"BREAST CANCER MULTI-THERAPY AND IMMUNE SYSTEM ACTIVATION, CHECKPOINT MODULATORS, SIGNAL INHIBITORS AND T CELLS REPROGRAMMING".

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Introduction

- Cancer is one of the leading causes of death worldwide, with approximately 24.1 million of new cases and 8.2 million of cancer-related deaths in 2018.
- The 70% are in Africa, Asia, Central America and South America.
- Novel approaches for breast cancer treatment included several molecules that block signaling pathways as CTLA-4 and PD-1.
- Combining immunotherapy, with new therapies which blocks signaling pathways, is expected to gradually reduce cancer mortality rates for the coming decades.

Siegel RL, et al. CA Cancer J Clin. 2018;68(1):7-30.

The immune system and cancer

- Targeted therapies that block or inhibit receptors and signaling pathways prevent cancer growth, progression and spread.
- The immune system has three main functions: to distinguish between the self and the exogenous, to contain external invading agents (pathogens, molecules, etc.) and to destroy abnormal cells such as cancer cells.
- Many of the new anti-cancer strategies aim to redirect immune protection against these abnormal cells.
- But the treatment of antibody-based adoptive immunotherapy has not developed as dramatically as expected, like the lack of markers in tumors.

Siegel RL, et al. CA Cancer J Clin. 2018;68(1):7-30.

The immune system and cancer

- However, PARP inhibitors and signaling pathways of tyrosine kinase src and Bcr-Abl and others.

- Also well as receptor blocking antibodies, such as blocking the activity of cytotoxic T lymphocyte antigen 4 (CTLA-4) and death protein are being used, and programmed 1 (PD-1) to activate the anti-tumor T-cell response, with good results in TNCB.

- A more effective immune response is necessary for the control and recognition of cancer, increasing the degree of activation by stimulating cytotoxic T-lymphocytes (CTL).

- And natural killer cells (NK), stimulated with cytokines such as: Interleukin (IL)-2, Interferon (IFN)-γ, tumor necrosis factor (TNF)-α and (IL)-12, plus the presentation of extracorporeal antigen

Mahoney KM. et al,. Nat Rev Drug Discov. 2015;14(8):561-84.

Breast cancer multi-therapy

- There are already several treatment strategies and their bases are thus:
- Anti-EGFR antibody therapy in breast cancer
- Monoclonal antibodies in breast cancer treatment:

  Blockade with cetuximab contributes to the suppression of several signaling pathways such as JAK/STAT, Raf/MEK/ERK, and PI3K/Akt.
- Signal transduction inhibitors
- Immunotherapy control point blocking in cancer with PD-1 and CTLA-4 blocking antibodies.

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Molecular targeted therapy in Breast Cancer treatment

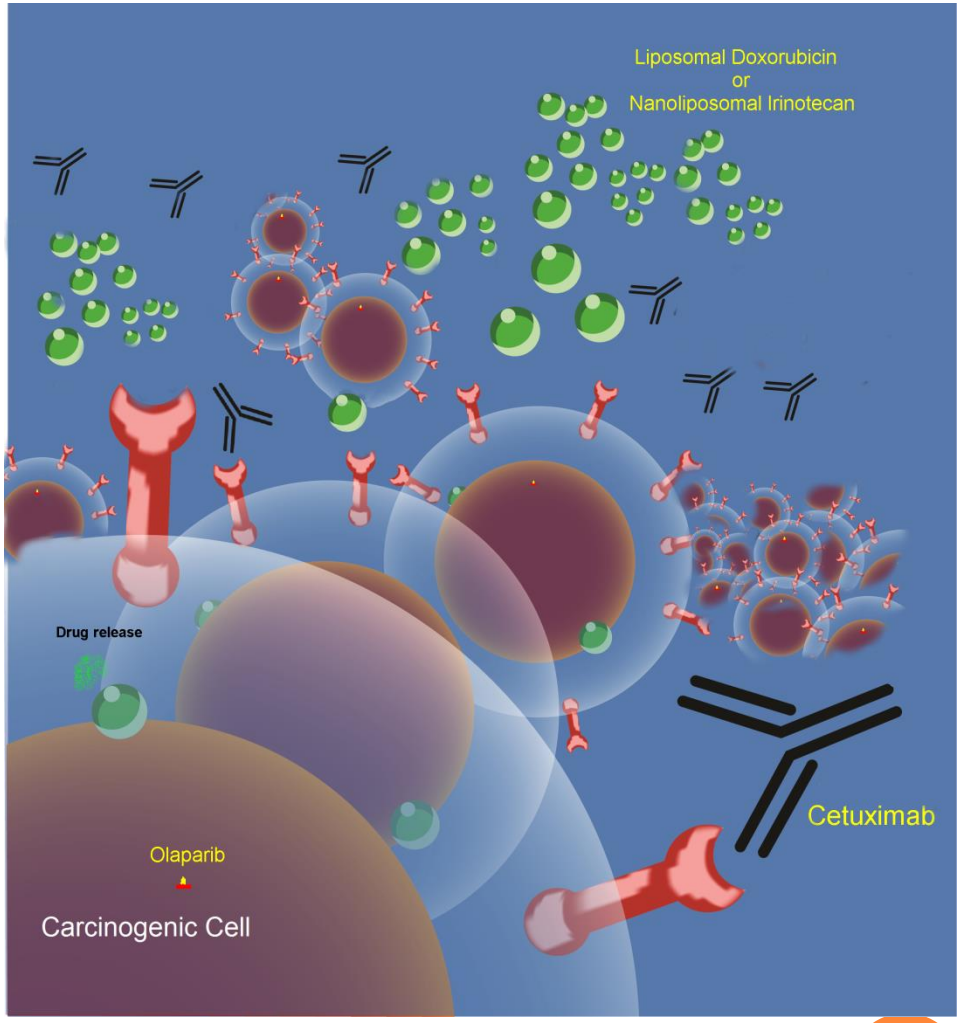
	Approved agents	Molecular targets	Mechanism of action
Monoclonal antibody	***Trastuzumab*** (Herceptin®)	HER2, HER3	RAS/Raf/MAPK Inhibition
	Pertuzumab (Perjeta®)	EGFR y HER4	
	Bevacizumab (Avastin®)	VEGF	VEGFR PI3K, PLCγ prevents revascularization
	Ranibizumab (Lucentis®)		
	Aflibercept (Zaltrap®)		
	Cetuximab (Erbitux®)	EGFR	
	Panitumumab (Vectibix®)		PI3K, RAS, STAT signaling inhibition
Antibody-drug conjugate	***T-DM1***	HER2	Cytotoxic agent
	Vinorelbine- (Navelbine®)		Vinca alkaloid
	Trastuzumab (Herceptin®)		RAS/Raf/MAPK
Inhibitors conjugate	**Fulvestrant-Palbociclib** (Ibrance®)	HR+(HER2-)	CDK) 4/6 inhibitor
	Palbociclib-Letrozole (Femara®)	(ER) Estrogen receptor positive	Cell cycle arrest
Signal transduction inhibitors			
Inhibitors PARP-1/2	**Iniparib** (Sanofi® BSI 201)	BRCA1 or BRCA2 mutation.	Not repair their DNA
	Talazoparib (BMN-673)		
	Niraparib (Tesaro®)		
	Olaparib (Lynparza® AZD-2281 y TOPARP-A)	PARP-1 selective inhibitor	
	Rucaparib (AG014699, PF-01367338)		
	Veliparib (ABT-888)		

	Approved agents	Molecular targets	Mechanism of action
Preclinical studies phase 1 of Inhibitors PARP-1/2	CEP-9722 MK-4827 MK-2206 NMS-P118	PARP-1/2 inhibitor	Not repair their DNA
Tyrosine Kinase Inhibitors	**Dasatinib** (Sprycel®)	Multiple tyrosine kinases (TK)	Bcr/Abl, Src, c-Kit and Eph receptor family
	Saracatinib (AZD0530)	Src protein	Src inhibitor
	Imatinib (Gleevec®)	Geminina y c-Abl nuclear	Bcr/Abl
	Nilotinib (Tasigna®)	Abl tyrosine kinases	Inhibitor Geminina y c-Abl nuclear Bcr/Abl
	Lapatinib (Tykerb®)	TK receptor	
	Palbociclib (Ibrance®) **Ribociclib** (Kisqali®)	Inhibitor kinases (CDK4,6)	Cell cycle
	MK-2206	AKT inhibitors	Cell cycle arrest
	Vemurafenib (Zelboraf®)	Inhibits the enzyme B-Raf. Serine/threonine-specific protein kinase	BRAF serine/threonine kinase inhibitor
	Cobimetinib (Cotellic®)	MEK1 protein kinase	Inhibits the activity of ERK2 transcriptional
Immunomodulators	**Nivolumab** (Opdivo®) **Pembrolizumab** (Keytruda®)	PD-1	Blocks ligands PD-L1 and PD-L2
	Durvalumab (Imfinzi®) **Atezolizumab** (Tecentriq®) **Avelumab** (Bavencio®)	PD-L1	Block activation of PD1
	Ipilimumab (Yervoy®) **Tremelimumab**	CTLA-4	B7-1/2
TKIs	Afatinib Erlotinib Gefitinib Dacomitinib Neratinib Sorafenib Alectinib	EGFR, HER2 y ErbB-4, VEGFR	PI3K/Akt/
	Crizotinib Ceritinib	competitive inhibitor Akt	ALK-fusión

Signal transduction inhibitors

- Combined therapy with antibody-based and immunotherapy is being incorporated into almost all oncological treatments.

- An inhibitory mAb and a PARP inhibitor such as olaparib, plus liposome chemotherapy, appears to be one of the most promising combinations in the cancer treatment.



Klapacz J. Mutat Res Rev. 2016;767:77-91. Wang B. J Med Chem. 2016;59(1):335-57. Robson M. N Engl J Med. 2017;377(6):523-533.

Immunotherapy control point blocking in cancer

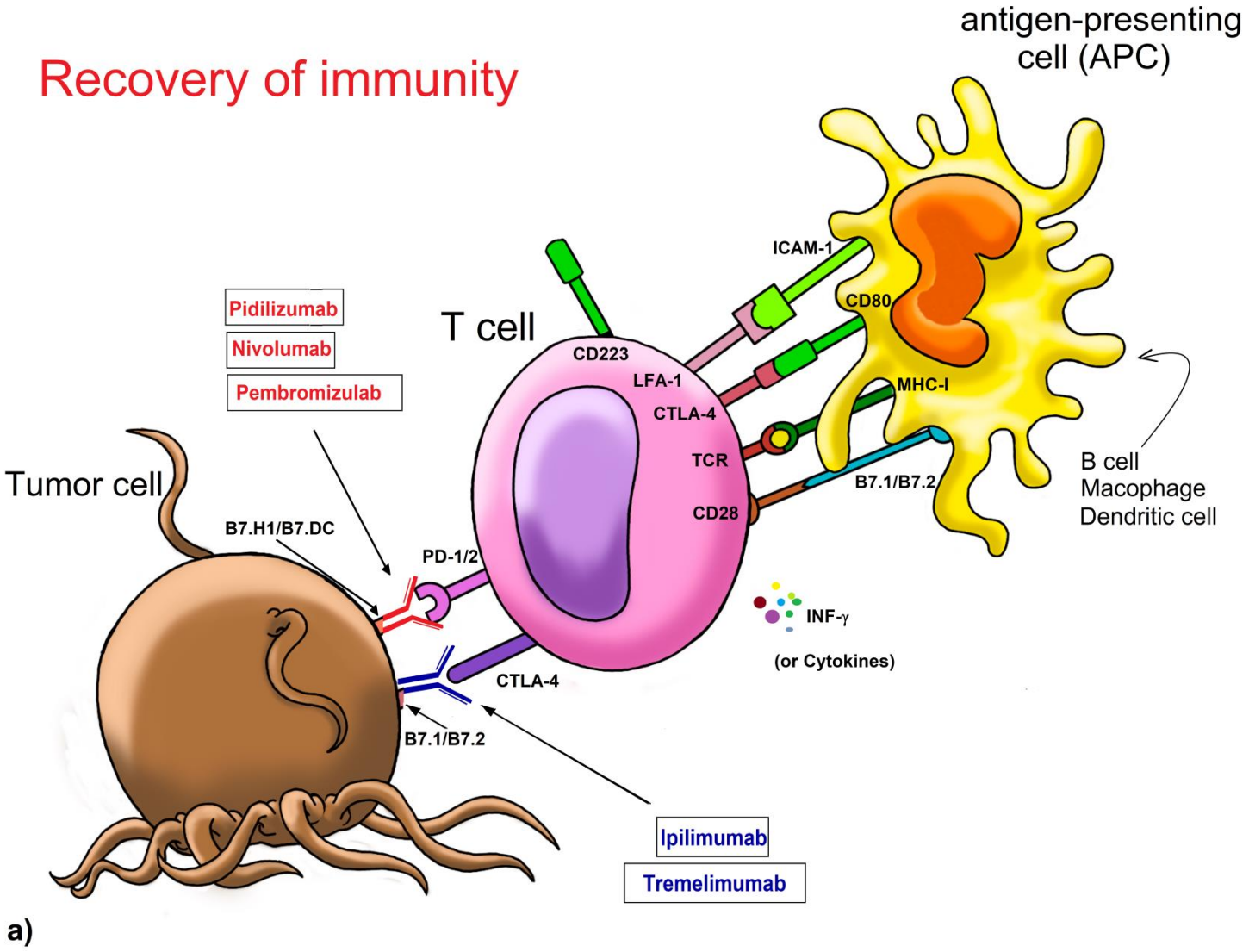
- In cancer, T cells are repressed and cannot respond against the tumor through the interaction between T cell receptors: PD-1 and its corresponding ligands (PD-L1/PD-L2 or B7.H1/B7.DC) and CTLA-4 (CD152) and its ligands CD80 (B7-1) and CD86 (B7-2) present in the cancer cell.

- Recent treatments with nivolumab (PD-1 target), ipilimumab (CTLA-4 target), durvalumab (PD-L1 target) and tremelimumab (CTLA-4 target) are used in breast tumors HER-2 negative and TNBC.

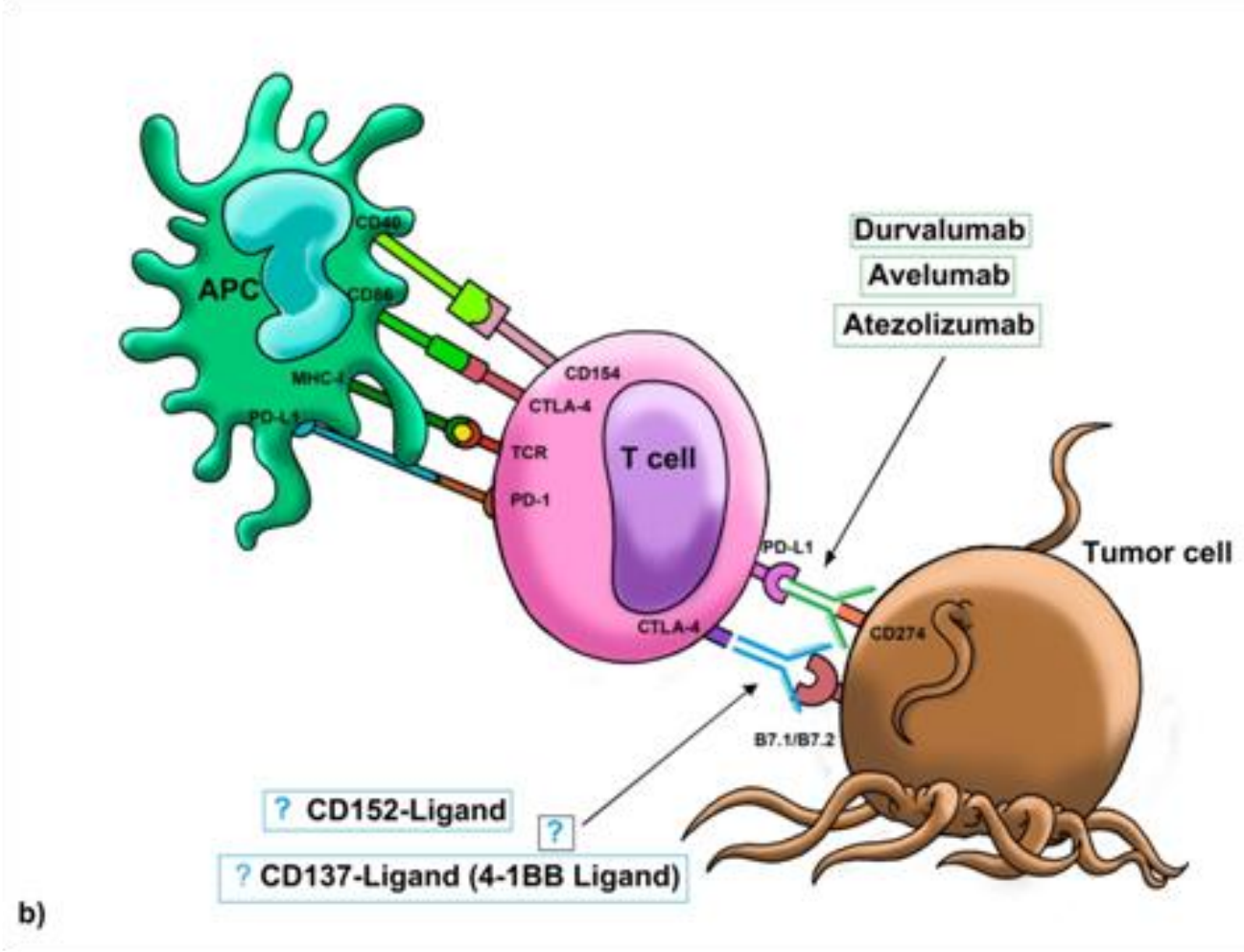
- Atezolizumab, a humanized monoclonal antibody of the isotype IgG1 against PD-1, and pembrolizumab, and which act by blocking PD-1.

Wang J. J Hematol Oncol. 2017;10(1):34. Santa-Maria CA. Oncotarget. 2018;9(27):18985-18996. Monneur A. Bull Cancer. 2018;105(3):263-274.

IMMUNOTHERAPY CONTROL POINT BLOCKING IN CANCER



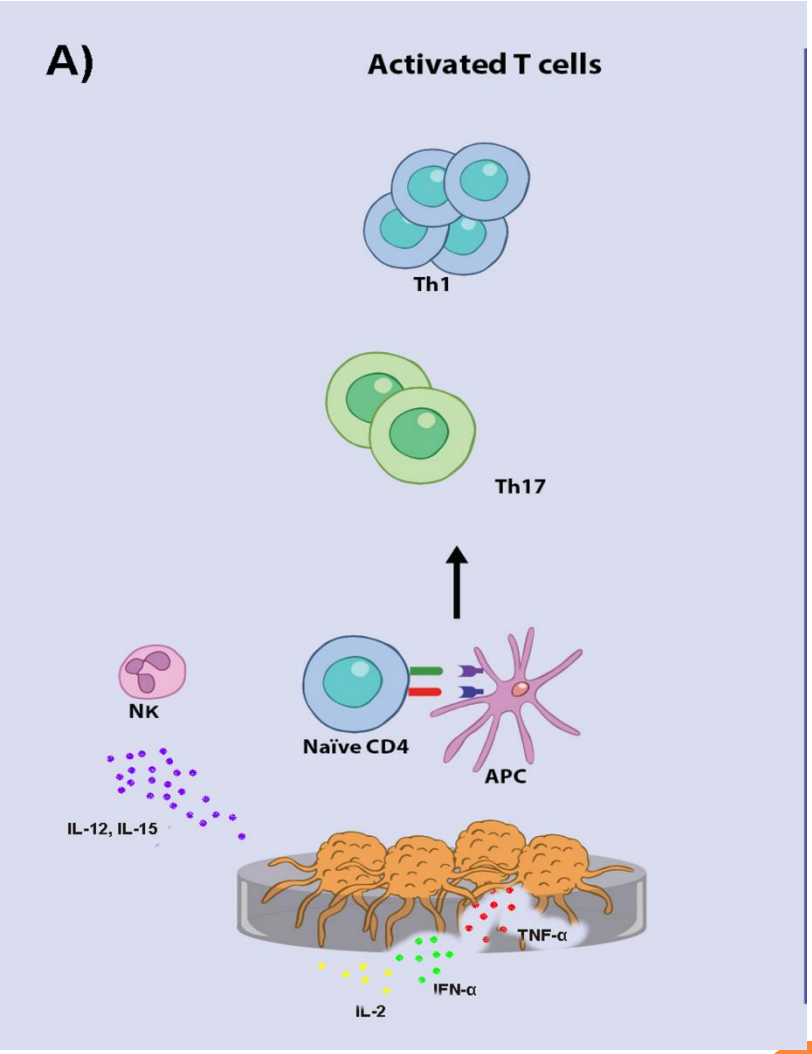
Immunotherapy control point blocking in cancer



Signal transduction inhibitors

- In an experimental proposal, autologous CD4+ T cells could be robustly polarized in vitro towards Th1 and Th17 subtypes, through cytokines and chemokines, to subsequently identify their activation with molecular adhesion profiles and surface markers.

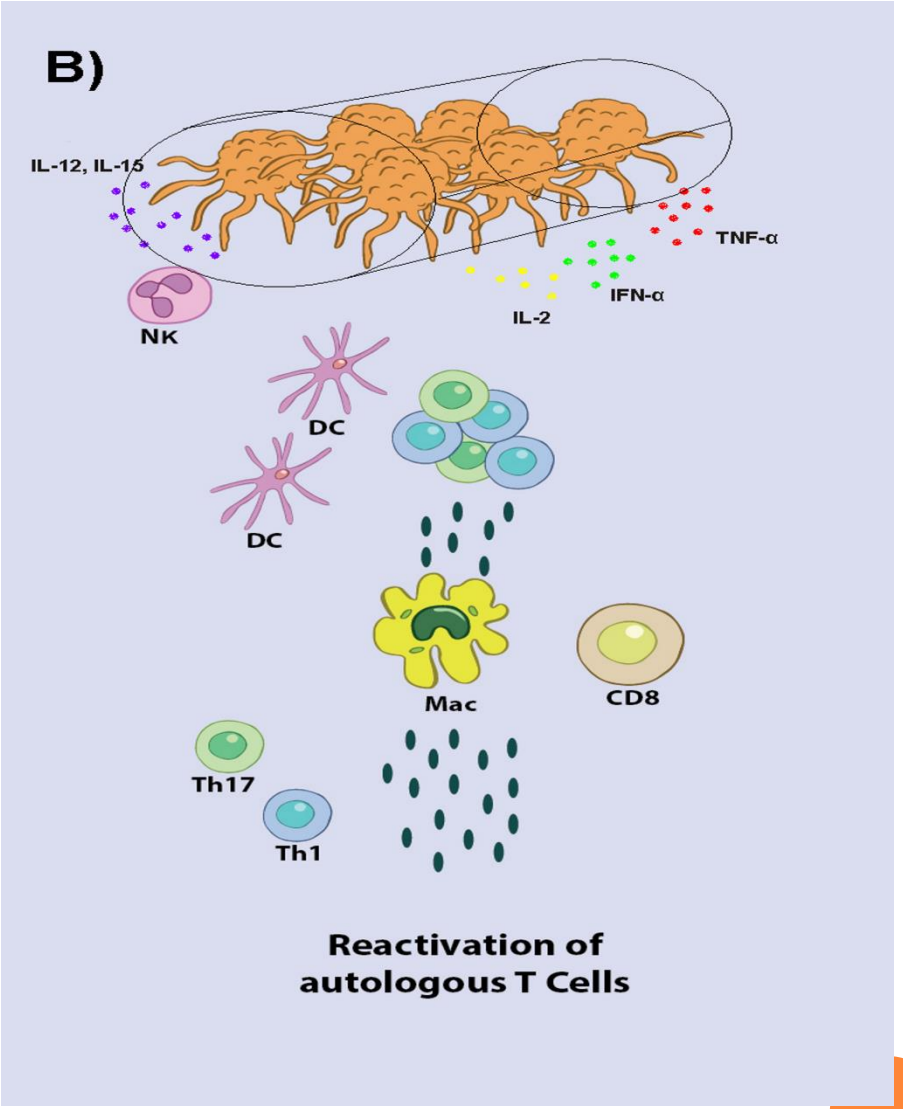
- Which will open the possibility of detecting effector function in vitro and then in vivo to treat cancer. Th1 response is generally considered as the main source of tumor rejection, but there is also evidence that Th17-polarized cells mediate the destruction of advanced B16 melanoma.



Pichler R. Cancer Immunol Immunother. 2017;66(4):427-440. Katz H. Med Oncol. 2017;35(1):13.

Signal transduction inhibitors

- The main objective of immunotherapy is to recognize and eradicate tumors by restoring the immune capacity of the host.
- One interesting approach is the activation of macrophages (MΦs) with the application of retinoic acid and stimulation of NK cells with IL-15, IL-22 and IL-23.
- And cytotoxic T cells (CTLs) stimulated with IL-2, TNF-α, IFN-γ, plus the presentation of the antigen in situ or with extracorporeal activation of autologous cells.



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CONCLUSION

- A therapeutic objective with mAbs that block both PD-1 and PD-L1 and CTLA-4 is being supported for the treatment of TNBC.

- In addition, several signalling pathway inhibitors (MAPKs) are being studied, as well as the application in the treatment of drugs that inhibit PARP-1/2. However, in many, the evolution of therapy does not improve the prognosis and only a partial resolution of the problem is achieved.

- Our proposal of immunotherapy against tumours includes the reactivation of the immune response, using activated T-cells and external cytokines, which can be given to the patient in order to establish an effective and lasting recognition of the tumor as a common treatment against cancer.

- Theoretically, no matter the type of cancer that will be treated, the treatment in question is based on the reactivation of the immune system for the recognition of new variants and types of cancer that were not recognized and the activation of the immune response Anti-tumor.

Wang J. J Hematol Oncol. 2017;10(1):34. Santa-Maria CA. Oncotarget. 2018;9(27):18985-18996. Monneur A. Bull Cancer. 2018;105(3):263-274.

- Recent advances in Antitumour Immunology and the development of new target molecule inhibitors, the implementation of cancer multitherapy seems to be the most promising option in the years to come.

- It requires more research and increasing the number of clinical studies to obtain the experience that will allow the future achievement of effective therapy against one of the diseases that cause many deaths in the world.

Thank you so much