CANCER IMMUNOTHERAPY AS A NEW TREATMENT OPTION

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INTRODUCTION

As we know, **CANCER CAN COAPTATE THE IMMUNE CONTROL**. However, some medications can disrupt immunological checkpoints and ''release'' anti-tumor immunity. This complex biological process still contains many **MYSTERIES** and is currently the subject of an intense study. By making the most of this, cancer immunotherapy could be a key part of the clinical management of cancer in a specific way: in cancer patients, **THE CANCER IMMUNITY CYCLE DOES NOT PERFORM OPTIMALLY** so the goal of cancer immunotherapy is to initiate itself – sustaining cycle of cancer immunity enabling it to amplify, propagate and generate unrestrained autoimmune inflammatory responses to overcome the negative feedback mechanisms of cancer; also, important inflection points in the history of cancer therapy: durable monotherapy responses are being reported (in different human cancers with several different ages), new drugs and implement clinical strategies are indicated in melanoma (a disease thought to be atypically immunogenic) and immunology therapy of cancer could report safety and more manageable profiles tan traditional cancer therapies (they act specifically). A successful approach will be to find a common rate – limiting step in the **TUMOR MICRO-ENVIRONMENT** so that we can act selectively targeting it in any given patient (because amplifying the entire cycle may provide anticancer activity but also could damage normal cells and tissues, as chemotherapy).

OBJECTIVE

Our main objective is to evaluate the current status of anti-tumor immunotherapy. To do this, we will expose the most promising lines of research and cutting – edge treatments; to be able to conclude whether, currently (or in the future), we can contemplate immunotherapy as a viable treatment option.

MATERIAL AND METHODS

The conduction of this narrative review, will be based on the conference about cancer immunotherapy ''Medicina de Precisión e Inmunoterapia: retos y oportunidades para el tratamiento del cáncer'' *Dr. Mariano Barbacid*. Also, we contacted Pedro Romero, who works at Ludwig Cancer Research at University of Lausanne, 1066 Epalinges, (Switzerland); and who recommended us the articles written on ''references'' (*key words:* cancer, immunotherapy and review; 5 years) which have been used and the publications quoted in those articles.

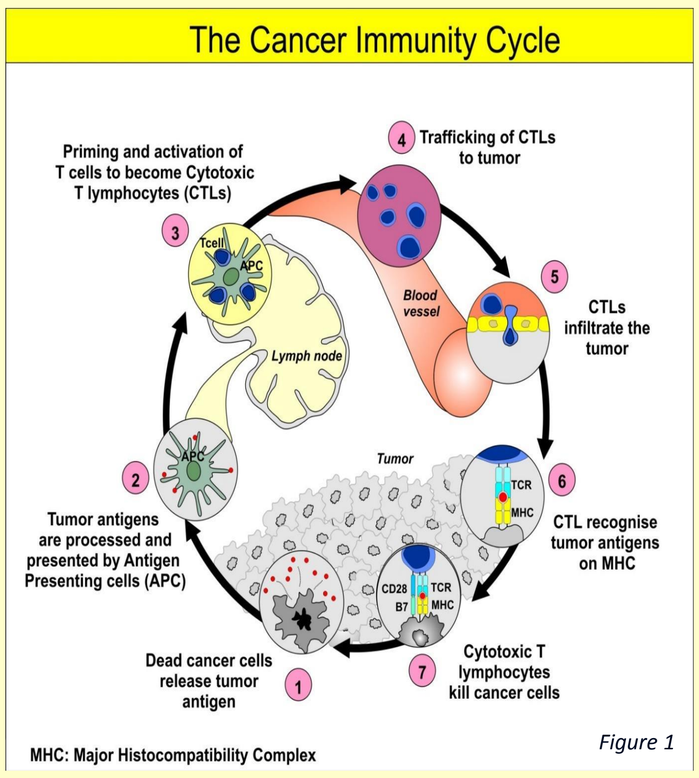


Figure 1

MONOCLONAL ANTIBODIES

The lack of CD28 activation by binding **CTLA-4** is a physiological phenomenon since it reacts with B7 with much higher affinity than CD28. So it interrupts the second activating signal, and **T cells** enter in a state of **ANERGY.**

Tremelimumab is a fully human IgG2 anti CTLA-4. It posed hopes in early melanoma.

Nivolumab is a fully human IgG4 anti PD-1, and it showed good responses in human melanoma, kidney and rectal cancers.

PD-1 has a role in **controlling the SUPPRESSIVE FUNCTION of Treg** playing a role in T cell recognition of antigens presented to T cells in secondary lymphoid organs.

Ipilimumab is a fully human IgG1 anti CTLA-4. Phase III trials showing improved survival so it was approved in 2011 in USA and Europe for the treatment of unresectable melanoma and a meta-analysis showed extended survival in 20% of patients, reaching 10 years in some cases.

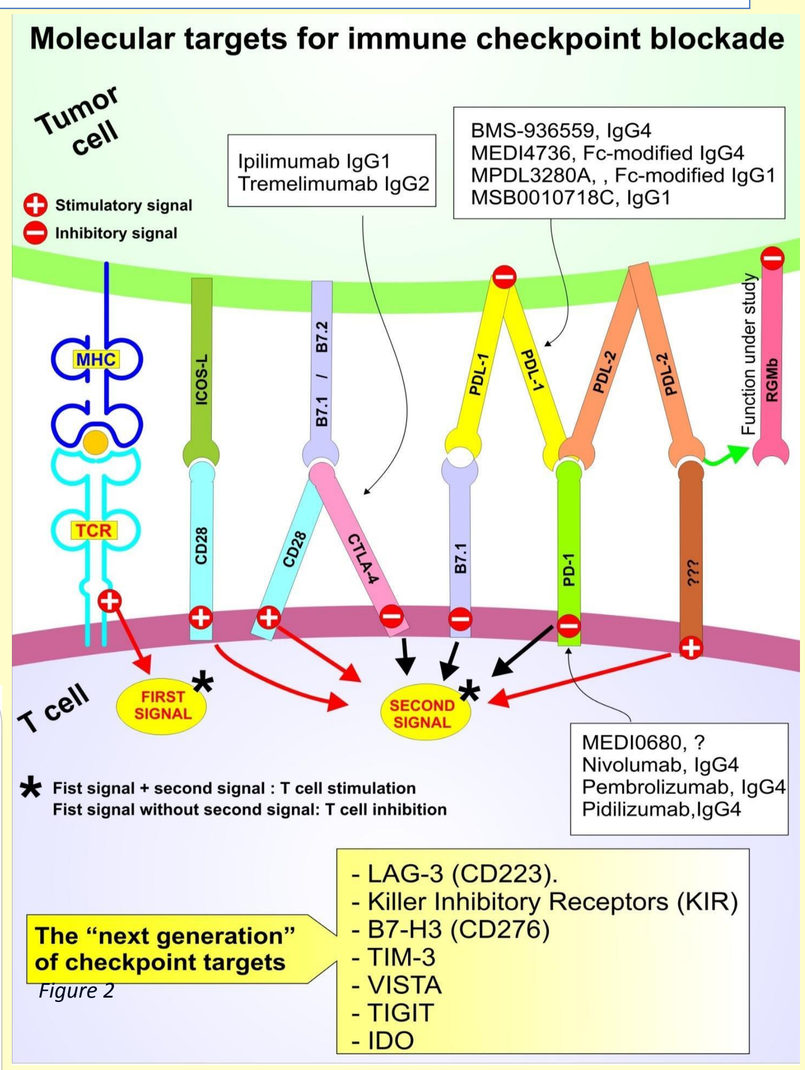
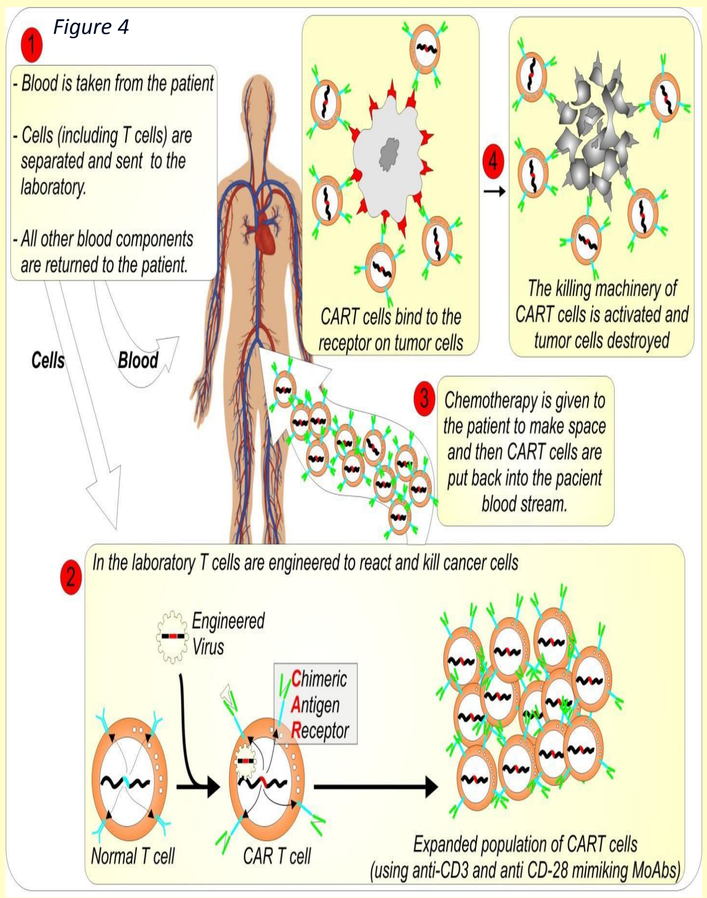


Figure 2



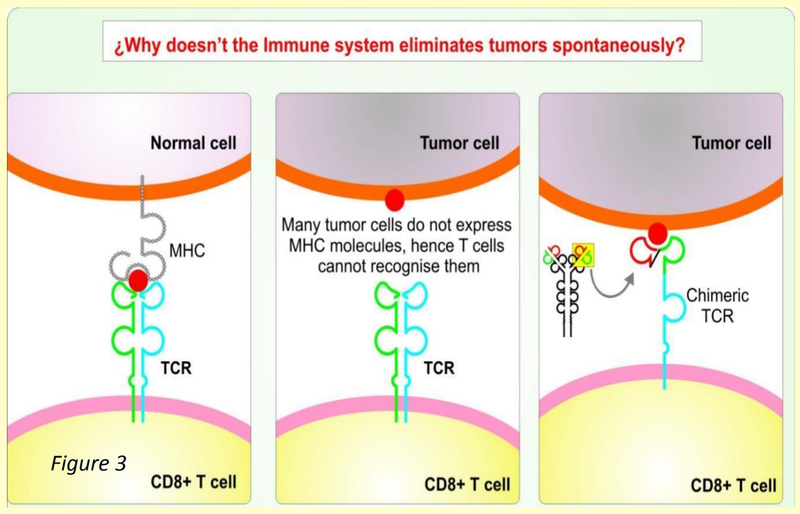


Figure 3

RESULTS AND DISCUSSION

CANCER REJECTION IS A 7-STEP PROCESS *(figure 1).* This cycle presents the anti-tumor response and, by dissecting it, we will know the potential points of attack in tumor immunotherapy.

So, **WHY DOES THE IMMUNE SYSTEM FAIL?**

As Chen & Mellman (2013) show in their article, the manipulation of the second activating signal could abrogate anti-cancer immune reactions (who apparently blocks B7 expression and over-express CTLA-4). The scientific community soon realized that this swarm of stimulatory and inhibitory molecules inter-playing in the anti-tumor immune response could be able manipulated to improve such response. This approach has been termed **IMMUNE CHECKPOINT BLOCKADE**, in other words, "molecules than can be blocked to free the immune system to destroy tumor cells" *(figure 2).*

CANCER VACCINES

Cancer vaccines seek to target a tumor-specific antigen and distinct from self-proteins. Tumor antigens have been divided into two categories: **shared tumor antigens** (expressed by many tumors) **and UNIQUE TUMOR ANTIGENS** (resulting from mutations induced through physical or chemical carcinogens, so they are expressed only by individual tumors). One approach could be vaccines containing whole tumor cells, but these vaccines have been less effective. Defined tumor antigens decrease the risk of autoimmunity, but tumors can evade destruction through antigen loss variance. A process called **"epitope spreading"** or ''provoked immunity'' may mitigate this weakness.

CHIMERIC ANTIGEN RECEPTOR T CELLS (CARTS)

Many tumor cells do not express HLA molecules, hence T cells cannot recognize them *(figure 3).* CAR T-cell therapy employs gene transfer techniques to reprogram endogenous T cells to target a specific tumor antigen. Patients typically receive chemotherapy, *figure 4,* the goal is to **INDUCE LYMPHODEPLETION** and thereby **ENHANCE CAR T-CELL EXPANSION** and persistence in vivo, lymphodepletion may have the additional benefit of tumor cytoreduction, which can potentially improve CAR T-cell treatment efficacy and minimize toxicity.

CONCLUSIONS

Cancer can avoid the IS and the NeoAg created by the tumors cells are involved in this scape (although AutoAg can also be a selective target) and they **have different expression patterns, signaling pathways, mechanisms of action**... So, **IMMUNOSUPPRESSION** is the natural history of cancer and multiple mechanisms are known that may work together or in parallel; consequently, there is a need to pursue other potential agents (vaccines, intratumoral injections of immune activators, agonists of co-stimulatory receptors...).

What is more, is reasonable to suspect that immunotherapy approaches from vaccines would be more effective when given in combination with, for example, a PD1-inhibitor. Subsequently, combination with agents, which must act in a **SYNERGY WAY** and that will enhance Tcell trafficking and infiltration into the tumor should be explored.

However, **IMMUNE – RELATED TOXICITIES** were also enhanced in their magnitude, frequency and onset (of course, increased activity due to combinations means also synergistic toxicity), but therapeutic targets that play an important role in mediating immune homeostasis and preventing autoimmunity must be selected.

The development of an effective cancer immunotherapy requires an **INTERNATIONAL AND MULTIDISCIPLINARY APPROACH** due to its enormous complexity. Taking advantage of those complex discoveries and technological advances, we must **DECODE THE HUMAN IMMUNE SYSTEM** so cancer could be conquered.

16th ASEICA INTERNATIONAL CONGRESS
Valencia, 6th - 7th - 8th November 2018