

Basic Principles of Cancer Immunotherapy

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Disclosures

- I have no relevant disclosures.
- I will not be discussing non-FDA approved indications during my presentation.

The Premise of Cancer Immunotherapy

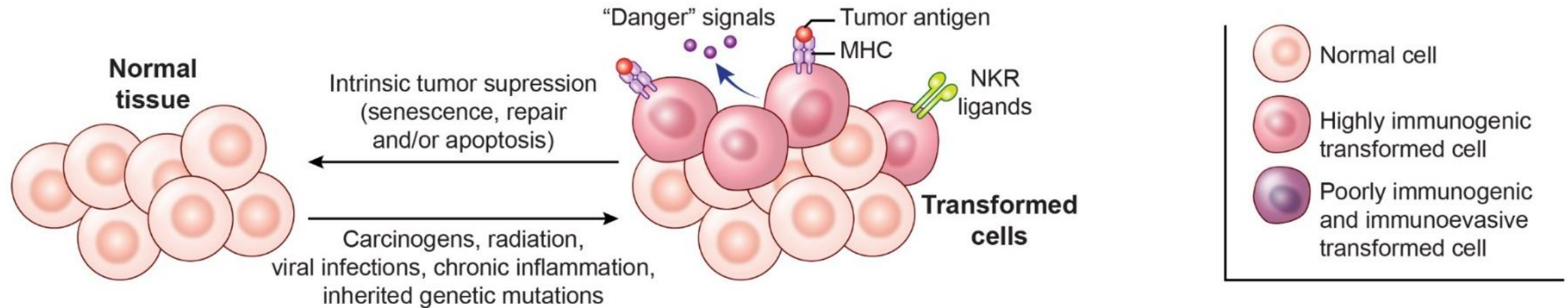
- Normally, the immune system eliminates mutated and/or damaged cells
- To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of immunotherapy is to restore the capacity of the immune system to recognize and reject cancer.

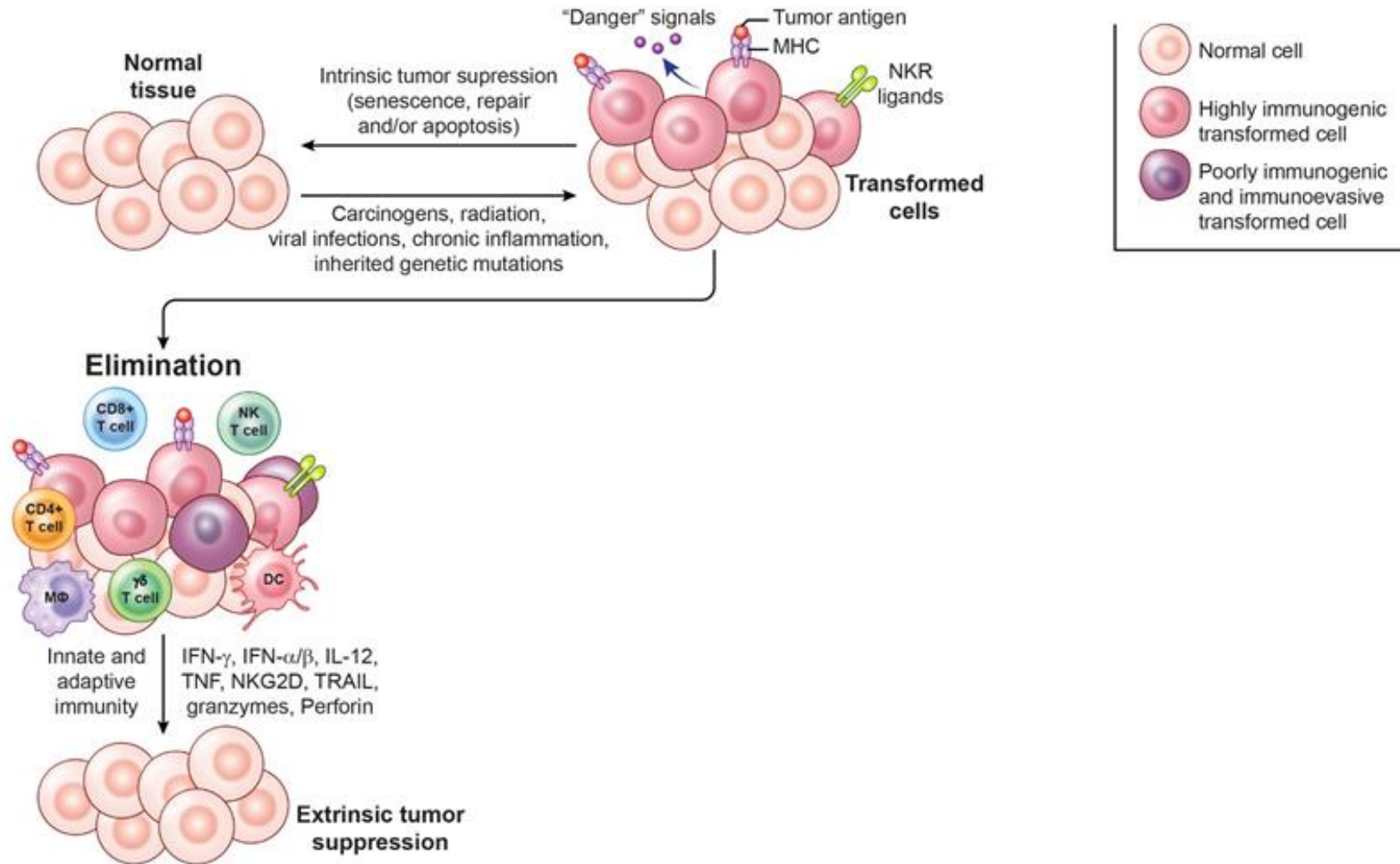
Why Does the Immune System Fail to Eliminate Cancer?

- Cancer cells grow progressively in immunocompetent hosts without evidence of systemic **T cell exhaustion** or **anergy**
 - **T cell Exhaustion:** CD8+ T cells often become dysfunctional, entering a state known as exhaustion, during certain chronic infections or when they enter a suppressive tumor microenvironment
 - **Anergy:** A state of immune unresponsiveness. Induced when the T cell's antigen receptor is stimulated, effectively freezing T cell responses pending a "second signal" from the antigen-presenting cell

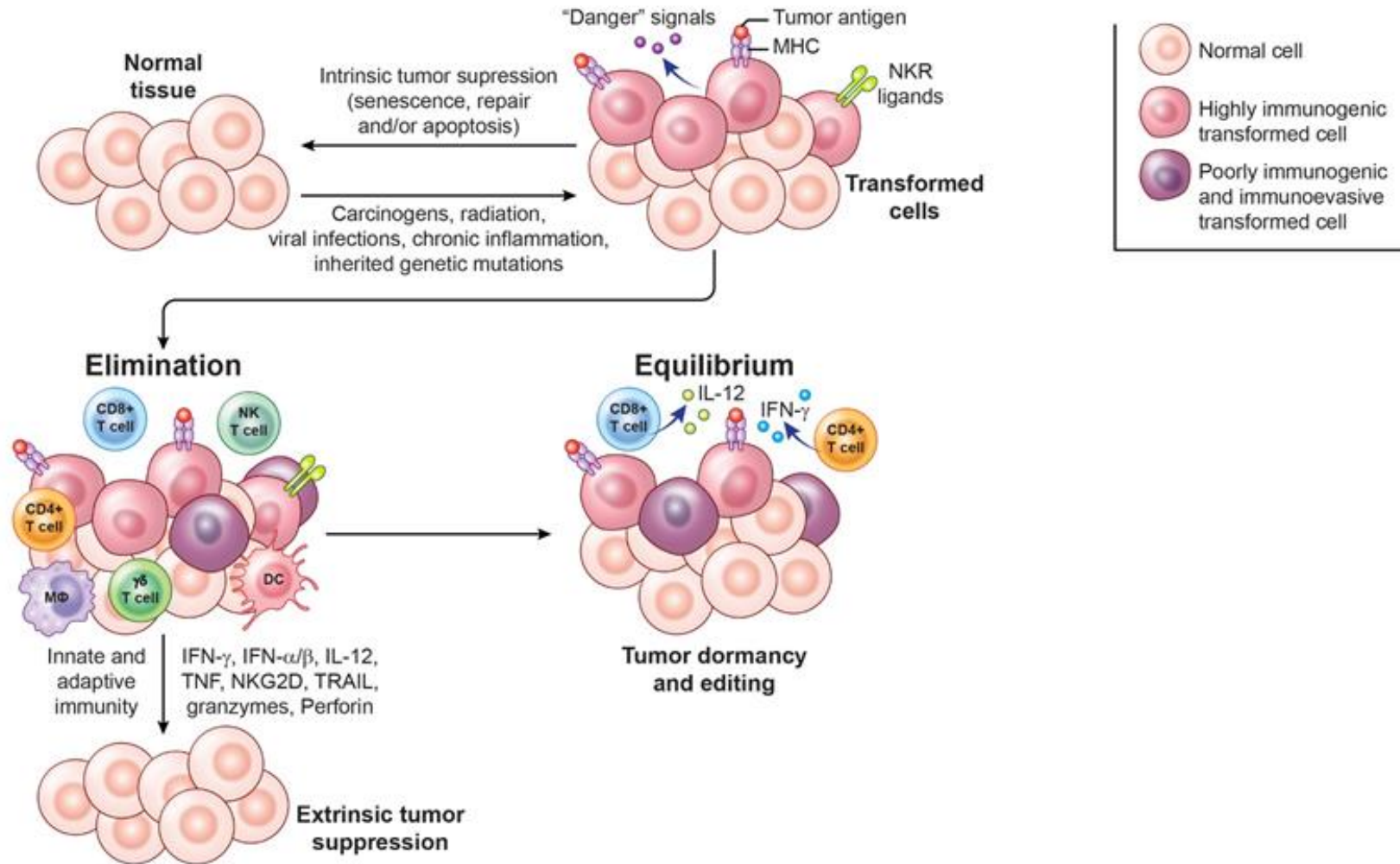
The 3 E's of Cancer Immunoediting



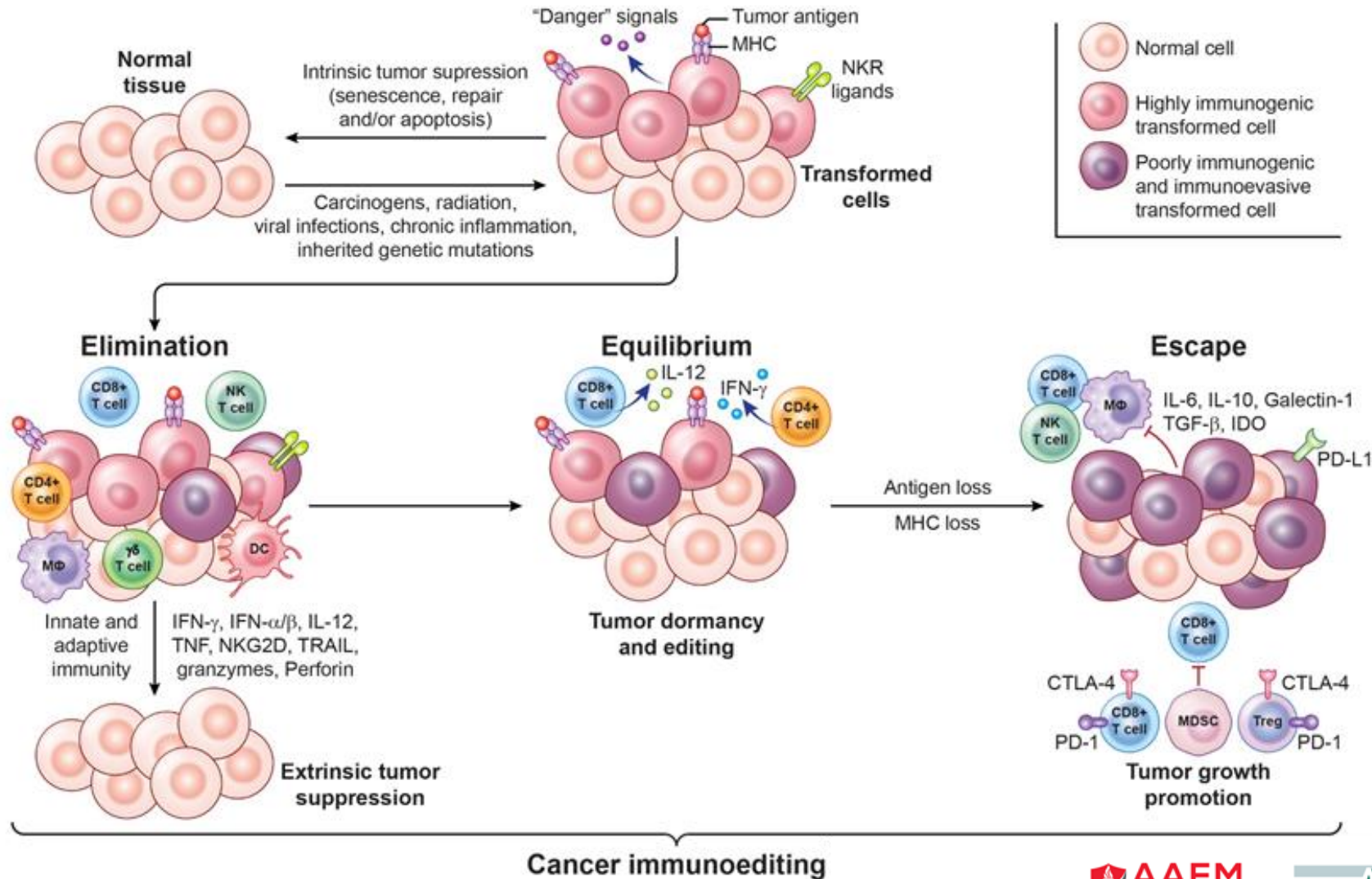
The 3 E's of Cancer Immunoediting



The 3 E's of Cancer Immunoediting

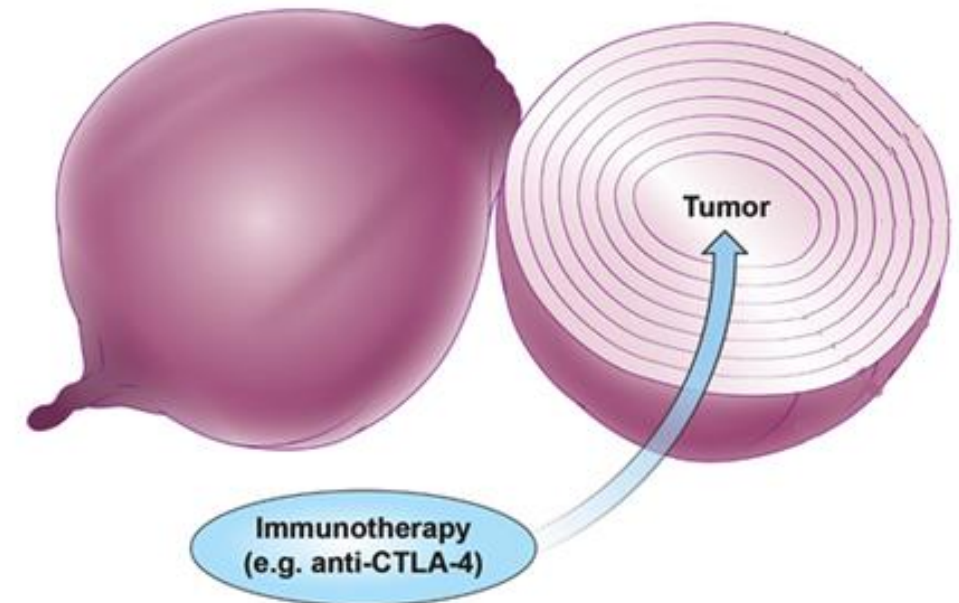


The 3 E's of Cancer Immunoediting

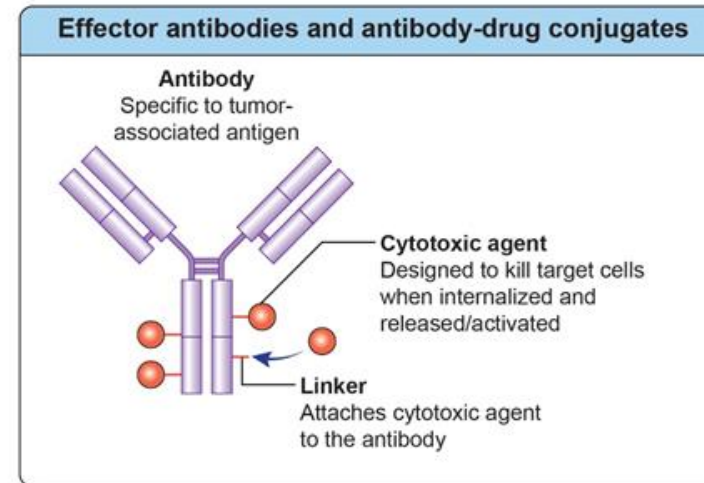
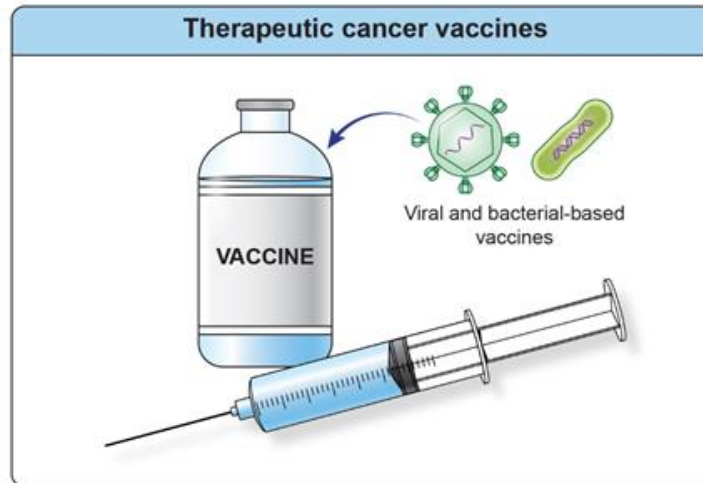
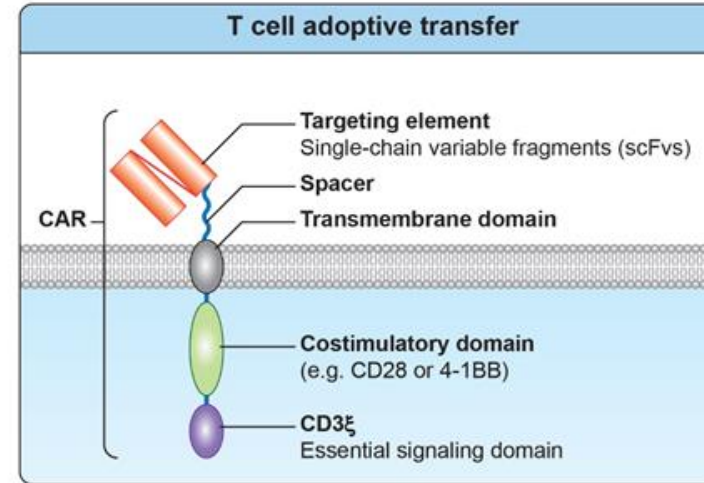
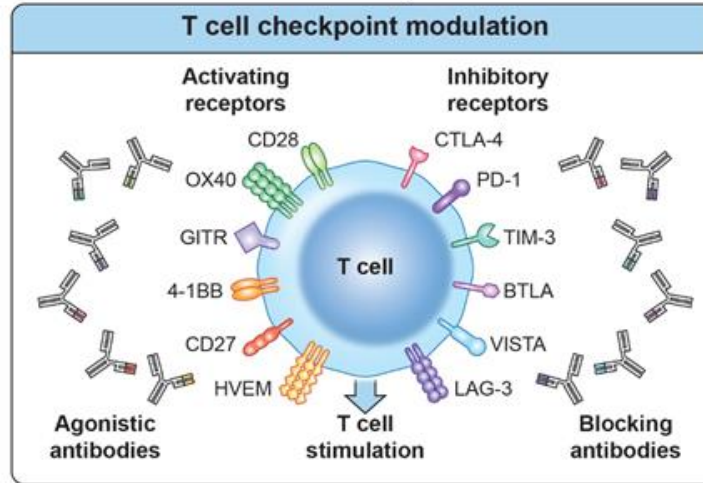


Multi-layered Immunosuppression

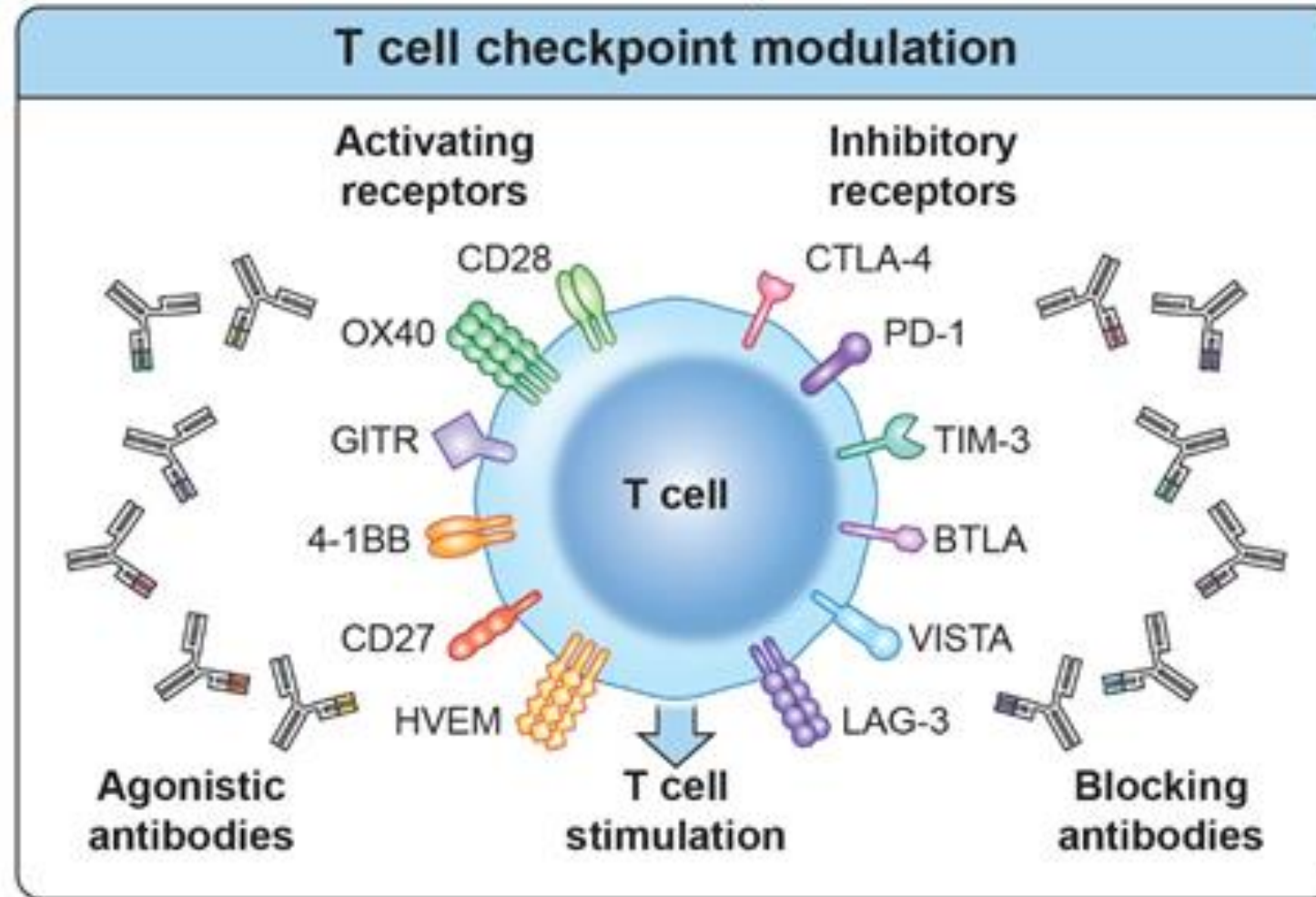
- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor



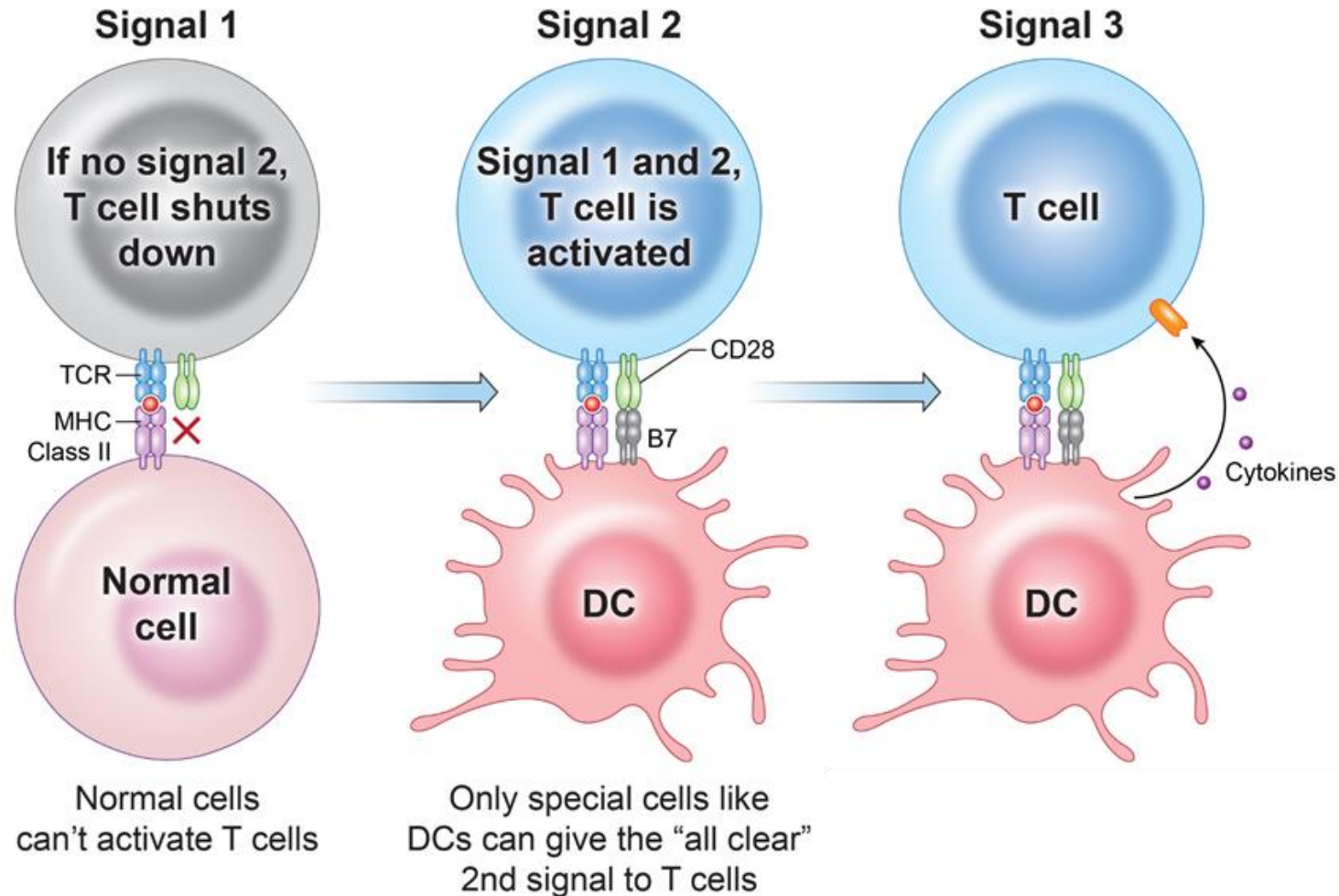
Types of Immunotherapy



T cell Checkpoint Modulation

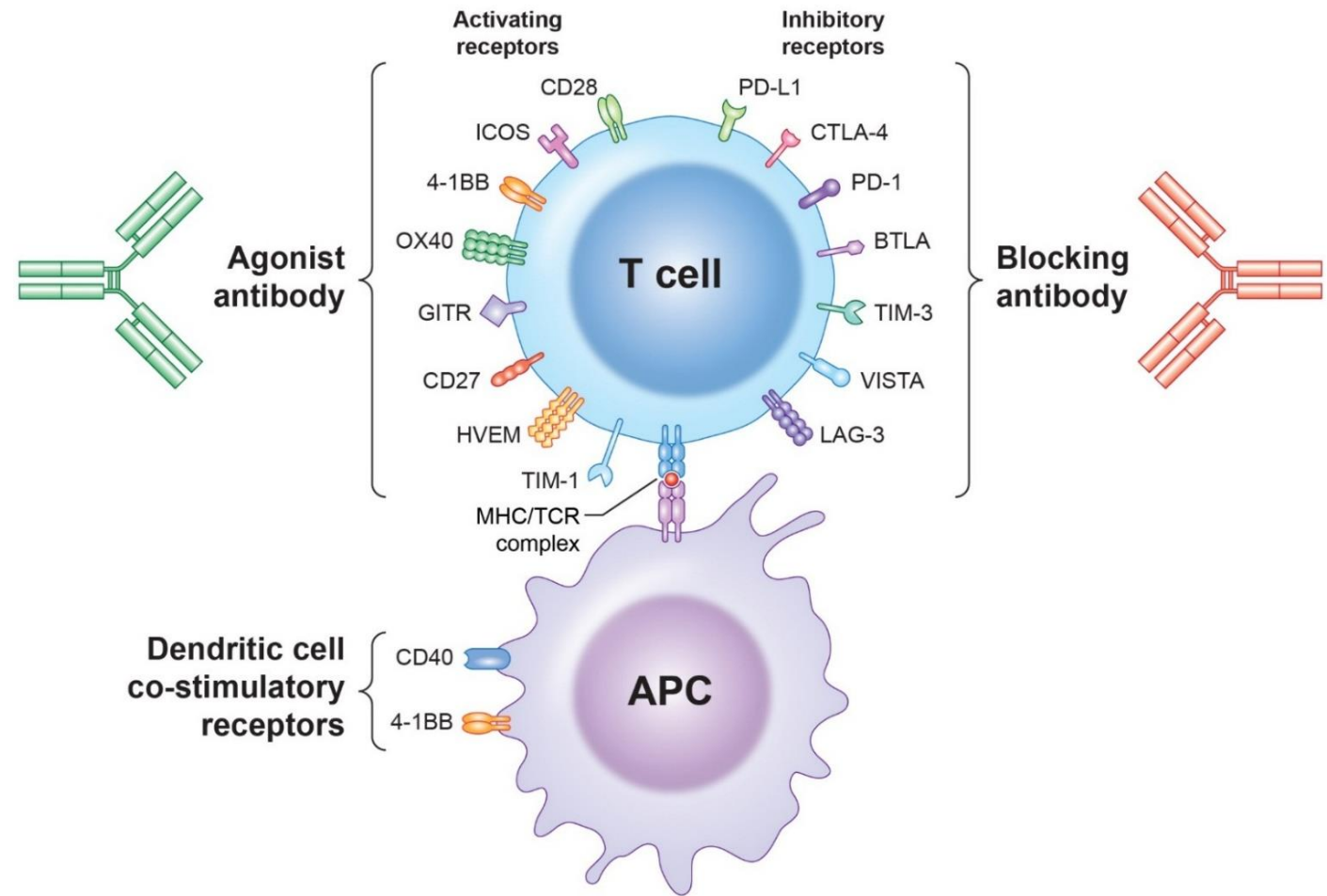


Antigen-specific T cell Activation



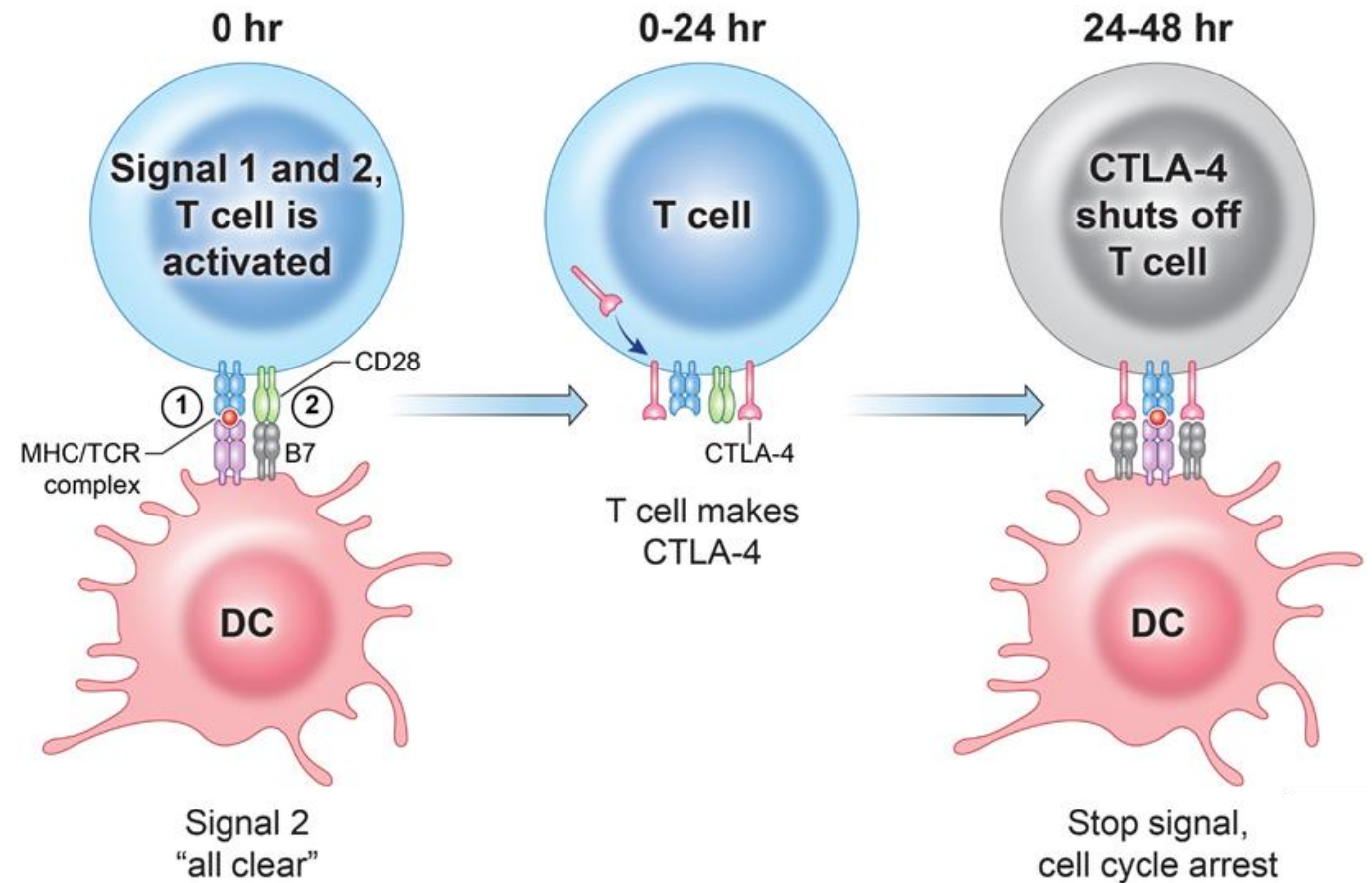
T Cell Checkpoint Modulation

- To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.
- The goal of T cell checkpoint blockade is to make T cell “off-switches” inaccessible to tumor cells, thus restoring tumor-specific immunity.

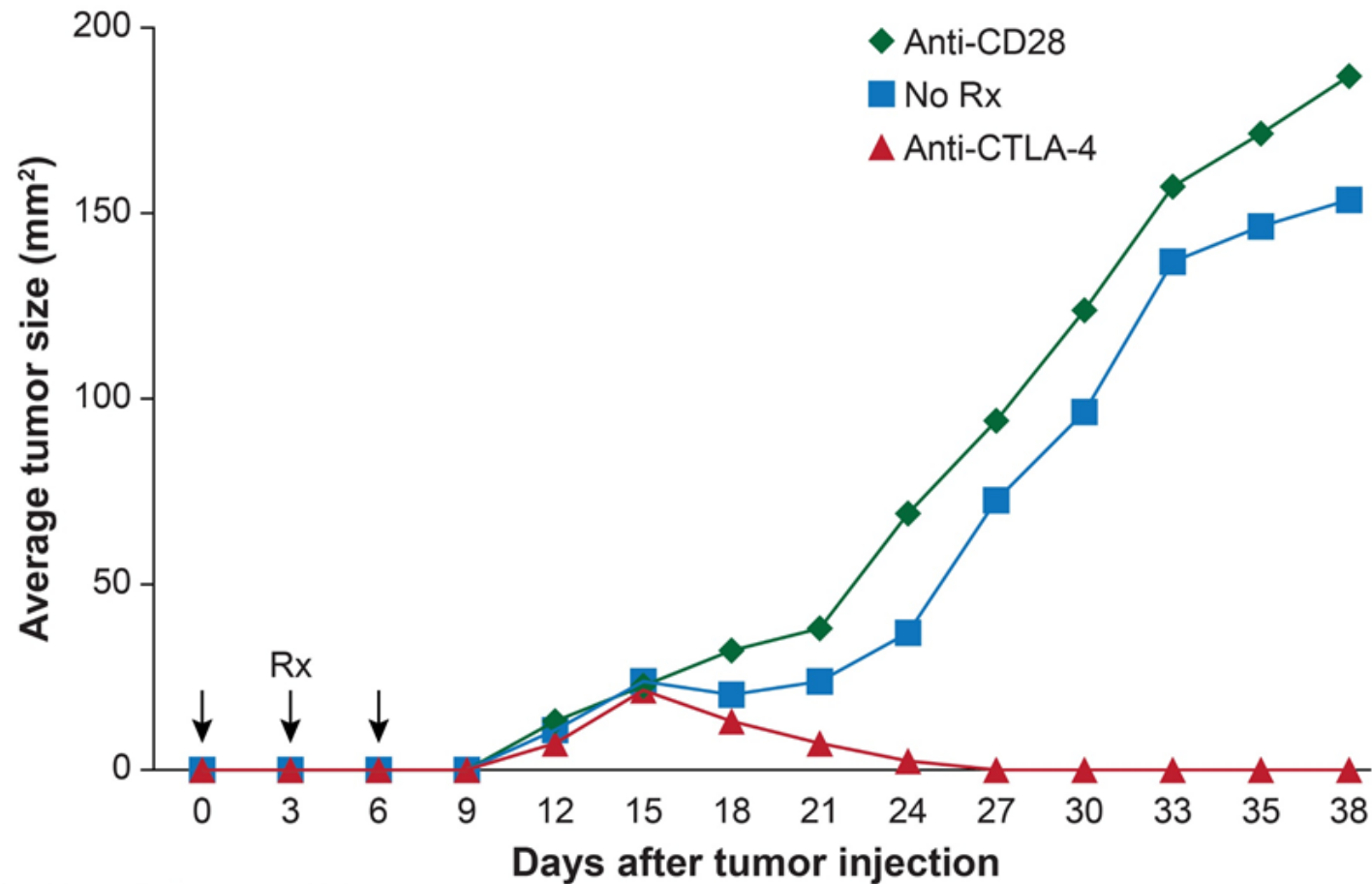


The CTLA-4 Checkpoint

- Cytotoxic T-Lymphocyte Associated Protein 4
- Also known as CD152
- Negative regulator of T cell activation



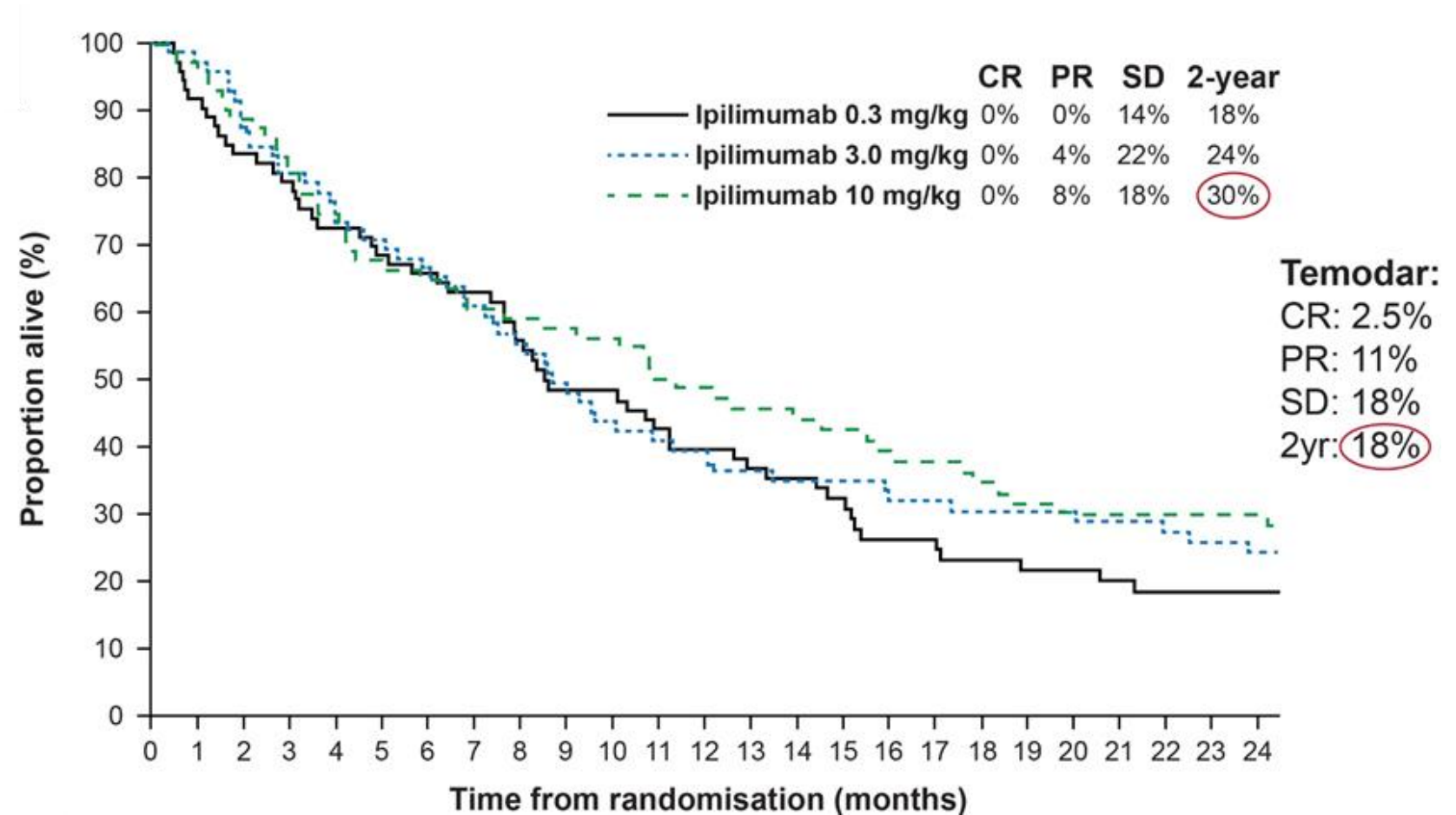
Anti-CTLA-4 induces regression of transplanted colon carcinoma



Leach DR, Krummel MF, Allison JP. 1996.
Enhancement of antitumor immunity by CTLA-4 blockade.
Science. 271(5256): 1734-6.

Ipilimumab (human anti CTLA-4)

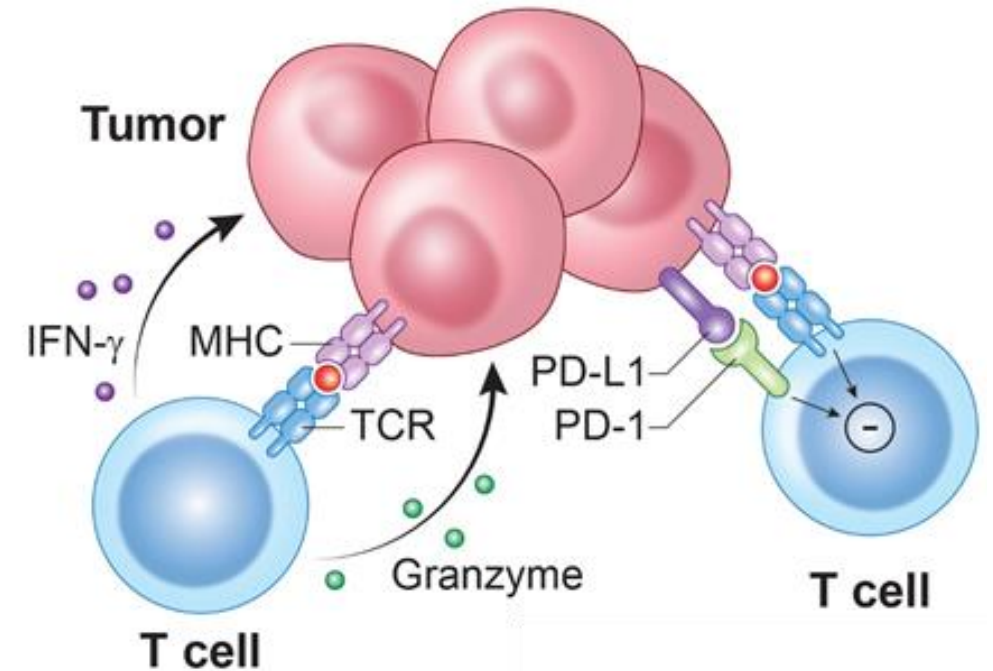
- Granted FDA approval for treatment of patients with metastatic melanoma in 2010



Wolchok et al. Lancet Oncol 2010

The PD-1/PD-L1 Checkpoint

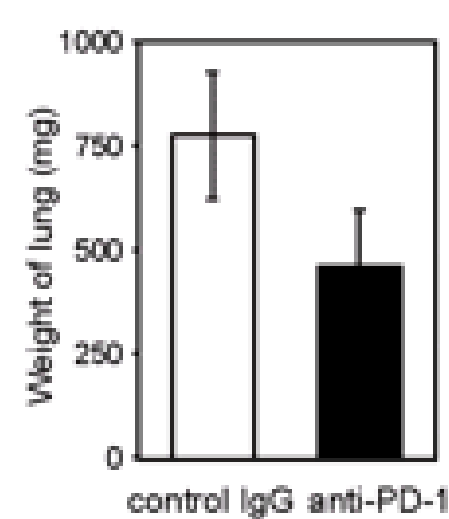
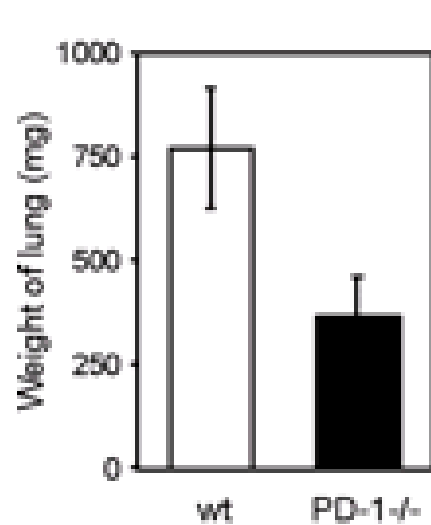
- PD-1 is induced upon T cell activation
- PD-1 promotes T cell tolerization through inhibiting activation signaling (negative feedback loop)
- T cell PD-1 interacts with PD-L1 and PD-L2
- Many cells express PD-L1 and can suppress T cell activation
- Tumors express PD-L1 through two primary mechanisms
 - TIL production of IFN- γ
 - Oncogenic signaling pathways



Francisco, L. et al. *Immunol Rev.* 2010. 236: 219.
Pardoll, D.M. *Nat Rev Cancer.* 2012. 12: 252.

Anti-PD-1 Slows Tumor Growth in Pre-clinical Models

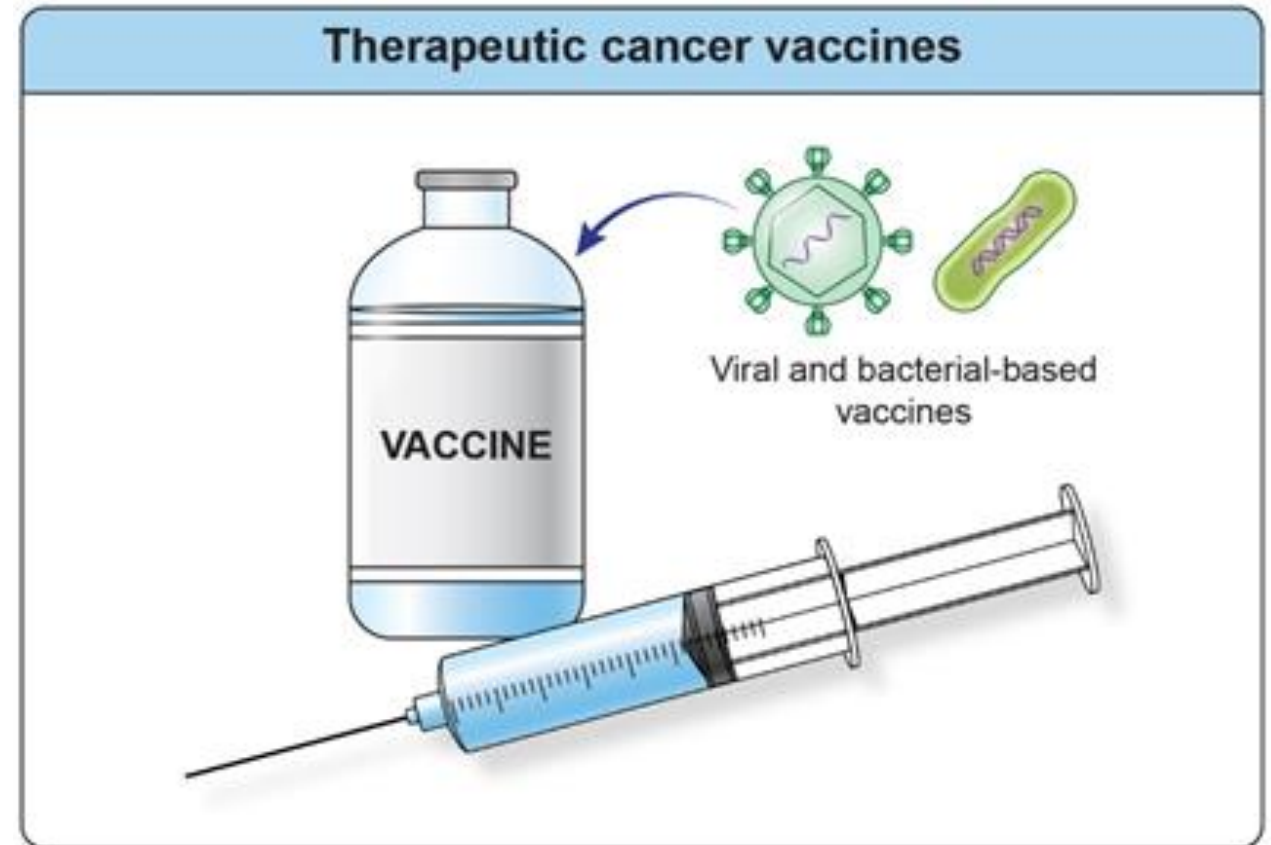
- PD-1 deletion or inhibition reduced CT26 colon cancer cell growth in BALB/c mice








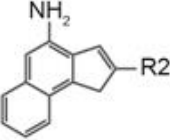
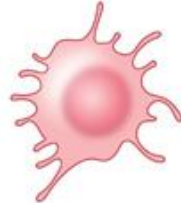
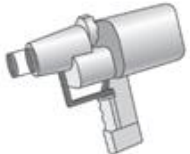
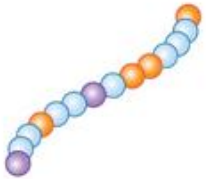
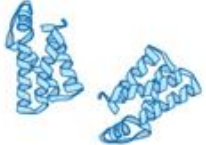




Iwai et al. Internat. Immunol 2004

Therapeutic Cancer Vaccines

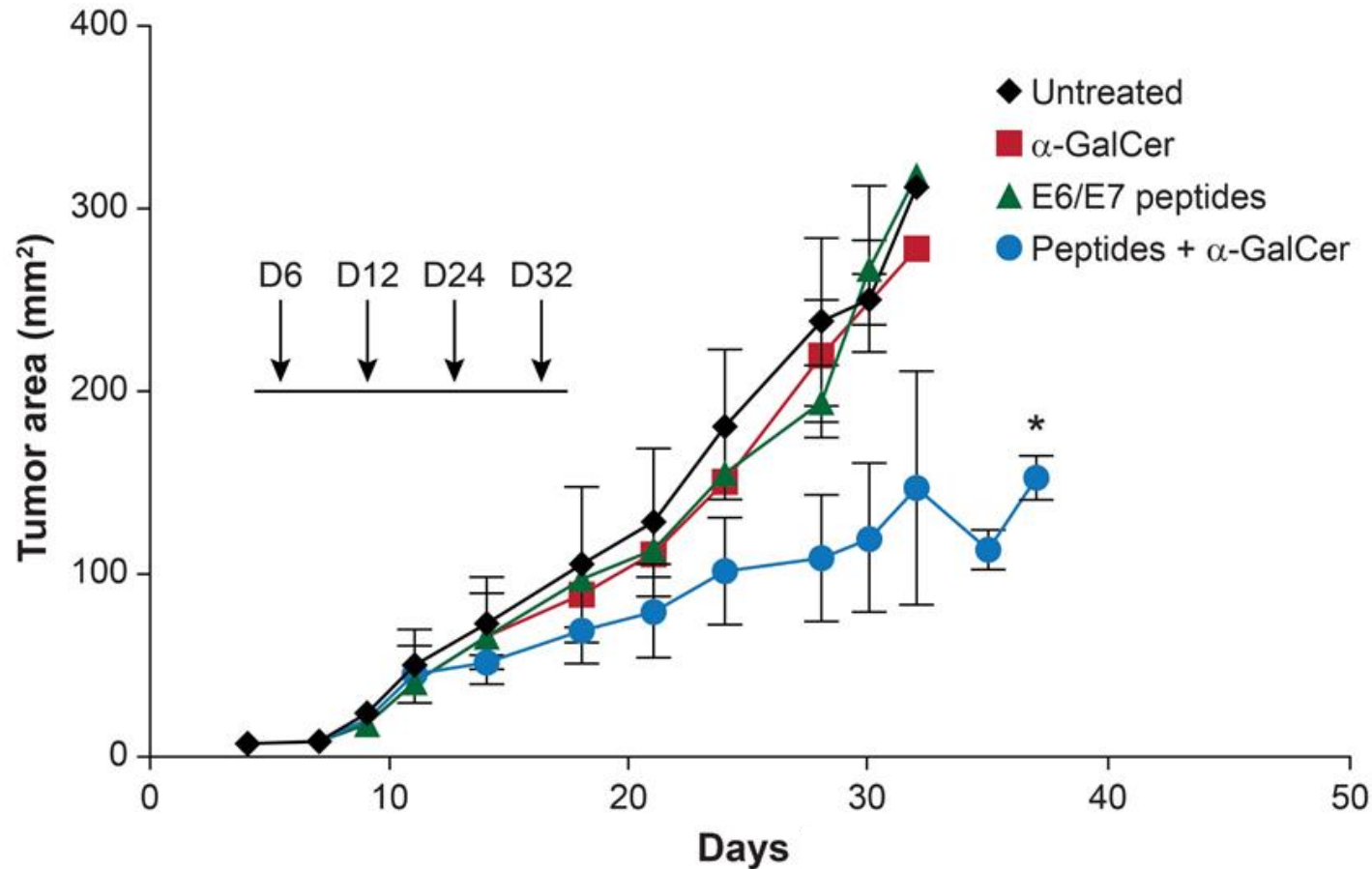
- The goal of therapeutic cancer vaccination is to increase the immunogenicity of tumor antigens in order to generate a high frequency of tumor-specific T cells.



Components of a Cancer Vaccine

Antigen	Adjuvant	Vector	Vehicle
 Whole tumor	 Emulsifiers	 Viral vectors	 Injection
 Protein antigen	 Innate agonists	 Dendritic cells	 Gene gun
 Antigenic peptide(s)	 Cytokines	 Attenuated bacteria	 Systemic infusion
	 Antibodies		 Nasal spray

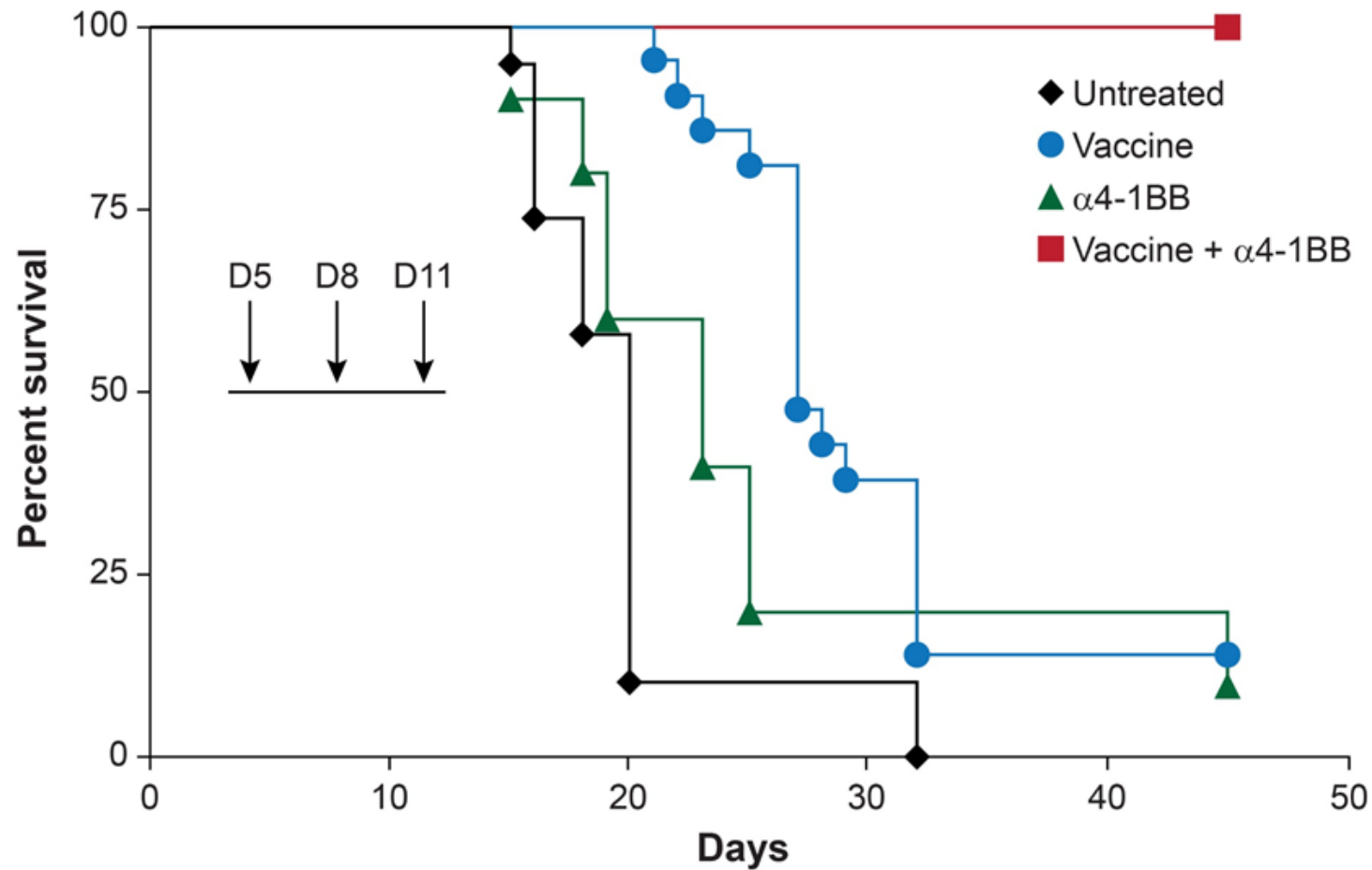
An intra-nasal HPV E6/E7: α -GalCer vaccine slows growth of TC-1 tumors



α -GalCer
activates
NKT cells

Shailbala Singh

4-1BB agonist antibody and HPV E6/E7 vaccine synergize in curing TC-1 Tumors

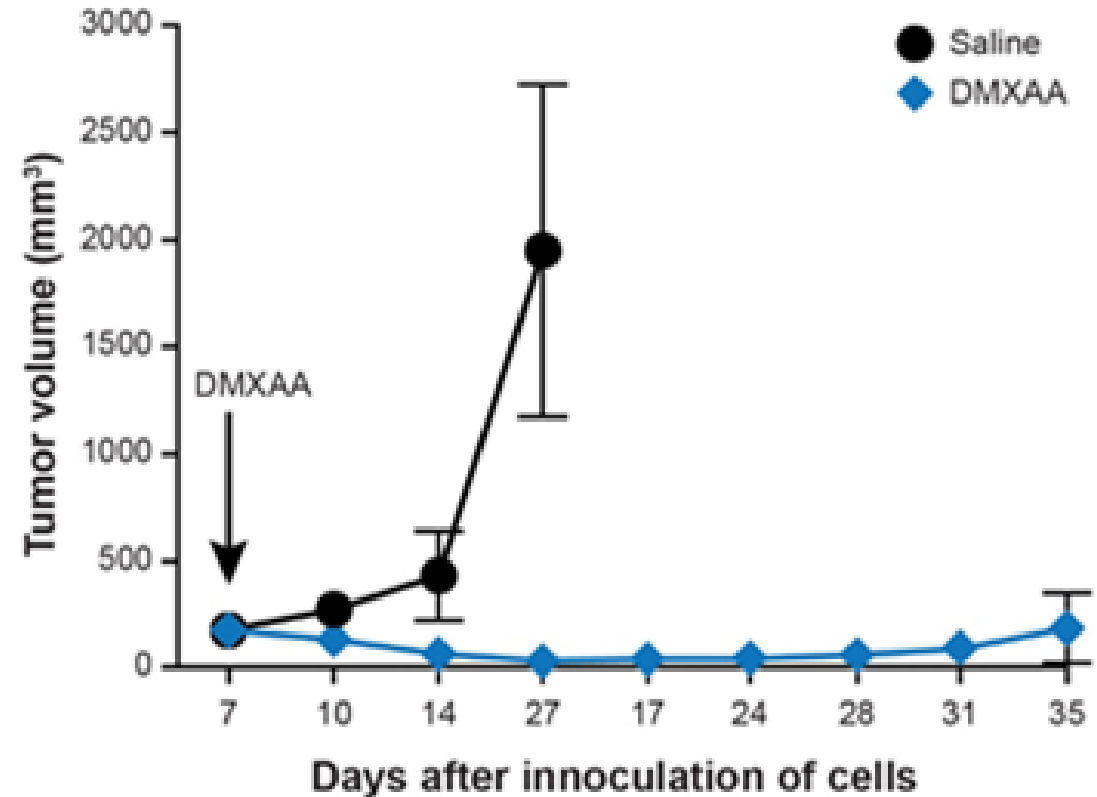
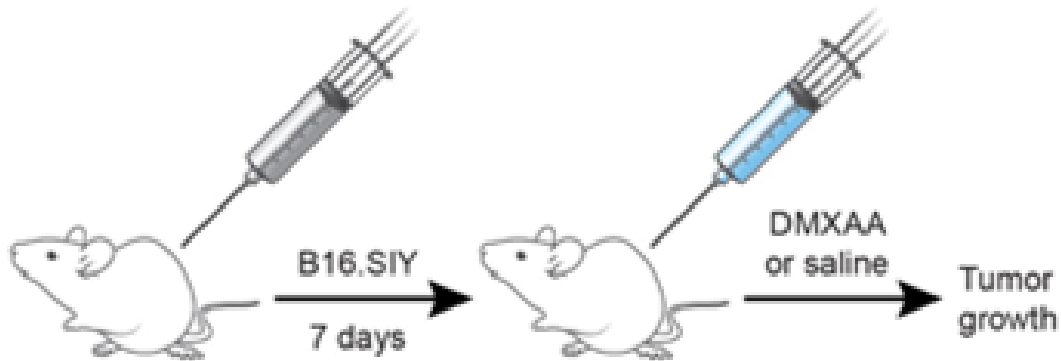


4-1BB is a
costimulatory
molecule on T cells

Todd Bartkowiak, M.S.

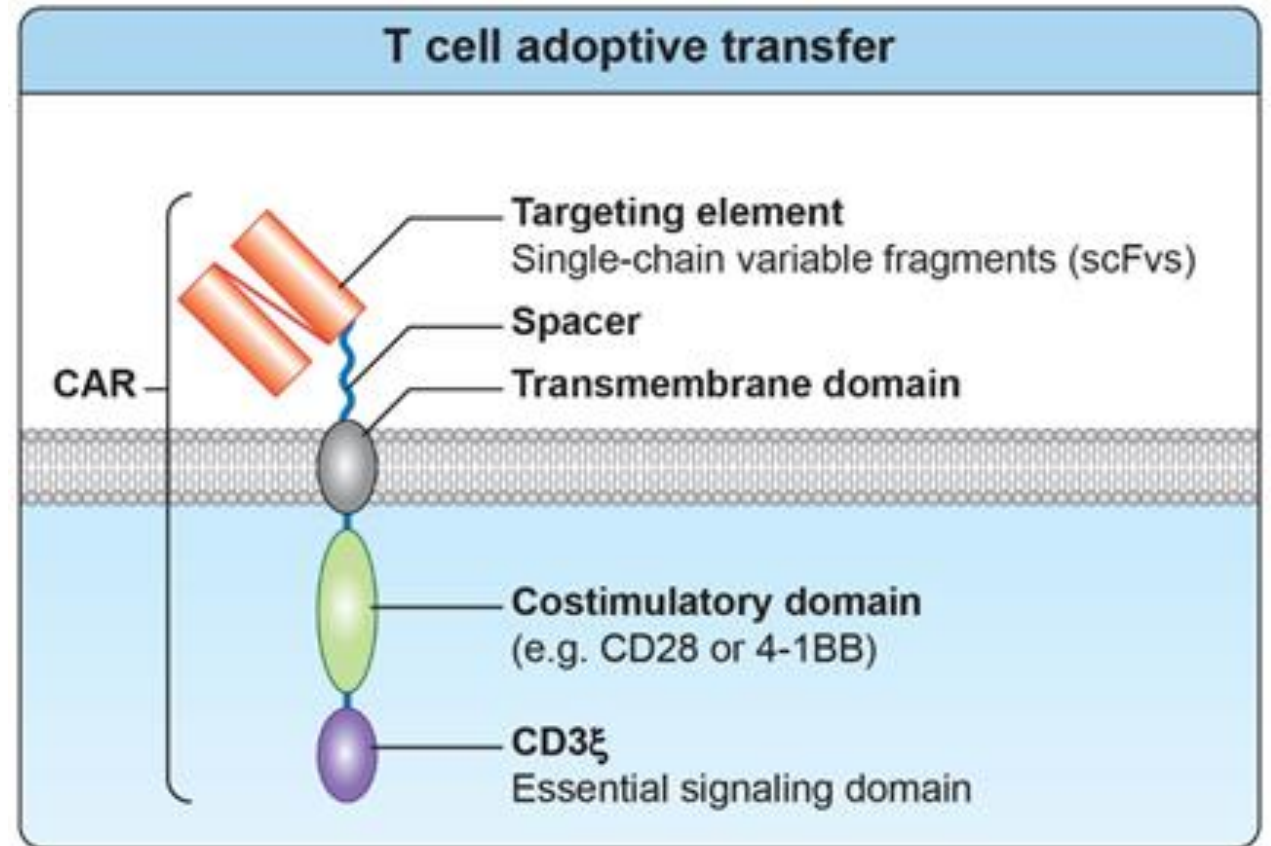
Intratumoral Injection of Innate Immune Agonists: *Direct Vaccination Approach*

- Intratumoral DMXAA (mouse STING agonist) triggers rejection of B16 melanoma

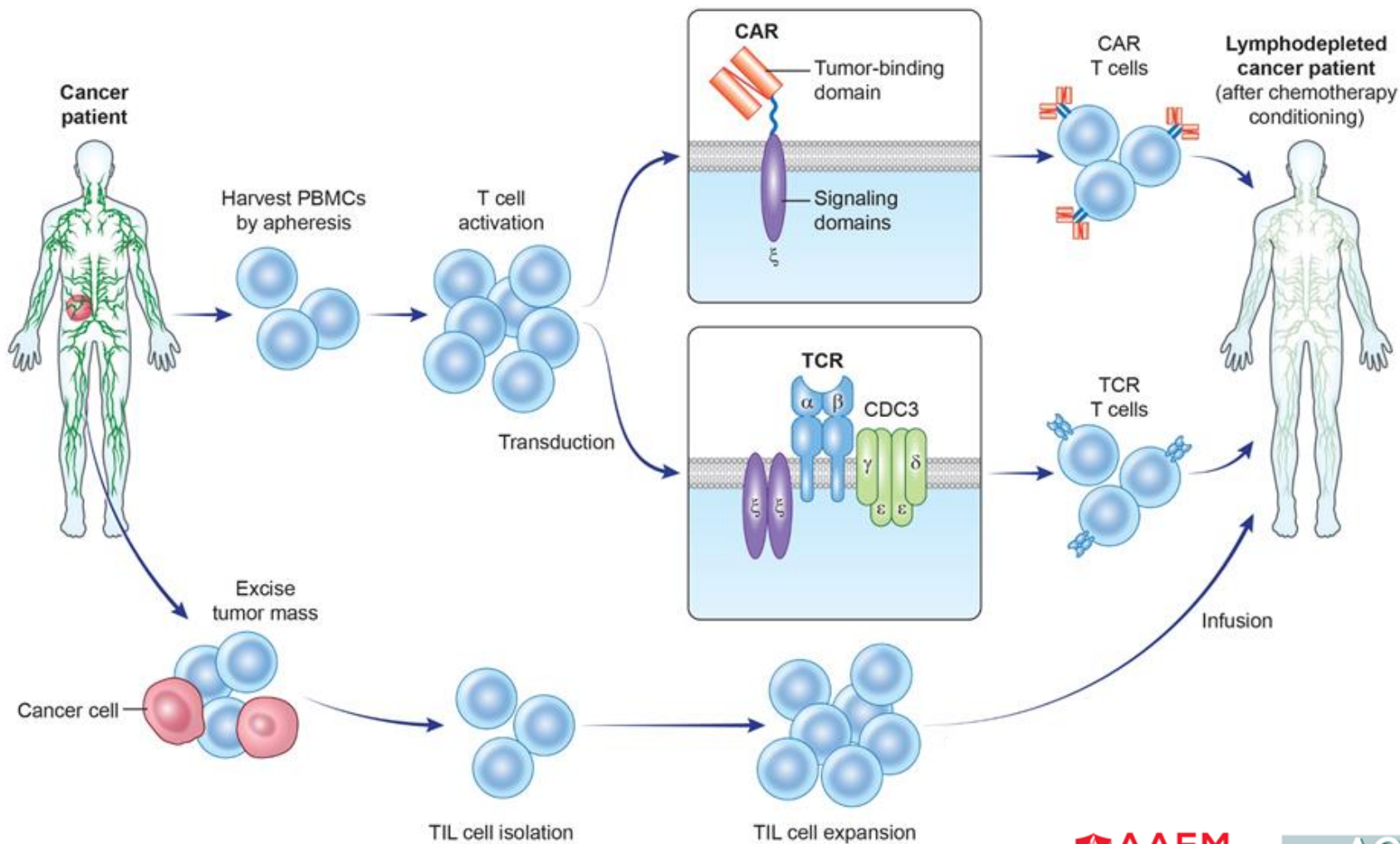


Adoptive Cell Transfer

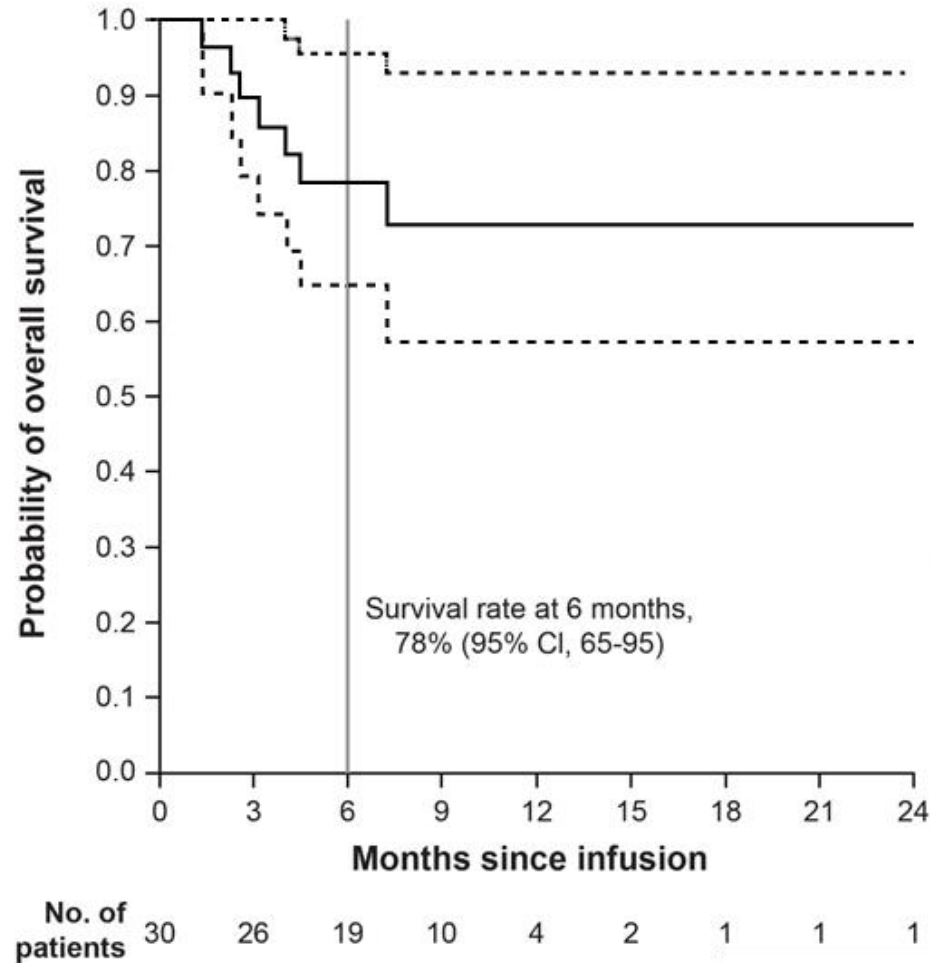
- The goal of adoptive cell transfer is to overwhelm the tumor with a higher frequency of tumor-specific immune cells and/or engineer immune cells to target cancer



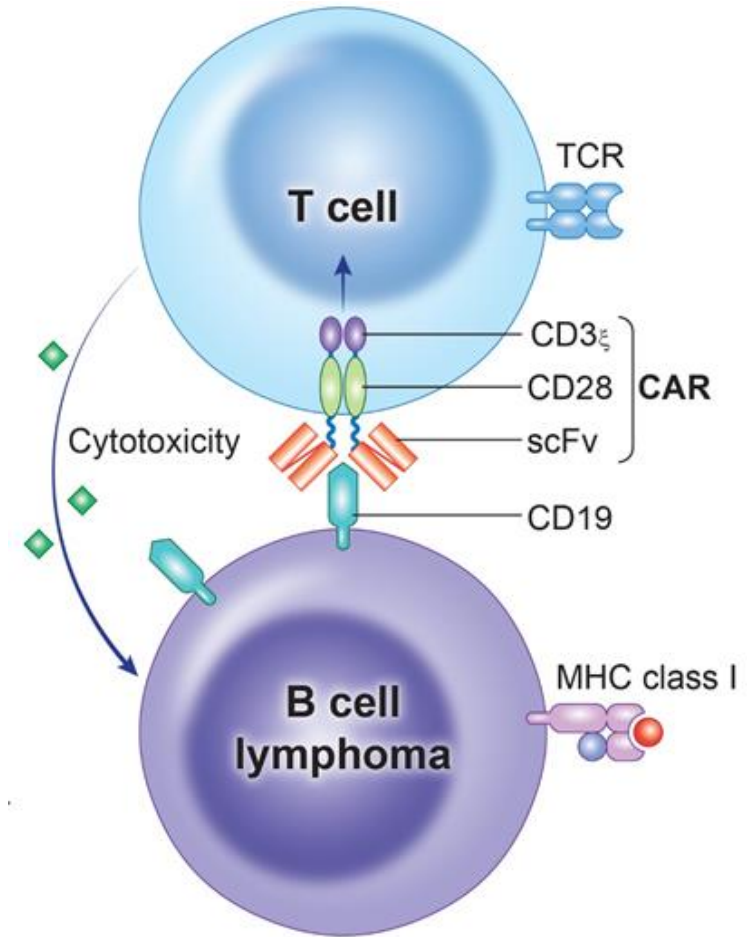
Adoptive Cell Therapy Process



CD19 CAR T Cell Therapy for Relapsed B Cell ALL

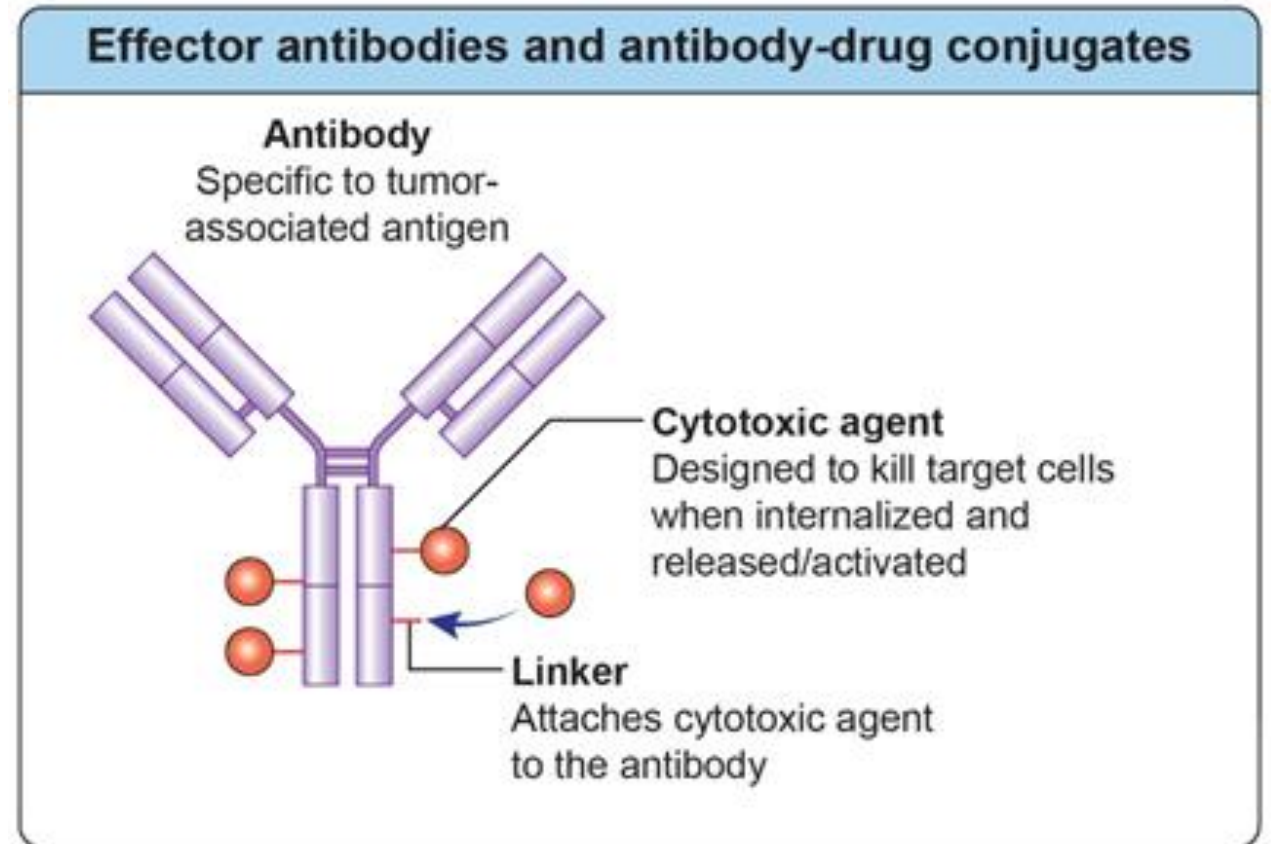


Maude S, Frey N, Shaw P, Aplenc R, Barrett D, Bunin N, Chew A, Gonzalez V, Zheng Z, Lacey S, et al. 2014. Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England Journal of Medicine. 374(10): 998.



Effector Antibodies and Antibody-drug Conjugates (ADCs)

- The goal of effector antibodies is to specifically target and kill tumor cells using innate mechanisms which are difficult to evade or through delivery of cytotoxic agents

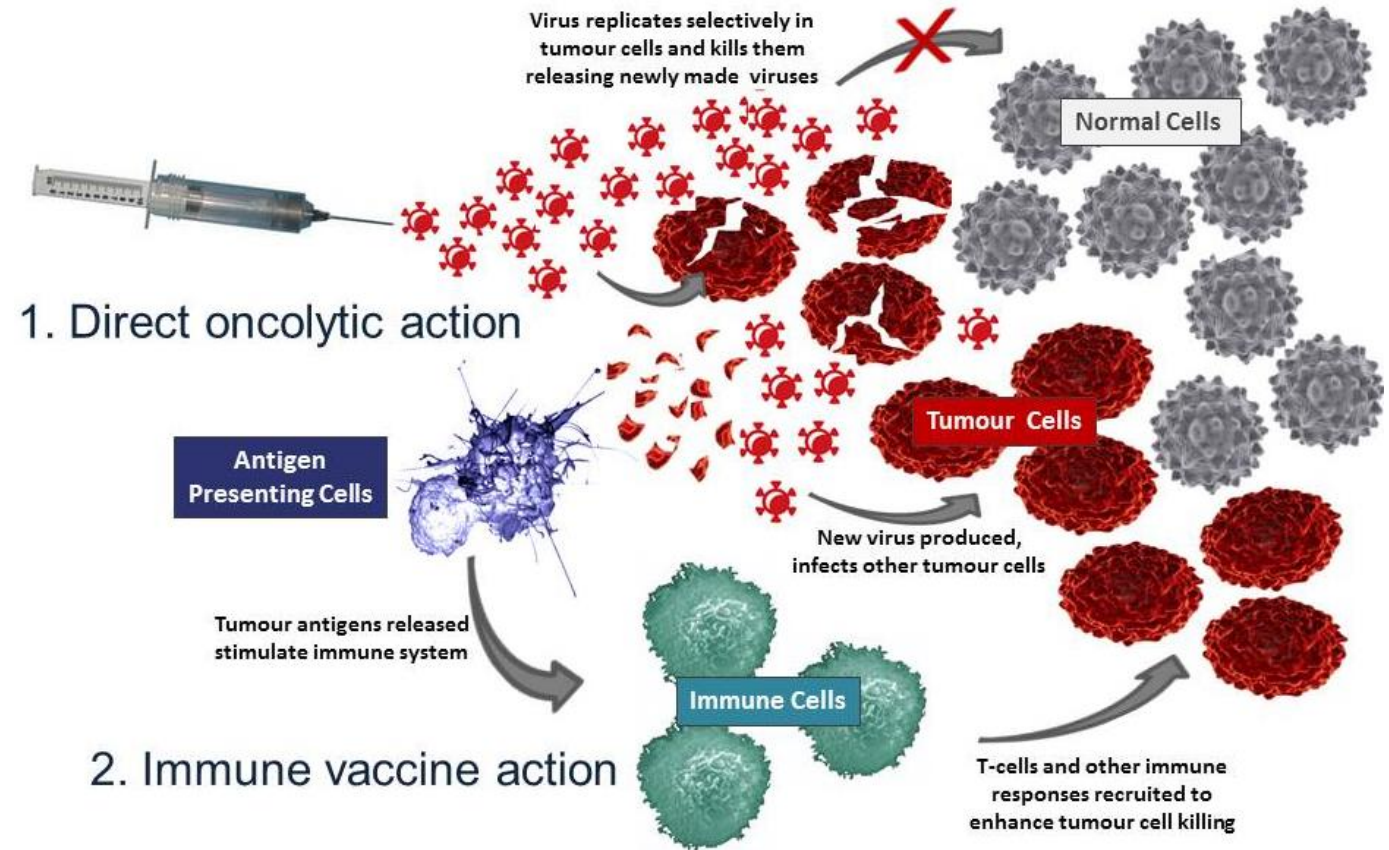


Key ADC/Antibody Principles

- **Specificity:** The more tumor specific the target antigen is, the higher the agent can be dosed without limiting toxicity
- **Internalization:** The target tumor surface protein must internalize to deliver the toxin – it should do so frequently and to a suitable endosomal compartment
- **Stability:** The toxin must remain inert and tethered to the antibody until it is delivered to its target cell

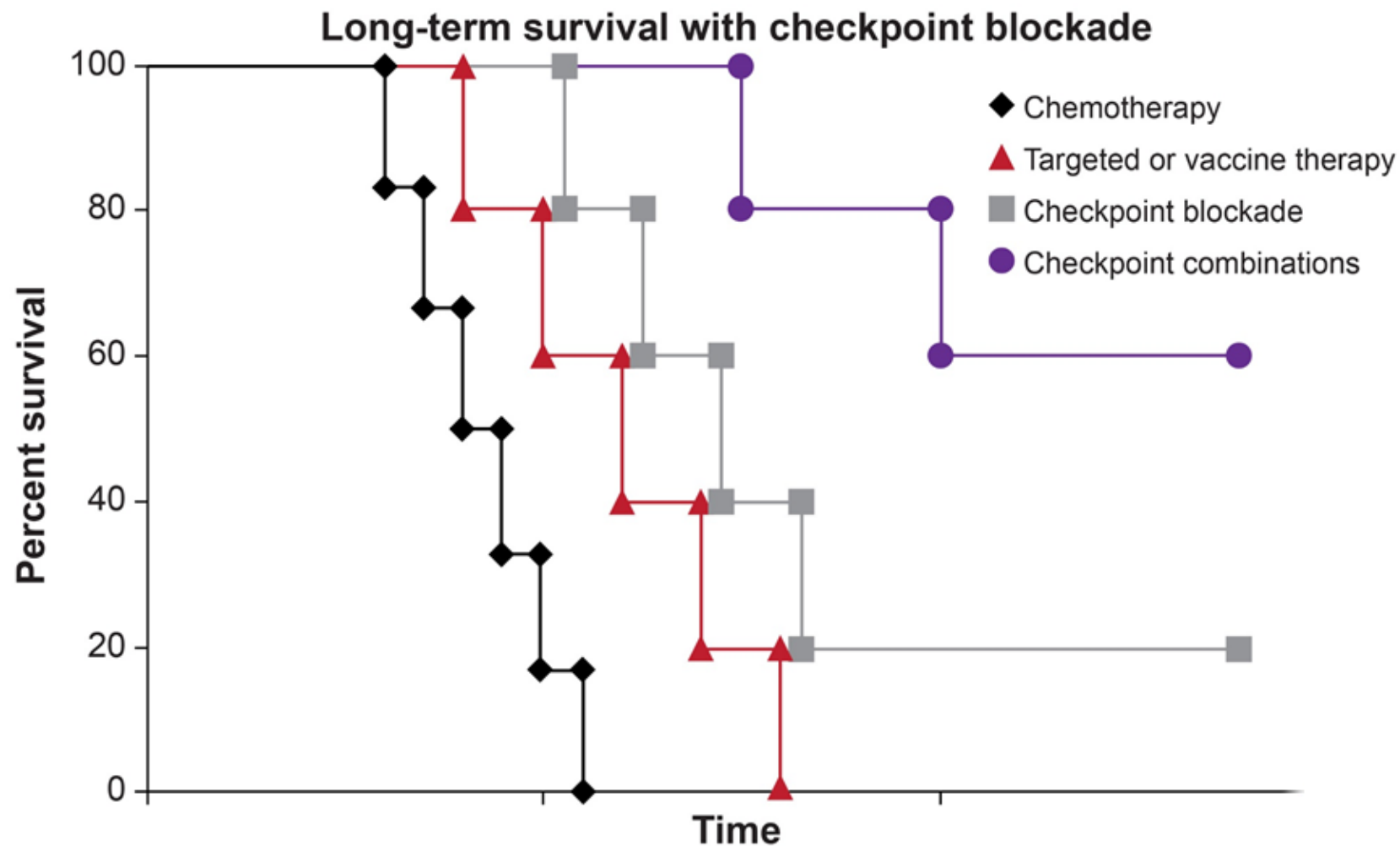
Oncolytic Viruses

- The goal of an oncolytic virus is to specifically target and kill tumor cells through viral replication



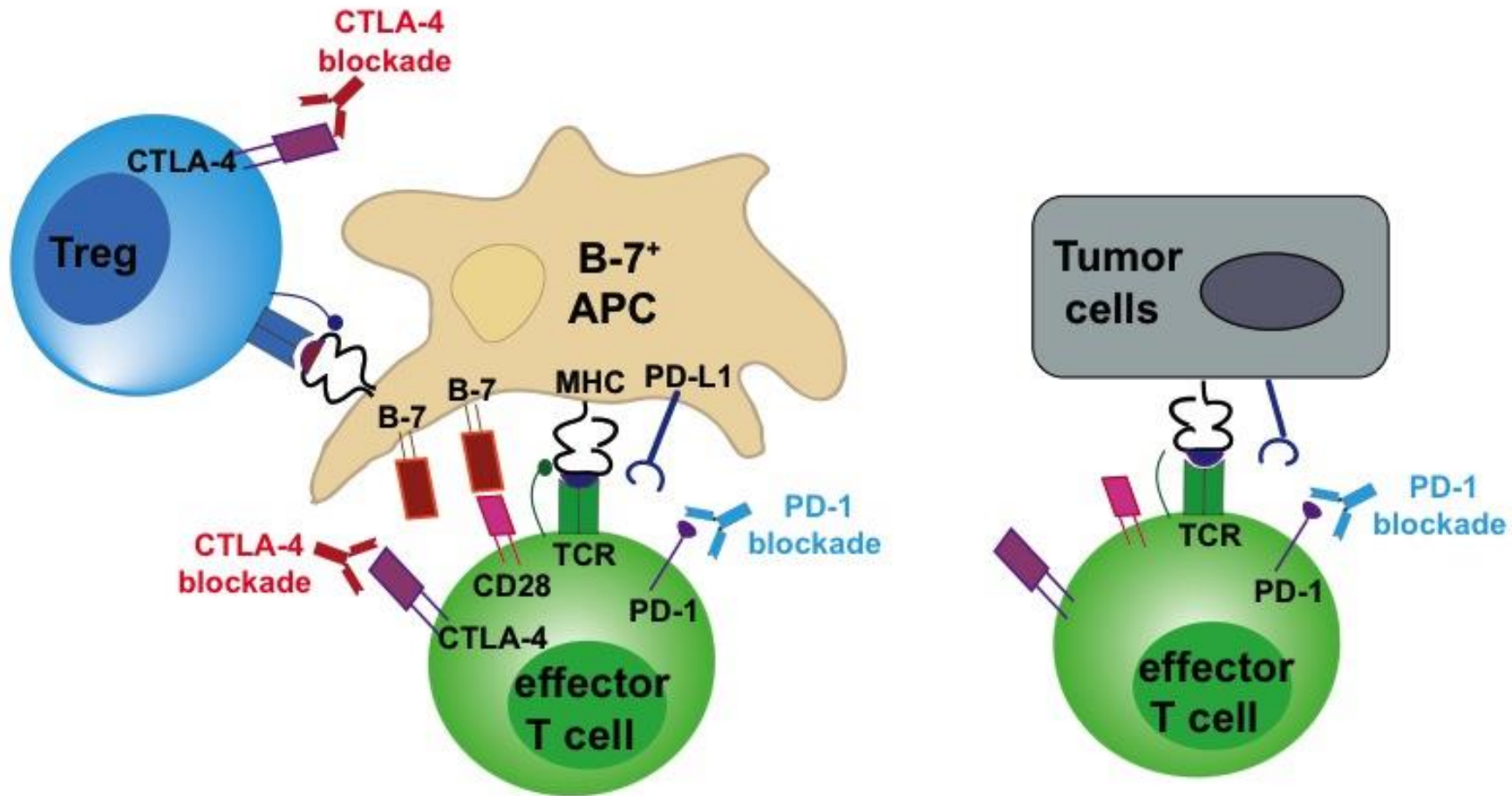
dddmag.com

Combination Immunotherapies



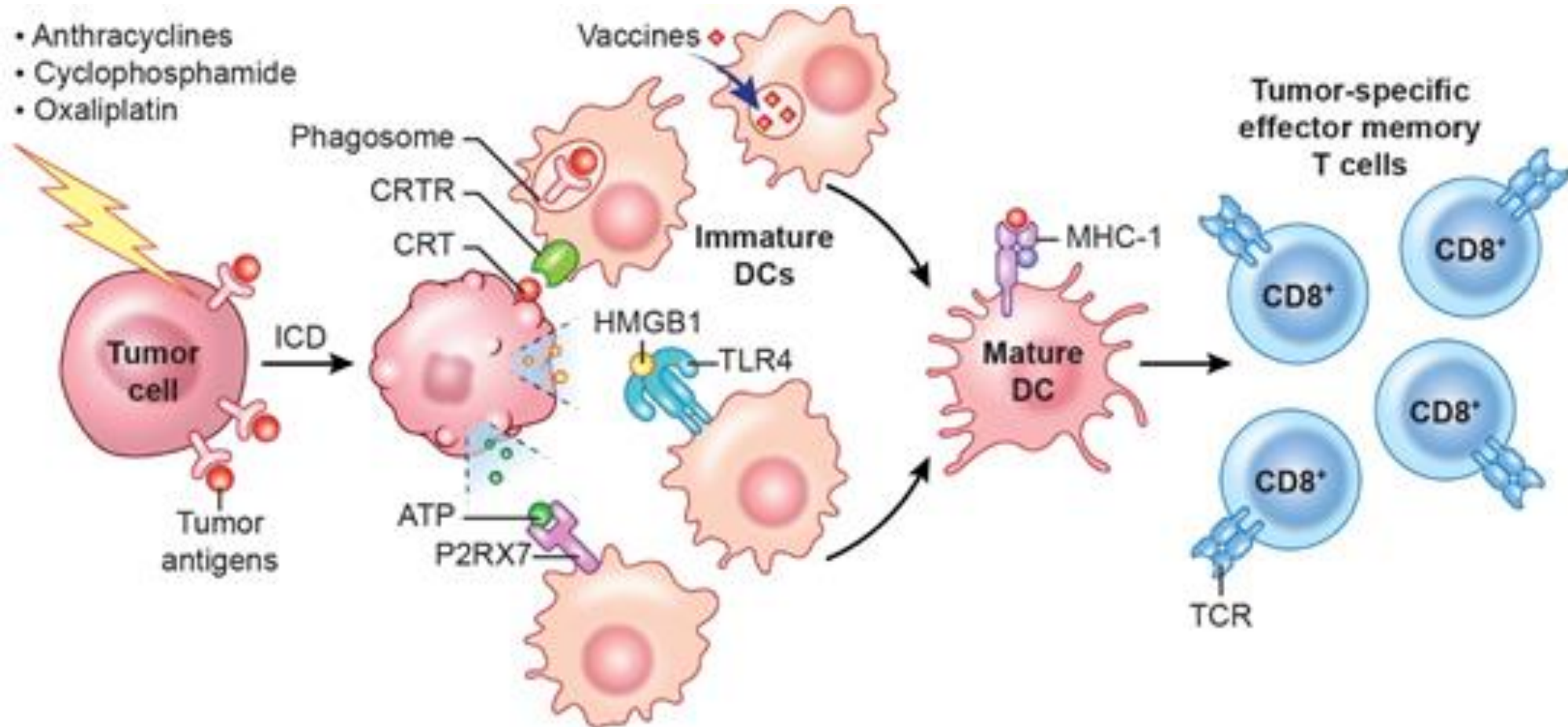
Combination Immunotherapies

Dual CTLA-4 and PD-1 inhibition



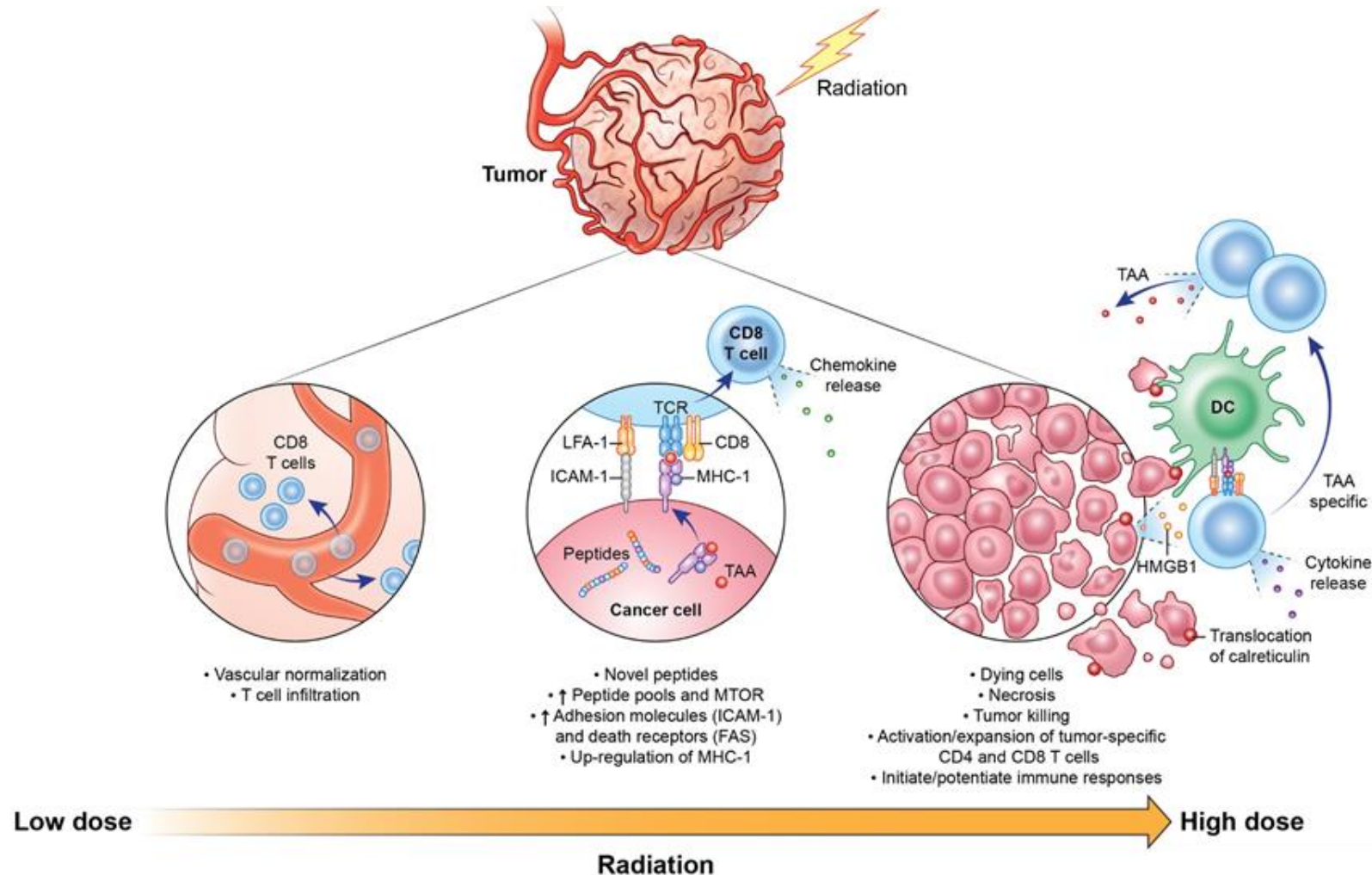
Combination Immunotherapies

Chemotherapy can induce an immune response



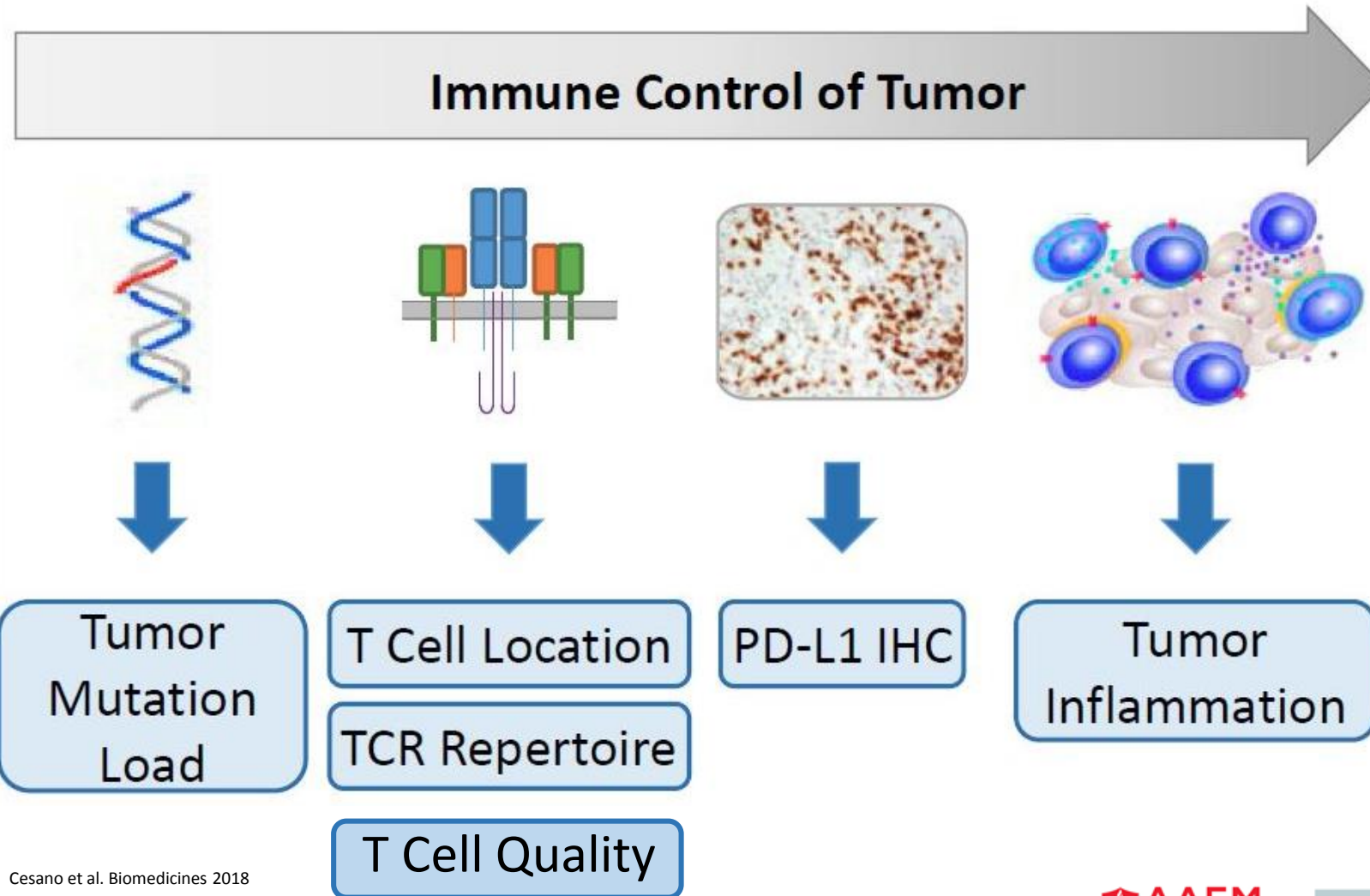
Combination Immunotherapies

Radiotherapy can induce an immune response



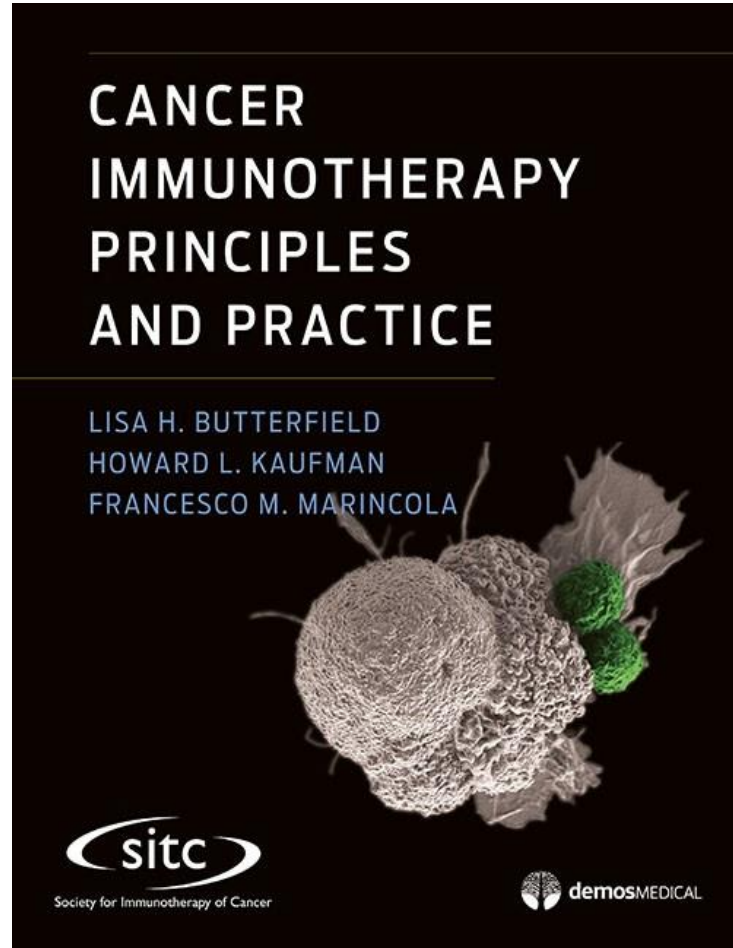
<http://www.ncbi.nlm.nih.gov/pubmed/18777956>

Immunotherapy Biomarkers



Cesano et al. Biomedicines 2018

Further Resources



SOCIETY FOR IMMUNOTHERAPY OF CANCER

