytosis happen?

Cells have to complete some steps in order to successfully phagocytize something. See the example of a macrophage phagocytizing a virus.

1. **The virus and the cell need to come into contact with each other.**
   - Sometimes the immune cell accidentally bumps into a virus in the blood stream. Other times, cells move by way of a process called "chemotaxis". Chemotaxis means the movement of an organism or cell in response to a chemical stimulus. Many immune system cells move in response to cytokines, small proteins used specifically for cell signaling. Cytokines signal cells to move to certain area in the body where the particle (in this case, a virus) is found. This is common with infections that are specific to a certain area (like a skin wound infected with bacteria). Those cytokines make all sorts of immune cells be attracted to where the virus or bacteria is found.
2. **The virus binds to the cell surface receptors on the macrophage.**
   - The macrophage will not initiate phagocytosis without successful binding of the cell surface receptors.

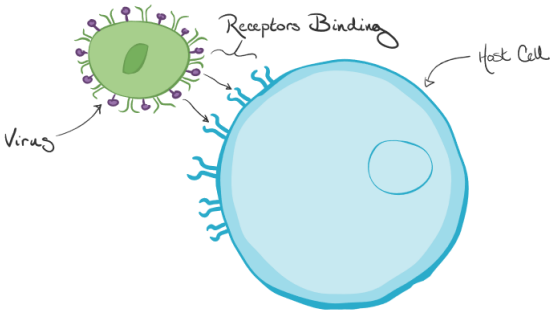


Image 7 The virus binds to the cell surface receptors on the macrophage.

3. **The macrophage starts to invaginate around the virus, engulfing it into a pocket.**
   - Instead of moving the large item across the plasma membrane, which might damage the membrane permanently, phagocytosis uses invagination to draw the particle inside while closing in around it.

     The macrophage and virus are bound at the cell surface. The cell pulls the virus inside, creating a pocket-like indentation without making any damage to the plasma membrane. And this is because the membrane of a cell is flexible.

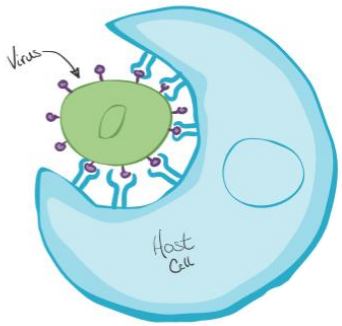


Image 8 The macrophage starts to invaginate around the virus, engulfing it into a pocket.

4. **The invaginated virus becomes completely enclosed in a bubble-like structure, called a "phagosome", within the cytoplasm.**
   - The lips of the pocket, formed as a result of invagination, extend towards each other in order to close the gap and fill the space. This action creates a phagosome, where the plasma membrane has moved around the particle, encasing it safely inside the cell.

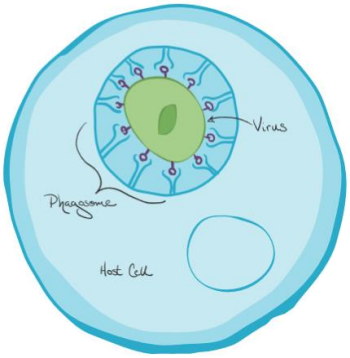


Image 9 The invaginated virus becomes completely enclosed in a bubble-like structure, called a "phagosome", within the cytoplasm.

5. **The phagosome fuses with a lysosome, becoming a "phagolysosome".**

   - Lysosomes are also bubble-like structures, similar to phagosomes, which process wastes inside the cell. "Lysis" means "to break down", which is the function of the lysosome. Without fusing with a lysosome, the phagosome would not be able to do anything with the contents inside.

6. **Phagolysosome lowers the pH to break down its contents.**

   - A lysosome or phagolysosome is able to break down the elements inside of itself by drastically lowering the pH of its internal environment. Lowering the pH makes the environment inside the phagolysosome very acidic. This is an effective way of killing whatever is inside the phagolysosome so it cannot infect them cell.

7. **Once the contents have been neutralized, the phagolysosome forms a residual body that contains the waste products from the phagolysosome.**

   - The residual body is eventually discharged from the cell.

5.2.2.3 Phagocytosis and the immune system

Phagocytosis is a critical part of the immune system. Several types of cells of the immune system perform phagocytosis, such as neutrophils, macrophages, dendritic cells, and B lymphocytes. The act of phagocytizing pathogenic or foreign particles allows cells of the immune system to know what they are fighting against. By knowing the enemy, the cells of the immune system can specifically target similar particles circulating in the body.

- *Macrophages*: Macrophages (and their precursors cells , monocytes) are the 'big eaters' of the immune system. These cells reside in every tissue of the body, where they engulf dead cells and pathogens and produce immune effector molecules. When there is an infection or tissue damage, monocytes are rapidly recruited to the tissue, where they differentiate into tissue macrophages.

The ability to go outside of the circulatory system is important, because it allows macrophages to hunt pathogens with less limits. Macrophages can also release cytokines in order to signal and recruit other cells to an area with pathogens.

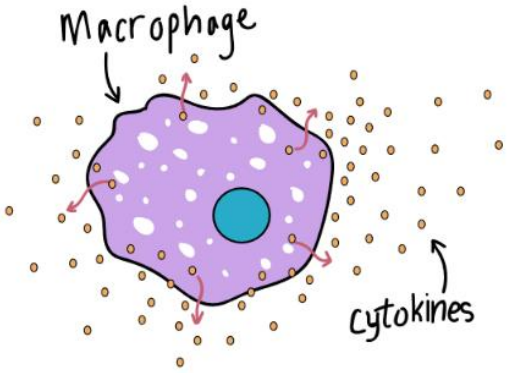


Image 10 Drawing of a macrophage.

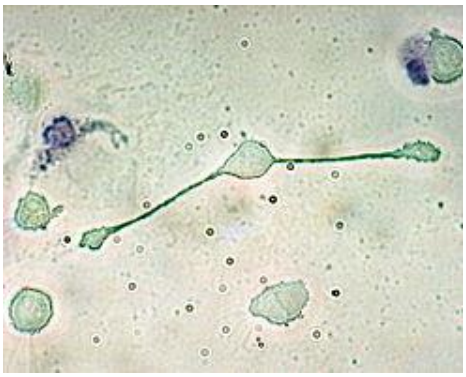


Image 11 A mouse macrophage forming two "arms" (pseudopodia) to engulf two possibly pathogenic particles.

- *Mast cells*: Mast cells are found in mucous membranes and connective tissues, and are important for wound healing and defense against pathogens via the inflammatory response. When mast cells are activated, they release cytokines and granules that contain chemical molecules to create an *inflammatory cascade*. Mediators, such as histamine[1], cause blood vessels to dilate, increasing blood flow and cell trafficking to the area of infection. The cytokines released during this process act as a messenger service, alerting other immune cells, like neutrophils and macrophages, to make their way to the area of infection, or to be on alert for circulating threats.

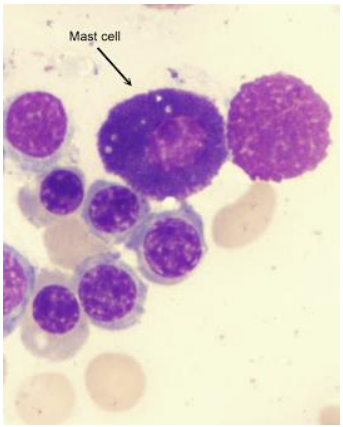


Image 12 A mast cell seen at the microscope.

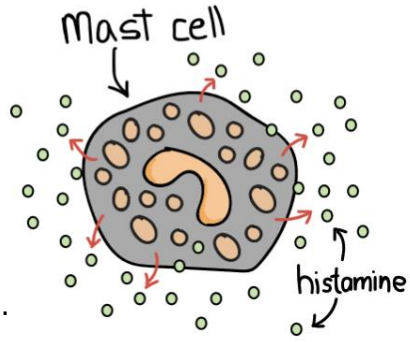


Image 13 Drawing of a mast cell.

[1] Chemical that causes many of the symptoms of allergies.

- *Neutrophils*: Neutrophils are phagocytic cells that are also classified as *granulocytes* because they contain granules in their cytoplasm. These granules are very toxic to bacteria and fungi, and cause them to stop proliferating or die on contact. Neutrophils are important because, unlike some of the other white blood cells, they aren't limited to a specific area of circulation. They can move freely through the walls of veins and into the tissues of the body to immediately attack all antigens. The force of attraction that determines the direction in which neutrophils will move is the chemotaxis. Neutrophils are typically the first cells to arrive at the site of an infection because there are so many of them in circulation at any given time.

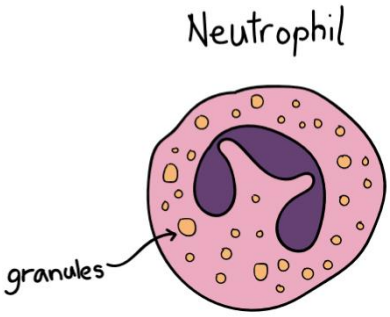


Image 15 Drawing of a neutrophil.

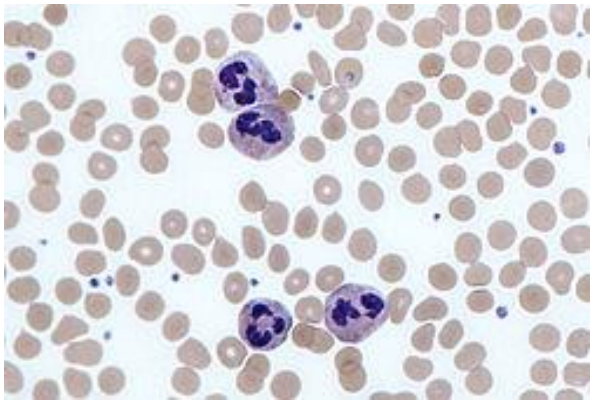


Image 14 Neutrophil in the blood stream.

- *Eosinophil:* The eosinophil is a specialized cell of the immune system. This proinflammatory white blood cell generally has a nucleus with two lobes (bilobed) and cytoplasm filled with approximately 200 large granules containing enzymes and proteins with different functions. Eosinophils are formed exclusively in the bone marrow where they spend about 8 days in the process of maturation before moving into the blood vessels. They travel through the vessels for 8 to 12 hours before they finally arrive at destination tissues, where they remain for 1 to 2 weeks. The functions of the eosinophil are varied, some of which are very similar to other white blood cells. They are implicated in numerous inflammatory processes, especially allergic disorders. Eosinophils only make up 1-6% of the white blood cells

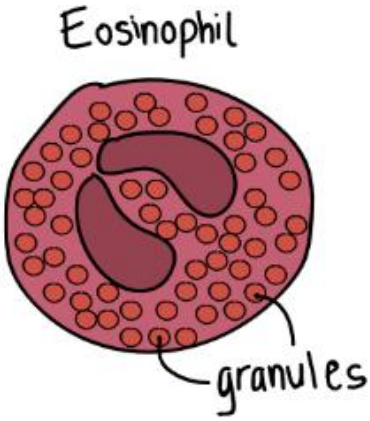


Image 17 Drawing of an eosinophil.

Image 16 The two lobes of an eosinophil.

- *Basophils*: Basophils are also granulocytes that attack multicellular parasites. Basophils release histamine, much like mast cells. The use of histamine makes basophils and mast cells key players in mounting an allergic response.

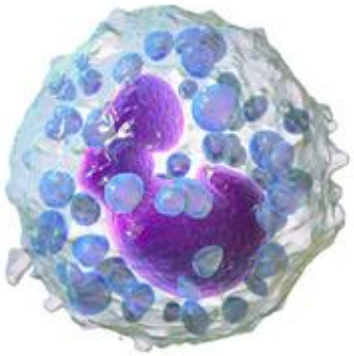


Image 19 3D rendering of a basophil.

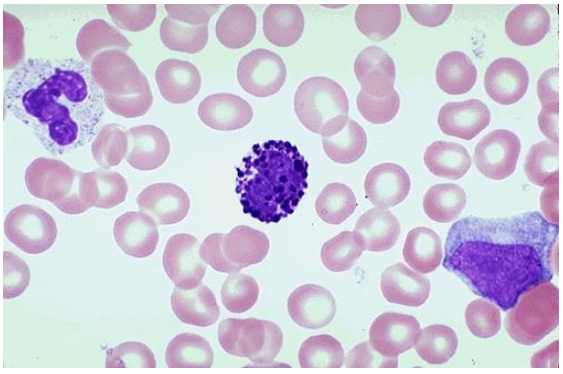


Image 18 Basophil in the blood stream.

- *Natural Killer cells*: NK cells play a major role in the host-rejection of both tumors and virally infected cells.

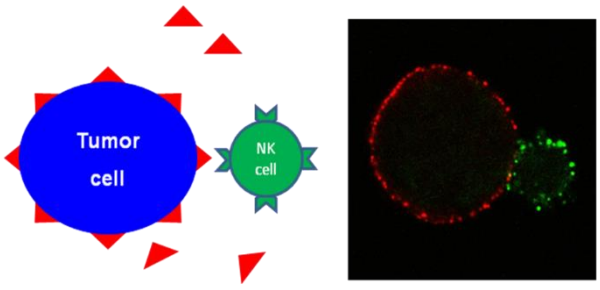


Image 20 On the left we can see a drawing of an NK cell, which has its target, a tumor cell, which has been recognized for its receptors. On the right a photo taken at the microscope showing how is the NK (in green) cell interacting with the tumor cell (in red).

NK cells are cytotoxic; they have small granules in their cytoplasm that contain special proteins such as perforin and proteases known as granzymes.

Perforin forms pores in the cell membrane of the target cell through which the granzymes and associated molecules can enter, inducing apoptosis. NK cells have been shown to kill an array of ‘stressed’ cells and secrete cytokines that participate in shaping adaptive immune responses. A key feature of NK cells resides in their ability to distinguish stressed cells (such as tumor cells, infected cells and damaged cells) from normal cells.

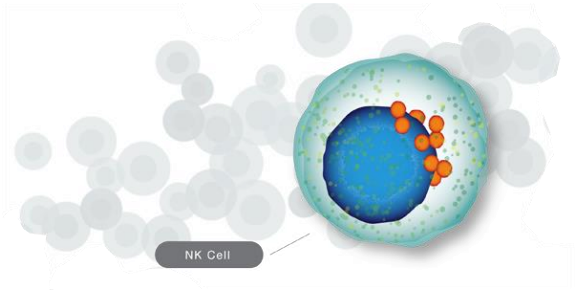


Image 21 Structure of a NK cell.

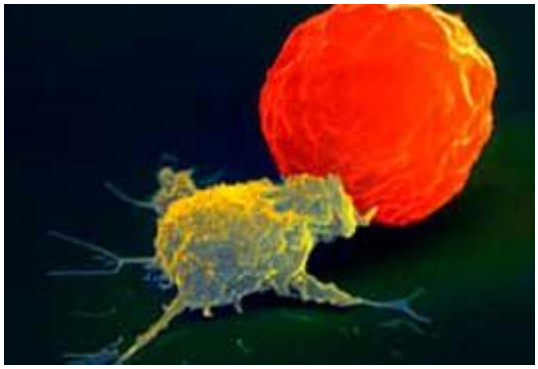


Image 22 NK cell interacting with tumor cell.

- *Dendritic cells*: Dendritic cells are antigen-presenting cells that are located in tissues, and can contact with external environments through the skin, the inner mucosal lining of the nose, lungs, stomach, and intestines. Since dendritic cells are located in tissues that are common points for initial infection, they can identify threats and act as messengers for the rest of the immune system by antigen presentation.

5.2.3 The Complement System

The complement system (also called the *complement cascade*) is a mechanism that *complements* other aspects of the immune response. Typically, the complement system acts as a part of the innate immune system, but it can work with the adaptive immune system if needed.

The complement system is made of a variety of proteins that, when inactive, circulate through the blood. When activated, these proteins come together to initiate the complement cascade, which contains the following steps:

1. *Opsonization*: Opsonization is a process in which foreign particles are marked for phagocytosis. All of the pathways require an antigen to signal that there is a threat present. Opsonization tags infected cells and identifies circulating pathogens expressing the same antigens.
2. *Chemotaxis*: Chemotaxis is the attraction and movement of macrophages to a chemical signal. Chemotaxis uses cytokines and chemokines to attract macrophages and neutrophils to the site of infection, ensuring that pathogens in the area will be destroyed. By bringing immune cells to an area with identified pathogens, it improves the likelihood that the threats will be destroyed and the infection will be treated.
3. *Cell Lysis*: Lysis is the destruction of the membrane of a cell. The proteins of the complement system puncture the membranes of foreign cells, destroying the integrity of the pathogen. Destroying the membrane of foreign cells or pathogens weakens their ability to proliferate, and helps to stop the spread of infection.
4. *Agglutination*: this process uses antibodies to pack and bind pathogens together. By bringing as many pathogens together in the same area, the cells of the immune system can mount an attack and weaken the infection easily, as they are all in the same place. Other innate immune system cells continue to circulate throughout the body in order to track down any other pathogens that have not been packed and bound for destruction.

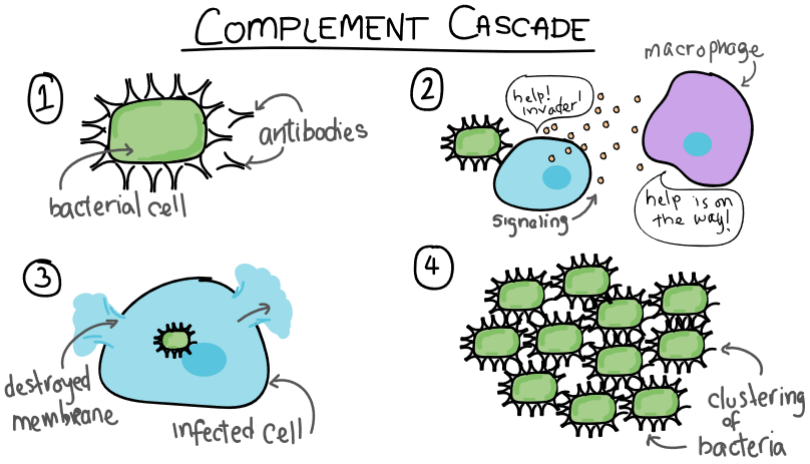


Image 23 Drawing of the complement cascade.

The innate immune system works to fight off pathogens before they can start an active infection. For some cases, the innate immune response is not enough, or the pathogen is able to exploit the innate immune response for a way into the host cells. In such situations, the innate immune system works with the adaptive immune system to reduce the severity of infection, and to fight off any additional invaders while the innate immune system is busy destroying the initial infection.

5.3 Adaptive immune system

It is curious how our recovery time for the common cold or the flu seems to get shorter after we have been exposed and successfully recovered the first time. The adaptive immune system, also called *acquired immunity*, uses specific antigens to strategically mount an immune response. Unlike the innate immune system, which attacks only based on the identification of general threats, the adaptive immunity is activated by exposure to pathogens, and uses an immunological memory to learn about the threat and improve the immune response accordingly. The adaptive immune response is much slower to respond to threats and infections than the innate immune response, which is primed and ready to fight at all times.

The adaptive immune system contains:

5.3.1Cells of the adaptive immune system

This system relies on fewer types of cells to carry out its tasks: *B cells* and *T cells*.

5.3.1.1 T cells

Once formed in the bone marrow, *T progenitor cells* migrate to the thymus (hence the name “T cell”) to mature and become T cells. While in the thymus, the developing T cells start to express *T cell receptors (TCRs)* and other receptors called *CD4* and *CD8* receptors. All T cells express T cell receptors, and either CD4 or CD8, not both. So, some T cells will be CD4+, if they have the CD4 receptor, or will be CD8+ if they have the CD8 receptor.

Unlike antibodies, which can bind to antigens directly, T cell receptors can only recognize antigens that are bound to certain receptor molecules, the MHC molecules, CD4 and CD8 play a role in T cell recognition and activation by binding to either MHCI or MHCII.

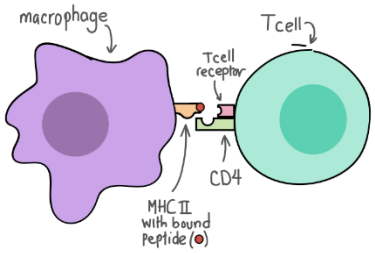


Image 24 Binding of TCR and MHC.

In order to make sure T cells will perform properly once they have matured and have been released from the thymus, they undergo two selection processes:

1. *Positive* selection ensures MHC restriction by testing the ability of MHCI and MHCII to distinguish between self and non-self-proteins. In order to pass the positive selection process, cells must be capable of binding only self-MHC molecules. If these cells bind non-self-molecules instead of self-MHC molecules, they fail the positive selection process and are eliminated by apoptosis.

2. *Negative* selection tests for self-tolerance. Negative selection tests the binding capabilities of CD4 and CD8 specifically. The ideal example of self-tolerance is when a T cell will only bind to self-MHC molecules presenting a foreign antigen. If a T cell binds, via CD4 or CD8, a self-MHC molecule that isn't presenting an antigen, or a self-MHC molecule that presents a self-antigen, it will fail negative selection and be eliminated by apoptosis.

   This two selection processes are put into place to protect own cells and tissues against your own immune response. Without this selection processes, autoimmune diseases would be much more common.

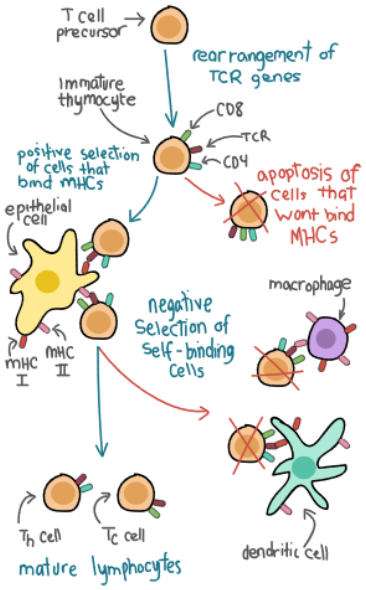


Image 25 Activation of a T cell

5.3.1.1.1 THE ACTIVATION OF A T CELL

A T cell is activated when it recognizes an antigen from an APC. Initially, the APC is presented as a naïve APC cell, because it has not yet come into contact with any antigen. When they do, they phagocytose the pathogenic molecule and kill it its cytoplasm. They express a protein from the pathogen in its MHC II molecule and are directed through the bloodstream to the lymph nodes where all naïve lymphocytes are found to find a specific T lymphocyte of that antigen. When they find it, the dendritic cell introduces it to the TCR of the lymphocyte, so that this lymphocyte can activate itself and begin a series of mechanisms to eliminate the pathogen in concrete. But, in order to activate itself the lymphocyte needs 3 signals. 1) Presentation of the antigen with the MHC II molecule 2) The co-stimulation signal with molecules CD80/86 and CD28 3)

The release of cytokines, which will cause lymphocytes to start a cloning process, so they can proliferate and have loads of T lymphocytes with the same TCR that matches the same antigen the one we are targeting.

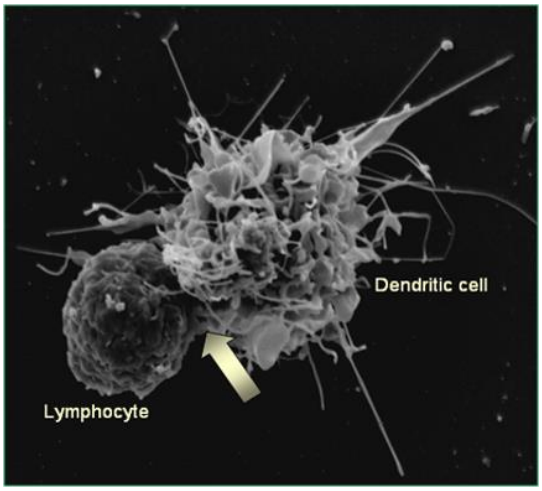


Image 26 T cell activation

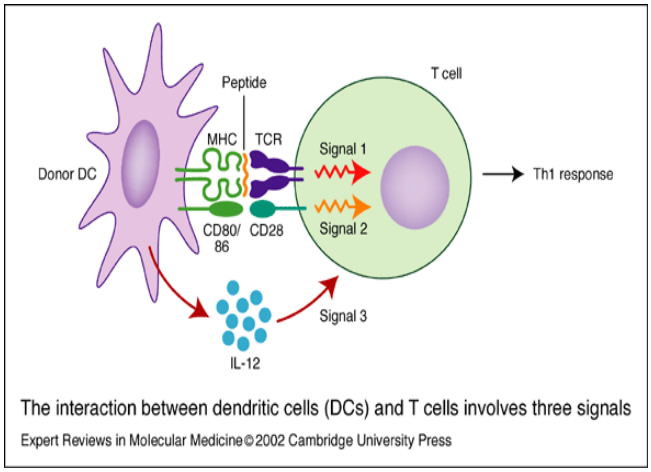


Image 27 The 3 signals for the activation of CD4+ T cells.

Interacción "Célula dendrítica-linfocito T"		
CMH-II (en la célula dendrítica)	-	**TCR (receptor de linfocito T)**
CD40	-	CD154 (CD40L)
CD80 (B7-1) /CD86 (B7-2)	-	CD28 (activación)
CD80 (B7-1) /CD86 (B7-2)	-	CD152 (CTLA4) (inactivación)
LFA-3 (CD58)	-	LFA-2 (CD2)
ICAM-1 (CD54)	-	LFA-1 (CD11a/CD18)
DC-SIGN (CD209)	-	ICAM-3 (CD50)

Image 28 Principal molecules involved in the interaction between dendritic cells and T lymphocytes.

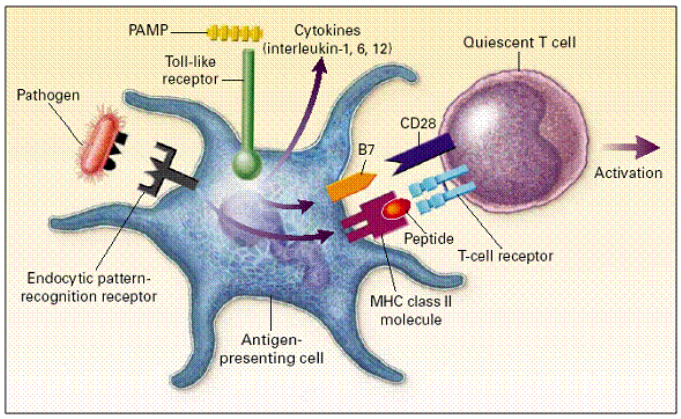


Image 29 Activated dendritic cells migrate and present antigens.

So, a T cell is activated when it recognizes an antigen from a APC and this activation results in the expansion of the antigen-specific lymphocyte pool and the differentiation of these cells into effector and memory cells. Effector cells include helper T cells, and cytotoxic T cells. In response to antigenic stimulation, helper T cells secrete cytokines for the stimulation of proliferation and differentiation of the T cells themselves, as well as other cells, including B cells, macrophages, and other leukocytes. Cytotoxic T cells kill cells that produce foreign antigens, such as cells infected by viruses and other intracellular microbes.

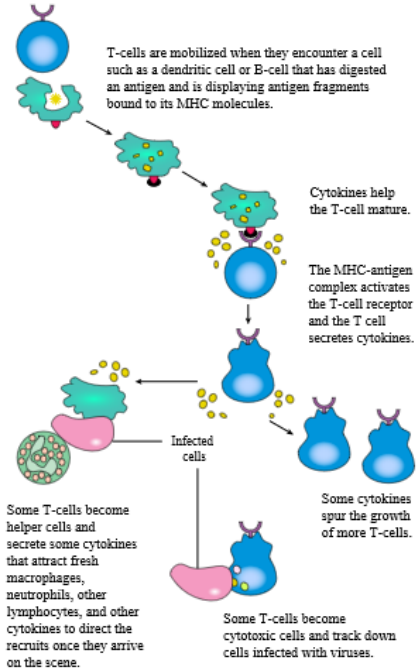


Image 30 T cell activation

Memory T cells are an expanded population of T cells specific for antigens that can respond rapidly to subsequent encounter with that antigen and differentiate into effector cell to eliminate the antigen. There is another class of T cells, called regulatory T cells, who have the function to inhibit immune response and resolve inflammation. Their major role is to shut down T cell-mediated immunity toward the end of an immune reaction.

To make a summary:

- Helper T cells express CD4, and help with the activation of T_C (cytotoxic) cells, B cells, and other immune cells.

- Cytotoxic T cells express CD8, and are responsible for removing pathogens and infected host cells.
- T regulatory cells express CD4 and another receptor, called CD25. T regulatory cells help distinguish between self and non-self-molecules, and by doing so, reduce the risk of autoimmune diseases. With the CD25, they slow down the immune response, until they deactivate all the lymphocytes, as they see that there is no longer a threat.
- T memory cells make the immune response quicker.

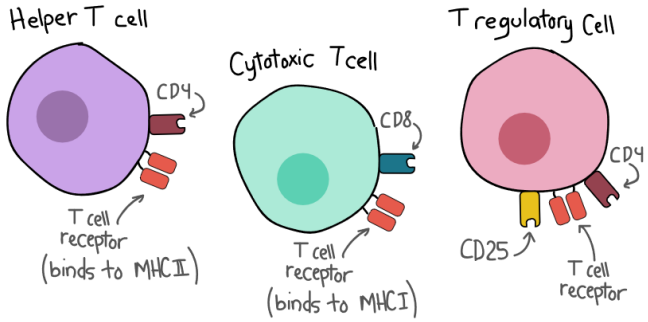


Image 31 Types of T cells.

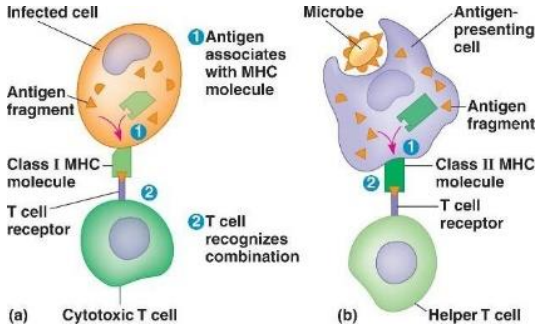


Image 32 Binding of TCR and MHC.

5.3.2B cells

After formation and maturation in the bone marrow (hence the name “B cell”), the naive *B cells* move into the lymphatic system to circulate throughout the body. In the lymphatic system, naive B cells encounter an antigen, which starts the maturation process for the B cell. B cells each have one of millions of distinctive surface antigen-specific receptors that are inherent to the organism’s DNA. For example, naive B cells express antibodies on their cell surface, which can also be called *membrane-bound antibodies*.

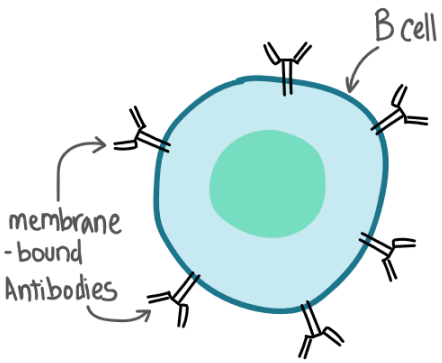


Image 33 Drawing of a B cell.

When a naive B cell encounters an antigen that fits or matches its membrane-bound antibody, it quickly divides in order to become either a *memory B cell* or an *effector B cell*, which is also called a *plasma cell*. Antibodies can bind to antigens directly.

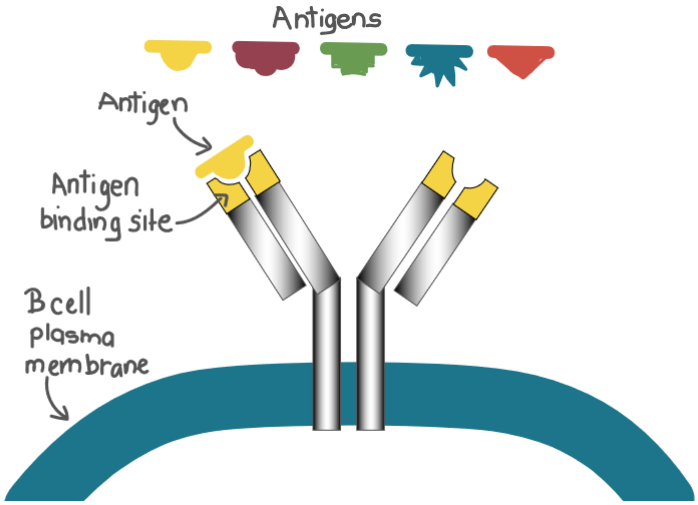


Image 34 An antibody from a B cell.

The antigen must effectively bind with a naive B cell's membrane-bound antibody in order to set off differentiation, or the process of becoming one of the new forms of a B cell.

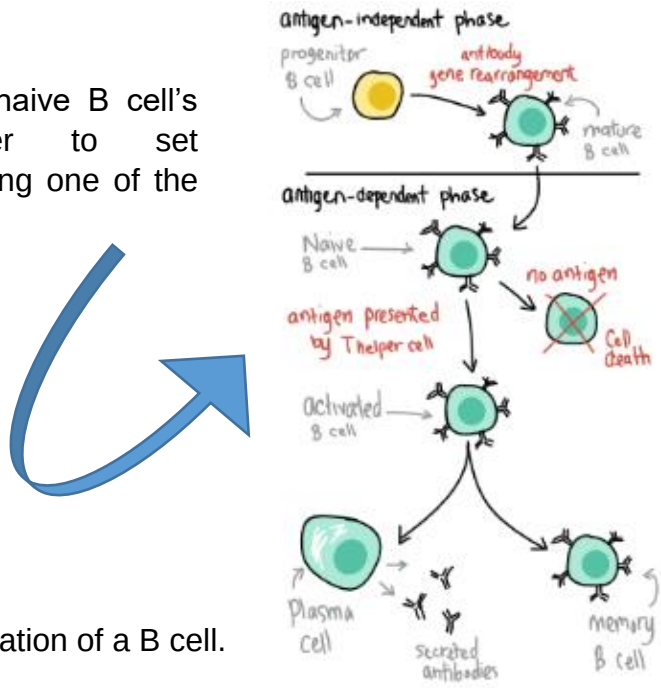


Image 35 Differentiation of a B cell.

Now that we have discussed the cells involved, and the types of immunity we have, you need to know which two types do the adaptive and innate system provide, and how those are dependent on the functions of B and T cells, as described above.

Humoral immunity:

How B cells recognize and respond to foreign antigens

B cells and their effector products make up the branch of adaptive immunity known as humoral immunity; this is a branch of the immune system that is especially good at dealing with extracellular microbes.

More specifically, someone who has never been exposed to a specific disease can gain humoral immunity through administration of antibodies from someone who has been exposed, and survived the same disease.

Steps of humoral immunity

STEP 1. ANTIGEN RECOGNITION: An antigen circulating in the body will only initiate a humoral response if it randomly encounters a complementary antibody receptor with a high affinity.

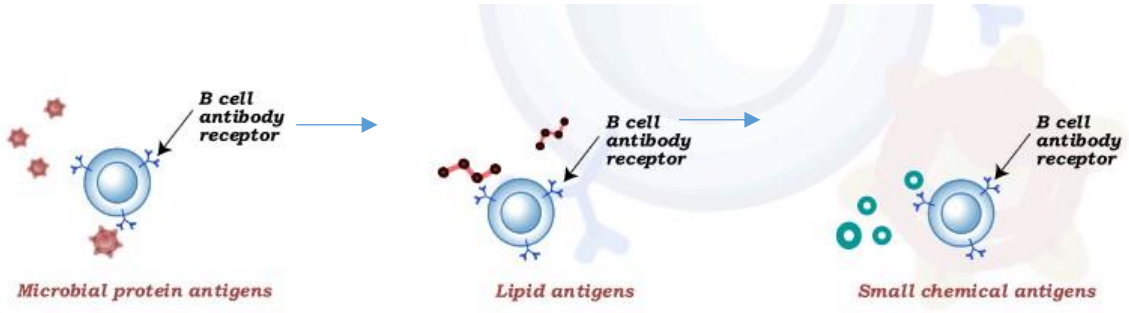


Image 36 Antigen recognition

- **STEP 2. CLONAL EXPANSION:** the process by which an antigen activates a single type of B cell is known as clonal selection. As we know, the body generates billions of lymphocytes that are able to recognize thousands of different potential antigens. Even though there are millions of different lymphocytes (because there are billions of cells), there must be some repeats. That is, within the total population of lymphocytes, there are only a few (1000 or so) of them that can recognize the same antigen. Those cells recognize the exact same antigen because they have the same antibody receptor, because they are genetically identical and developed from the same line. Those 1000 cells would be known as a clone. So, when an antigen activates one, two or forty of those 1000 cells, the entire clone is said to be activated. They need to

be activated because all the cells of this clone have the same BCR and can mount an effective immune response for the same antigen. This is called clonal selection, because the antigen “selected” cells of the clone with the correct specificity and activated them. Once cells of the clone are activated they begin to divide, this is known as clonal expansion.

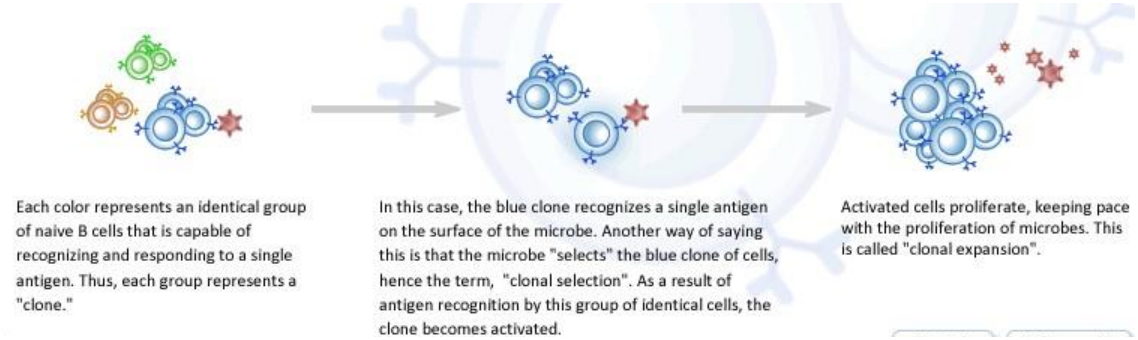


Image 37 Clonal expansion

- **Step 3. DIFFERENTIATION:** Once a clone of B cell has been activated, it is important to take into account two more important things. The first one is that the cells divide. By increasing in number, the clone ensures that it will have enough cells to mount an effective immune response. The second one is that those B cells will differentiate into plasma cells, and secrete antibodies (specific for the original antigen) to keep a “record” of what had happened, and that for the next time your body does not have to mount such a big immune response.

If the antigen is a protein it will also be phagocytosed by an APC and displayed to a T cell. This activates helper T cells and causes them to release mediators that improve the B cells’ response.

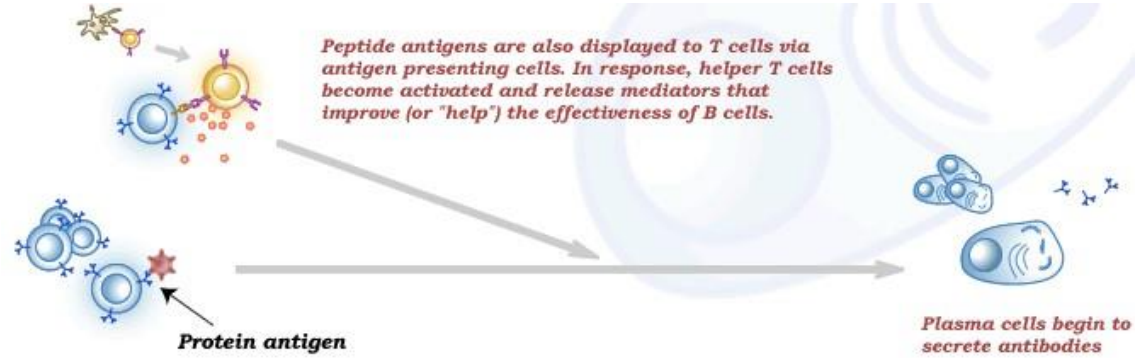


Image 38 Differentiation

- **Step 4. ANTIGEN ELIMINATION:** Antibodies are the effector mechanism of humoral immunity. They are capable of neutralizing antigens, marking them for destruction by macrophages, activating complement and instigating vigorous responses from the innate immune system. Has the humoral immune response winds down, some plasma cells undergo apoptosis. The other ones migrate to the bone marrow to keep secreting antibodies for several more years.

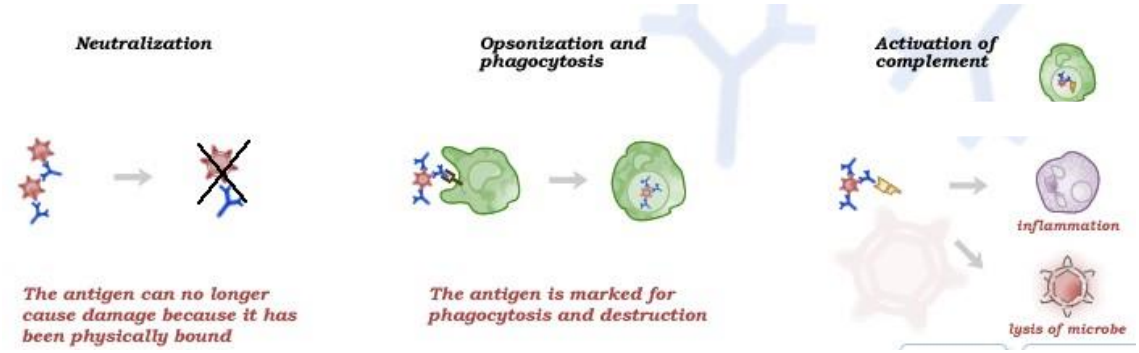


Image 39 Antigen elimination

Step 5. MEMORY: The initial activation of naïve lymphocytes also stimulates the proliferation of long-lived memory cells, which may survive after years of infection. This pool of memory cells is much larger than the pool of naïve lymphocytes for any one antigen that is present before encounter that specific antigen. This memory cells respond faster and more effectively against the antigen than naïve lymphocytes.

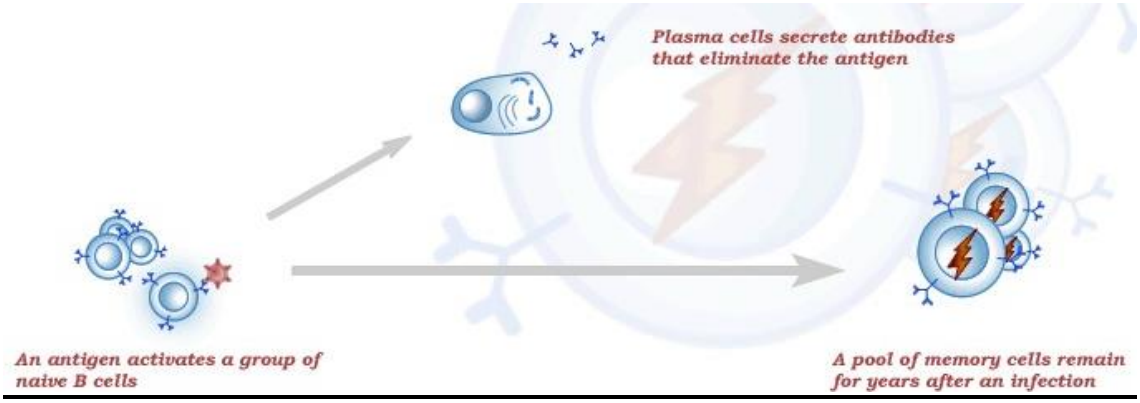


Image 40 Memory

Those pages above have the aim to explain how does the immune system work, which are its' functions, its' cells and which two types are involved in giving a strong immune response. Now we are going to enter to the main topic of this research project, which is the interaction of the immune system with cancer cells, and how potentiating this defense system we can get to eliminate cancer.

6 What is cancer?

Cancer is the name given to a collection of related diseases. In all types of cancer, the body cells begin to divide constantly and later on they emigrate to surrounding tissues.

Cancer can start anywhere in our body. Healthy cells grow and divide in order to form new cells that are needed because some of them had died due to apoptosis (induced death).

When cancer develops, this process breaks down. As they become more and more abnormal, old or damaged cells (which should die) resist, and new cells start to grow when they are not needed. These extra cells can divide without stopping and may form growths called tumors. Many cancers form solid tumors, which are masses of tissue.

There are two types of cancerous tumors: benign and malign. When talking about benign tumors we say that this ones do not spread into surrounding tissues, and even they can be quite large they do not usually grow back. Despite this, malign tumors do spread around, and they often grow back.

6.1 Differences between Cancer Cells and Normal Cells

Cancer cells differ from normal cells in many ways that allow them to grow out of control and become invasive. One important difference is that cancer cells are less specialized than normal cells. This is because of the non-stop division. Whereas normal cells divide into specialized cells, tumor cells do not.

Although the immune system normally removes those damaged or abnormal cells from the body, some cancer cells are able to “hide” from the immune system.

Tumors can also use the immune system to stay alive and grow. For example, with the help of certain immune system cells that normally prevent a

runaway immune response, cancer cells can actually keep the immune system from killing cancer cells.

Those malign cells may also be able to influence the normal cells, molecules, and blood vessels that surround and feed a tumor—an area known as the microenvironment. For instance, cancer cells can induce nearby normal cells to form blood vessels that supply tumors with oxygen and nutrients, which they need to grow. These blood vessels also remove waste products from tumors.

7 IMMUNOTHERAPY

We know that there are loads of different therapies to fight cancer, but what we do not know is that immunotherapy is one of them. But it is slightly different. In all the other therapies the emphasis is put in fighting the cancer with external factors, but with immunotherapy you are just potentiating your body to fight “naturally” against the cancer.

Immunotherapy uses the natural power of your immune system to fight diseases, including cancer. In the last few decades, it has become a key part of treatment for many different types of the disease. But not all immunotherapies work the same. Some of these drugs boost the immune system activity in a broad way, while others aim to teach it to attack very specific cell types which are found in tumors.

When talking about immunotherapy, we suppose that is a very new concept but in fact, it is not.

A brief story about immunotherapy

William B. Coley, now known as the Father of Immunotherapy, first attempted to harness the immune system for treating cancer in the late 19th century. Having noted a number of cases in which patients with cancer went into spontaneous remission after developing erysipelas, he began to inject mixtures of live and inactivated (done in a laboratory) Streptococcus pyogenes into patients’ tumors in 1891.

Coley achieved responses such as durable complete remission in several types of malignancies, including sarcoma, lymphoma, and testicular carcinoma, and this was the beginning of a new therapy to fight cancer. However, the lack of a known mechanism of action for ‘Coley’s toxins’ and the risks of deliberately infecting cancer patients with pathogenic bacteria, caused oncologists to adopt surgery and radiotherapy as standard treatments early in the 20th century.

One of the reasons why cancerous cells are successful is because they are able to hide from our immune system, to run away. Thus, the aim of immunotherapy is to “mark” those cells so the immune system can “see” them and destroy them. But this is the main aim of one of the two types of

immunotherapy, the second one is to potentiate your immune system so it can fight and kill the cancerous cells.

The natural capacity of the immune system to detect and destroy abnormal cells could prevent many types of cancer. However, some cancers manage to avoid being detected and destroyed by the immune system. It may be that they produce signals that reduce the ability of the immune system to detect and destroy tumor cells, or they may have modifications that make it more difficult that the immune system recognizes them and attack them. There are different types of therapies that are englobed by immunotherapy:

7.1 REMOVING THE BRAKE: THE CHECK POINT INHIBITORS. THE FIRST REVOLUTION.

This type of immunotherapy consists on blocking the activity of certain proteins which restrict the power of the immune responses. Those proteins are called monoclonal antibodies. In normal conditions, this proteins keep the immune response at bay, to prevent a reaction that could be excessively strong and damage the normal cells, and at the same time the cancerous ones. In cancer cells, these regulatory proteins may be abnormal, and it is possible that they help the tumor to escape from the immune response.

Blocking one of these regulatory proteins could enable the immune system again to destroy cancer cells. Those mechanisms are called the immune check points, and they are a therapy that involve monoclonal antibodies.

Those antibodies are artificially made in the laboratory, binding to special antigens which are expressed in the cell, like a protein expressed in the cancer cells surface, but which is absent or expressed in a lower extent in the normal cells.

In order to create those antibodies the researchers do inject into mice human antigen. These mice will create antibodies against this antigen, which, later, will be extracted to be used into individuals. This antibody producer of cells from mice are fused with cancer cell B, creating a hybridoma.

Once the monoclonal antibodies are obtained, they have to be administered to the patient, but How do this antibodies act in the human organism? The may act differently:

1. Stimulating an immune reaction against cancer, by using the immune system specific cells, which, as we know, are the T lymphocytes.

   These T lymphocytes have Membrane Receptors called PD-1 (among

   many others) that help them to recognize cancer cells. Despite this, those cancer cells are “intelligent” as well, and have another membrane receptor (PD-L1) which inhibits the receptor PD-1 from T-lymphocytes, giving to the cancer cells a way to escape from our immune system. Those murine antibodies bind to the PD-L1 receptor of the cancer cells surface, with the purpose of inhibiting the signals that prevent the immune cells to attack the malignant cells. One of this monoclonal antibodies, the *ipilimumab*, was approved by the FDA for the treatment of the metastatic melanoma, and some others are being reviewed in clinical trials.

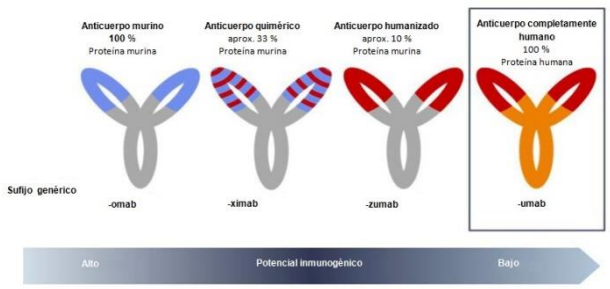


Image 41 diferent types of antibodies.

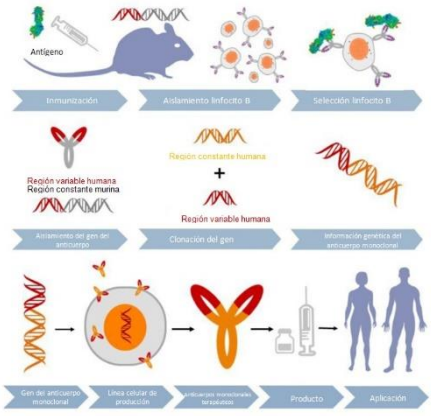


Image 42 steps of the infusion of monoclonal antibodies.

2. Some monoclonal antibodies stimulate an immune reaction that destroy cancer cells. In a similar way to the antibodies naturally produced by B lymphocytes, those monoclonal antibodies “recover”

the surface of cancer cells, what unleashes its destruction by the immune system. Monoclonal antibodies of this type, approved by FDA are *rituximab*, which aims to the antigen CD20 which is located in the cells of the Non-Hodgkin's lymphoma, and *alemtuzumab*, which aims to the antigen CD52 located on the cells of the chronic lymphocytic leukemia

(CLL) of B lymphocytes. Rituximab can directly trigger, as well, the cell death (apoptosis).

Image 43 Rituximab

3. Interfering with the action of proteins that are needed for the tumor growth. For instance, *bevacizumab* aims to the vascular endothelial growth factor (VEGF), a protein secreted by tumor cells and other cells in the microenvironment of the tumor that promotes the creation of tumor blood vessels. When it binds to bevacizumab, VEGF is not able to interact with its cell receptor, which impedes the signaling that turns into the growth of new blood vessels.

   Finally, see below two tables the gather the action mechanisms of monoclonal antibodies and its target antigens (table 2 and table 1 respectively).

Direct tumor cell killing
• cell surface receptor agonist activity (leading to apoptosis) • cell surface receptor antagonist activity (inhibit signaling, reduce proliferation, induce apoptosis) • cell surface enzyme neutralization (leading to signaling abrogation) • conjugated antibody, delivery of payload (drug, toxin, radio-isotope, leading to cell death)
Immune-mediated tumor cell killing
• induction of phagocytosis • complement activation • antibody-dependent cell-mediated cytotoxicity (ADCC) • target gene-modified T cells • activate T cells (through inhibition of T cell inhibitory receptors, such as CTLA-4, or antibody-mediated cross presentation of antigen to dendritic cells)
Vascular and stromal ablation
• vessel receptor antagonism or ligand trap • stromal cell inhibition • conjugated antibody, delivery of payload

Image 44 Table 1

Antigen category	Examples of antigens	Tumor types expressing antigen
Cluster of differentiation (CD) antigens	CD20	non-Hodgkin lymphoma
	CD30	Hodgkin lymphoma
	CD33	Acute myelogenous leukemia
	CD52	Chronic lymphocytic leukemia
Glycoproteins	EpCAM	Epithelial tumors (breast, colon, lung)
	CEA	Epithelial tumors (breast, colon, lung)
	gpA33	Colorectal carcinoma
	Mucins	Epithelial tumors (breast, colon, lung, ovarian)
	TAG-72	Epithelial tumors (breast, colon, lung)
	Carbonic anhydrase IX	Renal cell carcinoma
	PSMA	Prostate carcinoma
	Folate binding protein	Ovarian tumors
Glycolipids	Gangliosides (e.g., GD2, GD3, GM2)	Neuroectodermal tumors, some epithelial tumors
Carbohydrates	Lewis-Y[27]	Epithelial tumors (breast, colon, lung, prostate)
Vascular targets	VEGF	Tumor vasculature
	VEGFR	Epithelium-derived solid tumors
	αVβ3	Tumor vasculature
	α5β1	Tumor vasculature
Growth factors	ErbB1/EGFR	Glioma, lung, breast, colon, head and neck tumors
	ErbB2/HER2	Breast, colon, lung, ovarian, prostate tumors
	ErbB3	Breast, colon, lung, ovarian, prostate tumors
	c-MET	Epithelial tumors (breast, ovary, lung)
	IGF1R	Lung, breast, head and neck, prostate, thyroid, glioma
	EphA3	Lung, kidney, colon, melanoma, glioma, hematological malignancies
	TRAIL-R1, TRAIL-R2	Solid tumors (colon, lung, pancreas) and hematological malignancies
	RANKL	Prostate cancer and bone metastases
Stromal and extracellular matrix antigens	FAP	Epithelial tumors (colon, breast, lung, head and neck, pancreas)
	Tenascin	Glioma, epithelial tumors (breast, prostate)

Image 45 Table 2

7.2 CHIMERIC ANTIGEN RECEPTOR (CAR). THE SECOND REVOLUTION

The use of CAR T-cell therapy has been restricted to small clinical trials, largely in patients with advanced blood cancers. But these treatments have nevertheless captured the attention of researchers and the public alike because of the remarkable responses they have produced in some patients—both children and adults—for whom all other treatments had stopped working.

As its name implies, the backbone of CAR T-cell therapy is T cells, which are often called the workhorses of the immune system because of their critical role in orchestrating the immune response and killing cells infected by pathogens.

These T cells are then genetically modified in the laboratory to express a synthetic, or man-made, protein on their surface known as a chimeric antigen receptor, or CAR. The CARs on the T cells are designed to bind to specific proteins on the surface of cancer cells. Having the ability to bind to the cancer cells allows the modified T cells to attack these cells. This process also spurs the production of other T cells in the body capable of targeting cancer cells.

After the immune cells are engineered to express a CAR, they are then grown in the laboratory until there are hundreds of millions of them. When they are ready to be given to patients, patients first receive chemotherapy and other drugs that deplete the body of existing T cells. The entire batch of CAR T cells is subsequently infused into the patient in a single dose.

7.2.1THE MAKING OF A CAR T CELL

The CAR on the cell's surface is composed of fragments, or domains, of synthetic antibodies. The domains that are used can affect how well the receptor recognizes or binds to the antigen on the tumor cell.

The receptors rely on stimulation signals from inside the cell to do their job. So each CAR T cell has signaling and "co-stimulatory" domains inside the cell that signal the cell from the surface receptor. The different domains that are used can affect the cells' overall function.

Over time, advances in the intracellular engineering of CAR T cells have improved the engineered T cells' ability to produce more T cells after infusion into the patient (expansion) and survive longer in the circulation (persistence).

Advances have also been made in how long it takes to produce a batch of CAR T cells. Although it initially took several weeks, many labs have now reduced the time to less than 7 days.

7.2.1.1 A Possible Option Where None Had Existed

The good news are that, Dr. Grupp, M.D., Ph.D., of the Children's Hospital of Philadelphia (CHOP), has led several trials of CAR T cells in children and young adults with ALL that had recurred or was not responding to existing therapies. In one of these earlier trials, which used CD19-targeted CAR T cells, all signs of cancer disappeared (a complete response) in 27 of the 30 patients treated in the study, with many of these patients continuing to show no signs of recurrence long after the treatment.

These early successes laid the foundation for a larger trial Exit Disclaimer of a CD19-targeted CAR T-cell therapy, called tisagenlecleucel , for children and adolescents with ALL. Many of the patients who participated in the trial, funded by Novartis, had complete and long-lasting remissions.

The rapid advances in and growth of CAR T-cell therapy has exceeded the expectations of even those who were early believers in its potential.

7.2.2Understanding, Managing Side Effects

Like all cancer therapies, CAR T-cell therapy can cause several worrisome, and sometimes fatal, side effects. One of the most frequent is cytokine release syndrome (CRS).

As part of their immune-related duties, T cells release cytokines, chemical messengers that help to stimulate and direct the immune response. In the case of CRS, there is a rapid and massive release of cytokines into the bloodstream, which can lead to dangerously high fevers and precipitous drops in blood pressure.

Ironically, CRS is considered an “on-target” effect of CAR T-cell therapy—that is, its presence demonstrates that active T cells are at work in the body. Generally, patients with the most extensive disease prior to receiving CAR T cells are more likely to experience severe CRS.

In many patients, both children and adults, CRS can be managed with standard supportive therapies, including steroids. And as researchers have gained more experience with CAR T-cell therapy, they’ve learned how to better manage the more serious cases of CRS.

Another potential side effect of CAR T-cell therapy (an off-target effect), is a mass die off of B cells, known as B-cell aplasia. CD19 is also expressed on normal B cells, which are responsible for producing antibodies that kill pathogens. These normal B cells are also often killed by the infused CAR T cells. To compensate, many patients must receive immunoglobulin therapy, which provides them with the necessary antibodies to fight off infections.

More recently, another serious and potentially fatal side effect, swelling in the brain, or cerebral edema, has been seen in some of the larger trials being conducted to support potential FDA approval of CAR T-cell therapies for patients with advanced leukemias. One company, in fact, decided to halt further

development of their leading CAR T-cell therapy after several patients in clinical trials died as a result of treatment-induced cerebral edema.

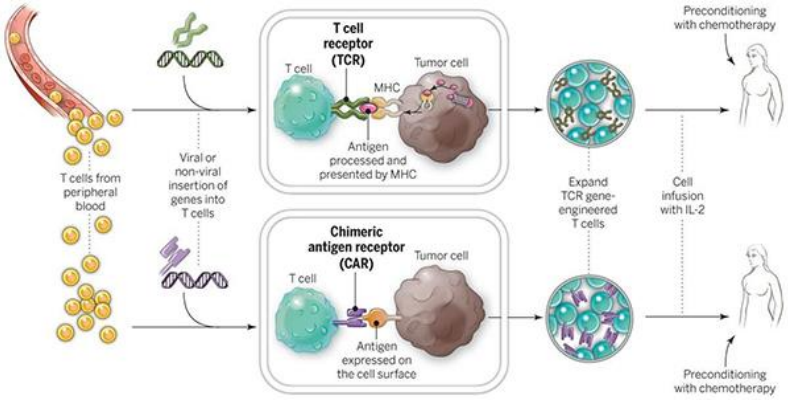


Image 46 The making of car t cell

7.3 Antitumor T response: tumor-infiltrating lymphocytes (TILs)

Researchers have found immune system cells deep inside some tumors and have named these cells *tumor-infiltrating lymphocytes* (TILs).Esta terapia consiste en reforzar “naturalmente” la capacidad de las células T para combatir el cáncer.

In TIL therapy, TILs are collected from a patients’ tumor sample and tested in the laboratory to identify those with the best ability to recognize the patient's tumor cells. Unlike CARs, they don’t need any further modifications or any type of engineering. As with CARs, however, large populations of these TILs are grown in the laboratory.

The expanded TILs are then turned on, or activated, by treatment with immune system signaling proteins called cytokines. After the patient receives chemotherapy to destroy their existing T cells, the activated cells are infused into the patient in a single dose.
The idea behind this approach is that the TILs have already shown the ability to target tumor cells, but there may not have been enough of these immune cells in and around the tumor (known as the tumor microenvironment) to eradicate it or overcome the signals being released by tumor cells that block the immune

cells' activity. Introducing massive amounts of activated TILs can help to overcome these barriers, leading to tumor destruction.

Treatments using TILs are being tested in clinical trials in people with melanoma, kidney cancer, ovarian cancer, and other cancers. Early studies of this approach by researchers from the National Cancer Institute have been promising, but its use may be limited because doctors might not be able to get TILs from all patients.

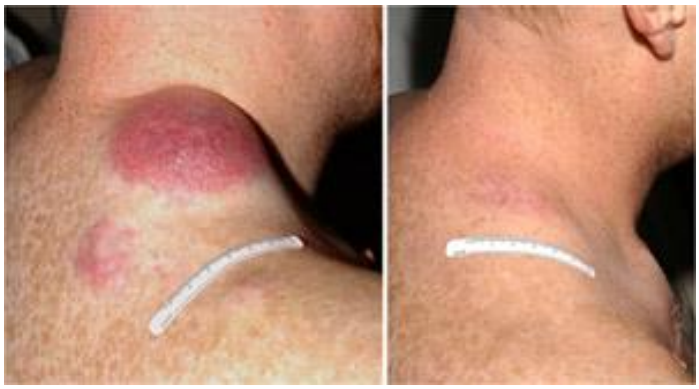


Image 47 Before and after pictures of a patient with advanced melanoma who underwent treatment with tumor-infiltrating lymphocytes. With 2 weeks of treatment, the large tumor had disappeared.

7.4 CANCER VACCINES

Vaccines are not yet a major type of immunotherapy. Researchers have been trying to develop vaccines to fight cancer for decades, but this has proven to be harder than was first thought. As researchers have learned over the years, the immune system is very complex. It has also become clear that cancer cells have different ways of eluding the immune system, which makes creating effective vaccines difficult.

Researchers are using the knowledge gained in recent years to improve how they develop cancer vaccines. For example, vaccines are now often given along with other substances (called adjuvants) that help boost the body's immune response, which might help the vaccines work better.

Researchers are also studying the best way to give vaccines, looking to see if they work better when used alone or with other types of cancer treatments.

Types of cancer vaccines

Many different types of vaccines are now being studied to treat a variety of cancers.

Tumor cell vaccines: These vaccines are made from actual cancer cells that have been removed from the patient during surgery. The cells are altered (and killed) in the lab to make them more likely to be attacked by the immune system and then injected back into the patient. The patient's immune system then attacks these cells and any similar cells still in the body.

Most tumor cell vaccines are autologous, meaning the vaccine is made from killed tumor cells taken from the same person in whom they will later be used. Other vaccines are allogeneic, meaning the cells for the vaccine come from someone other than the patient being treated. Allogeneic vaccines are easier to make than autologous vaccines, but it's not yet clear if one type works better than the other.

Antigen vaccines: These vaccines boost the immune system by using only one antigen (or a few), rather than whole tumor cells. The antigens are usually proteins or pieces of proteins called peptides.

Antigen vaccines can be specific for a certain type of cancer, but they are not made for a specific patient like autologous tumor cell vaccines are.

Dendritic cell vaccines: These vaccines have shown the most success so far in treating cancer. Sipuleucel-T (Provenge), which is approved for the treatment of advanced prostate cancer, is an example of a dendritic cell vaccine.

Dendritic cells are special immune cells in the body that help the immune system recognize cancer cells. They break down cancer cells into smaller pieces (including antigens), and then hold out these antigens so other immune cells called T cells can see them. The T cells then start an immune reaction against any cells in the body that contain these antigens.

Dendritic cell vaccines are made from the person in whom they will be used. The process used to create this type of vaccine (known as an autologous vaccine) is complex and expensive. Doctors remove some immune cells from the patient's blood and expose them in the lab to cancer cells or cancer antigens, as well as to other chemicals that turn the immune cells into dendritic cells and help them grow. The dendritic cells are then injected back into the patient, where they should cause an immune response to cancer cells in the body.

Vector-based vaccines: These vaccines use special delivery systems (called vectors) to make them more effective. They aren't really a separate category of vaccine; for example, there are vector-based antigen vaccines.

Vectors are special viruses, bacteria, yeast cells, or other structures that can be used to get antigens into the body. The vectors are often germs that have been altered to make sure they can no longer cause disease.

Vectors can be helpful in making vaccines for a number of reasons. First, they can be used to deliver more than one cancer antigen at a time, which might make the body's immune system more likely to mount a response. Second, vectors such as viruses and bacteria might trigger their own immune responses from the body, which could help make the overall immune response even stronger. Finally, these vaccines might be easier and less expensive to make than some other vaccines.

Some common cancers in which vaccines are being tested

Some of the more common types of cancer in which vaccines are now being studied include:

Brain tumors (especially glioblastoma)

Breast cancer

Cervical cancer

Colorectal cancer

Kidney cancer

Lung cancer

Lymphoma

Melanoma

Pancreas cancer

Prostate cancer

8 PRACTICE PART

8.1 ARTICLE: IS THE CURE OF CANCER INSIDE OF US?

We live in a very advanced society at scientific and technological level. We can create insulin artificially through bacteria, we can transplant healthy kidneys to patients who need it ... etc., but there are many things that we still cannot solve, and one of them, maybe one of the more relevant, is the disease with the highest mortality rate in our days; the cancer

It is true that in some cases, we are able to cure it, or rather, to chronicle it; with chemotherapy, surgery and other conventional therapies, but we do not have something that eradicates it completely 100%.

Normally, if in a group of 20 people we ask how many people have a relative or an acquaintance who has suffered from cancer, about 18 people will raise their hands. We talk very easily about cancer and what this entails, but how would we define cancer? Surely, from the room of 20 people, only 2 would give a rough definition of what it is.

To define the word cancer, we will associate it with another term; Organ, And why this? So let's see, when we wonder of a good definition for the word organ, we think of a system formed by a set of cells that are constantly dividing themselves to form daughters cells, which are able to survive thanks to the oxygen that the blood brings and the nutrients also provided by it. Given this definition, then, we can observe that we may have difficulty in saying whether it identifies only an organ or a cancer as well.

And this difficulty comes from the fact that cancer is very intelligent. It is made up of a set of cells that have a disproportionate division, which is able to build blood vessels around it that provide them with oxygen and nutrients, and that it is also able to deceive the immune system, and to say that its cells are not a potential threat. Cancer acts as if it were another organ of our body, of which we are not "conscious" until it is in an advanced stage of its development.

And that’s how these cancer cells manage to survive even though our body has enough mechanisms to get rid of them.

Previously, we mentioned the immune system. Many of us do not know that it plays a fundamental role in the development of this disease. What we also don’t know is that right now we could be developing cancer, but that our defense system (immune system) is eradicating it.

And how does this happen? First, we will briefly define what is the immune system and its functions. To do so, we will look at the composition of this term; System and Immune. System, comes from a Latin word that serves to refer to an ordered module of interrelated elements that interact with each other. It can be used to talk about real objects or abstract concepts that are endowed with organization.
The concept of Immune, for its part, serves to refer to what is not susceptible to being affected by certain diseases or that is free of charges or penalties.

In the area of medicine and biology, immunity is associated with the state of resistance to the pathogenic action of foreign organisms or substances, such as our cancer cells.

The immune system, also known as an immunological system, is formed by the set of structures and biological processes that protect the organism. These processes are capable of identifying and destroying pathogenic cells, viruses, parasites, etc.

The proper functioning of the immune system requires it to be able to distinguish foreign substances and differentiate them from the healthy cells and tissues of the organism. For this, it will lie on the use of antibodies, lymphocytes, leukocytes and other components, which later we will see how they are able to help fight a cancer.

The immune system, therefore, must appeal to various mechanisms that allow it to recognize and neutralize the pathogens, which could be, indeed, cancer cells.
Having said all this, we can think that if we already have mechanisms that help us to eliminate the abnormal cells of our body, how it is possible that so many people suffer from cancer every day?

Well, this is because, as we have said before, the cancer is intelligent, it has developed mechanisms that are called "escape mechanisms", with which it deceives the immune system and does not appear as an antigen. And these escape mechanisms are precisely those that doctors and researchers will use to fight the existing cancer.

And it's here where the main topic of the article goes into, the immunotherapy.

Immunotherapy is a biological therapy that is aided by the immune system to fight cancer, that is, it uses the mechanism that should first have worked properly and enhances its activity so as to avoid side effects and not punish that much the body the other conventional therapies do.

Within this immunotherapy we will focus on different types/techniques that we will explain further below: monoclonal antibodies, TILS or infiltrating tumor lymphocytes and finally the CAR T cells, or chimeric antigen receptors.

First, we will explain the concept of monoclonal antibodies.
We did previously, referred to the fact that doctors and researchers would use the escape mechanisms of cancer cells as a benefit to eradicate existing cancer. And this is because one of the escape mechanisms, found on the surface of cancerous cells and lymphocytes (cells of the immune system that are responsible for making holes in the surface of the pathogenic cells, thus causing their death). These mechanisms (which in fact are Membrane

Receptors), are called PD-1 and PD-L1, in the immune and cancer cells respectively.

PD-1, located in the lymphocytes, detects the presence of non-natural organisms of our organism and "gives the order" to begin the immune response against this organism. PD-L1(Membrane Receptors of cancer cells), inhibits the function of PD-1, causing the carcinogenic cell to become invisible to our defense system.
The therapy that has been designed based on this concept, is based on the design of a murine antibody (that is, from mice) that manages to bind with the membrane receptor PD-L1, inhibiting it. Then we would be talking about a therapy that would inhibit the inhibitor, called anti-PD-L1.

The second therapy we will discuss is the infiltrating tumor lymphocytes, or ITLS.
This therapy is conceptual and technically very simple. It consists in performing a biopsy of the patient's tumor, and observing which lymphocytes have been able to penetrate into the tumor and begin what could be considered as an attempt to respond against cancer.

These lymphocytes are isolated and their growth is stimulated in the laboratory. Subsequently, they are injected into the patient and an immune response is expected to be sufficiently potent to eliminate the tumor.

Finally, we have the therapy known as CARS, or chimeric antigen receptors.

In this treatment, T lymphocytes are modified to attack cancer cells. This is because in analyzing the tumor it has been observed that there are no lymphocytes that have managed to enter into the tumor. T cells are extracted from the patient's blood, and in the laboratory, the gene for a special receptor that binds to a certain protein in the patient's cancer cells is added to (but that this protein is only expressed in cancer cells and not in other normal cells of our body, a very common problem in this type of therapy, since many times the

cancer does not express any protein that can be recognized by our immune cells).
This special receptor is called CAR, that is, "chimeric antigen receptor". Large quantities of T cells with CAR are produced in the laboratory and administered to the patient by infusion. And, again, these cells are expected to potentiate a very strong response that is capable of eradicating the cancer of the patient.

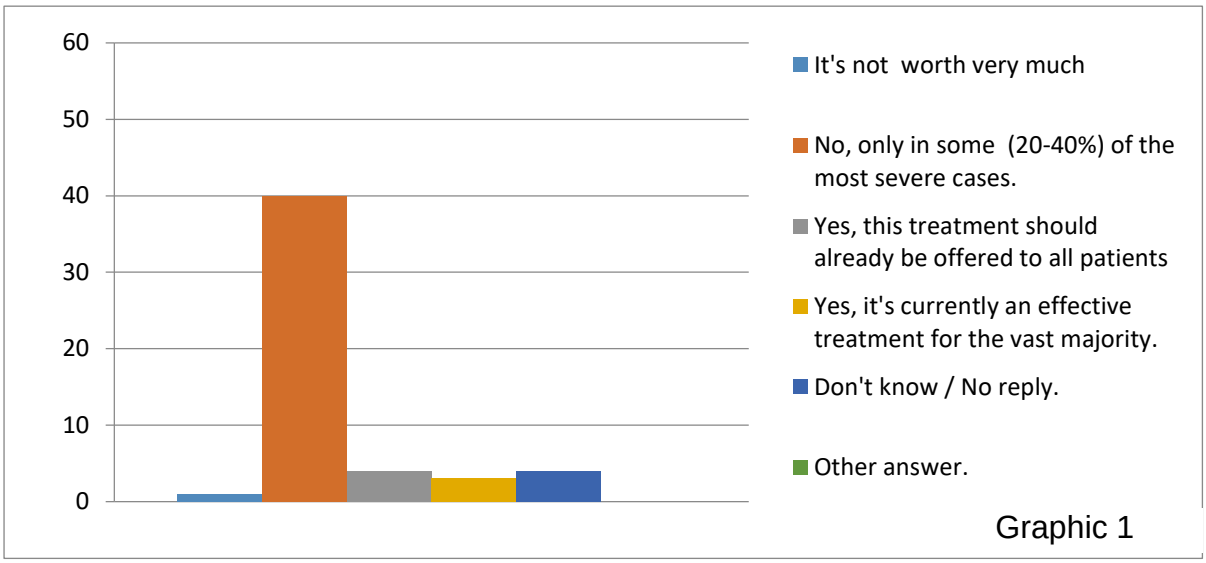
All in all, immunotherapy is considered one of the main hopes in the treatments of cancer, as it uses the body’s potential to fight cancer. It is difficult though to apply immunotherapy, because it is considered an expensive therapy and very personal, as the doctor has to study each tumour and see which particularity it has.

9 GRAPHICS

9.1 TABLES ATTACHMENT

1. WILL THE IMMUNOTERAPY BE ABLE TO TREAT EFFECTIVELY TO ALL PATIENTS IN THE FUTURE?

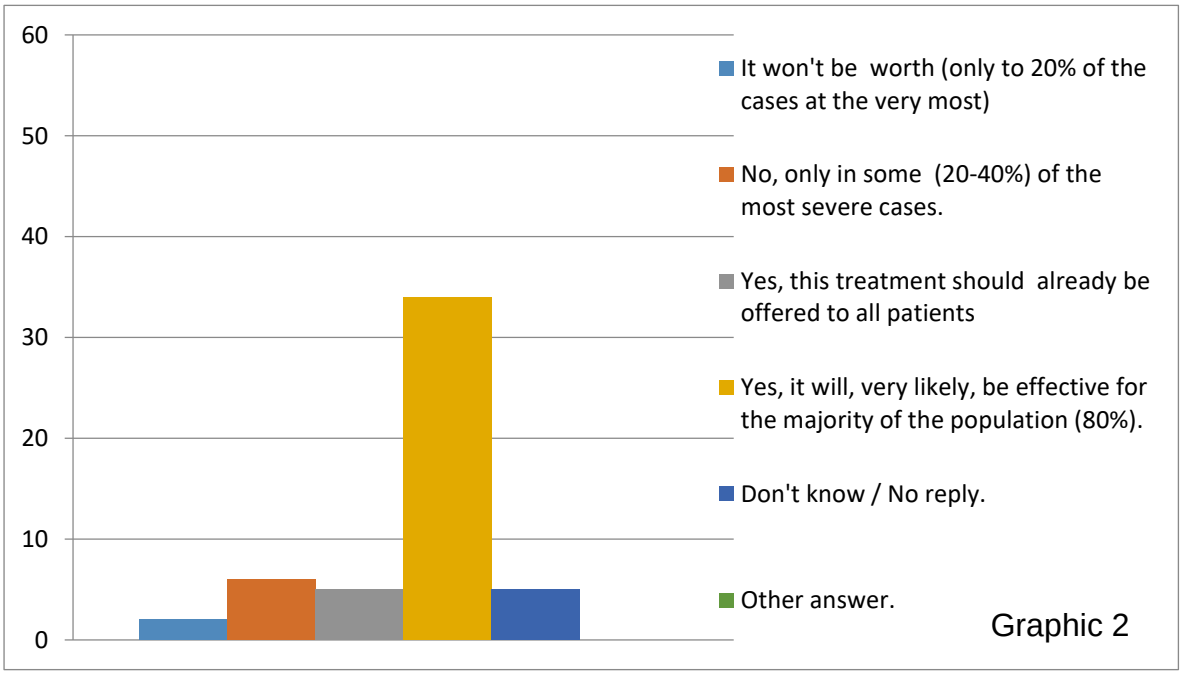
NOW (next 1-2 years):



Graphic 1

As we can see in this graph, most respondents (76.92%) do not believe that in the recent future (1-2 years) immunotherapy is going to be effective for treating all patients and all types of tumors, but do think that it will for 20 or 40% of the most serious. On the other hand, two small groups of 7.69% each, think that it would be a therapy that should be given as a first treatment, and the other small group does not know what the evolution of this new therapy will be.

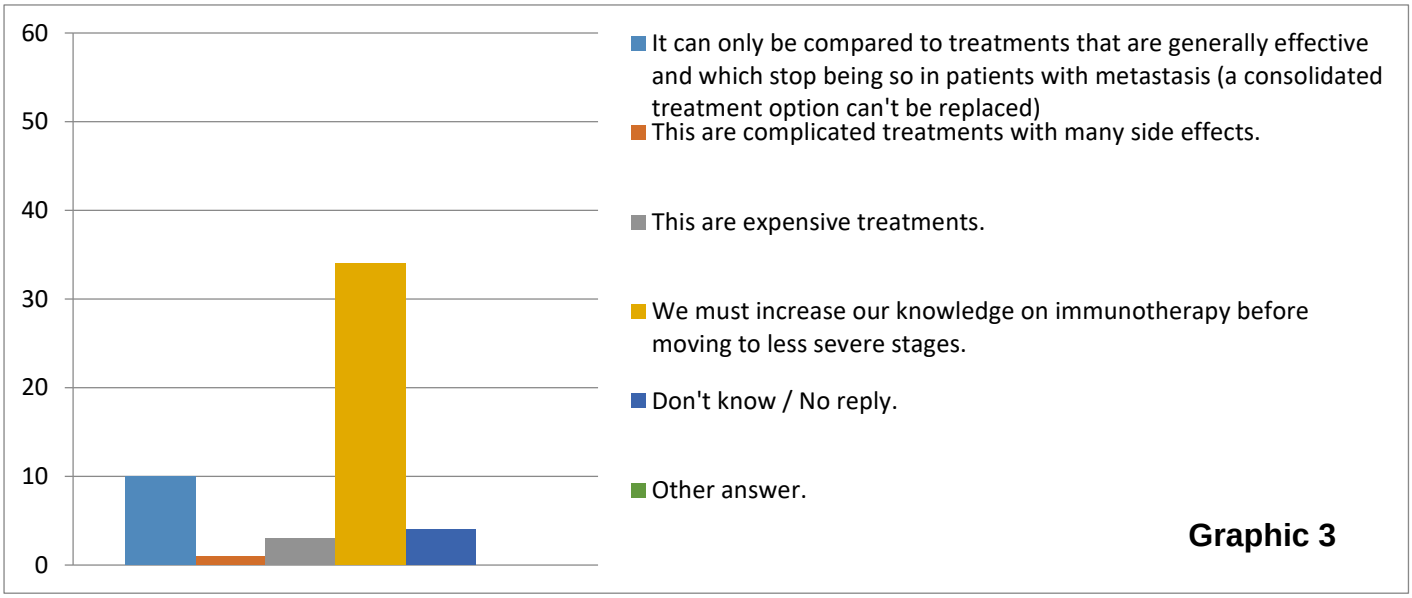
IN THE FUTURE (in 10 years):



Graphic 2

The main idea of this graphic in which 34 respondents agree (65.38%), is that in the future (within 10 years) it will be possible to effectively treat 80% of the population with immunotherapy. The second most followed idea for the respondents is that immunotherapy will only be effective in 20-40% of the most serious cases.

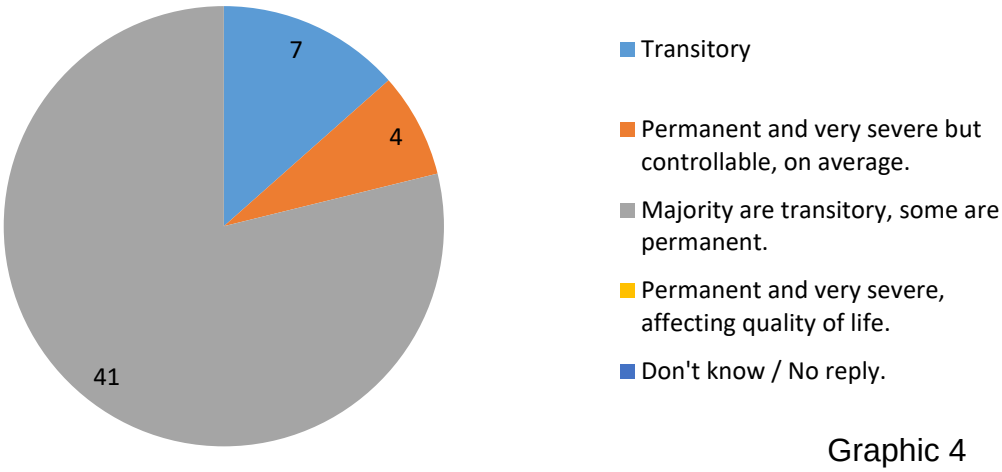
2. WHY IS THIS THERAPY ONLY APPLIED TO PATIENTS WITH METHASTASYS



Graphic 3

The 65% of the survey respondents think that before going in an adjuvant stage they must increase the knowledge about this therapy. However, the 19% of the survey respondents think that this treatment can only be compared with treatment that is effective and stops being so in patients with a metastasis. There is a 7% that does not now or has not answer the question, or they don't know the answer.

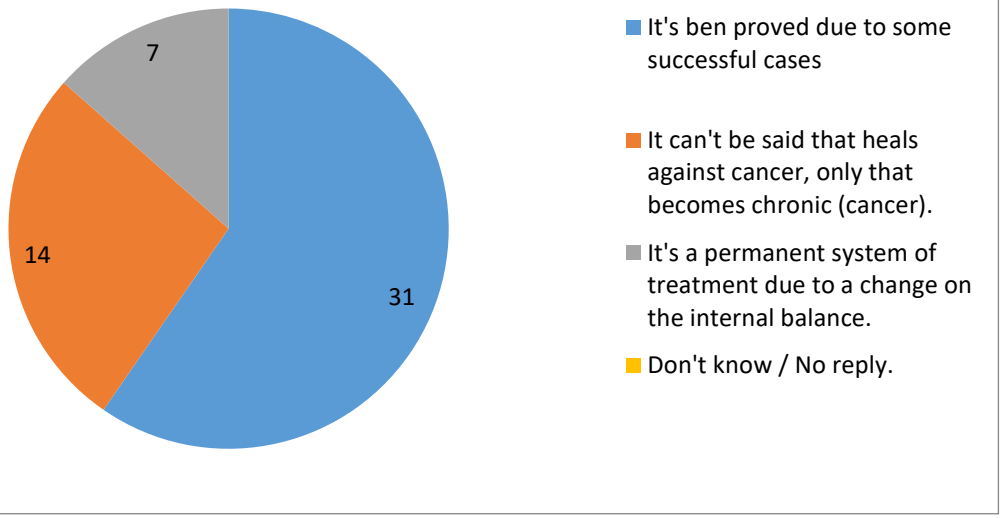
3. ARE THE SIDE EFFECTS OF IMMUNOTHERAPY TRANSITORY, OR MAY THEY END UP BEING PERMANENT AND THEREFORE AFFECTING QUALITY OF LIFE OF THE INDIVIDUAL?



Graphic 4

Most of the respondents (78.85%) believe that many of the side effects of immunotherapy are transient, although there are also some permanent ones. There is a small minority (13.46%) who thinks that they are all transient and another even smaller group (7.69%) who think they are permanent and very serious but they can be controlled normally.

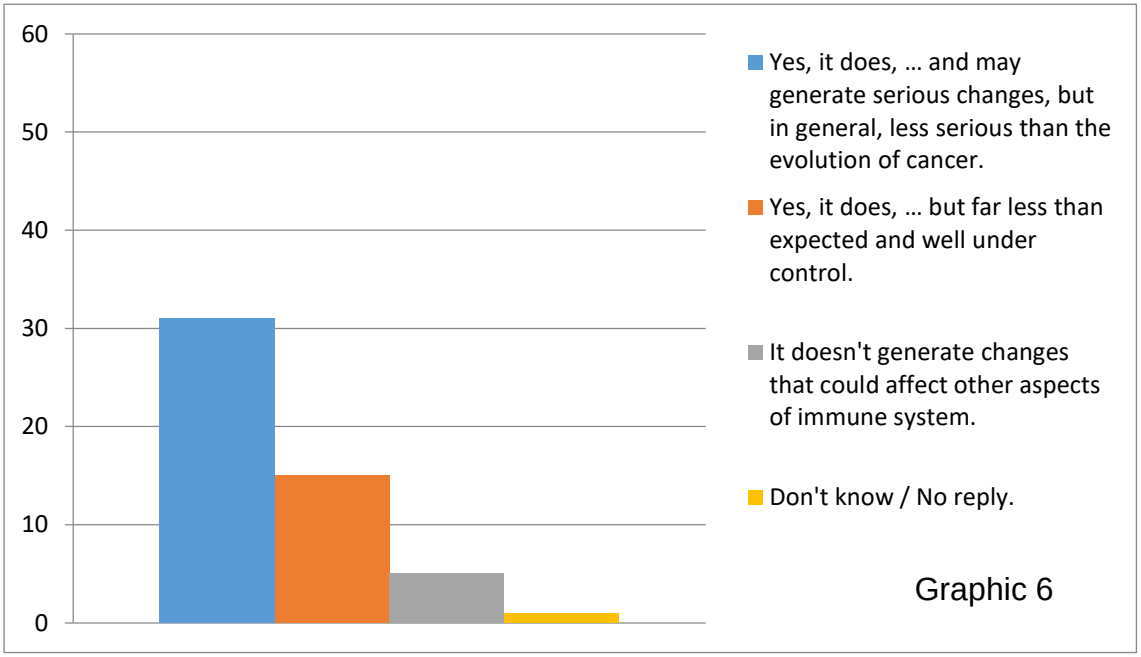
4. WHY DO YOU THINK CANCER CAN BE TREATED SUCCESSFULLY WITH THIS THERAPY?



Graphic 5

Although it is not a very high percentage, the answer given by respondents with 59.62% is that they believe that it is a therapy that can cure cancer because it is well-proven in some cases successfully. The second most valued idea with 26.92% is the following, we cannot say that it cures cancer, only chronicles it. Finally, the other group with 13.46% believes that it is a permanent treatment system as it changes the internal balance.

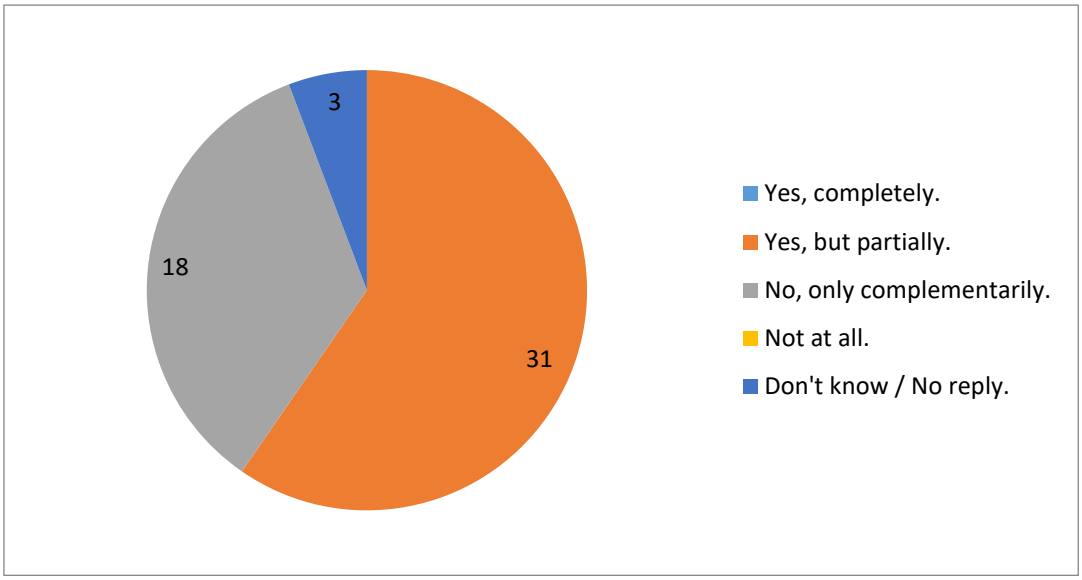
5. MAY THE IMMUNOTHERAPY CHANGE OUR IMMUNE SYSTEM IN A WAY THAT ITS ACTIVITYCOULD BE AFFECTED IN FRONT OF OTHER PATHOLOGIES UNLEASHED IN OUR BODY?



Graphic 6

As can be seen in the graph, the most voted answer (with 59.62%) refers to whether it can cause serious changes but that these changes are usually less harmful than the evolution of cancer. Another 28.85% of respondents believe that it can cause, indeed, serious changes but that it does much less than expected and that they are well controlled. A small percentage of 9.62% have responded that immunotherapy does not generate changes that affect other aspects of the immune system.

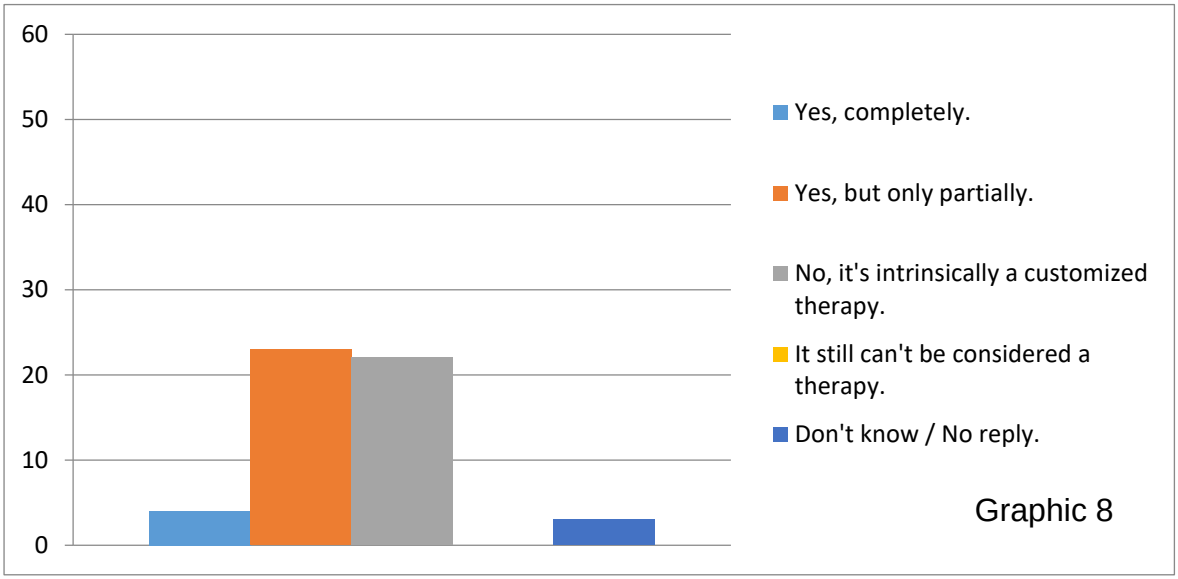
6. WILL THE IMMUNOTHERAPY BE ABLE TO REPLACE THE CURRENT THERAPIES AGAINST CANCER (CHEMOTHERAPY, RADIOTHERAPY...)?



Graphic 7

As it can be seen, the opinion answered most by respondents (with 59.62%) says that immunotherapy will be able to partially replace existing cancer treatment therapies. On the other hand, 34.62% have responded that immunotherapy can only complement these current therapies.

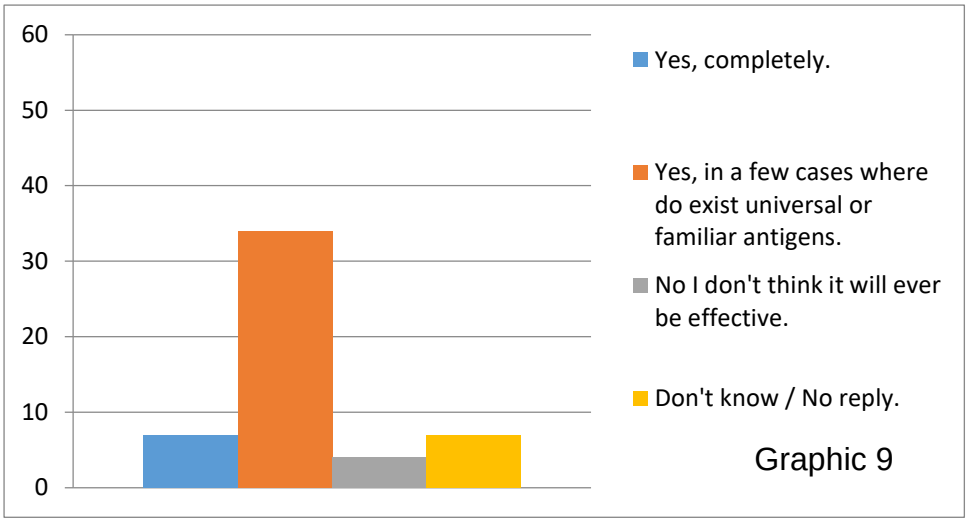
7. DO YOU THINK IT WILL CEASED TO BE A CUSTOMIZED THERAPY AND BECOME UNIVERSAL?



Graphic 8

Regarding this question the opinion of the respondents has been split almost equally into two answers. The first of them (44.23%) says that immunotherapy will no longer be a personalized therapy and will become universal even though only partially. The other most voted response with 42.31% did not agree because it believes that immunotherapy is intrinsically a personalized therapy. Apart from these two answers, 7.69% responded that they totally agreed that immunotherapy will no longer be a personalized therapy and will become universal.

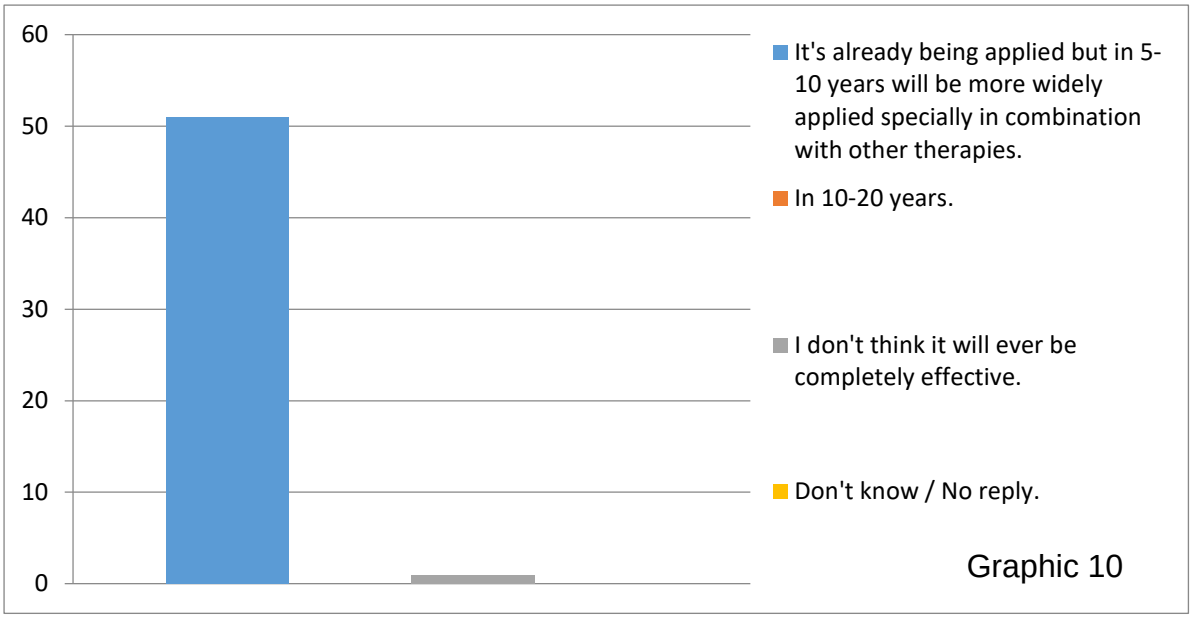
8. DO YOU THINK THERE WILL BE A POSSIBILITY TO DEVELOP A VACCINE (PROPHYLACTIC VACCINE) AGAINST CANCER?



Graphic 9

The general opinion of the respondents with 65.38% believe that yes, there can be a cancer vaccine in a few cases where universal or family antigens do exist. Although the majority of respondents have responded to this option, there are two more options that have been answered with the same percentage of 13.46%. The first of them completely states that there will be this cancer vaccine, and second of them are people who do not know if it can exist. It should also be mentioned that 7.69% believe that this vaccine will never be effective.

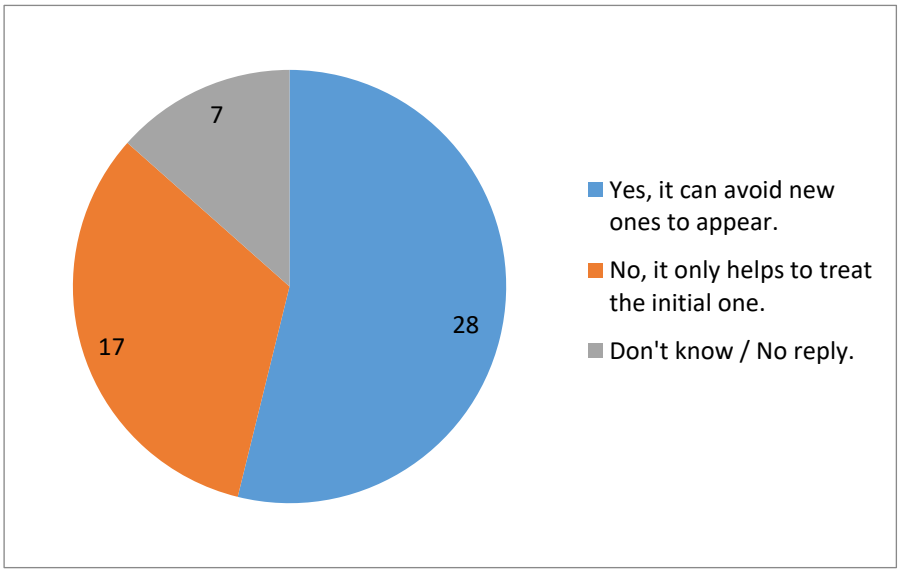
9.HOW LONG WILL IT TAKE TO GLOBALLY APPLY THIS THERAPY IN THE HEALTH SYSTEM SPHERE



Graphic 10

In this question, almost the absolute majority agreed with 98.08% in their response that says that immunotherapy is already applied generically to the healthcare sector but that it will be more widely applied from about 5-10 years, especially in combination with other therapies. The other minimum group of 1.92% believe that immunotherapy will never be effective at all.

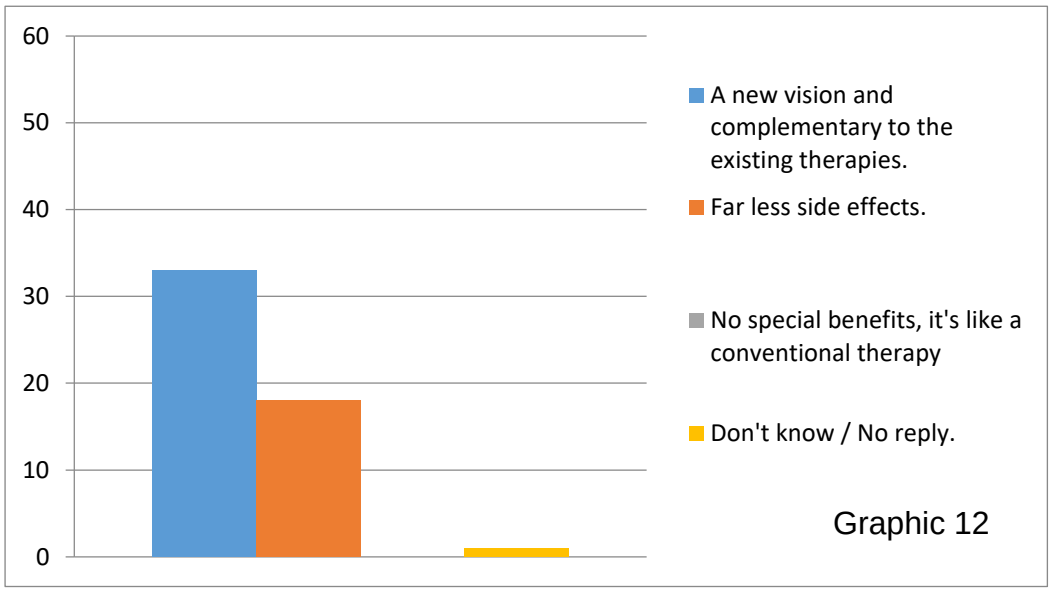
10. DOES IMMUNOTHERAPY ELIMINATES TUMOURS AND AVOIDS NEW ONES TO APPEAR, OR JUST INTENDS TO ELIMINATE THE ALREADY EXISTING ONES?



Graphic 11

The opinion in this question is quite diverse; however, the most common response given by respondents (with 53.85%) is that immunotherapy can prevent new tumors from appearing in the future. On the other hand, 32.69% believe that immunotherapy only intends to eliminate the initial and does not prevent them from appearing more. Finally, 13.46% of respondents do not know what to answer this question.

11. WHICH BENEFITS/ADVANTAGES BRINGS THE IMMUNOTHERAPY VERSUS THE CURRENT THERAPIES AGAINST CANCER?



Graphic 12

In this question the respondents' answers are classified in almost two large groups, excluding those who have not been able to respond. The first group, with 63.46%, believes that immunotherapy provides a new and complementary vision to current therapies. The other group with 34.62% believed that the greatest advantage of immunotherapy with regard to existing cancer treatment therapies is that it produces many less side effects.

9.2 INTERVIEWS

9.2.1INTERVIEW WITH DOCTOR TABERNERO

1- AL LLEGIR EN ELS DIARIS, SEMPRE ES SENT PARLAR DE UNA MATEIXA IMMUNOTERÀPIA, QUE SÓN ELS ANTICOSSOS MONOCLONALS, PERQUÈ NO ES FA REFERÈNCIA TAMBÉ ALS TILS O ALS CARS?

- Doncs perquè el que tenim avui en dia és la punta del iceberg, és a dir, tenim un 15% de la immunoteràpia que tindrem, entre cometes és el més fàcil el que s'està desenvolupant ara, buscar anticossos que desactiven les proteïnes que paralitzen els limfòcits que ja hi ha a dintre dels tumors. Però ara la lluita es què fem amb aquells tumor son no hi hagin TILS que reconeguin el tumor, i ara aquí s'està treballant amb CARS, TILS, vacunes… però tots ells són productes en investigació, no n'hi ha cap de comercialitzat. O sigui resumint, amb el que hem estat molt bons és amb reactivar aquests limfòcits.

2- EL DOCTOR PERE GASCÓN EN L'ALTRE XERRADA NO VA PARLAR DE LA IMMUNOTERÀPIA COM A TERÀPIA JA EXISTENT, PERQUÈ?

- Bueno, és una visió més clàssica potser, més consolidada, però…la immunoteràpia s'està donant, però clar és una teràpia més moderna, que supera els tractaments més moderns del càncer, com la cirurgia la quimioteràpia o la radioteràpia, però el fet és que la immunoteràpia sí que es pot considerar una teràpia actualment.

3- PODRÀ LA IMMUNOTERÀPIA TRACTAR AMB EFICÀCIA A TOTS ELS PACIENTS AMB CÀNCER EN UN FUTUR?

- Bueno, es depèn si mires un futur més proper o més llunyà. En un futur proper, tots els càncer no es podran curar, però si que es farà

un gran avanç en el camp d'aquesta malaltia. En un futur més llunyà en canvi, hi ha una gran possibilitat que la ciència hagi avançat tant, que ja no hagin ni malalties.

4- Perquè només s'aplica aquesta teràpia en pacients amb metàstasi?

- No s'aplica només en pacients amb metàstasi, però la veritat és que en un 90% sí, i això és perquè no és un tractament que es pugui donar en adjuvància per un tema legal i ètic, es clar. Si jo avui tinc un pacient a la consulta i sé que no en necessita d'immunoteràpia, sinó que necessita quimio, no li donaré aquest tractament.

5- Són els efectes de la immunoteràpia transitoris o permanents afectant la qualitat de vida de l'individu?

- Jo diria que són transitoris la gran majoria. T'explico un cas. Hi ha una nena als Estats Units que patia de leucèmia. Se la va tractar amb els CAR T cells i va estar a punt de morir. Va patir un quadre d'alliberament de citocines i no podíem fer res per treure-la d'aquella situació. Al cap de dos dies a la nena ja li havia desaparegut la meitat del tumor, i semblava que en uns pocs dies més estaria totalment fora de perill. Ara cada any ens envia una foto a tots els metges que vam col·laborar amb el cas, que diu quants anys porta sense càncer, i a data d'avui en porta 6. Per tant, si que hi ha algun cas on els efectes siguin permanents (però no és cap situació greu) , però ara podem dir que la majoria són transitoris i es produeixen durant el tractament.

9.2.2INTERVIEW WITH DOCTOR GASCÓN

1- PODRÀ LA IMMUNOTERÀPIA TRACTAR AMB EFICÀCIA A TOTS ELS PACIENTS AMB CÀNCER EN UN FUTUR?

   - ✓ No se si dir que arribarem a tractar a tots els pacients ni tots els tipus de càncer, ja que ara funciona molt bé amb alguns tipus de càncer però no funciona tant be amb altres tipus de càncer, llavors el que necessitem és esbrinar que necessitem més d'una molècula per destruir el tumor, i ara ja s'està fent amb assajos clínics, ajuntem la pròpiament immunoteràpia amb quimioteràpia o amb altres inhibidors d'altres passos de senyals de transmissió dintre de la cèl·lula. Per tant, sí és molt important, sí que és alguna cosa que tractarem, però no et sé dir si a tots els pacients. El que sé segur és que haurem d'afegir alguna cosa més del que ara tenim.

2- Perquè només s'aplica aquesta teràpia en pacients amb metàstasi?

   - ✓ Doncs això és un tema molt senzill, no podem donar tractaments experimentals quan ja tenim tractaments que funcionen, per una qüestió ètica. Per tant sempre, sempre, qualsevol producte que nosaltres hem utilitzat amb quimioteràpia ho hem provat en metàstasi, quan hem vist resultats importants, ja hem passat a l'adjuvància, però mai comencem en adjuvància per qüestions ètiques.

3- Però també perquè la persona no té cap opció més...

   - ✓ Si, si, òbviament, això és la veritat però fundamentalment és que un tractament nou mai es comença en adjuvància, per exemple, se li dona a un malalt que no té cap més esperança.

Però mai, mai fem cap tractament inicial en adjuvància sense haver passat per alguna cosa prèviament, perquè pensa una cosa, hi ha una cosa molt important, si hi haguessin efectes secundaris, que a vegades n'hi ha, tu no pots permetre't el luxe d'una malalta que igual està curada, fer-ho en adjuvància, ja que això vol dir tractament complementari, fer-ho a 100 malaltes perquè només se'n beneficiïn 20 o 30, ara gràcies a la genètica sabem esbrinar a qui donar-li quimioterapia i a qui no, per això no podem fer res experimental en adjuvància, ja que aquests efectes secundaris podrien afectar les dones o els homes que ja estarien sans, però si que ho podríem justificar en una persona que no té res més a perdre.

4- Són els efectes de la immunoteràpia transitoris o permanents afectant la qualitat de vida de l'individu?

Ara diria que la majoria son severs però també transitoris. Perquè ara sabem com contraatacar-los. Quan vam començar, que jo vaig ser aquí, vam començar amb melanoma, ens trobàvem que molts pacients tenien diarrees tremendes, nosaltres cridàvem al gastroenteòleg, perquè això ens era nou a nosaltres, era un malalt de protocol, el doctor venia al dia següent i demanava una biòpsia. Esperant els resultats ja passaven uns deu dies, en aquest temps el malalt ja se'ns havia desmadrat, i alguns cops (bastants) es moria.

Un cop se'ns va morir un noi de 23 anys per les diarrees constants, era tot aigua aigua aigua, no es quedava al cos ni 5 minuts, i se'ns va acabar deshidratant i morint per això. Ara aquest noi podria estar curat. Però ara què passa? Ara sabem com actuar en aquests casos, i podem donar un tractament el més ràpid possible. Imaginat, pel que dèiem abans si això, aquest tractament li haguéssim donat a algú en adjuvància.

5- Perquè creu que amb aquesta teràpia es pot curar el càncer?

Es curiós però la gran majoria de malalts, amb un tractament de 4 mesos, modulen el seu sistema immunològic fent així que el tumor erradiqui. Nosaltres mai diem curar el càncer, perquè tenim sempre advocats al darrere, i si tens una recaiguda i diem que t'has curat, pot acabar el metge arruïnat. En càncer ens estem molt de dir curar, diem que són bons supervivents, i cronificar és una paraula molt mediàtica, que queda molt bé, però de fet el que busquem és ficar els malats en remissió prolongada. Si està curat o no, no ho sabem però està en remissió prolongada.

6- Pot la immunoteràpia alterar el nostre sistema immunològic de manera que es pugui veure afectada la seva activitat davant d'altres patologies que es desencadenin al nostre cos?

Et fico l'exemple dels CARS, amb ells ens carreguem els limfòcits B, però generalment no es veu afectat el nostre sistema immunològic.

7- Podrà la immunoteràpia substituir les teràpies de tractament de càncer actualment existents?

Sí en part, perquè avui he fet una xerrada i m'he adonat que cada vegada tenim més productes, del que diem anti-diana, que no és quimioteràpia, però que si actuen per si sols tenen una resposta molt feble.

10 CONCLUSIONS

At the beginning of this research, I asked to myself some questions to which I hoped to give an answer. What is immunotherapy? How it works? Who is it administered? Is it able to overcome cancer cells? To these questions I have been able to give them an answer that has helped me to understand the great complexity of our body, and of this disease. But there have been a number of things that I did not expect……The intense and close interaction in a personalized (face to face) way with internationally renowned researchers in the field of immunotherapy, the feeling of what's behind a scientific research, the complex world of the hospital environment ... and all the experiences that, thanks to the contact with professionals I have had access to, far beyond the scientific side itself.

There are still many questions for those professionals to answer, and probably as the knowledge and application will become broader, new ones will emerge, but this is the essence of research and this is what allows us to move forward.
On a personal level, work has been very enriching, not only because of the scientific knowledge acquired, but also because of the human side of the disease and those who day to day dedicate their efforts to overcome it.

That is why some of the questions that I had at the beginning of the work have been fading away, and those who don't have an answer to this date will surely have it in the near future, and I, in one way or another, hope be part of this great group.

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12 ATTACHMENTS

12.1 SURVEY

COL·LEGI SAGRADA FAMÍLIA Horta

ENQUESTA TREBALL DE RECERCA BATXILLERAT- TEMA: IMMUNOTERÀPIA ANTITUMORAL.

Identificació de la resposta: (Nom i cognoms -no necessaris-, càrrec / situació laboral, camp de treball, centre de treball).

……
……
……
……
……

1. **PODRÀ LA IMMUNOTERÀPIA TRACTAR AMB EFICÀCIA A TOTS ELS PACIENTS AMB CÀNCER EN UN FUTUR?**
   ARA (propers 1-2 anys):
   - ☐ **No serveix de gaire**
   - ☐ **No, però si alguns (20-40%) dels més greus**
   - ☐ **Sí, és un tractament que caldria oferir ja a tots el pacients**
   - ☐ **Sí, ja és un tractament efectiu per la majoria**
   - ☐ **No sap / no contesta**

   Altra resposta: **……**
   ……
   ……
   ……

   EN EL FUTUR (en 10 anys):
   - ☐ **No servirà de gaire (com a molt per un 20% dels pacients)**
   - ☐ **No, però si per alguns (20-40%) dels més greus**
   - ☐ **Sí, serà un tractament que s'oferirà d'entrada a tots el pacients**
   - ☐ **Sí, possiblement será útil per a la majoria de la població (80 %)**
   - ☐ **No sap / no contesta**

Altra resposta: **……**
……
……
……

2. PER QUÈ NOMÉS S'APLICA AQUESTA TERÀPIA A PACIENTS AMB METÀSTASI?

☐ **Només es pot comparar amb tractaments que en general són efectius i que deixen de ser-ho en pacients amb metástasis (no es pot treure una opció de tractament consolidada)**

☐ **Són tractaments amb molts efectes secundaris i complicats**

☐ **Són tractament cars**

☐ **Cal millorar el coneixement sobre la immunoteràpia abans de pasar a situacions menys greus**

☐ **No sap / no contesta**

Altra resposta: **……**
……
……
……

3. SÓN ELS EFECTES SECUNDARIS DE LA IMMUNOTERÀPIA TRANSITORIS O PODEN ARRIBAR A SER PERMANENTS AFECTANT A LA QUALITAT DE VIDA DE L'INDIVIDU?

☐ **Transitoris**

☐ **Permanents però controlables en general**

☐ **La majoria transitoris, alguns permanents**

☐ **Permanents i molt greus afectant la qualitat de vida**

☐ **No sap / no contesta**

Altra resposta: **……**
……

4. PER QUÈ CREU QUE AMB AQUESTA TERÀPIA ES POT CURAR EL CÀNCER?

☐ **Ho ha demostrat per alguns casos**

☐ **No podem dir que cura el cáncer, només el cronifica**

☐ **Es un sistema permanent de tractament al canviar l'equilibri intern**

☐ **No sap / no contesta**

***Altra resposta:* …… ……**

5. POT LA IMMUNOTERÀPIA ALTERAR EL NOSTRE SISTEMA IMMUNOLÒGIC DE MANERA QUE ES PUGUI VEURE AFECTADA LA SEVA ACTIVITAT DAVANT D'ALTRES PATOLOGIES QUE ES DESENCADENIN AL NOSTRE COS?

☐ **Sí, ho fa, … i pot generar greus canvis, però en general menys greus que l'evolució del càncer**

☐ **Sí, ho fa però molt menys de l'esperable i ben controlats**

☐ **No genera canvis que afectin altres aspectos del Sistema Immunitari**

☐ **No sap / no contesta**

Altra resposta (incloent el "per què?"):……

6. PODRÀ LA IMMUNOTERÀPIA SUBSTITUIR LES TERÀPIES DE TRACTAMENT DE CÀNCER (QUIMIOTERÀPIA, RADIOTERÀPIA...) ACTUALMENT EXISTENTS?

☐ **Sí del tot.**

☐ **Sí en part.**

☐ **No, només complementar**

☐ **No, en absolut**

☐ **No sap / no contesta**

***Altra resposta:* ……**

7. CREU QUE DEIXARÀ DE SER UNA TERÀPIA PERSONALITZADA I ESDEVINDRÀ UNIVERSAL ?

☐ **Sí del tot.**

☐ **Sí/no en part només.**

☐ **No, és intrinsecament una teràpia personalitzada**

☐ **No, es pot considerar una terapia encara**

☐ **No sap / no contesta**

***Altra resposta:* ……**

8. CREU QUE HI HAURÀ LA POSSIBILITAT DE VACUNAR-SE (VACUNA PROFILÀCTICA) CONTRA EL CÀNCER?

- ☐ **Sí del tot.**
- ☐ **Sí per alguns pocs casos a on hi hagin antígens universals o familiars.**
- ☐ **No, no crec que sigui efectiva mai**
- ☐ **No sap / no contesta**

***Altra resposta:* ……**

9. EN QUANT TEMPS CREU QUE AQUESTA TERÀPIA ES PODRÀ APLICAR DE MANERA MÉS GENÈRICA EN L'ÀMBIT SANITARI?

- ☐ **Ja s'aplica, però en 5-10 anys serà més ampliament aplicada, especialmente amb combinacions.**
- ☐ **En 10-20 anys.**
- ☐ **No, crec que sigui efectiva mai del tot**
- ☐ **No sap / no contesta**

***Altra resposta:* ……**

10. LA IMMUNOTERÀPIA ELIMINA EL TUMOR I IMPEDEIX QUE N'APAREGUIN DE NOUS, O NOMÉS PRETÉN ELIMINAR L'EXISTENT?

- ☐ **Sí, pot impedir que apareguin nous tumors**
- ☐ **No només ajuda a tractar sobre el tumor inicial**
- ☐ **No sap / no contesta**

***Altra resposta:* ……**

11. QUINS BENEFICIS/ AVANTATGES COMPORTA LA IMMUNOTERÀPIA RESPECTE LES TERÀPIES ACTUALMENT EXISTENTS DE TRACTAMENT DEL CÀNCER?

- ☐ **Una visió nova i complementària a les teràpies habituals.**
- ☐ **Molts menys efectes secundaris.**
- ☐ **Cap benefici especial, és com tota la terapia convencional**
- ☐ **No sap / no contesta**

***Altra resposta:* ……**