

# Basic Principles of Cancer Immunotherapy

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# Disclosures

- Contracted Research: Lilly USA, LLC
- I will not be discussing non-FDA approved indications during my presentation.

# The Premise of Cancer Immunotherapy

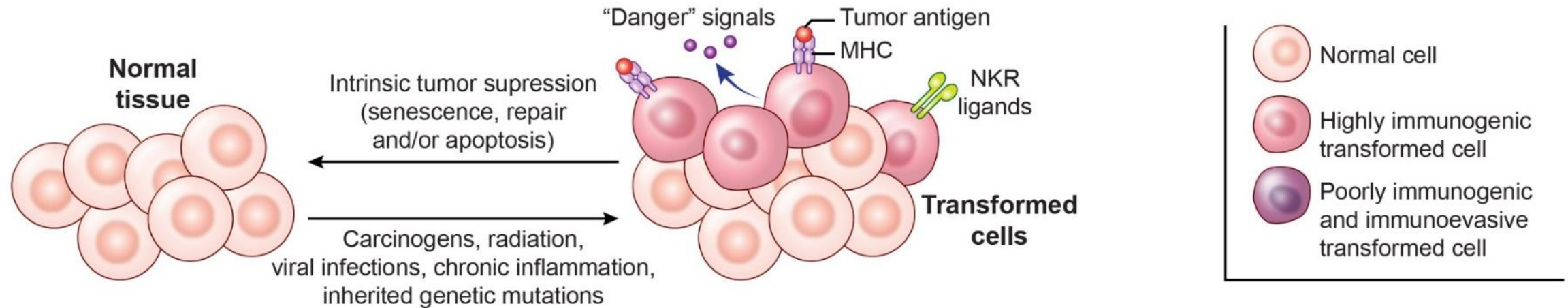
- Normally, the immune system eliminates mutated and/or damaged cells
- To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

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

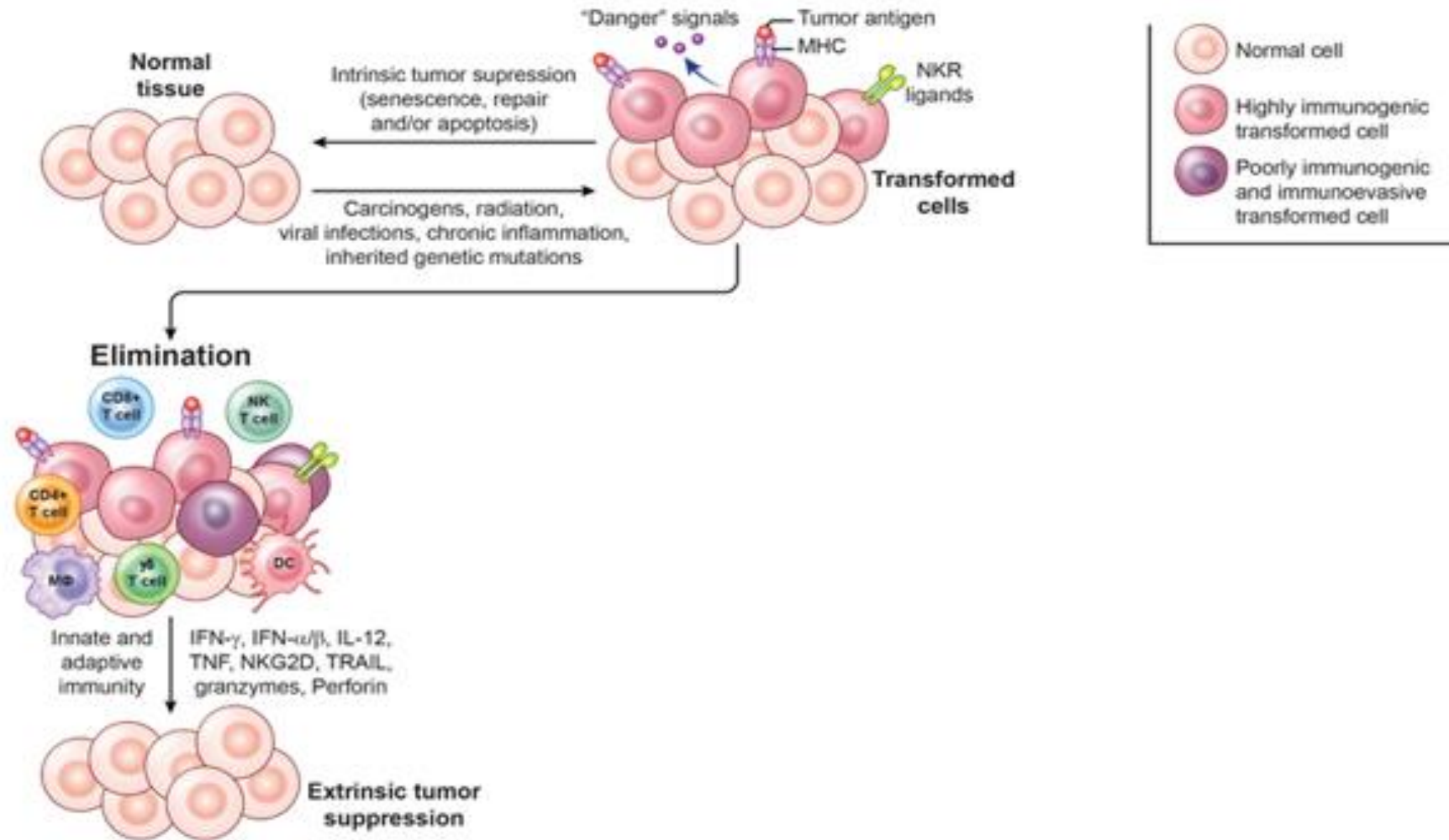
# Why Does the Immune System Fail to Eliminate Cancer?

- Cancer cells grow progressively in immunocompetent hosts without evidence of **T cell exhaustion** or **systemic 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
  - **Systemic 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

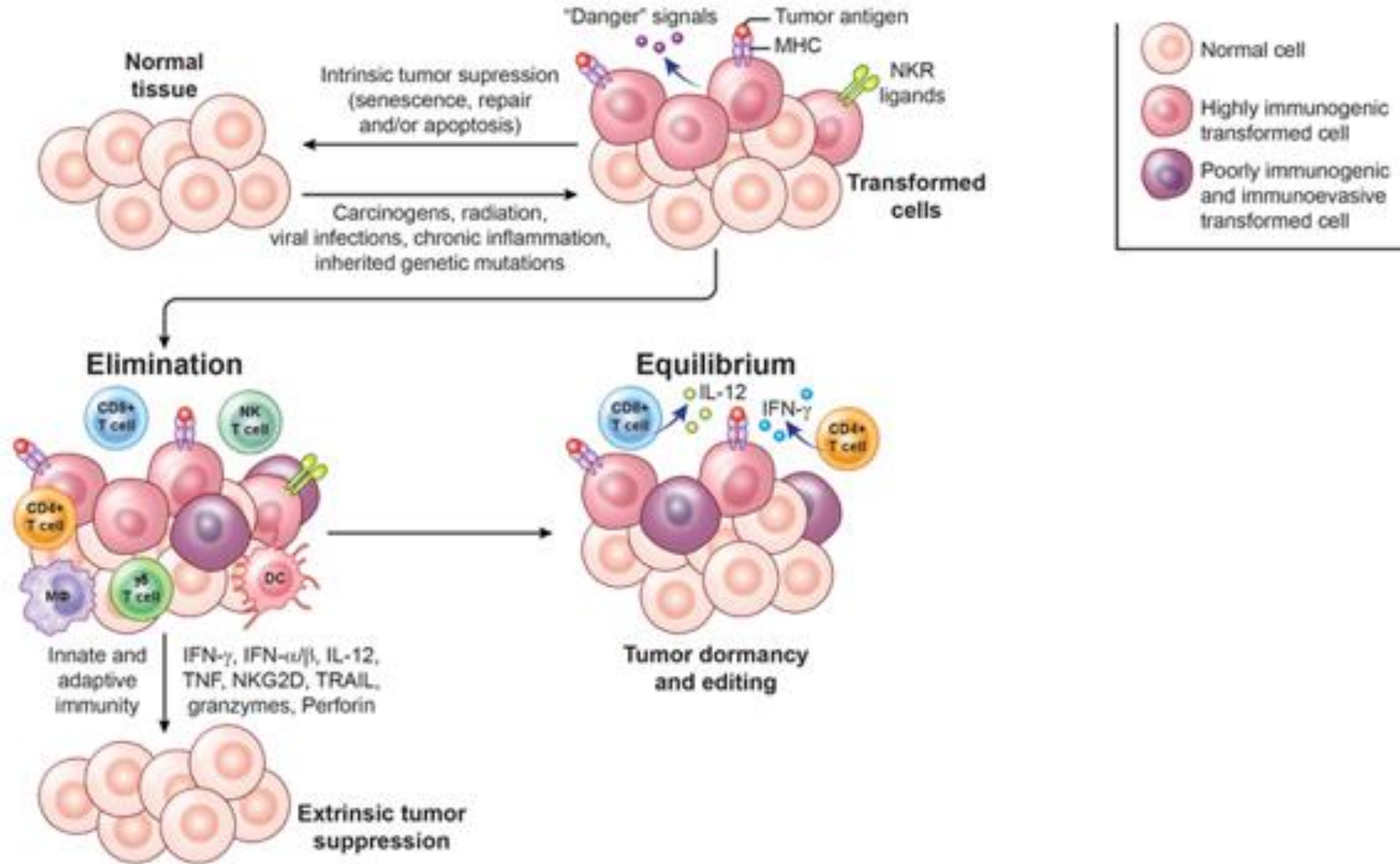


# The 3 E's of Cancer Immunoeediting

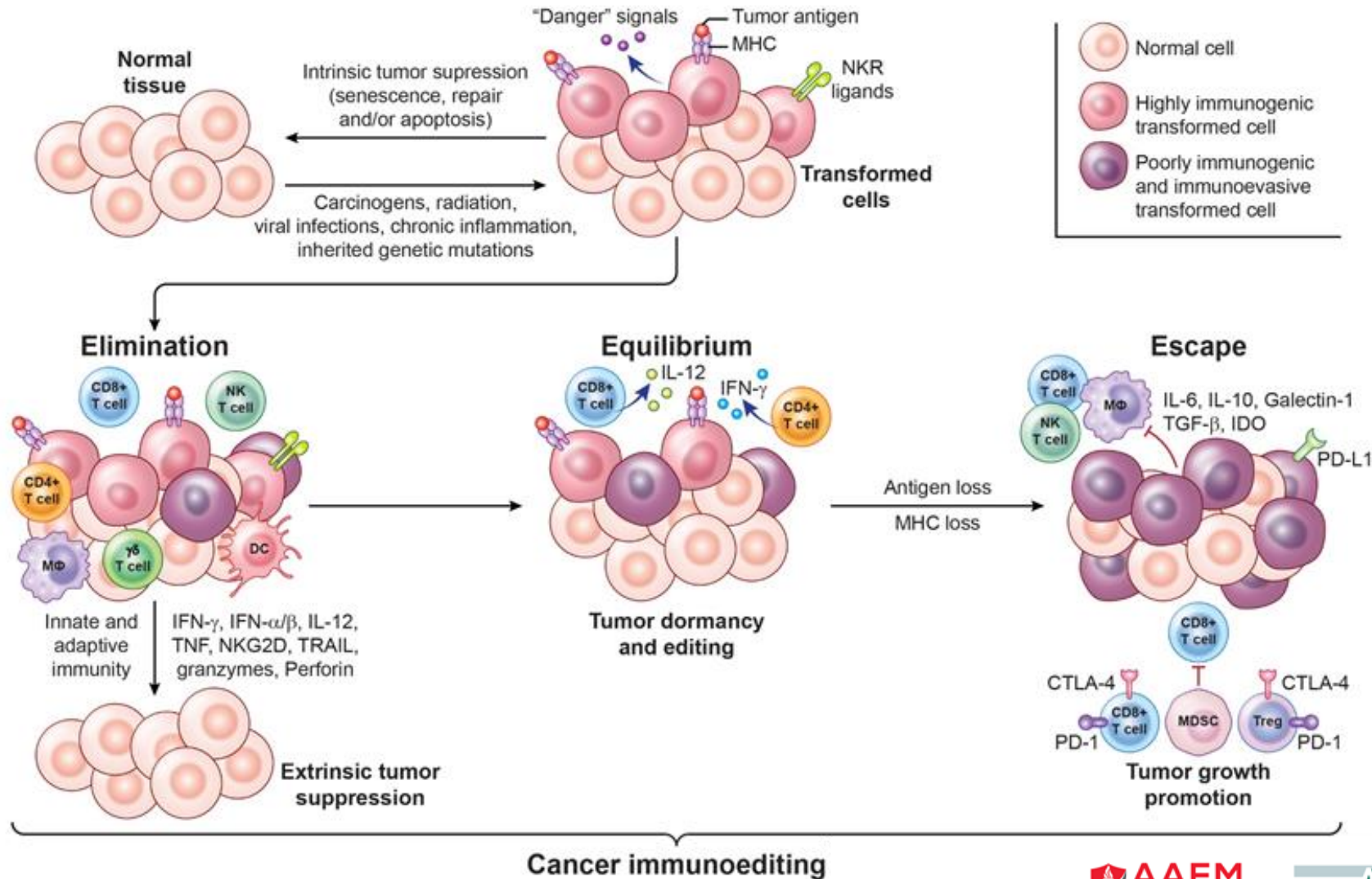




# The 3 E's of Cancer Immunoeediting



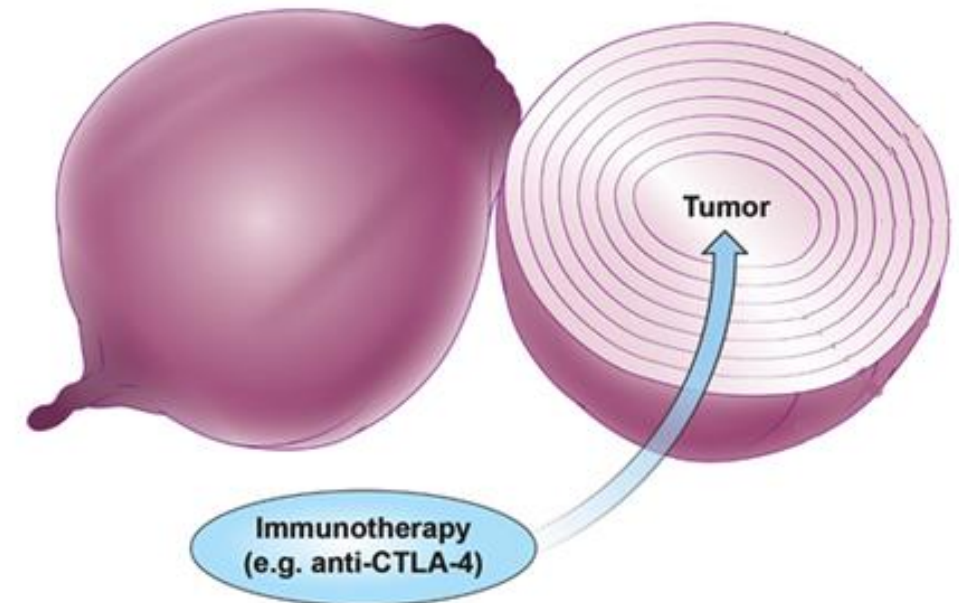
# The 3 E's of Cancer Immunoediting



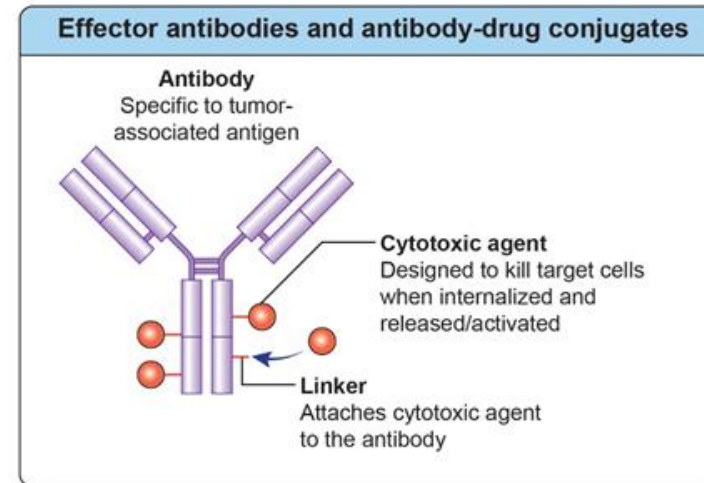
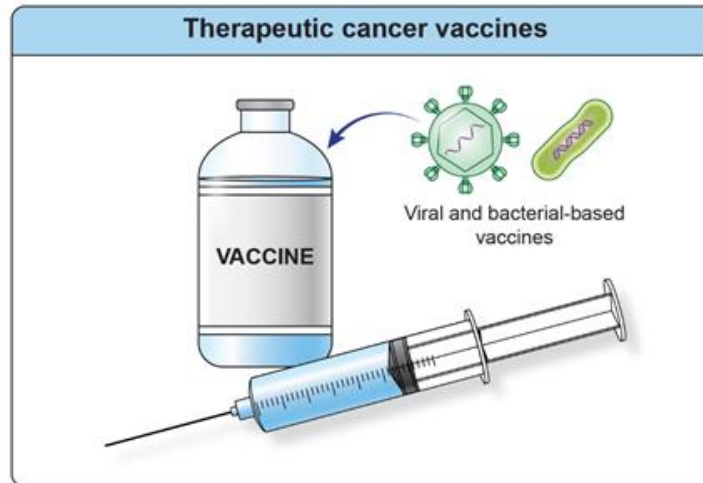
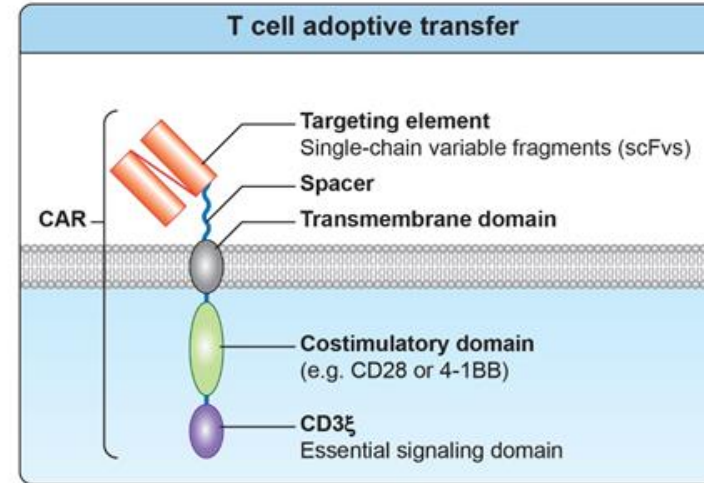
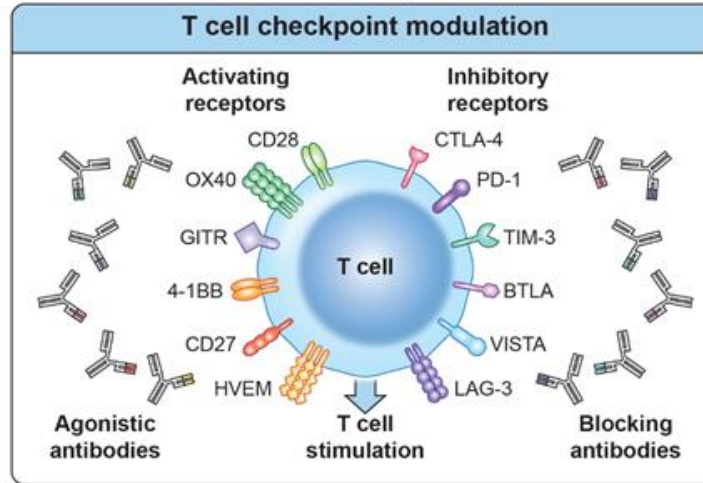


# Multi-layered Immunosuppression

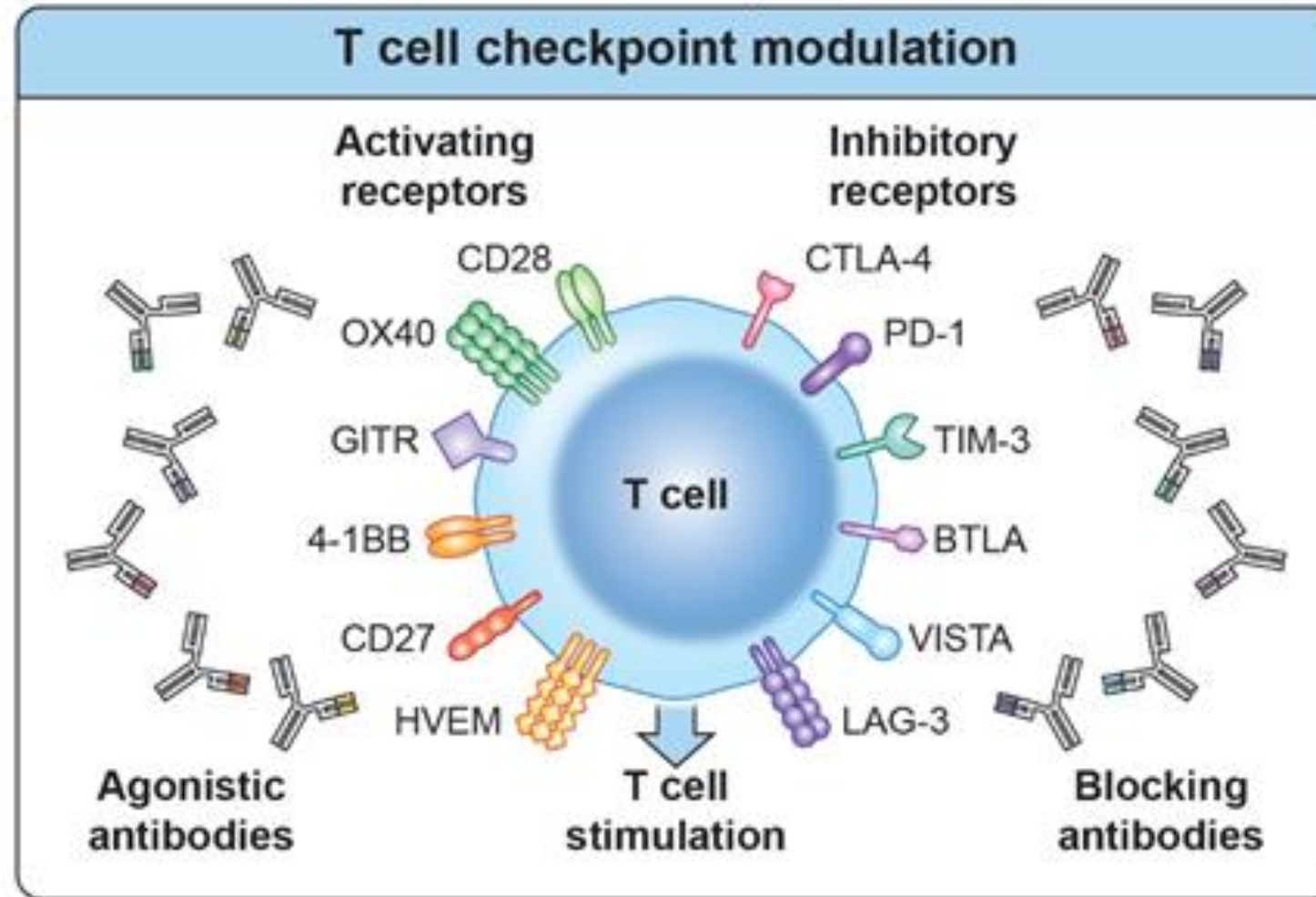
- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune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



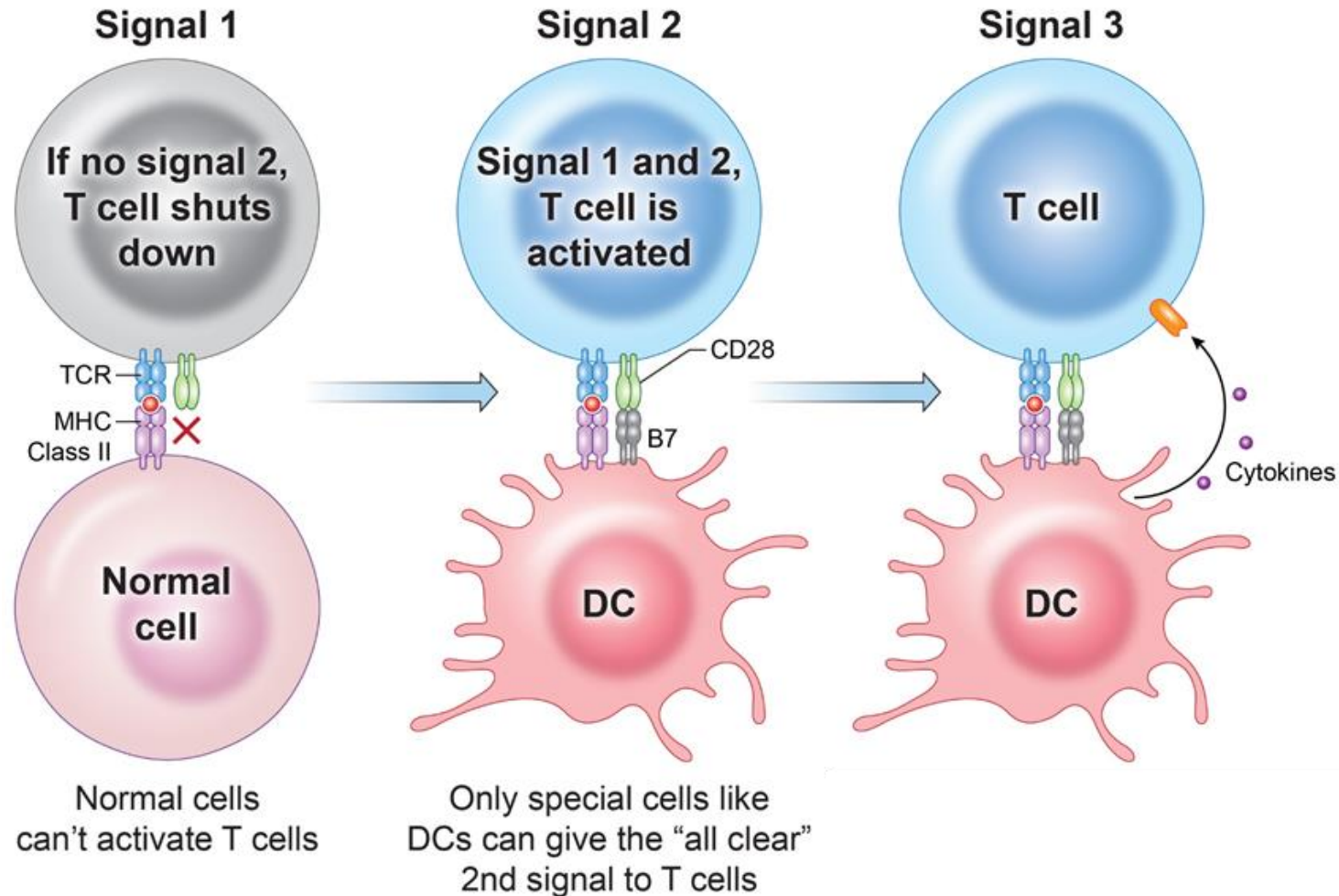
# Types of Immunotherapy



# T cell Checkpoint Modulation



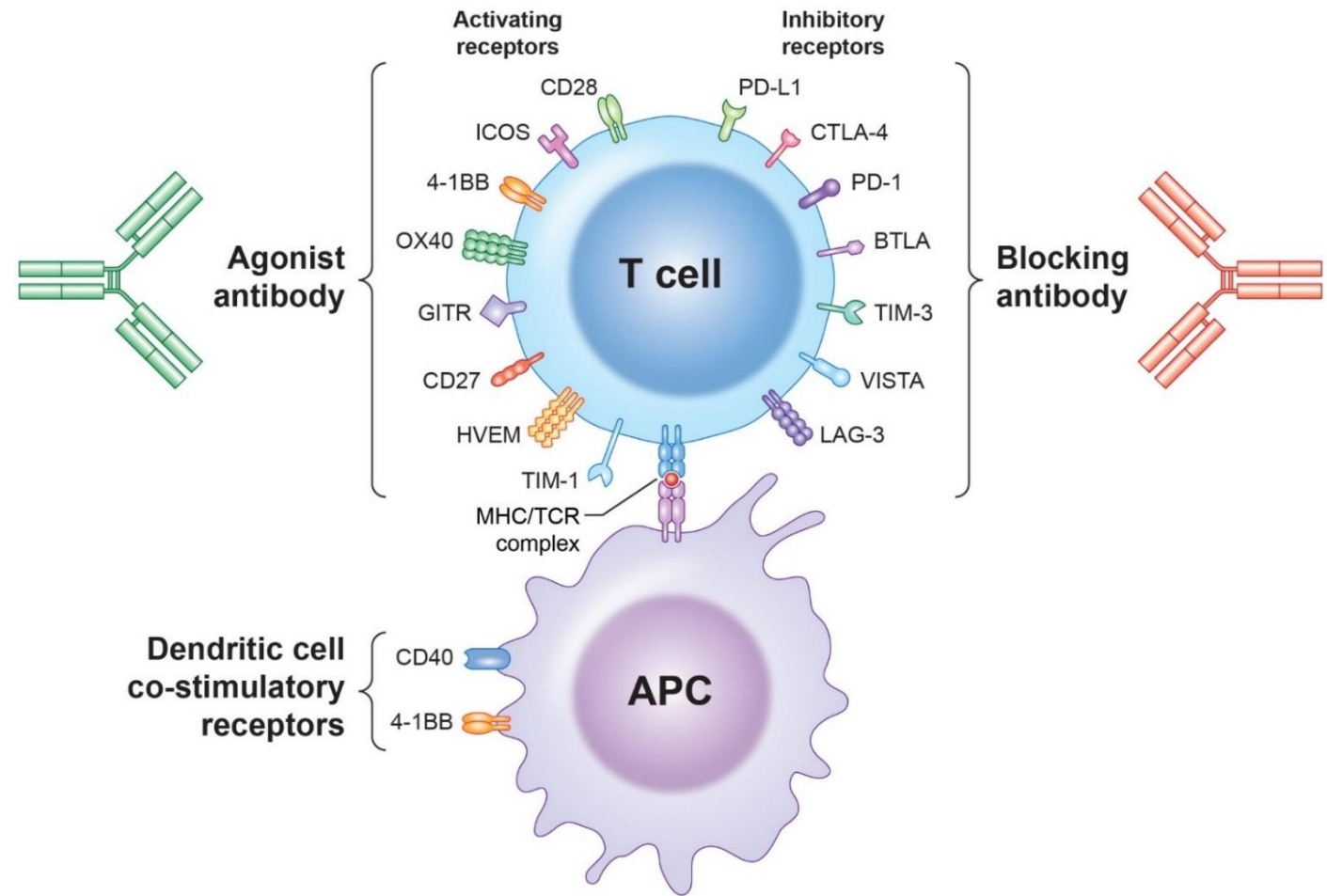
# Antigen-specific T cell Activation





# T Cell Checkpoint Modulation

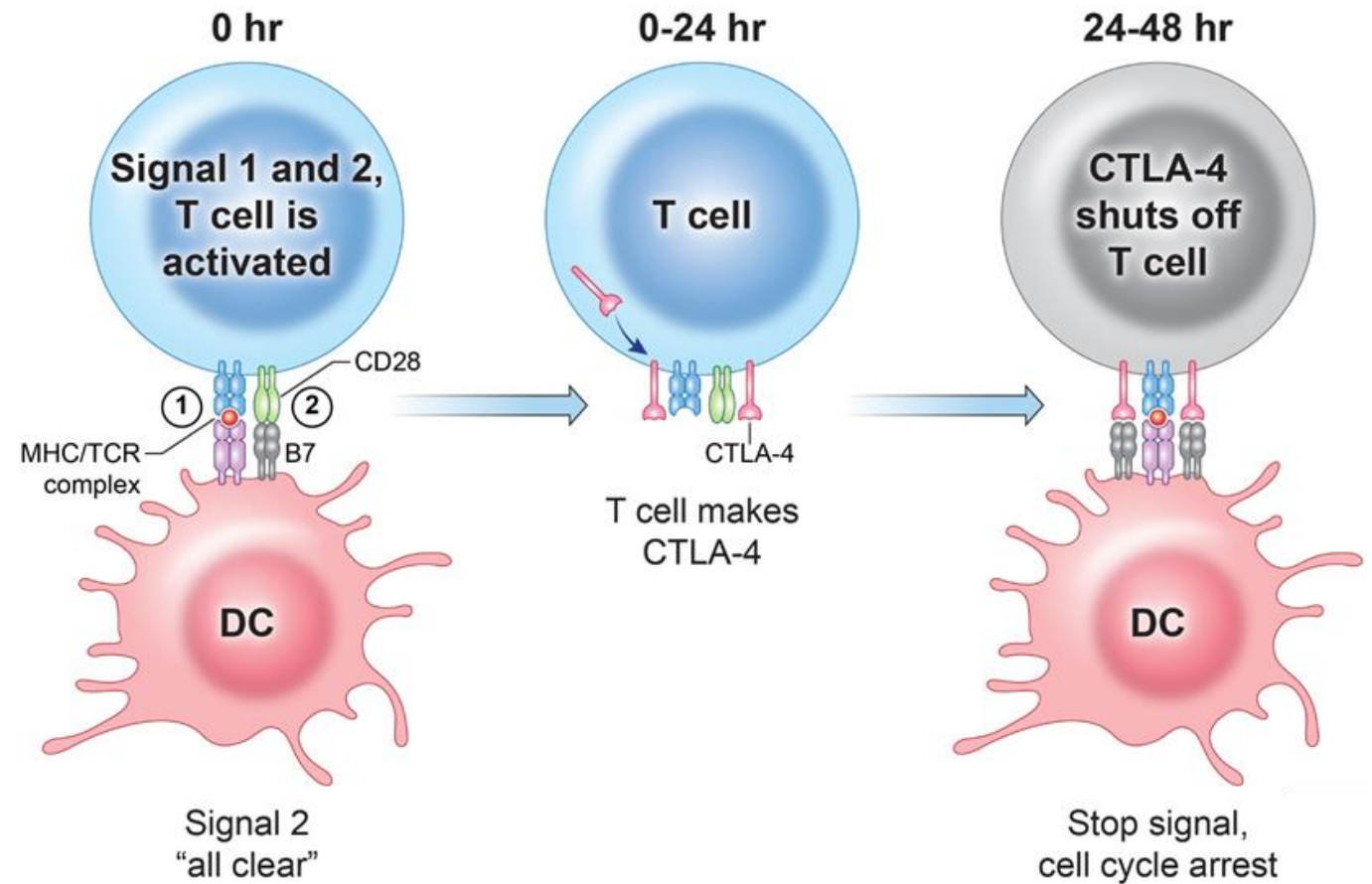
- To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.
- The goal of T cell checkpoint blockade is to make T cell “off-switches” inaccessible to tumor cells, thus restoring tumor-specific immunity.



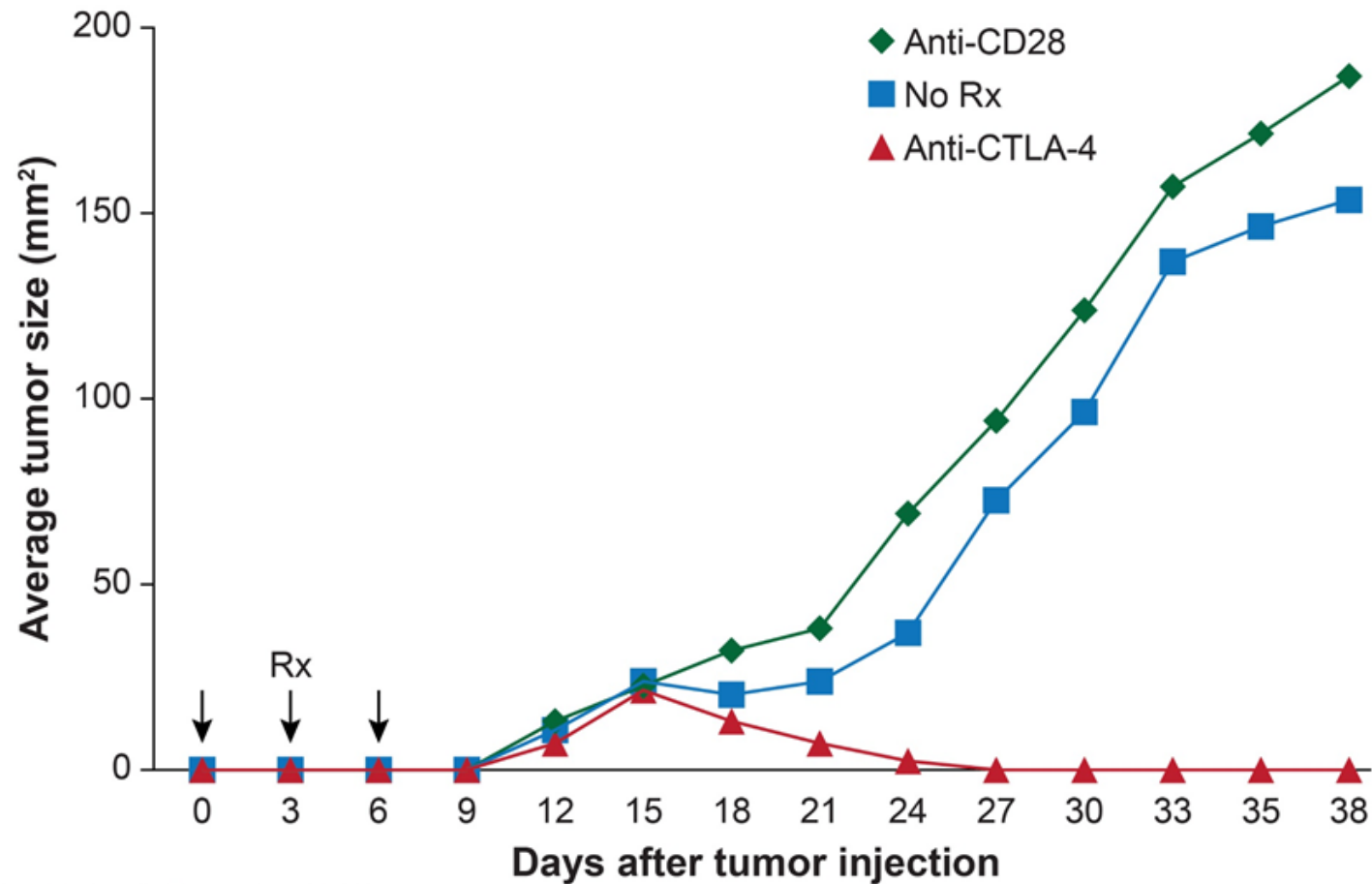


# The CTLA-4 Checkpoint

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



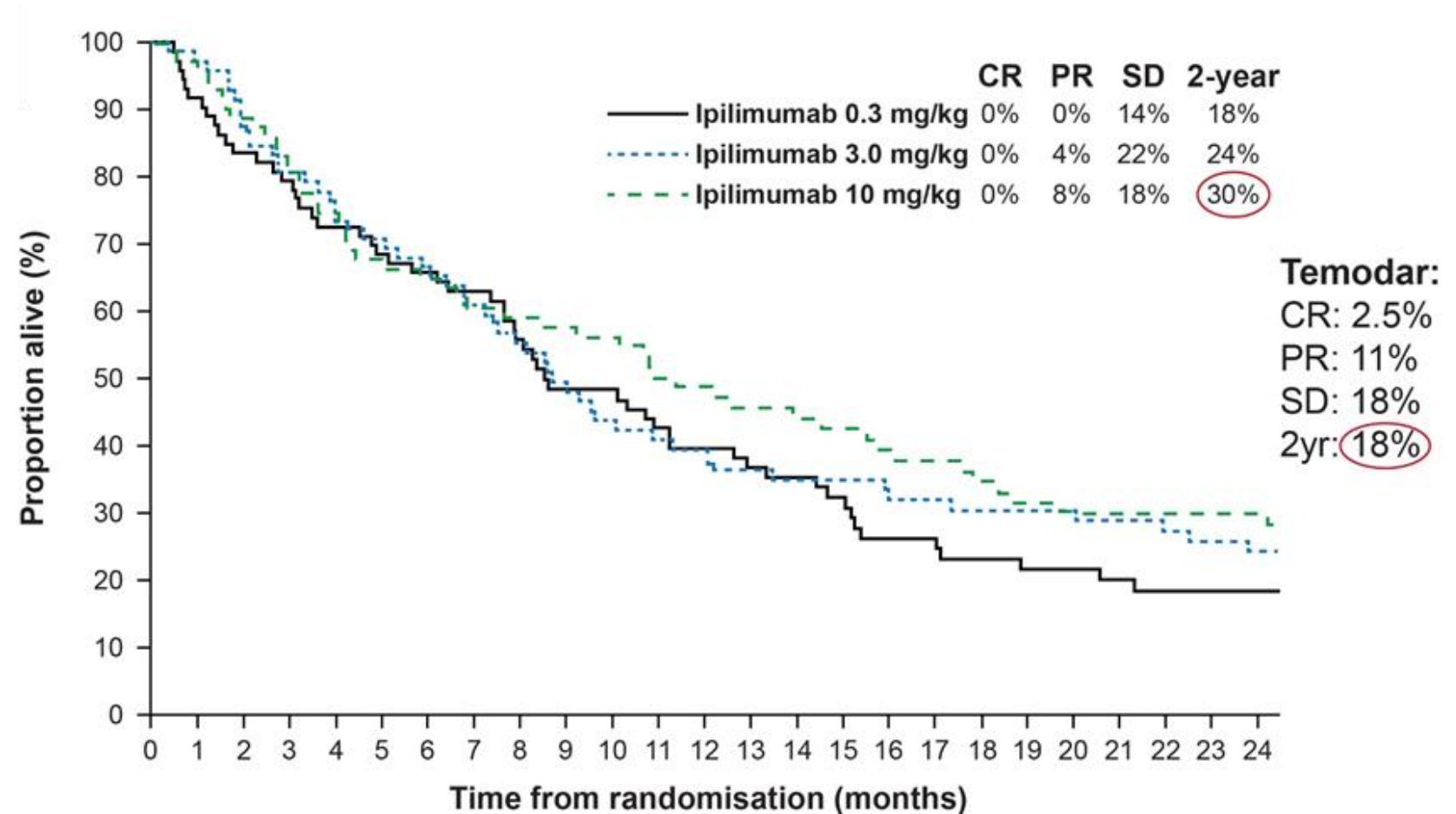
# Anti-CTLA-4 induces regression of transplanted colon carcinoma



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)

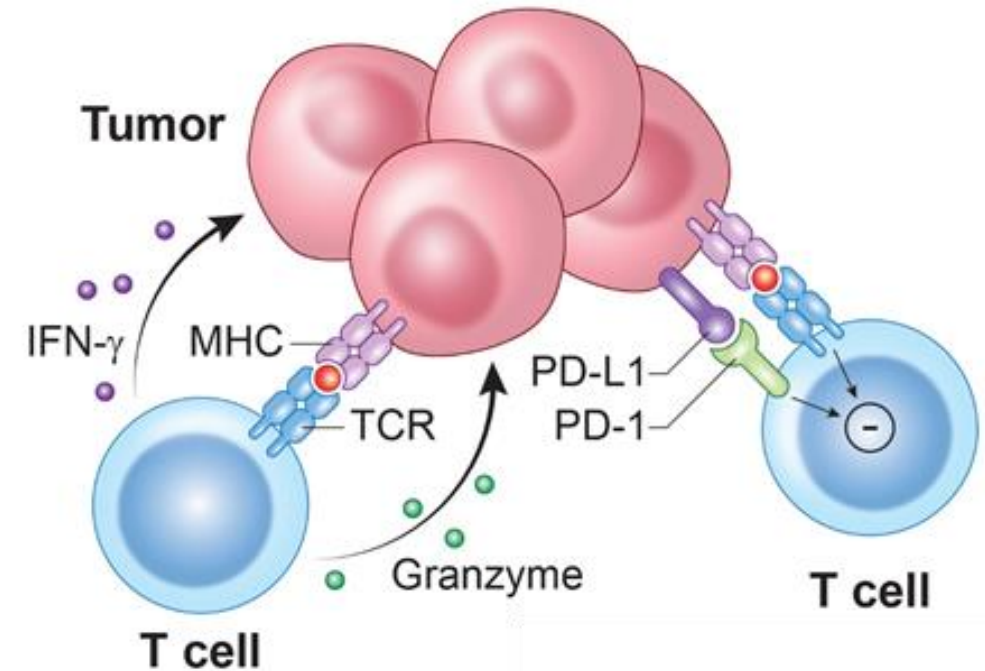
- Granted FDA approval for treatment of patients with metastatic melanoma in 2010



Wolchok et al. Lancet Oncol 2010

# The PD-1/PD-L1 Checkpoint

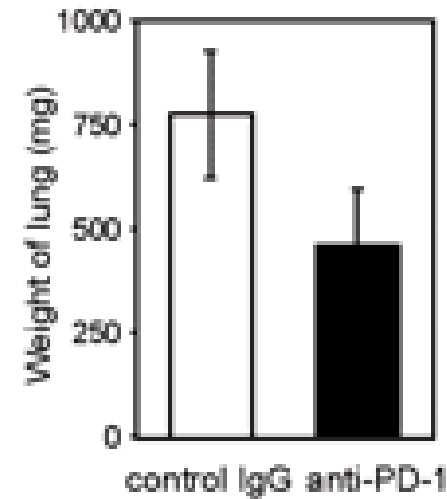
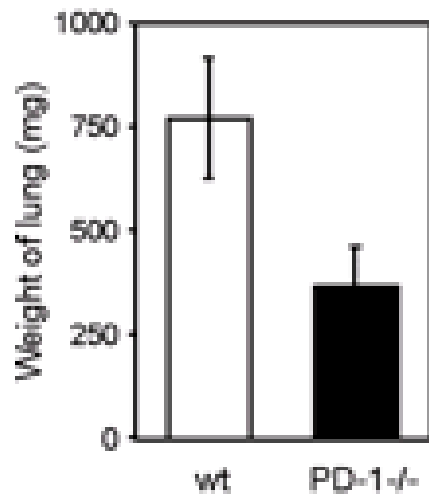
- Promotes T cell tolerization through inhibiting activation signaling
- T cell PD-1 interacts with PD-L1 and PD-L2
- Many cells express PD-L1/PD-L2 and can suppress T cell activation
- Tumors express PD-L1 through two primary mechanisms
  - TIL production of IFN- $\gamma$
  - Oncogenic signaling pathways



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

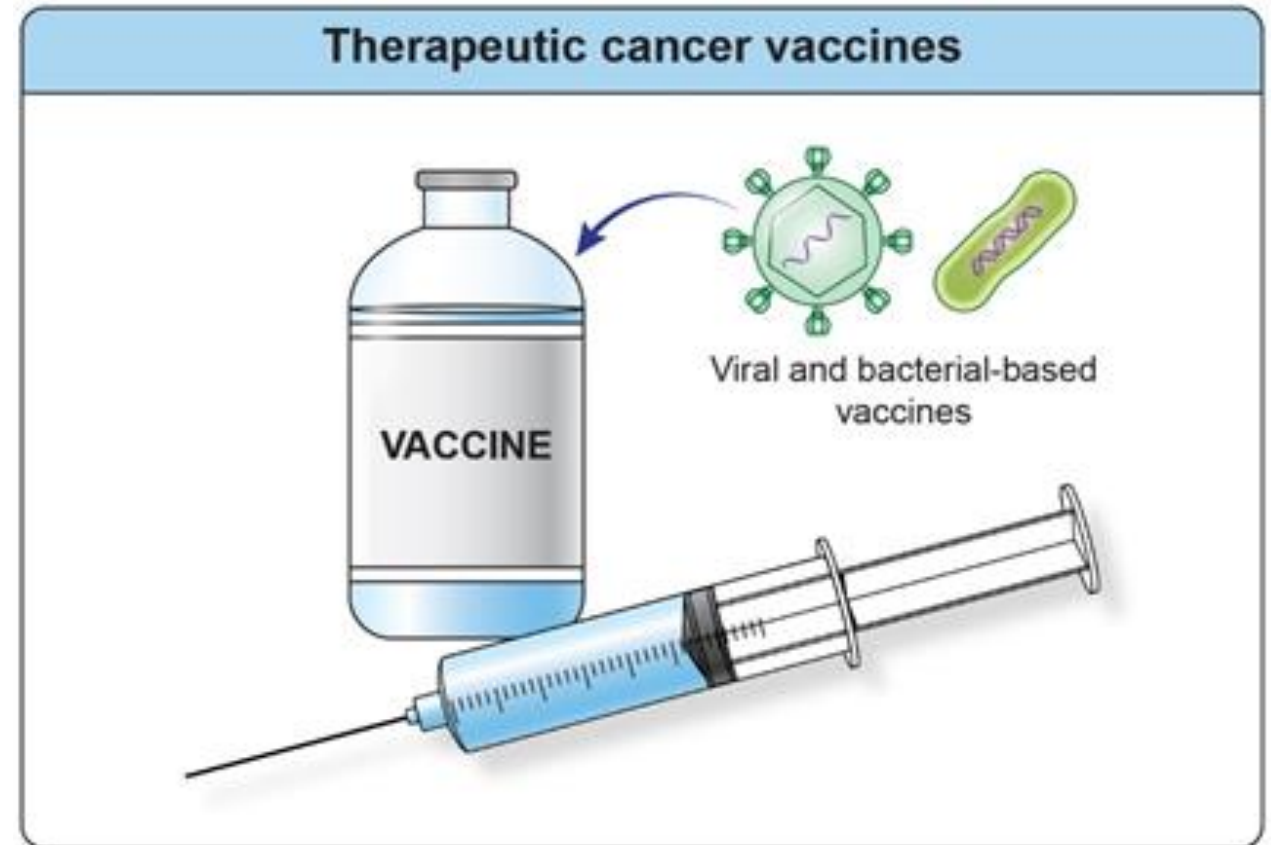


Iwai et al. Internat. Immunol 2004






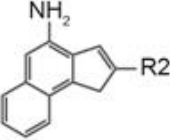
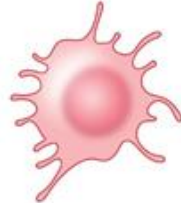
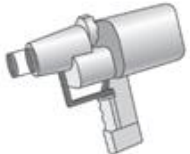
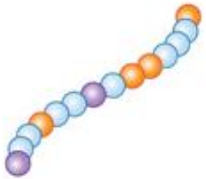
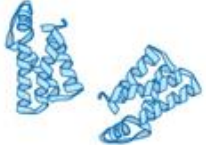






# Therapeutic Cancer Vaccines

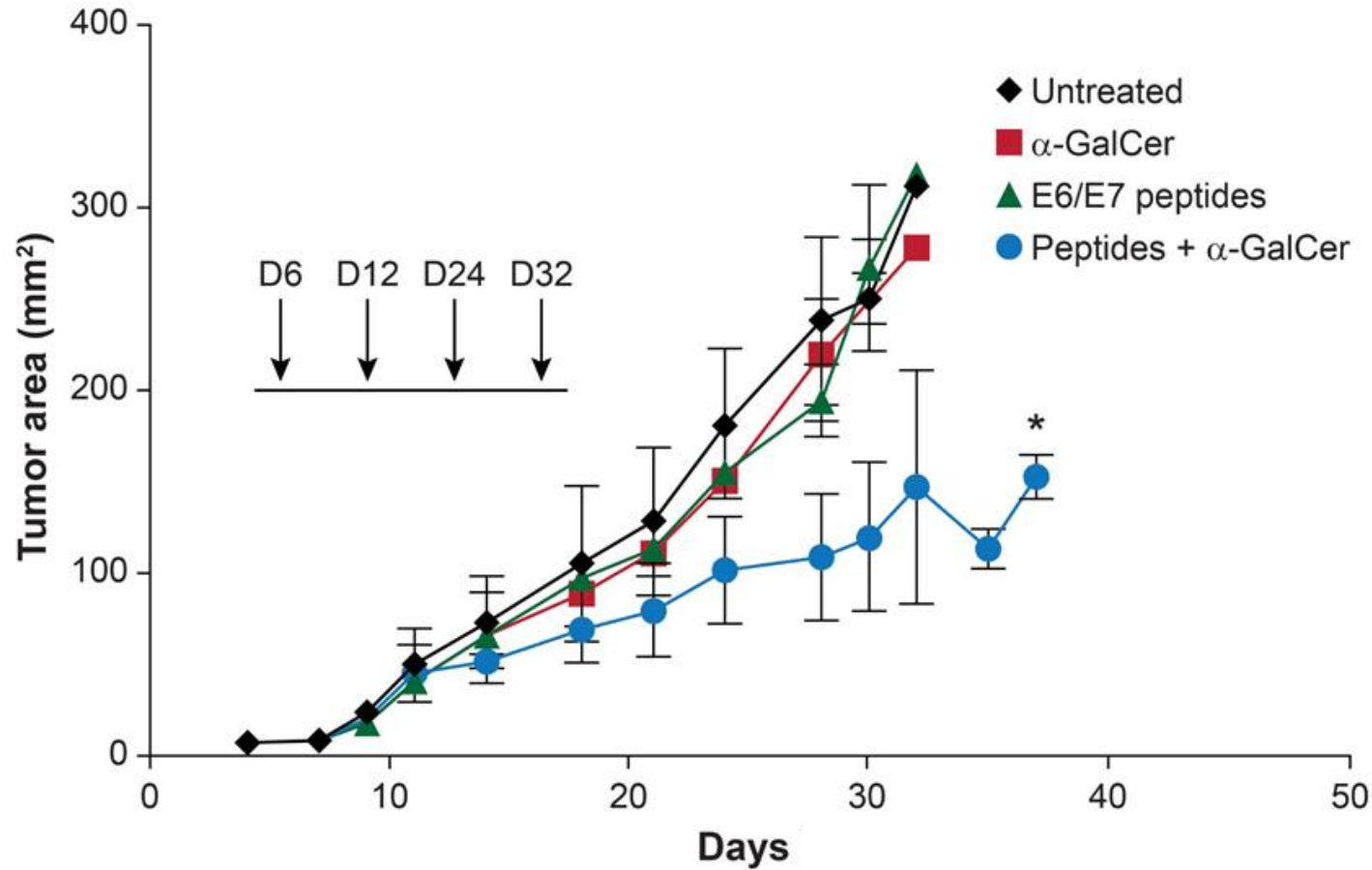
- The goal of therapeutic cancer vaccination is to increase the immunogenicity of tumor antigens in order to generate a high frequency of tumor-specific T cells.



# Components of a Cancer Vaccine

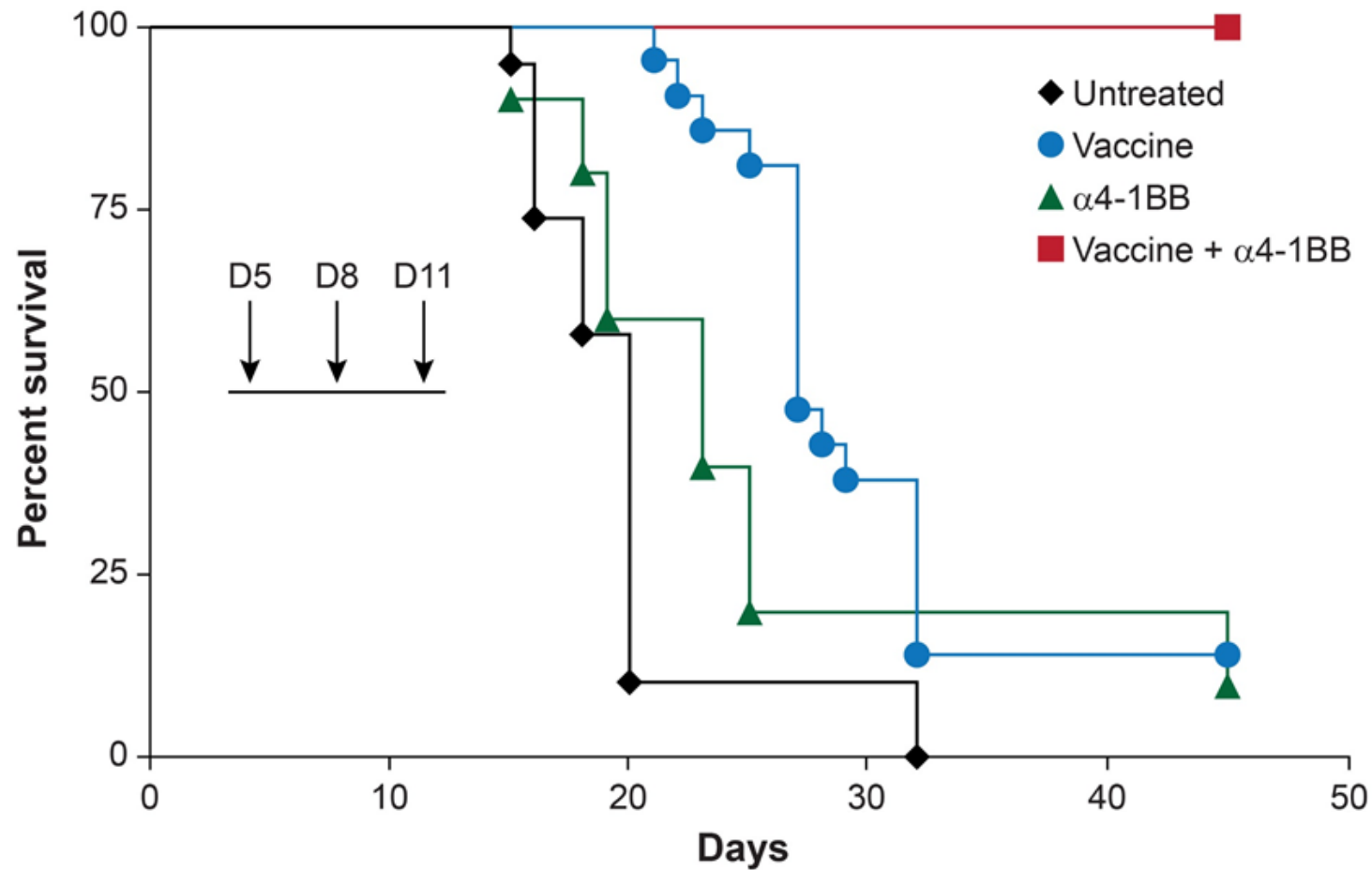
Antigen	Adjuvant	Vector	Vehicle
 Whole tumor	 Emulsifiers	 Viral vectors	 Injection
 Protein antigen	 Innate agonists	 Dendritic cells	 Gene gun
 Antigenic peptide(s)	 Cytokines	 Attenuated bacteria	 Systemic infusion
	 Antibodies		 Nasal spray

# An intra-nasal HPV E6/E7: $\alpha$ -GalCer vaccine slows growth of TC-1 tumors



Shailbala Singh

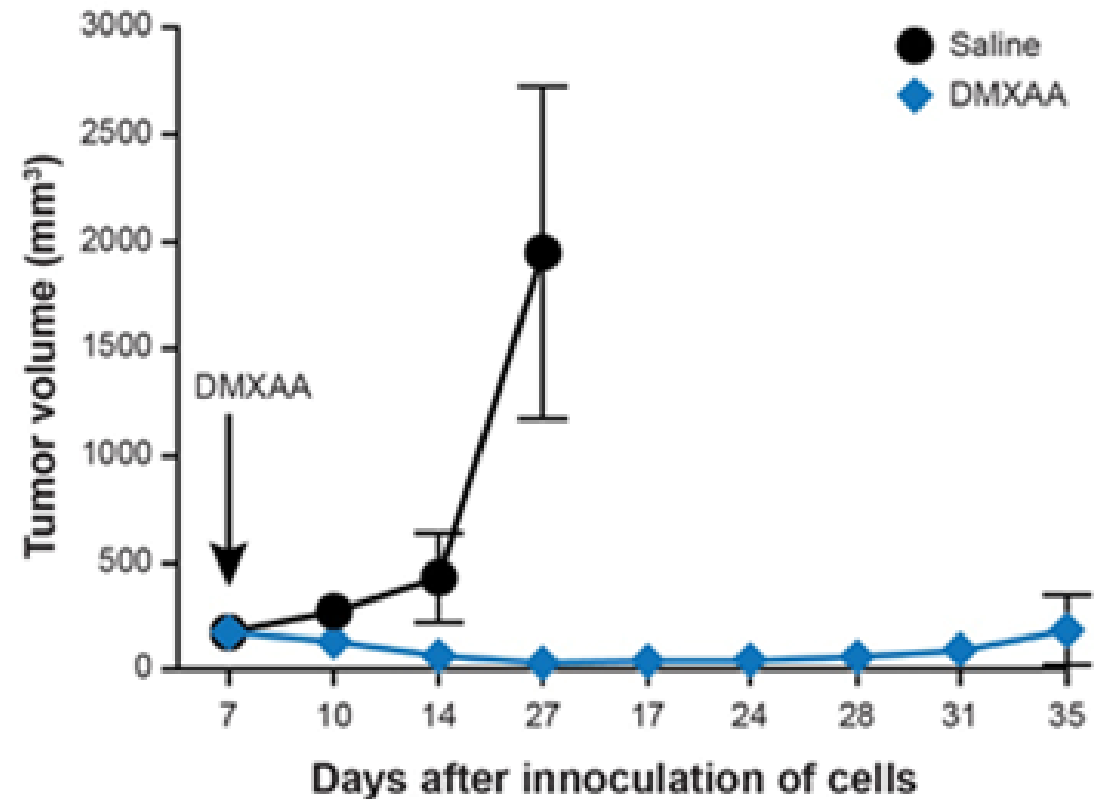
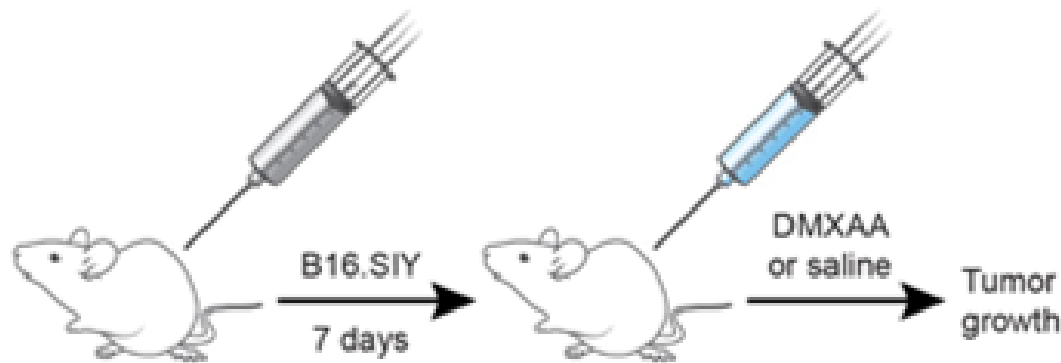
# 4-1BB agonist antibody and HPV E6/E7 vaccine synergize in curing TC-1 Tumors



Todd Bartkowiak, M.S.

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

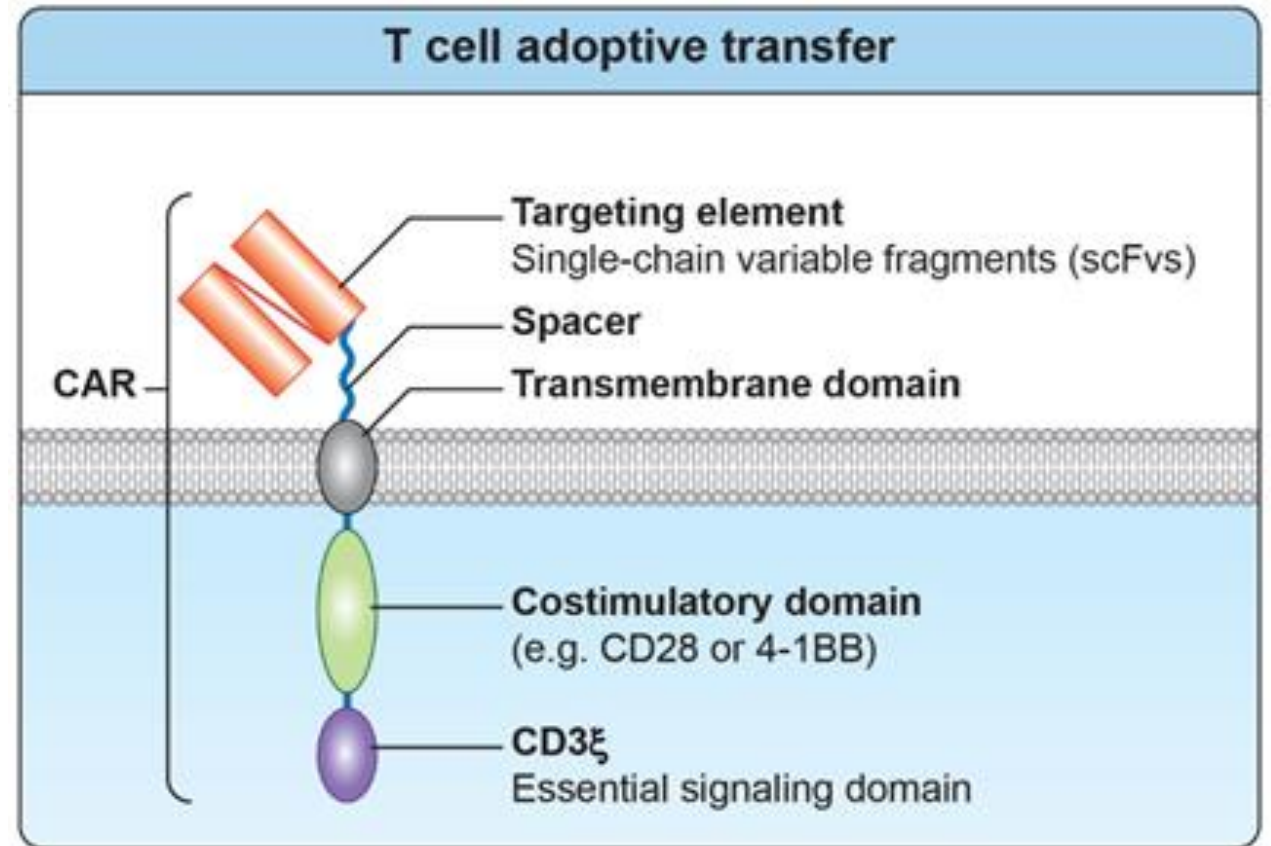
- Intratumoral DMXAA (mouse STING agonist) triggers rejection of B16 melanoma



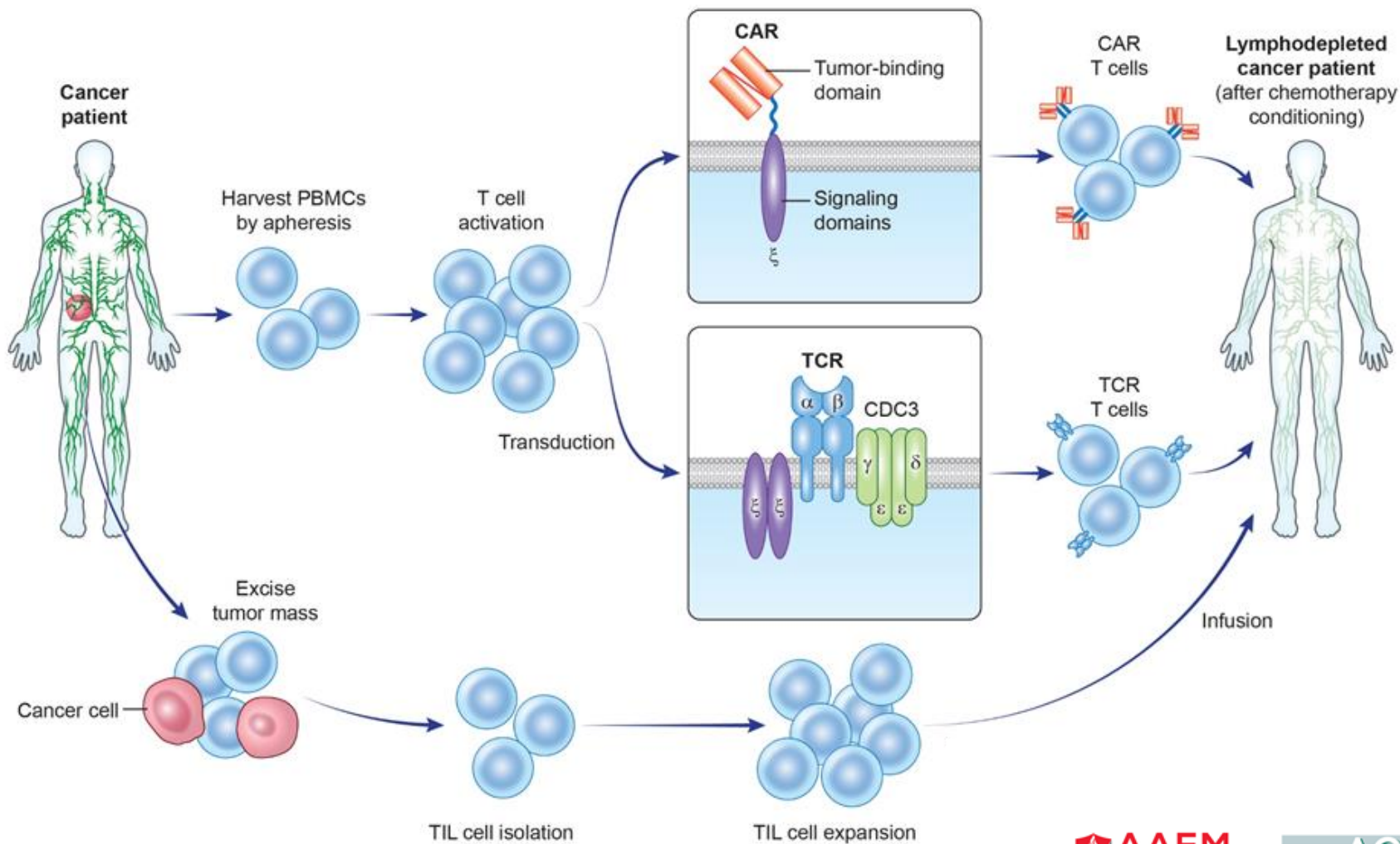


# Adoptive Cell Transfer

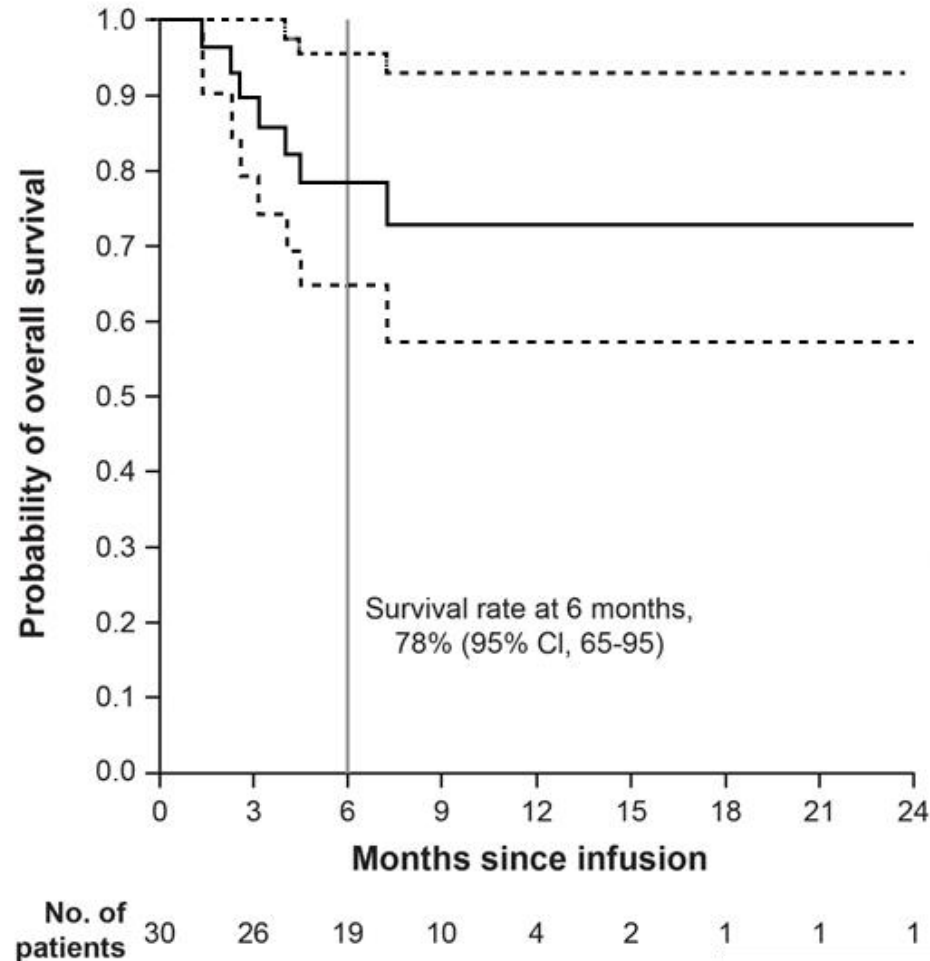
- The goal of adoptive cell transfer is to overwhelm the tumor with a higher frequency of tumor-specific immune cells and/or engineer immune cells to target cancer



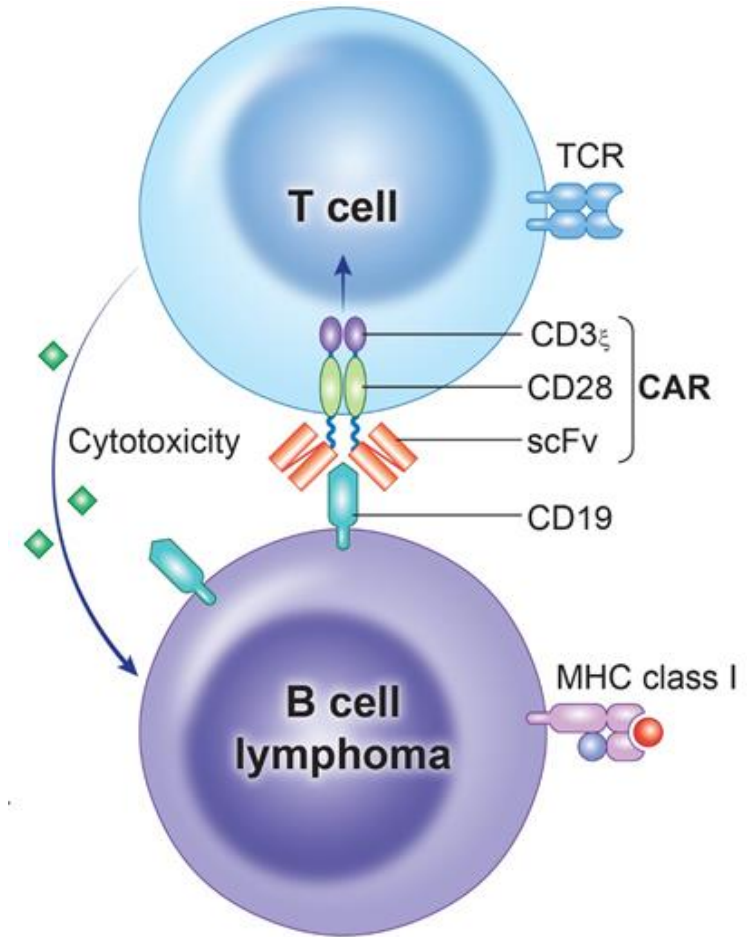
# Adoptive Cell Therapy Process



# CD19 CAR T Cell Therapy for Relapsed B Cell ALL

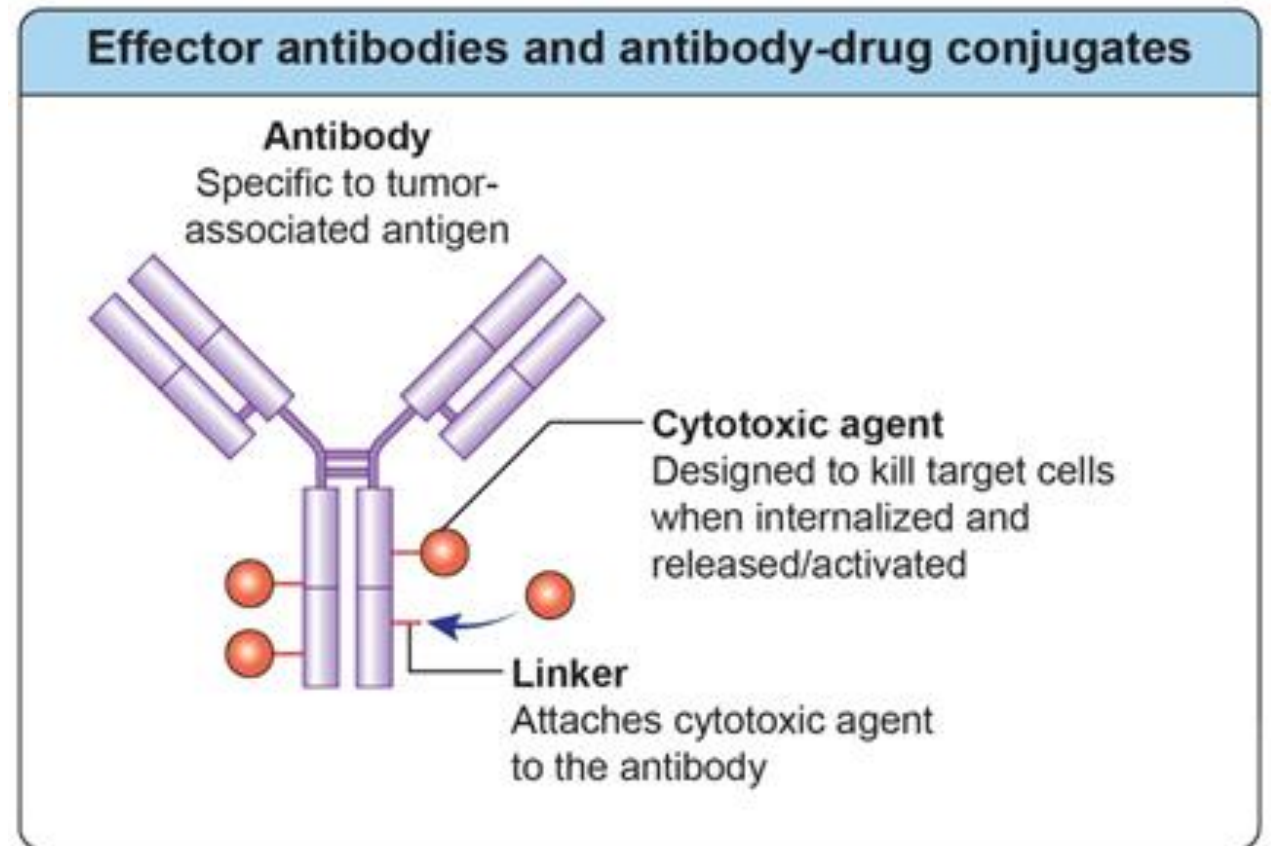


Maude S, Frey N, Shaw P, Aplenc R, Barrett D, Bunin N, Chew A, Gonzalez V, Zheng Z, Lacey S, et al. 2014. Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England Journal of Medicine. 374(10): 998.



# 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



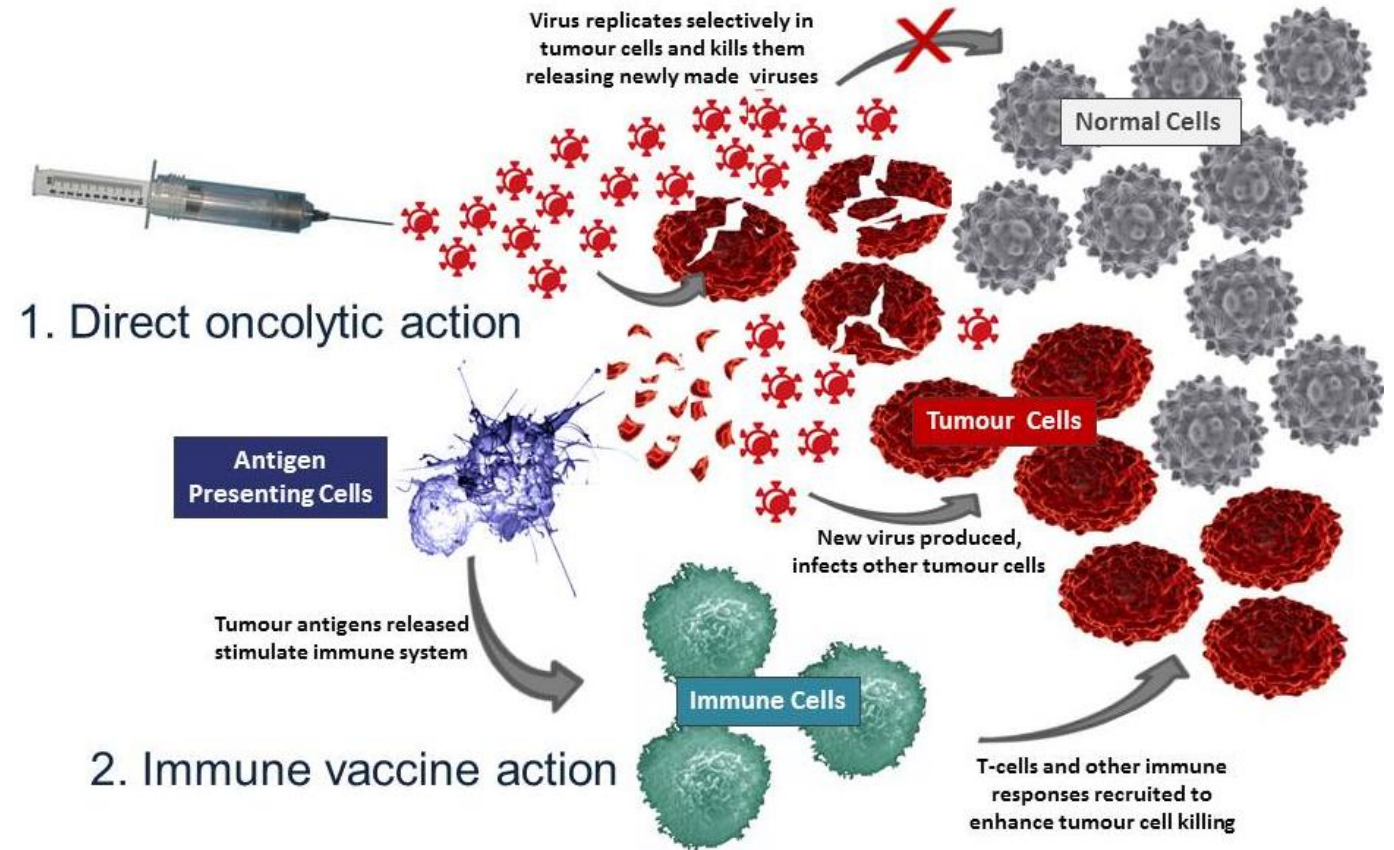
# Key ADC/Antibody Principles

- **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



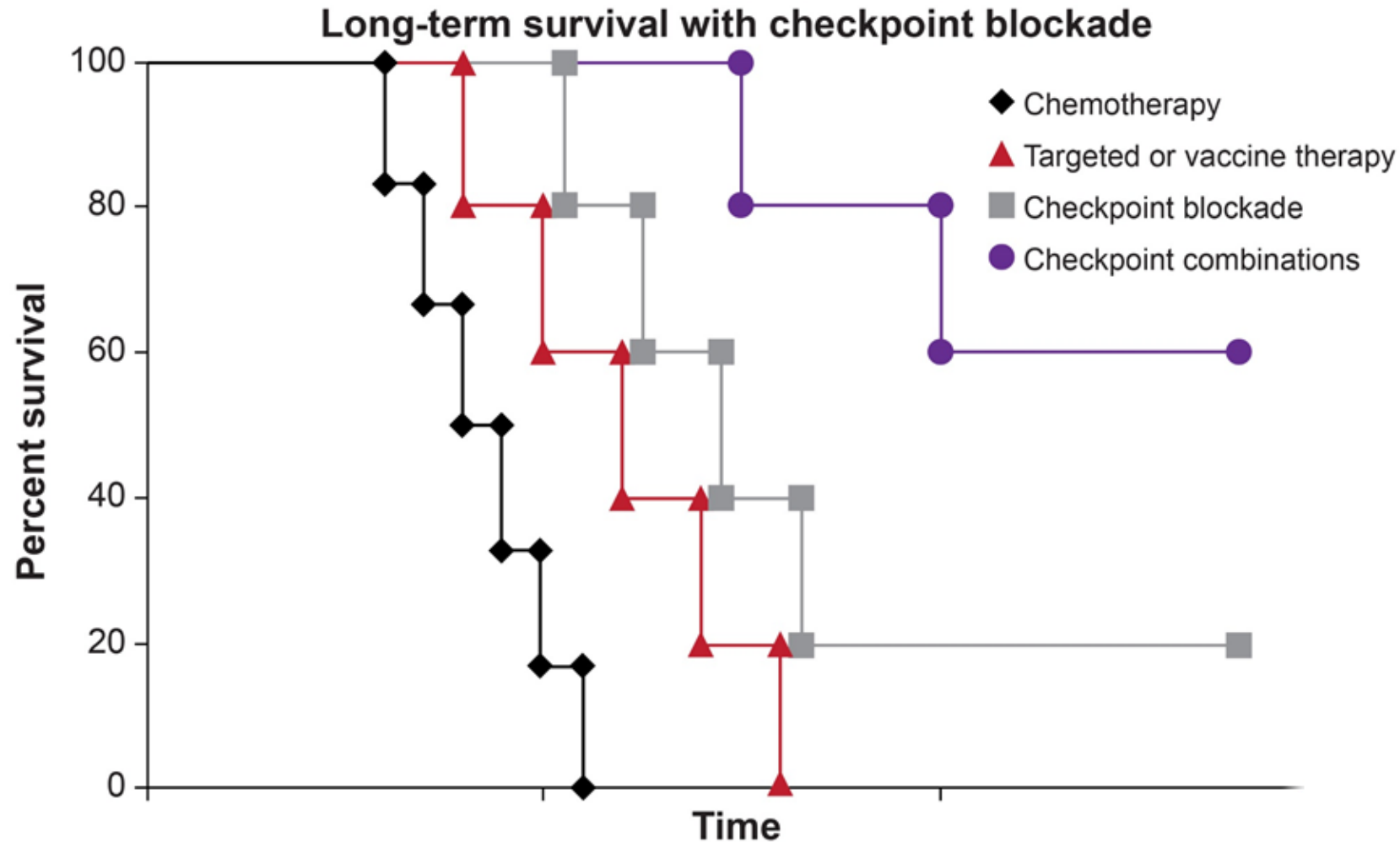
# Oncolytic Viruses

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



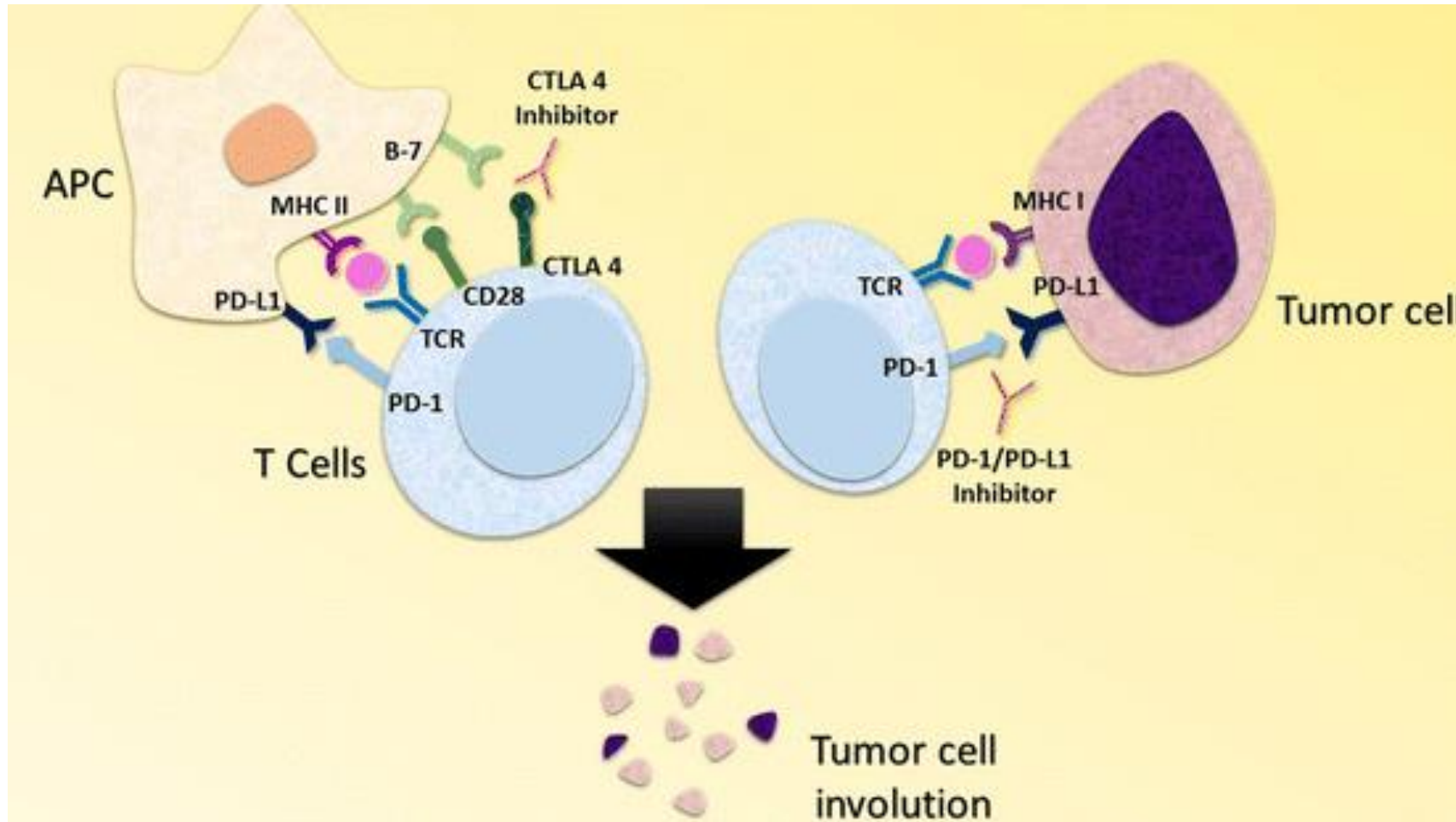
dddmag.com

# Combination Immunotherapies



# Combination Immunotherapies

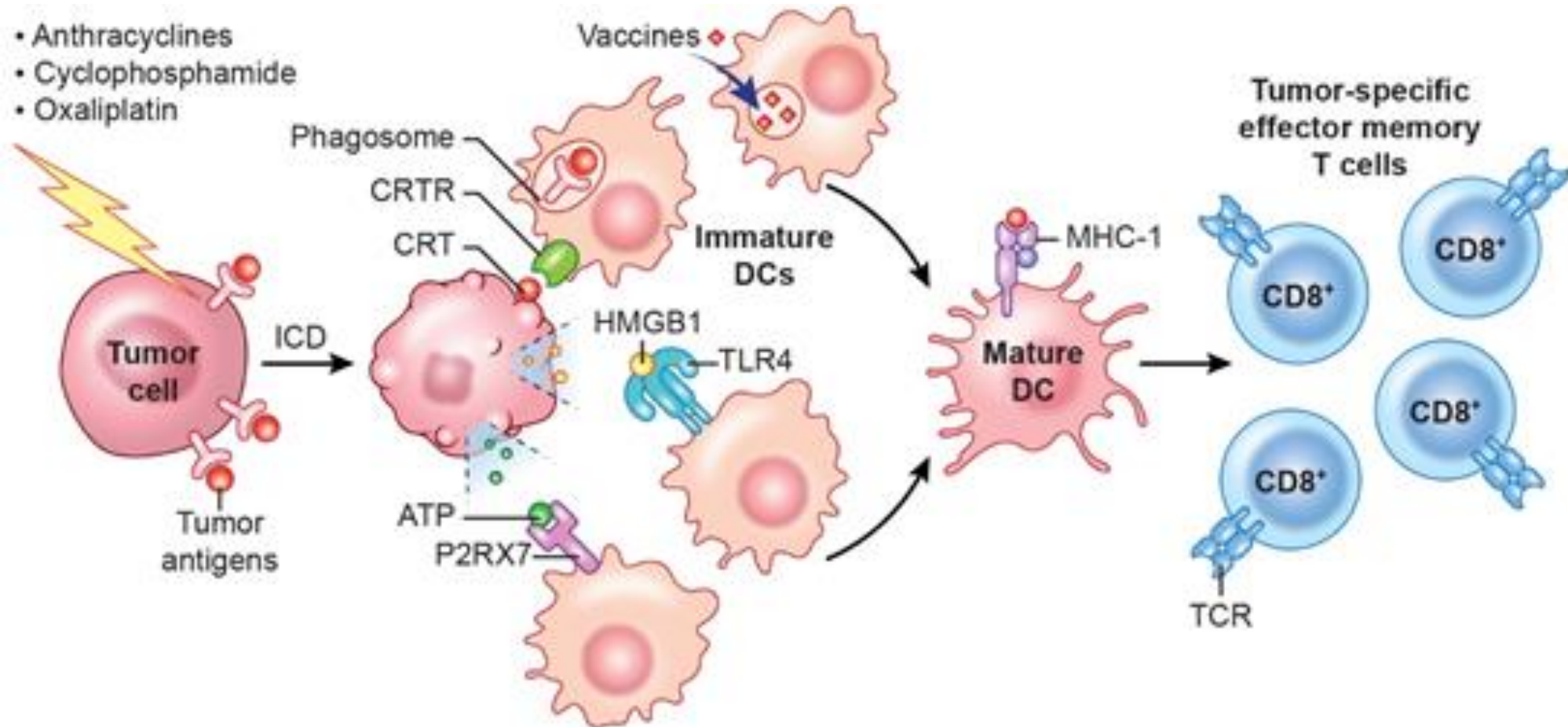
## *Dual CTLA-4 and PD-1 inhibition*



Chae et al. JITC 2018

# Combination Immunotherapies

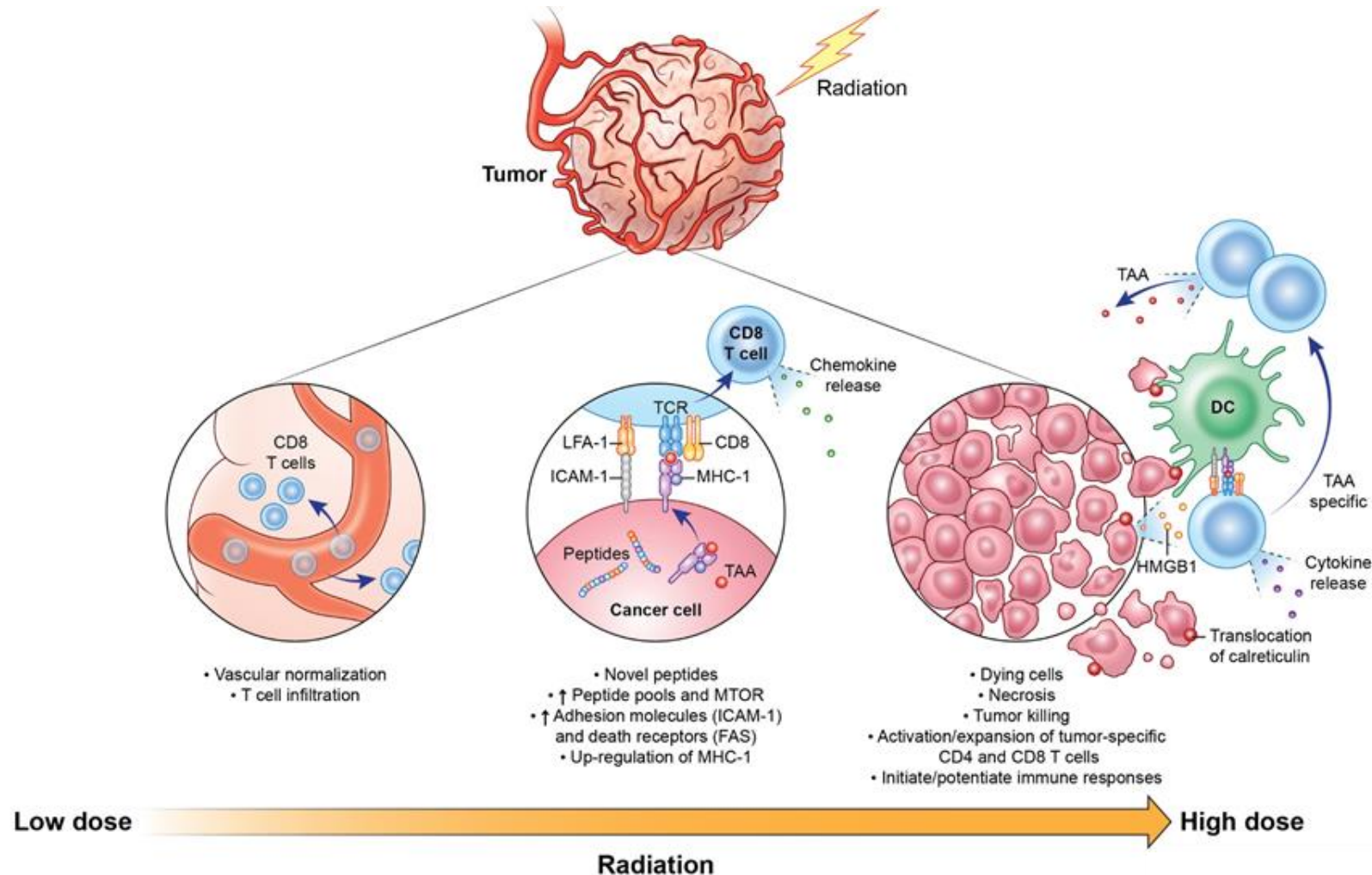
*Chemotherapy can induce an immune response*





# Combination Immunotherapies

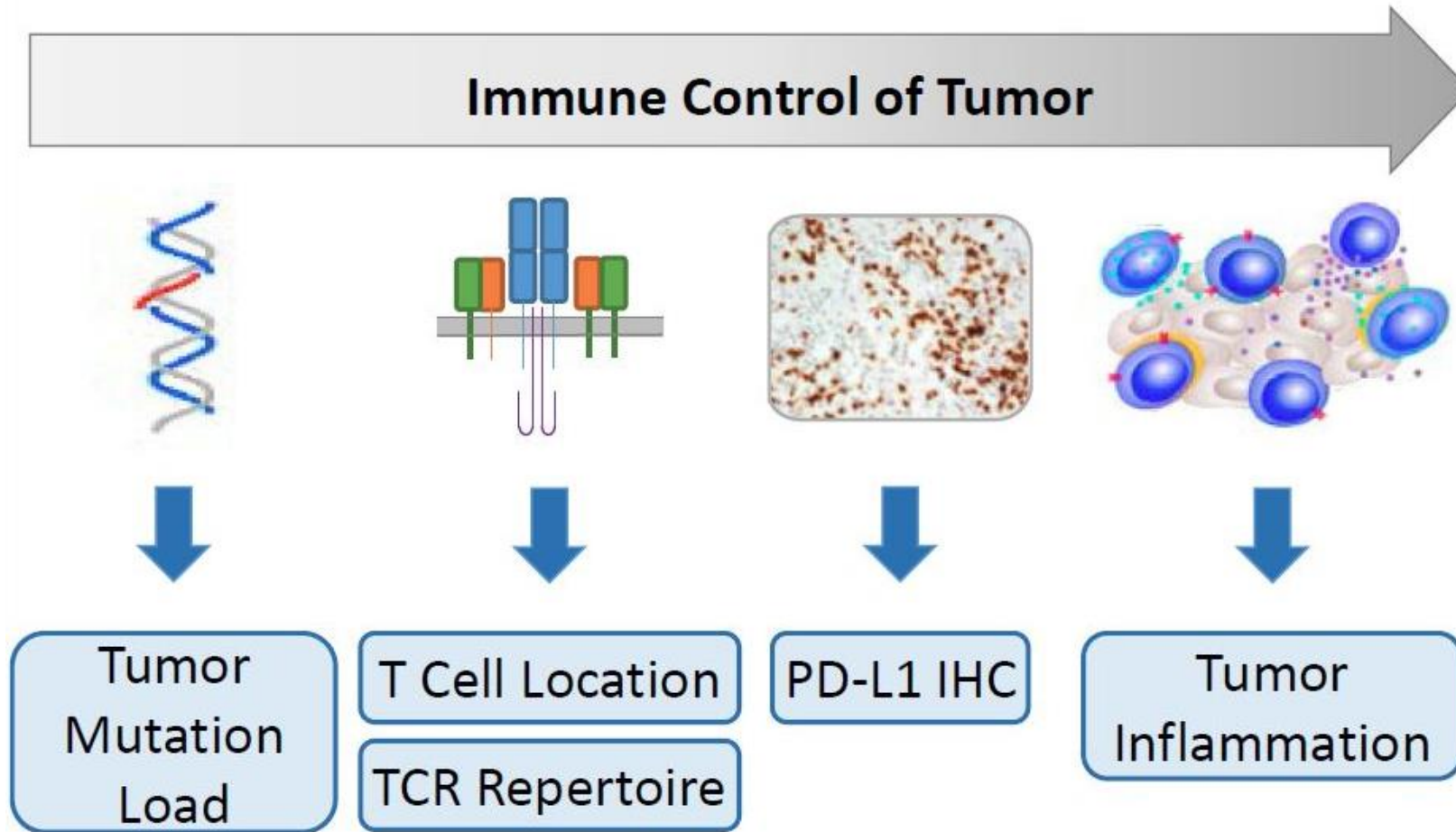
## *Radiotherapy can induce an immune response*



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

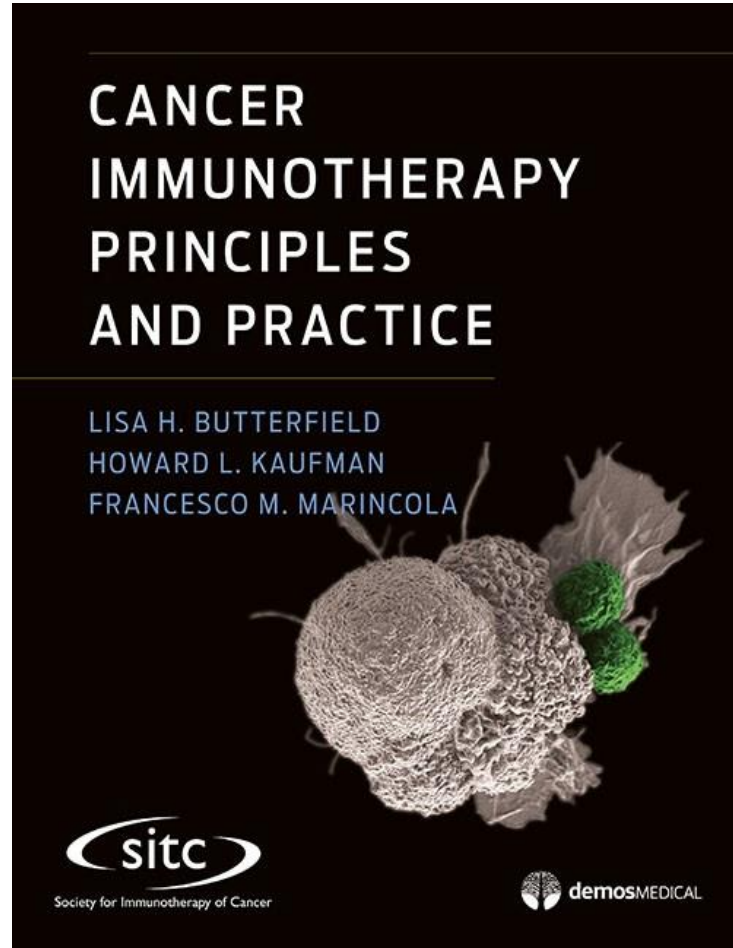


# Immunotherapy Biomarkers



Cesano et al. Biomedicines 2018

# Further Resources



SOCIETY FOR IMMUNOTHERAPY OF CANCER

