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ADVANCES IN Cancer IMMUNOTHERAPY™

Basic Principles of Cancer Immunotherapy

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

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Disclosures

- Disclosures: Advisory board for Symphogen, Providence
- I will be discussing non-FDA approved indications during my presentation.

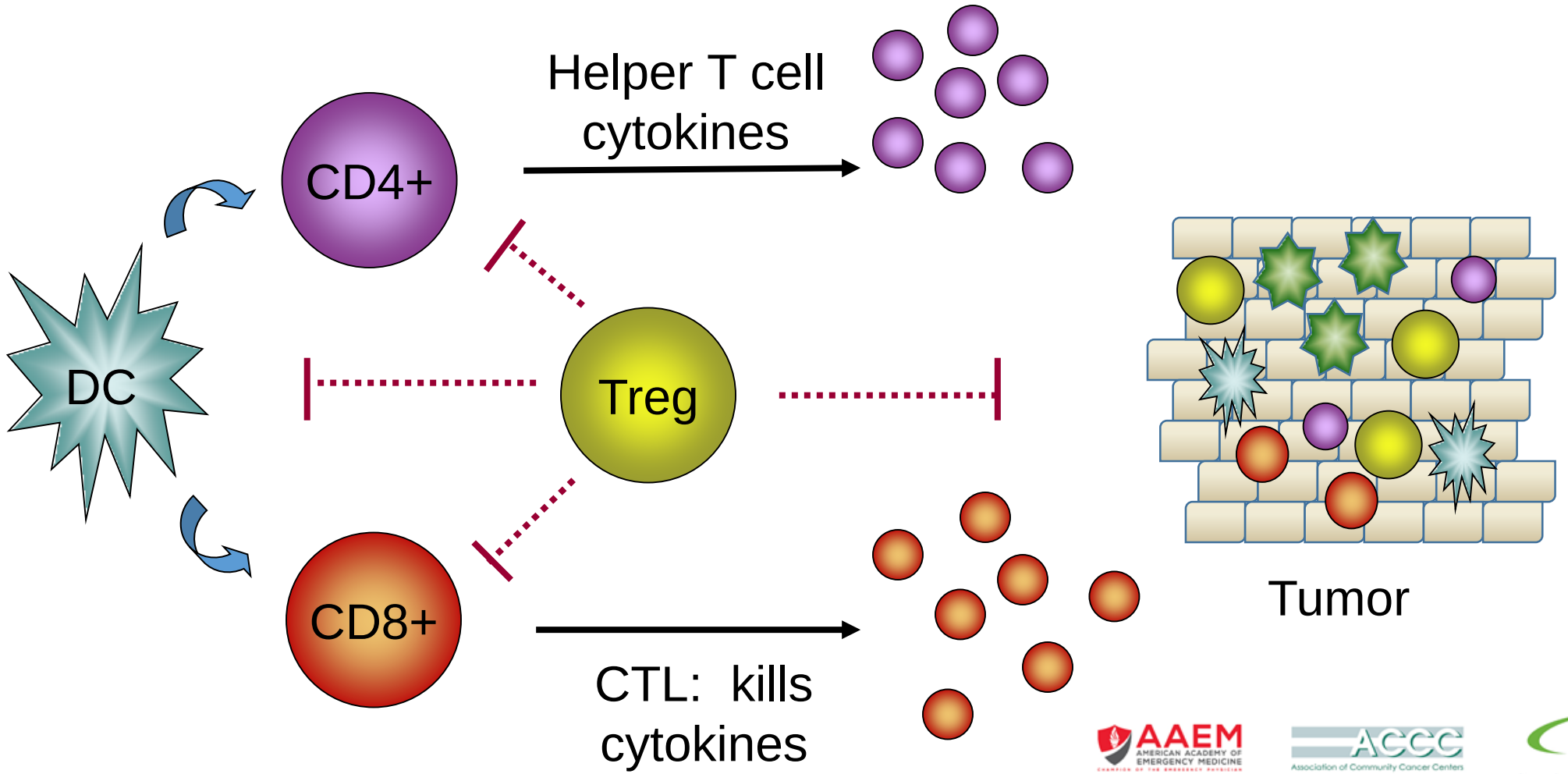
- Data being presented concerns immunotherapies approved by the U.S Food and Drug Administration for marketing and usage in the United States

The Premise of Cancer Immunotherapy

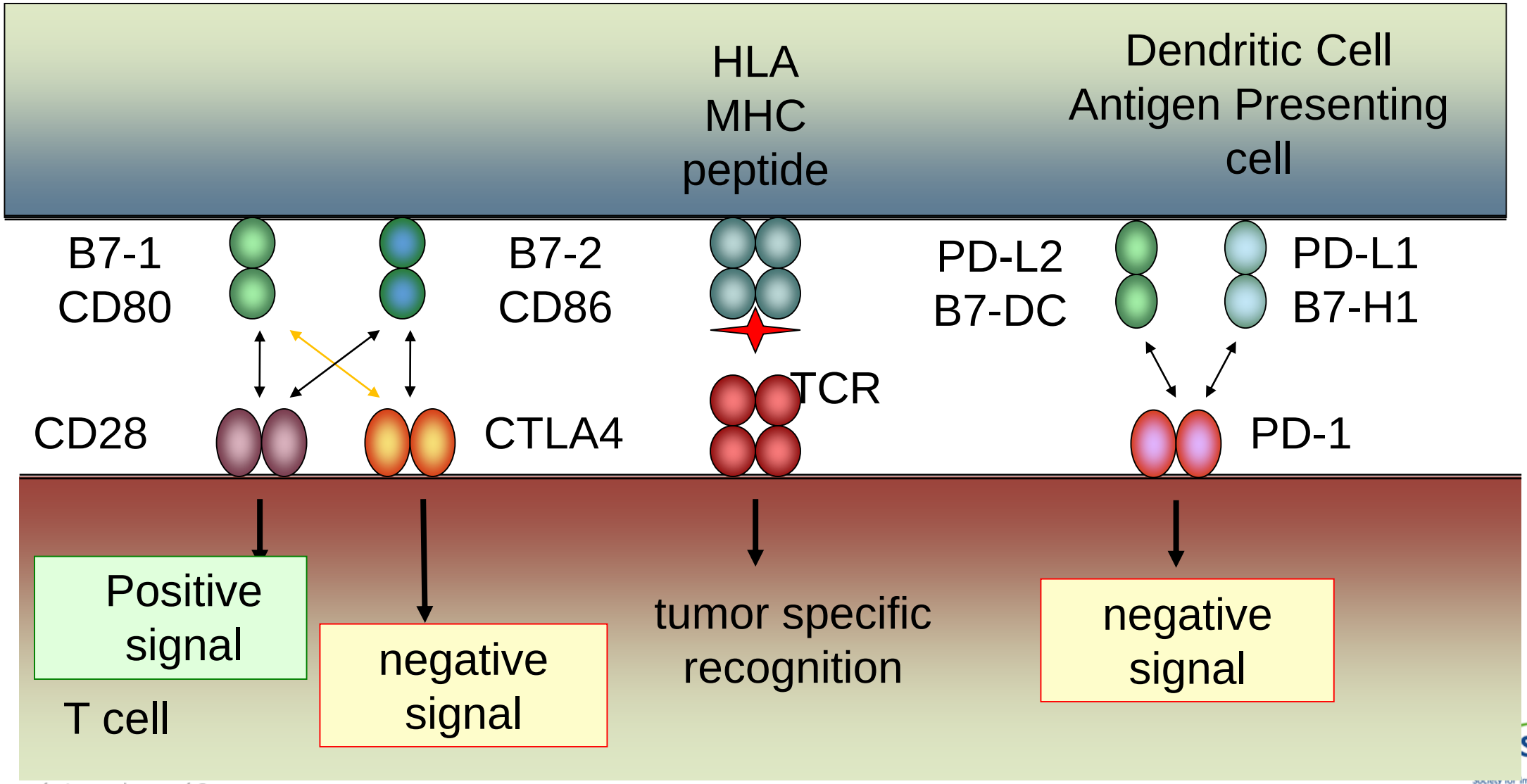
- Normally, the immune system eliminates infection and has the potential to recognize and destroy tumor cells
- Tumors evolve mechanisms to locally disable and/or evade the immune system.

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

Orchestrating the Immune Response



Activation: balancing positive and negative signals to regulate immune responses



Why Does the Immune System Fail to Eliminate Cancer?

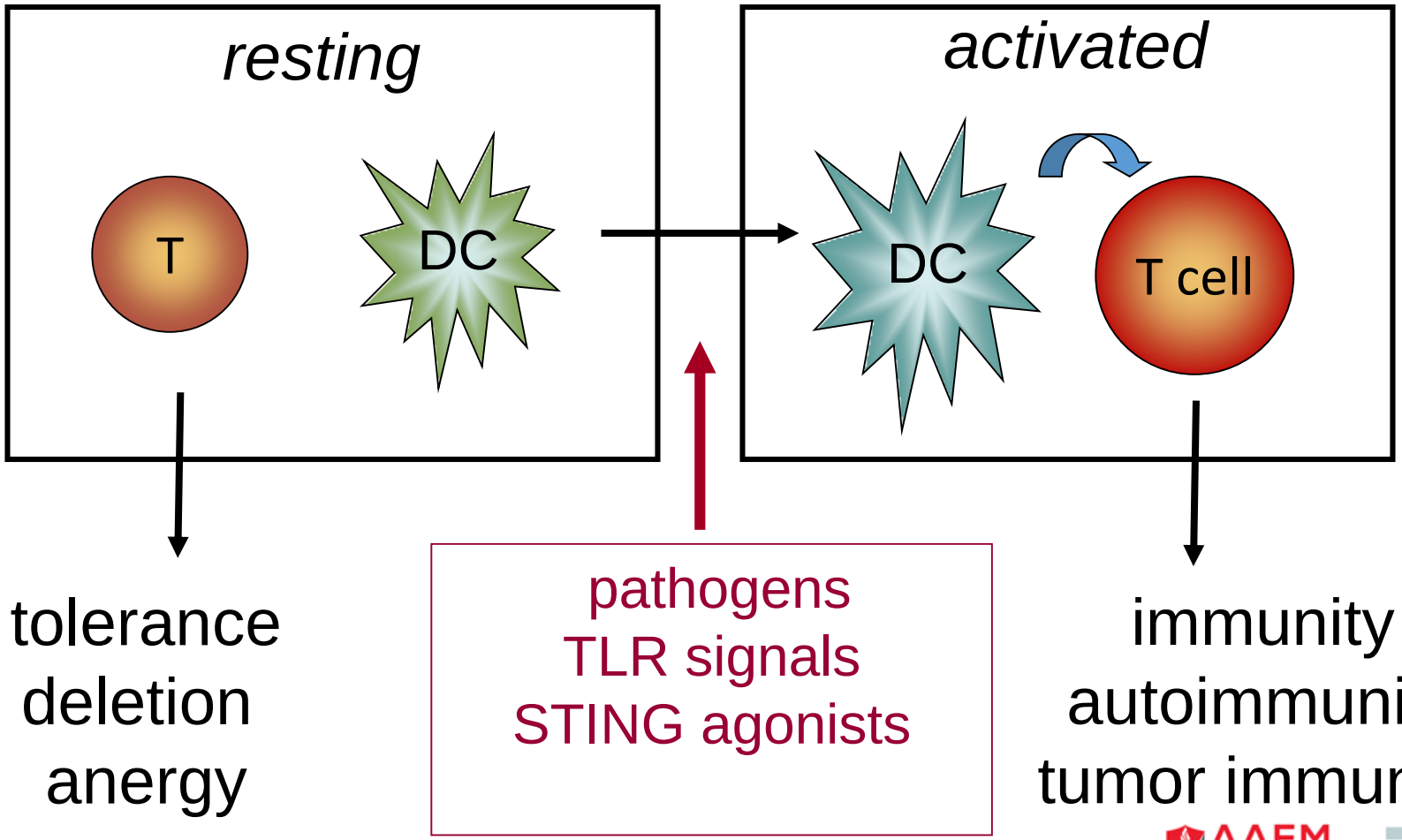
1) T cell Exhaustion: CD8+ T cells often become dysfunctional, entering a state known as exhaustion, during certain chronic infections

2) Tolerance: Can occur in the periphery in response to TCR engaging antigen on immature antigen presenting cells.

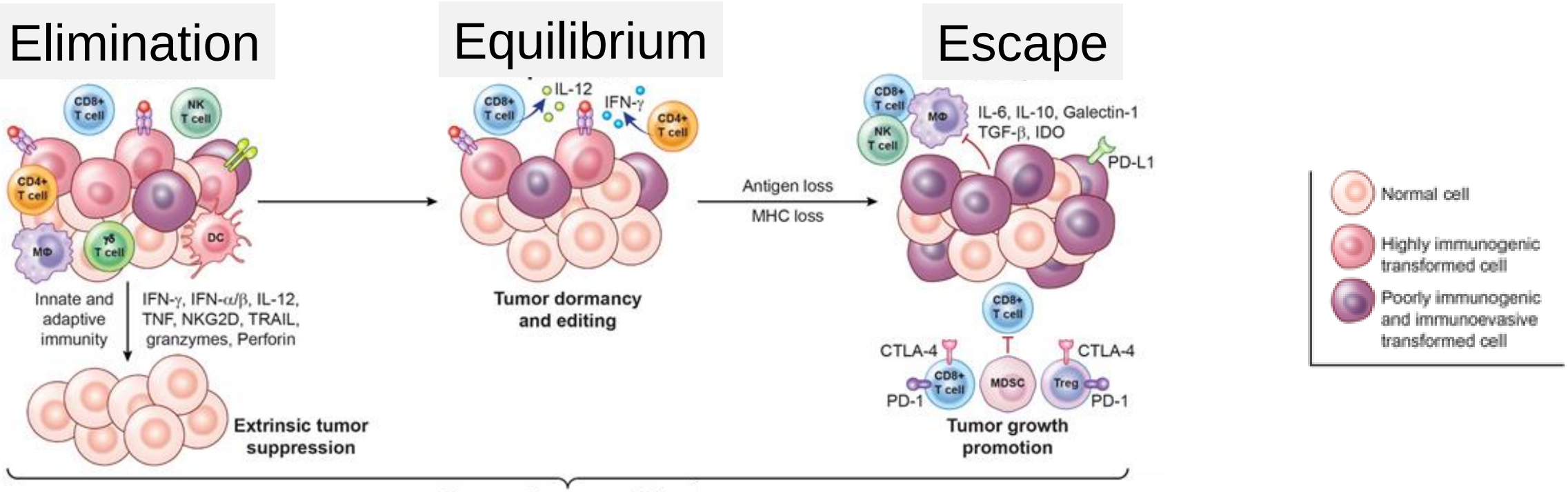
- occurs either by clonal deletion or induction of anergy: A state of immune unresponsivenesss

3) Inhibitory mechanisms: multiple mechanisms exist that inhibit the immune response

TCR stimulation can lead to the induction of tolerance or activation



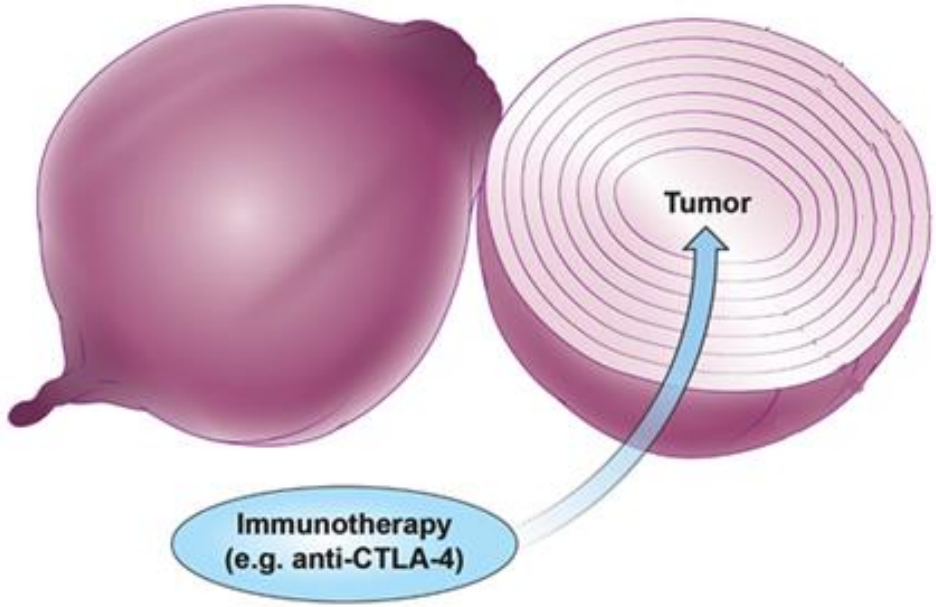
The 3 E's of Cancer Immunoediting
Robert Schreiber



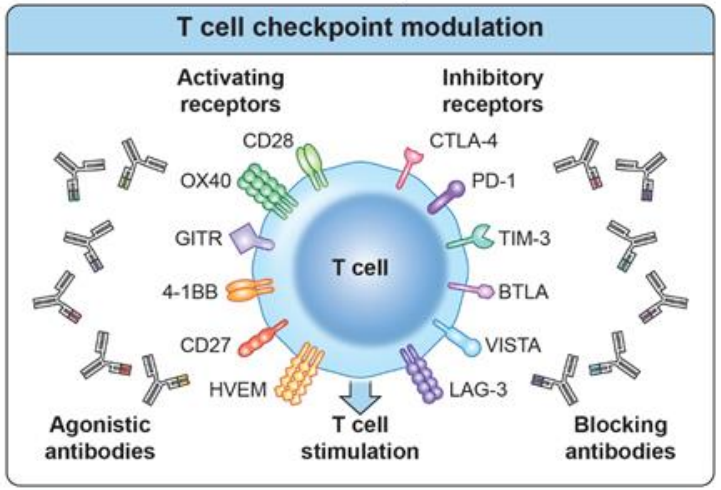
Cancer Immunoediting

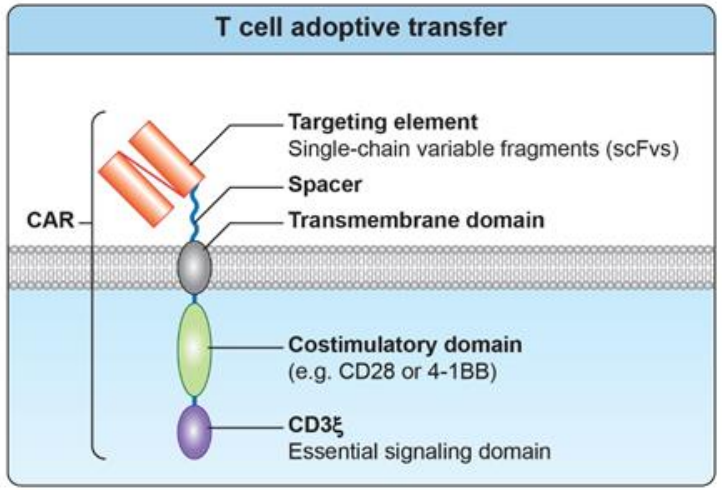
Multi-layered Immunosuppression

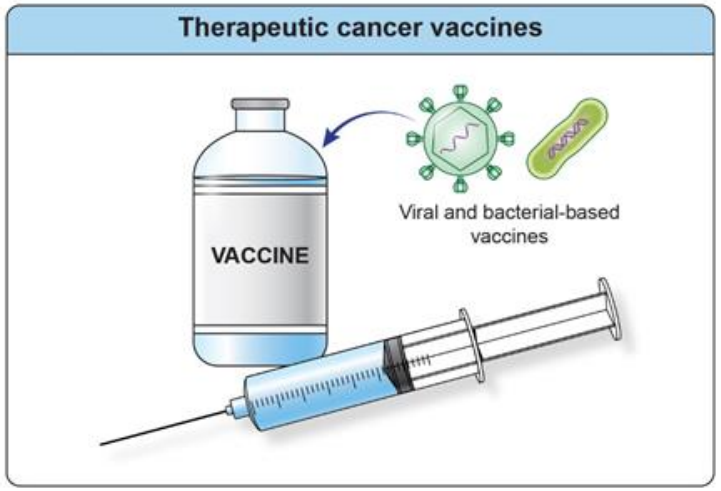
- Tumors include the presence of immunosuppressive stroma
- Multiple inhibitory mechanisms also exist including regulatory T cells and inhibitory macrophage populations
- Immunotherapy attempts to “peel back” the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor

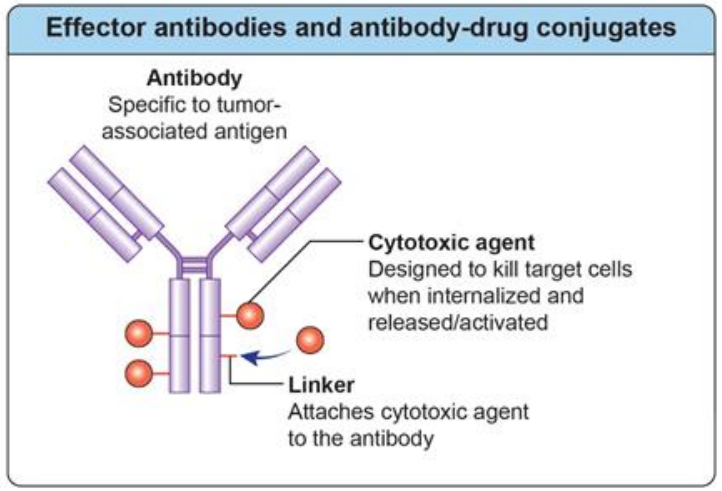


Types of Immunotherapy

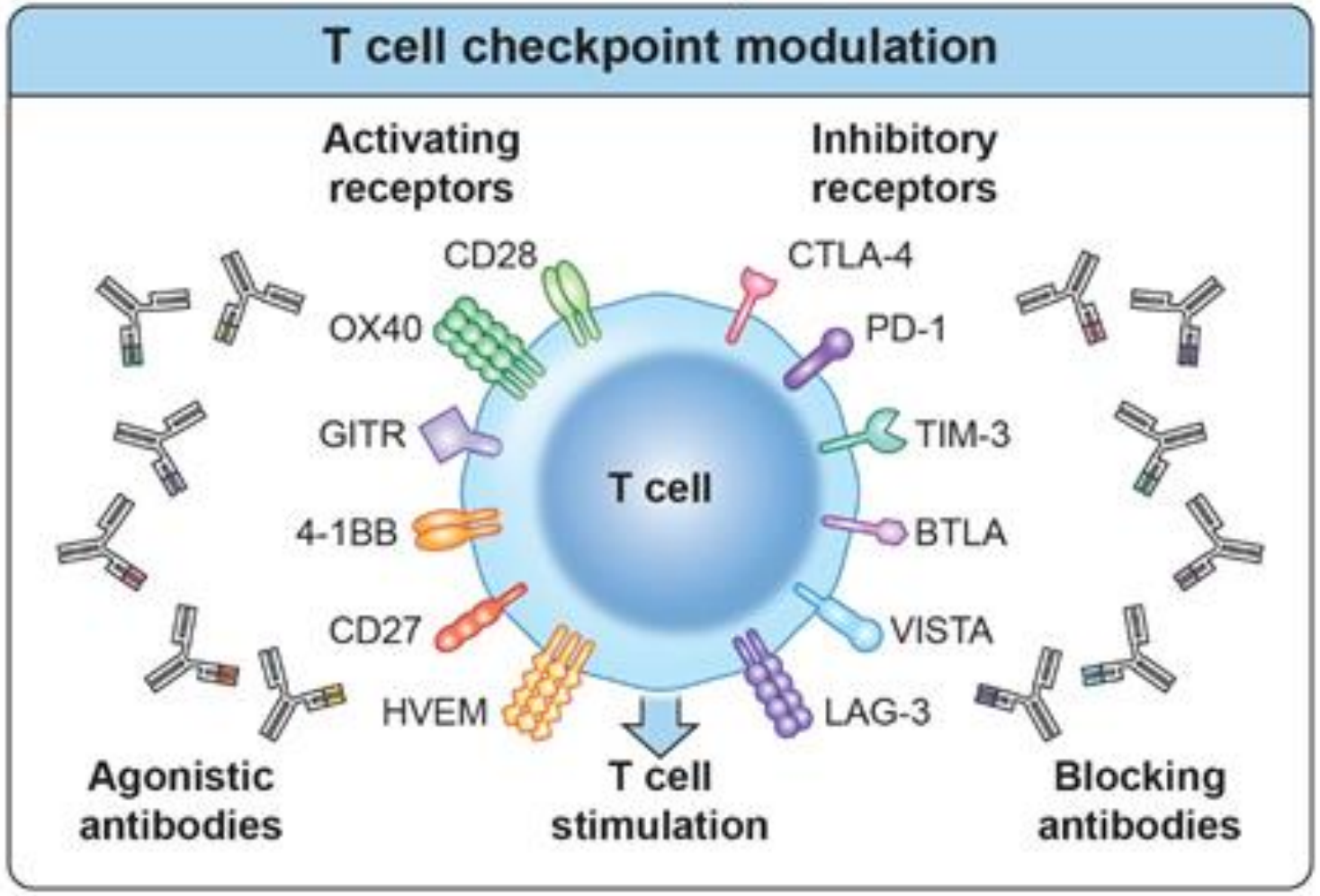






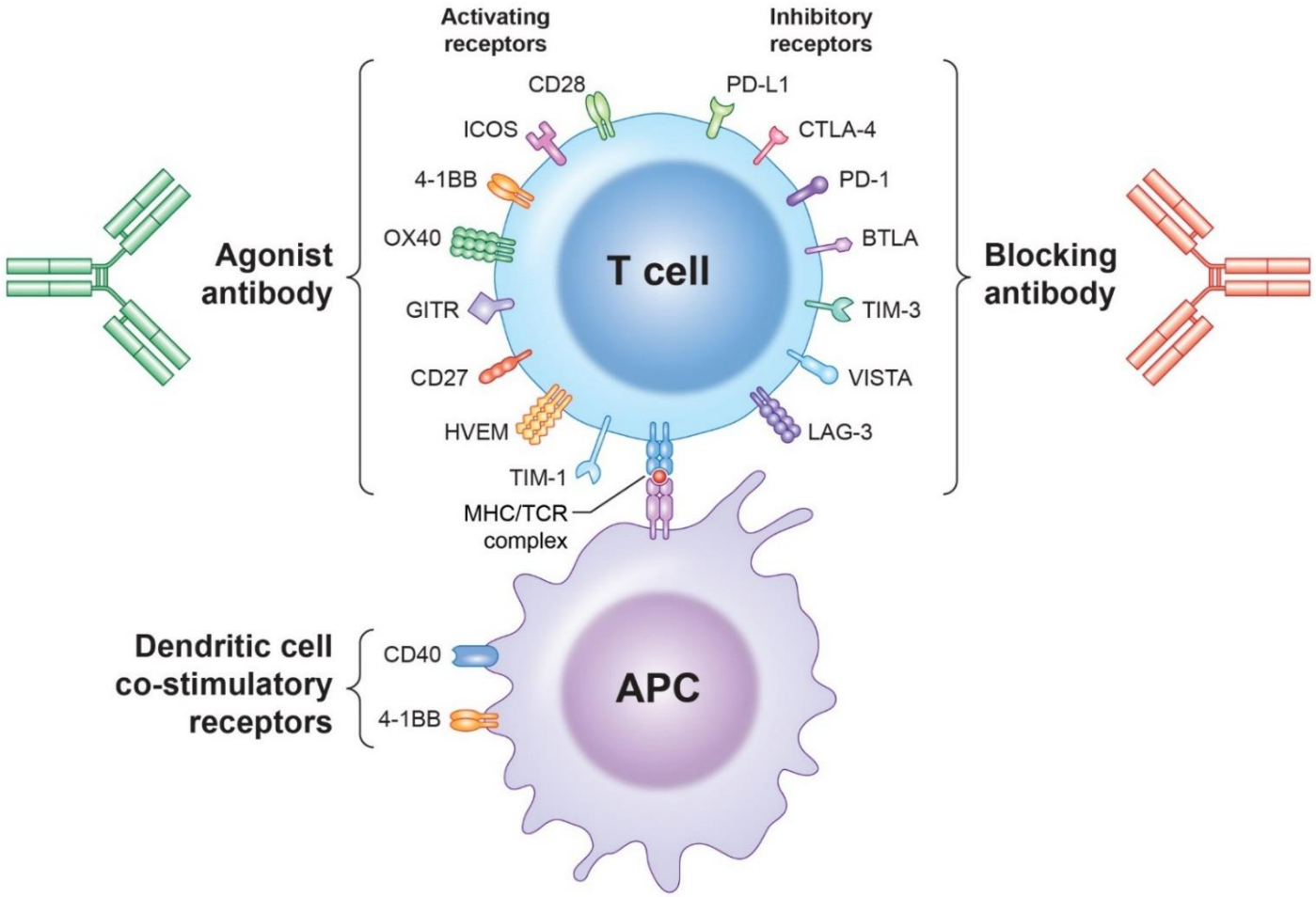


T cell Checkpoint Modulation

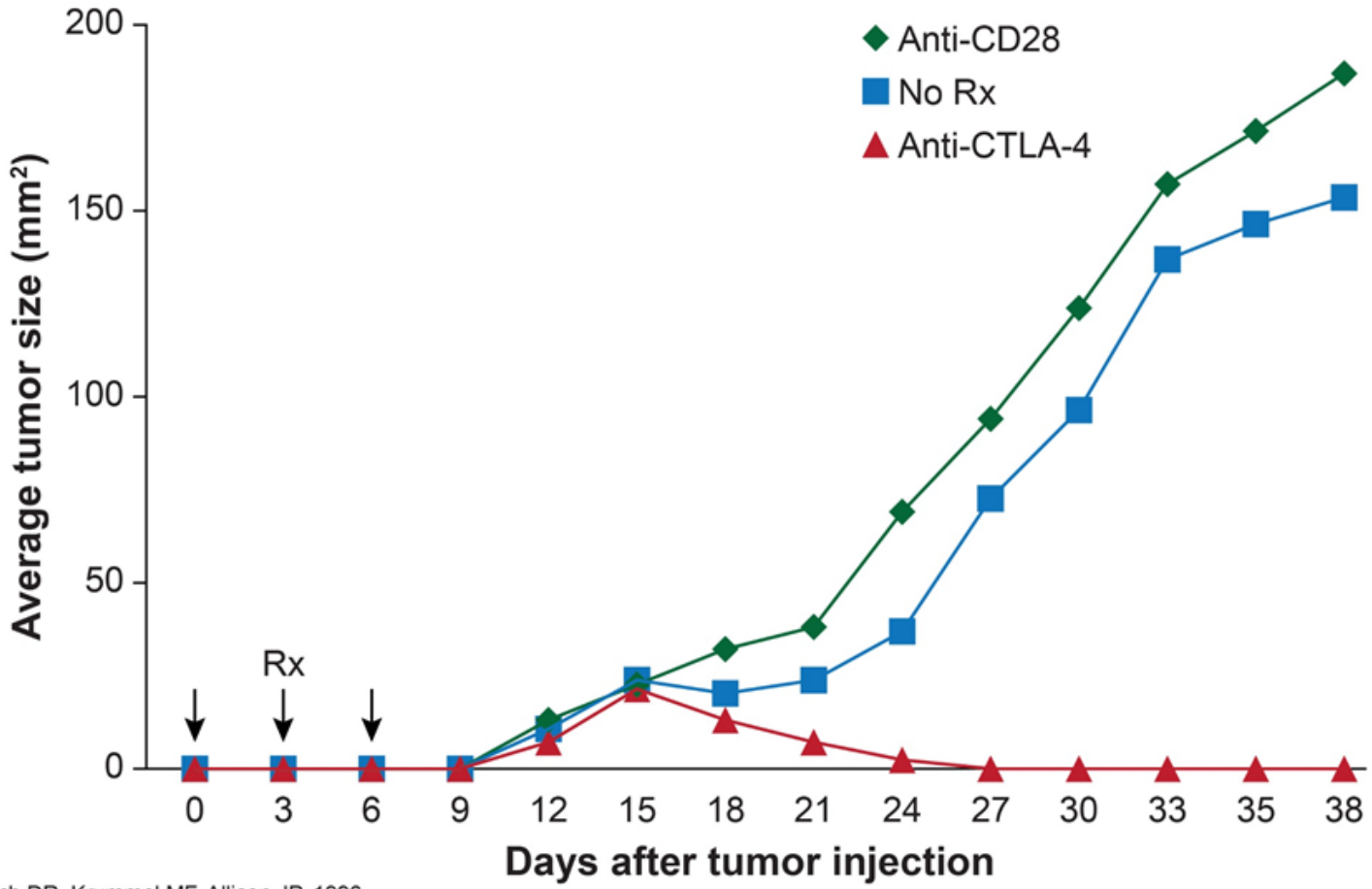


T Cell Checkpoint Modulation

- The goal of T cell checkpoint blockade is to inhibit negative signaling to T cells.



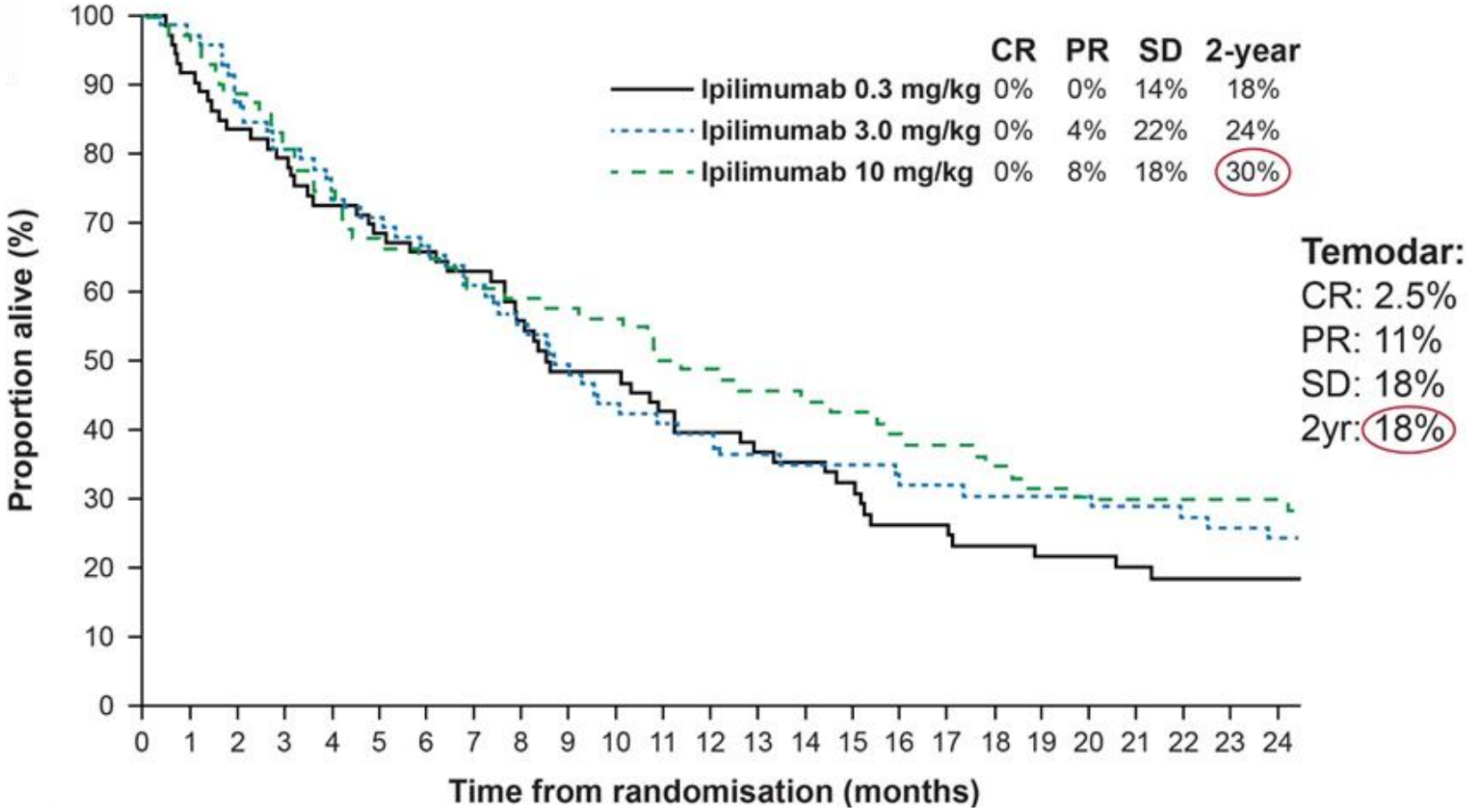
Anti-CTLA-4 induces regression of transplantable colon carcinoma



Leach DR, Krummel MF, Allison JP. 1996.
Enhancement of antitumor immunity by CTLA-4 blockade.
Science. 217(5256): 1734-6.

Clinical trial in Metastatic Melanoma: Ipilimumab (human anti CTLA-4)

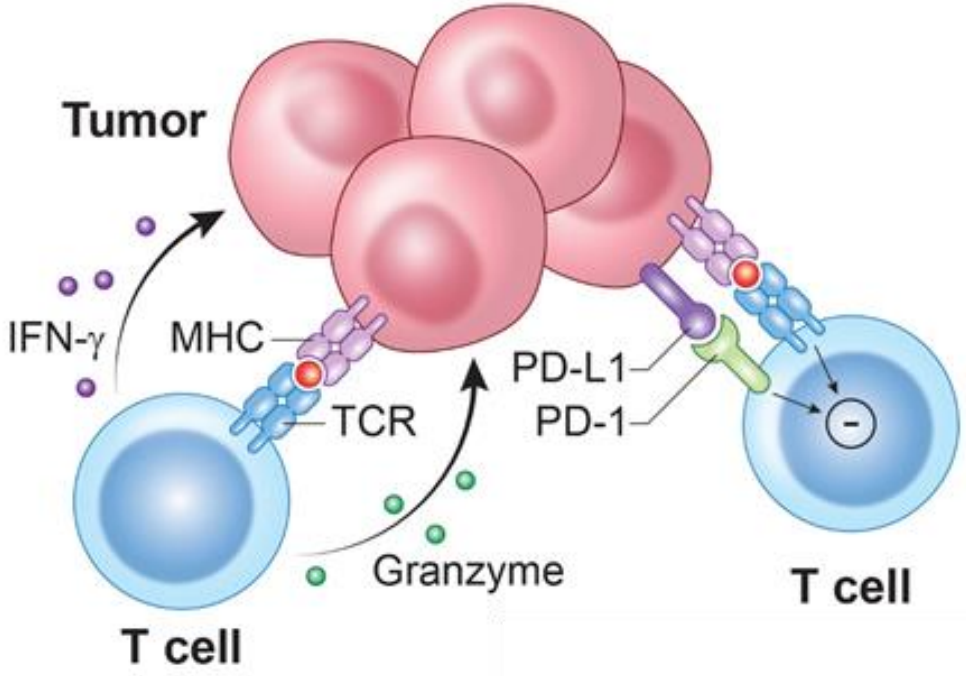
- Granted FDA approval for treatment of patients with metastatic melanoma in 2010
- Hodi et al NEJM 2010



Wolchok et al. Lancet Oncol 2010

The PD-1/PD-L1 Checkpoint

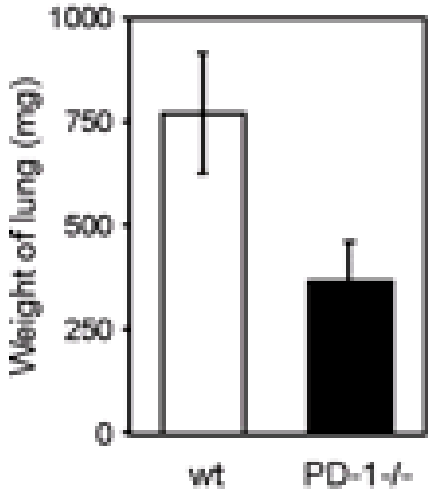
- T cell PD-1 interacts with PD-L1 and PD-L2
- Many cells express PD-L1/PD-L2 and can suppress T cell activation
- Tumors express PD-L1 through two primary mechanisms
  - TIL production of IFN-γ
  - Oncogenic signaling pathways

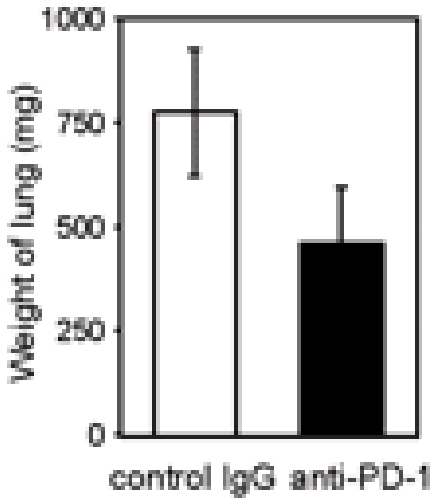


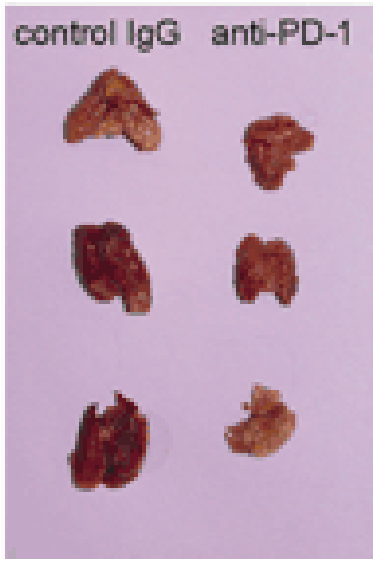
Francisco, L. et al. *Immunol Rev.* 2010. 236: 219.
Pardoll, D.M. *Nat Rev Cancer.* 2012. 12: 252.

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







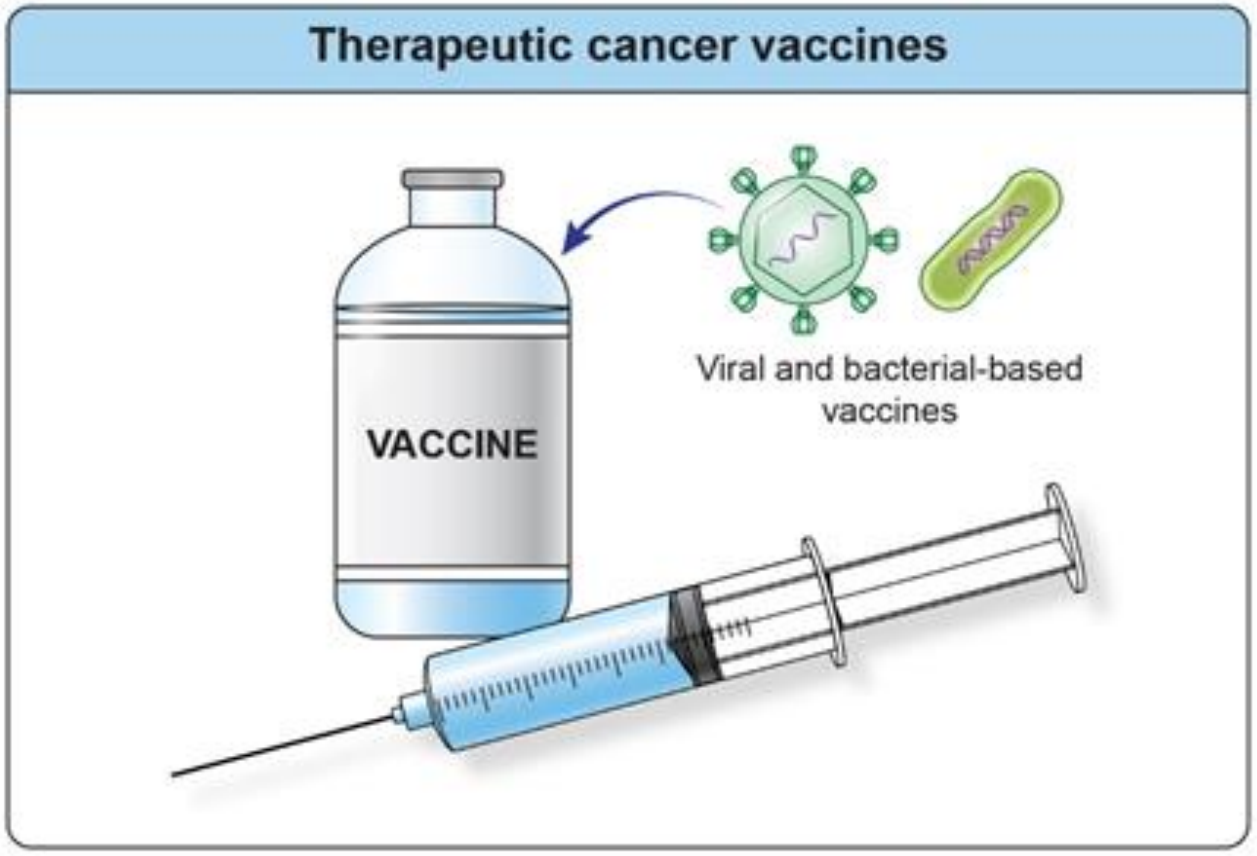
Iwai et al. Int. Immunol 2004

PD-1 Blockade: Objective responses in multiple cancers

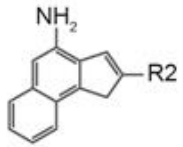
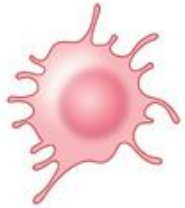
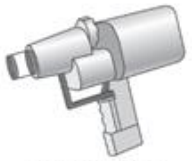
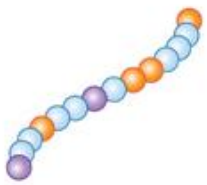
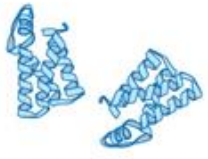
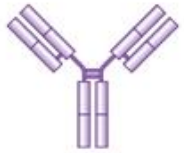
- Metastatic melanoma – 38% OR (Hamid, NEJM 2013)
- Non-small cell lung cancer – 17% OR (Rizvi, Lancet 2015)
- Kidney cancer – 27% OR (Topalian, NEJM 2012)
- Bladder cancer – 52% OR (Powles, Nature 2014)
- Hodgkin's Lymphoma – 87% OR (Ansell, NEJM 2015)
- Colorectal cancer (MSI) – 40% OR (Le, NEJM 2015)
- Merkel Cell Lymphoma – 56% OR (Nghiem, NEJM 2016)
- Head and Neck – 13.3% OR (Ferris, NEJM 2016)

Therapeutic Cancer Vaccines

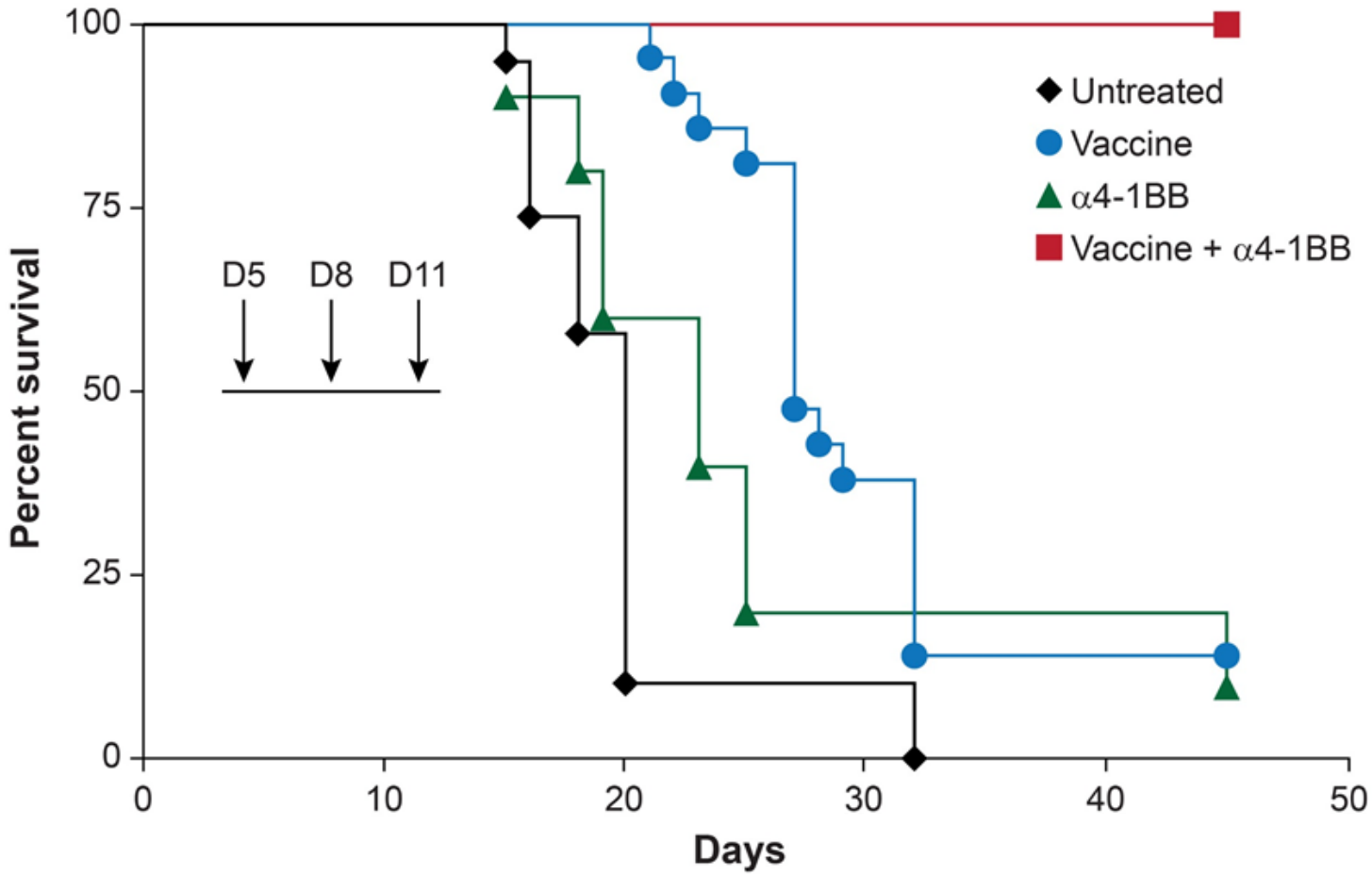
- The goal of therapeutic cancer vaccination is to activate and generate a high frequency of tumor-specific T cells.



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

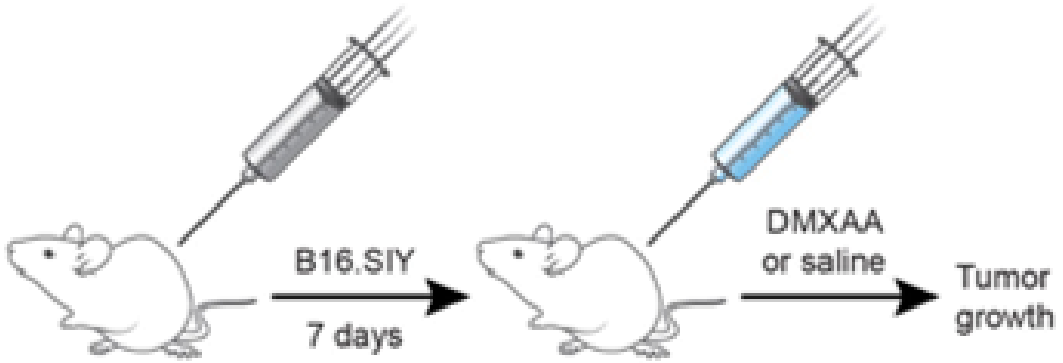
4-1BB agonist antibody and HPV E6/E7 vaccine synergize in curing TC-1 Tumors

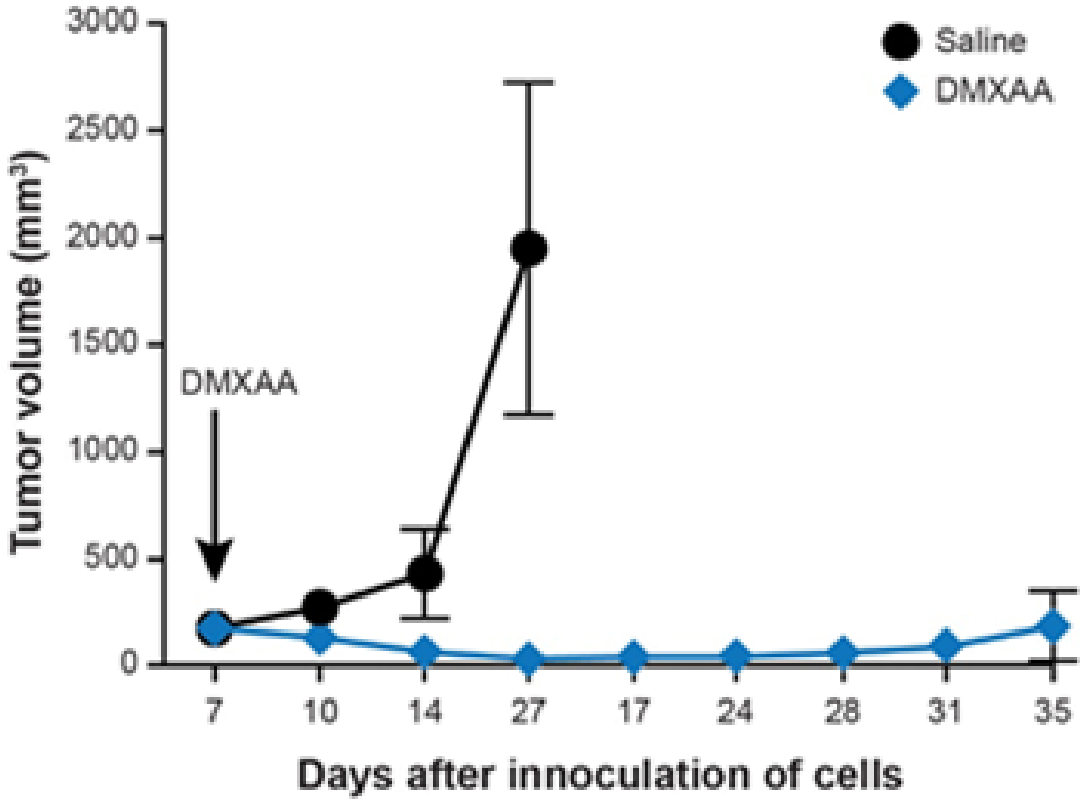


Todd Bartkowiak, M.S.

Intratumoral Injection of Innate Immune Agonists:
Direct Vaccination Approach

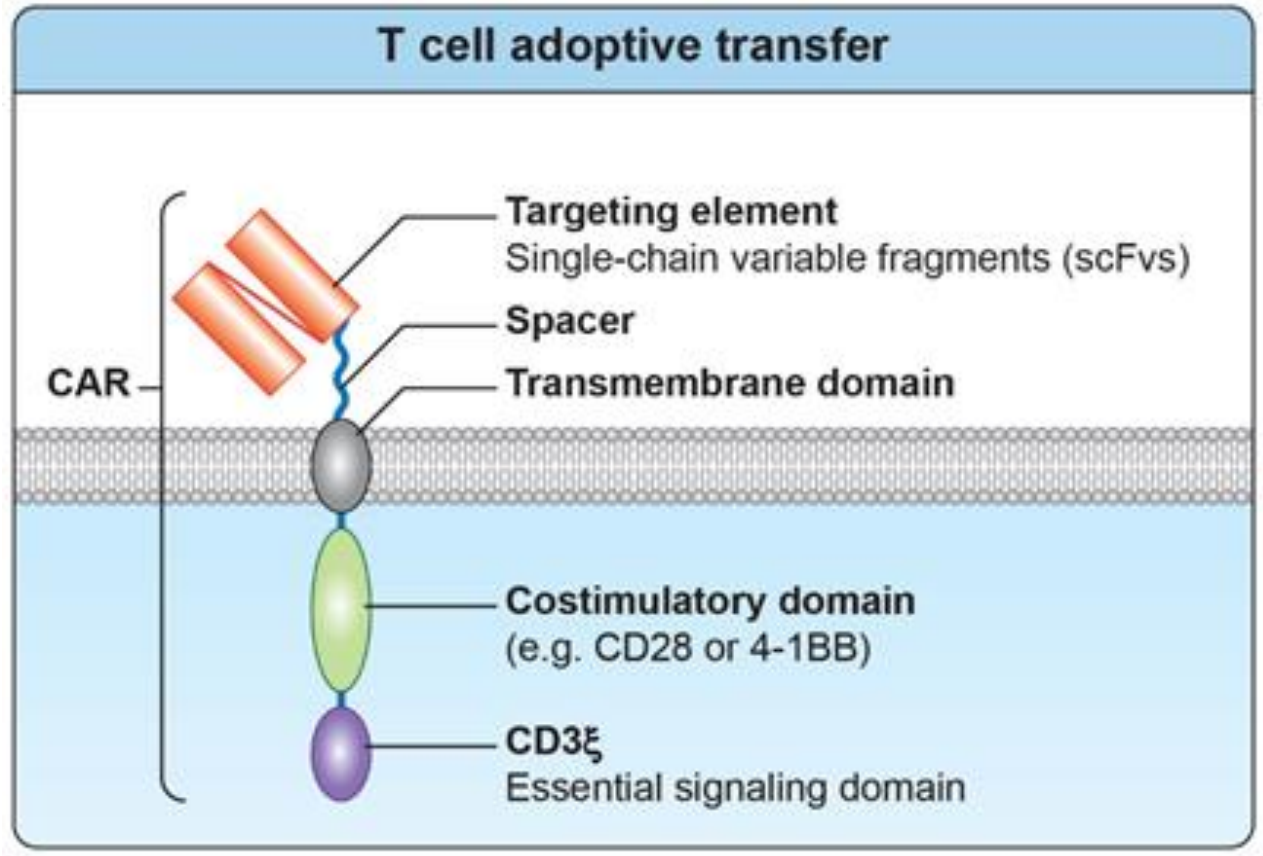
- Intratumoral DMXAA (mouse STING agonist) triggers rejection of B16 melanoma



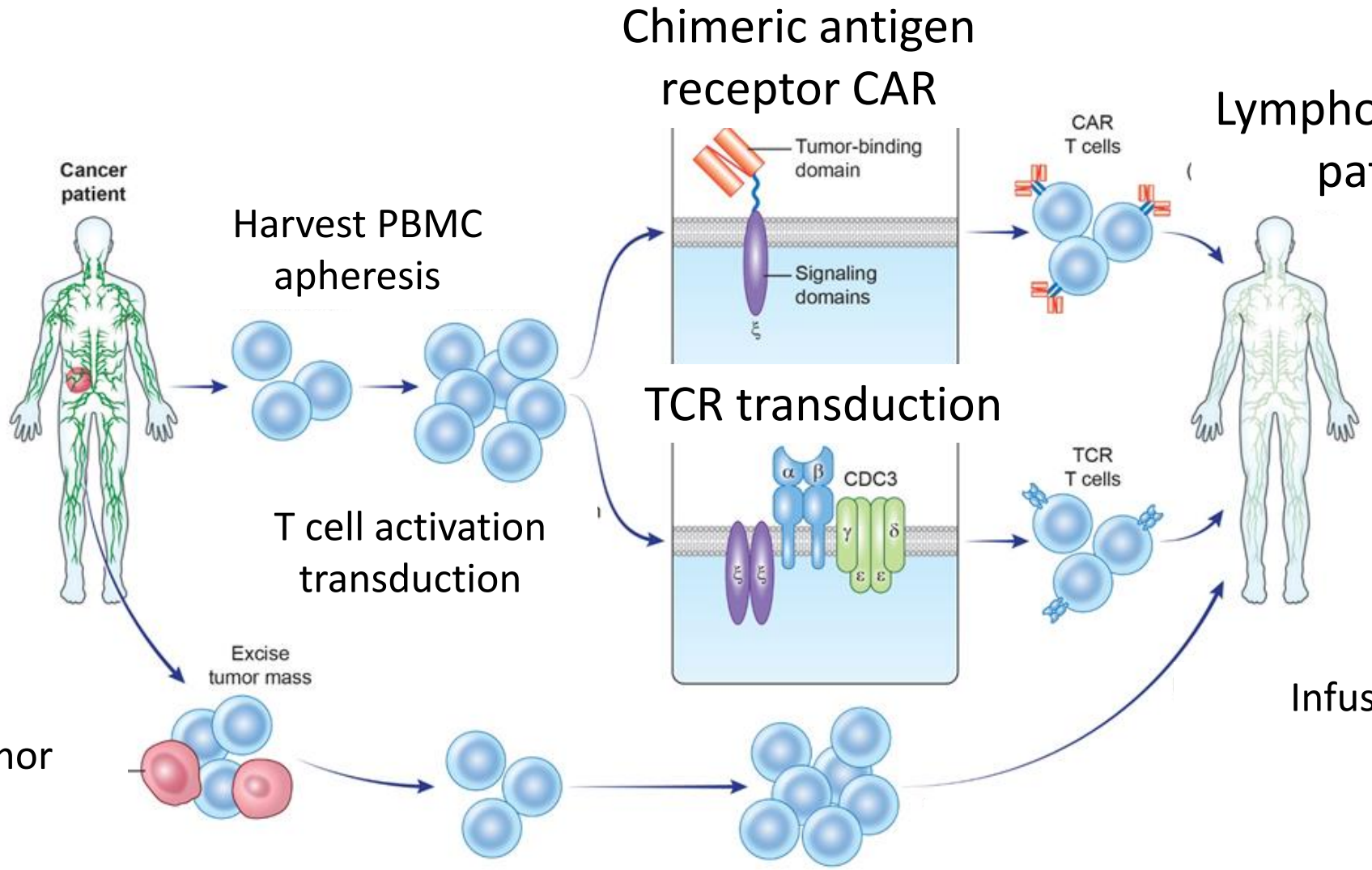


Adoptive cell therapy: Chimeric Antigen Receptors CARs

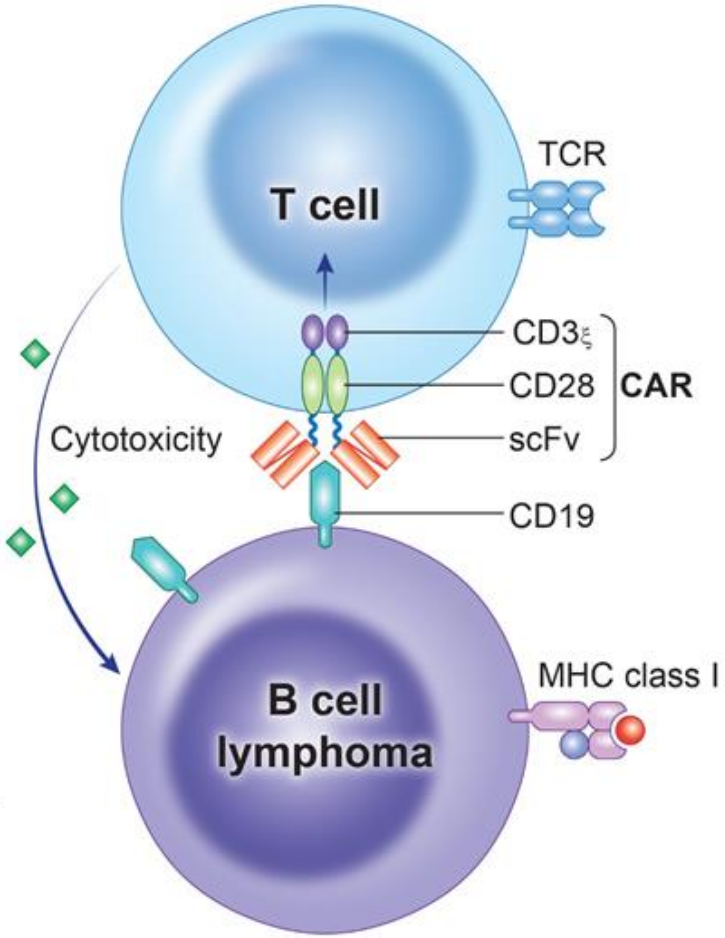
- The goal of adoptive cell transfer is to provide a high frequency of tumor-specific immune cells and/or engineer immune cells to target cancer



Adoptive Cell Therapy Process



CD19 CAR T Cell Therapy



Chimeric antigen receptors

CD19 CARs

June (Novartis) ALL, 90% CR

Maude SL NEJM (2014)

Sadelain (Juno) 88% CR, B-ALL

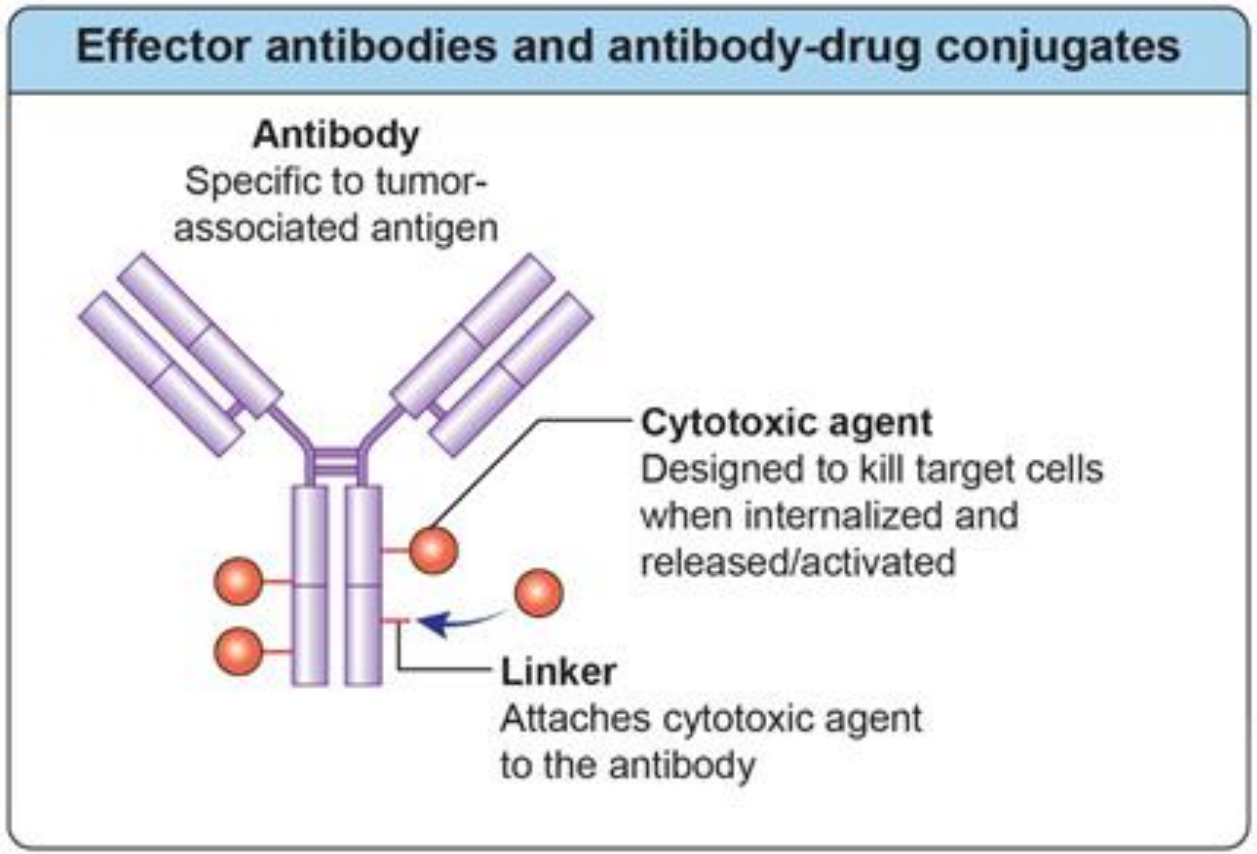
Davilia ML Sci Trans Med (2014)

Rosenberg (Kite) DLBCL, 92%

Kochendefer JN JCO (2014)

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 of suppress and/or through delivery of cytotoxic agents

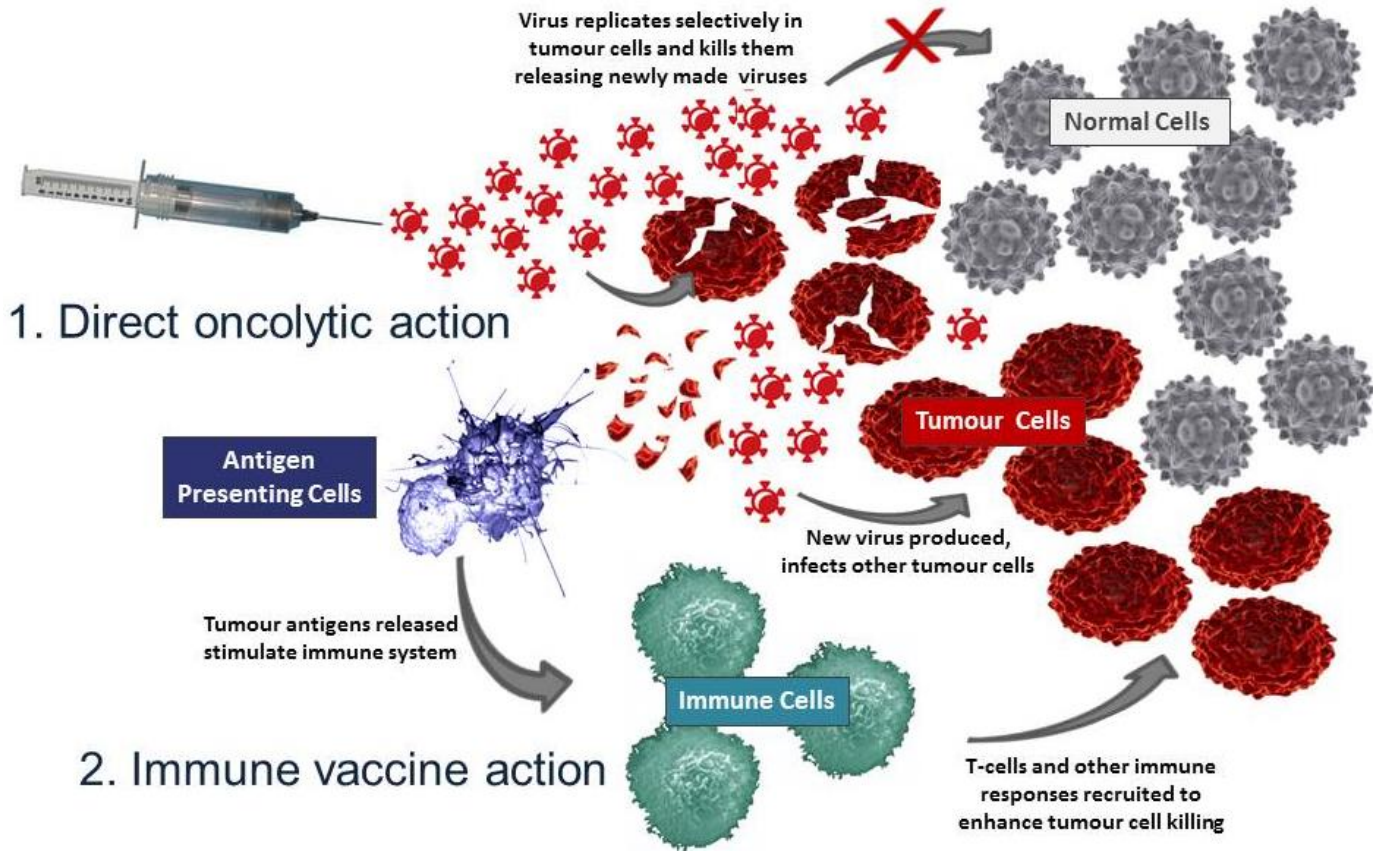


Key ADC/Antibody Principles

- **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

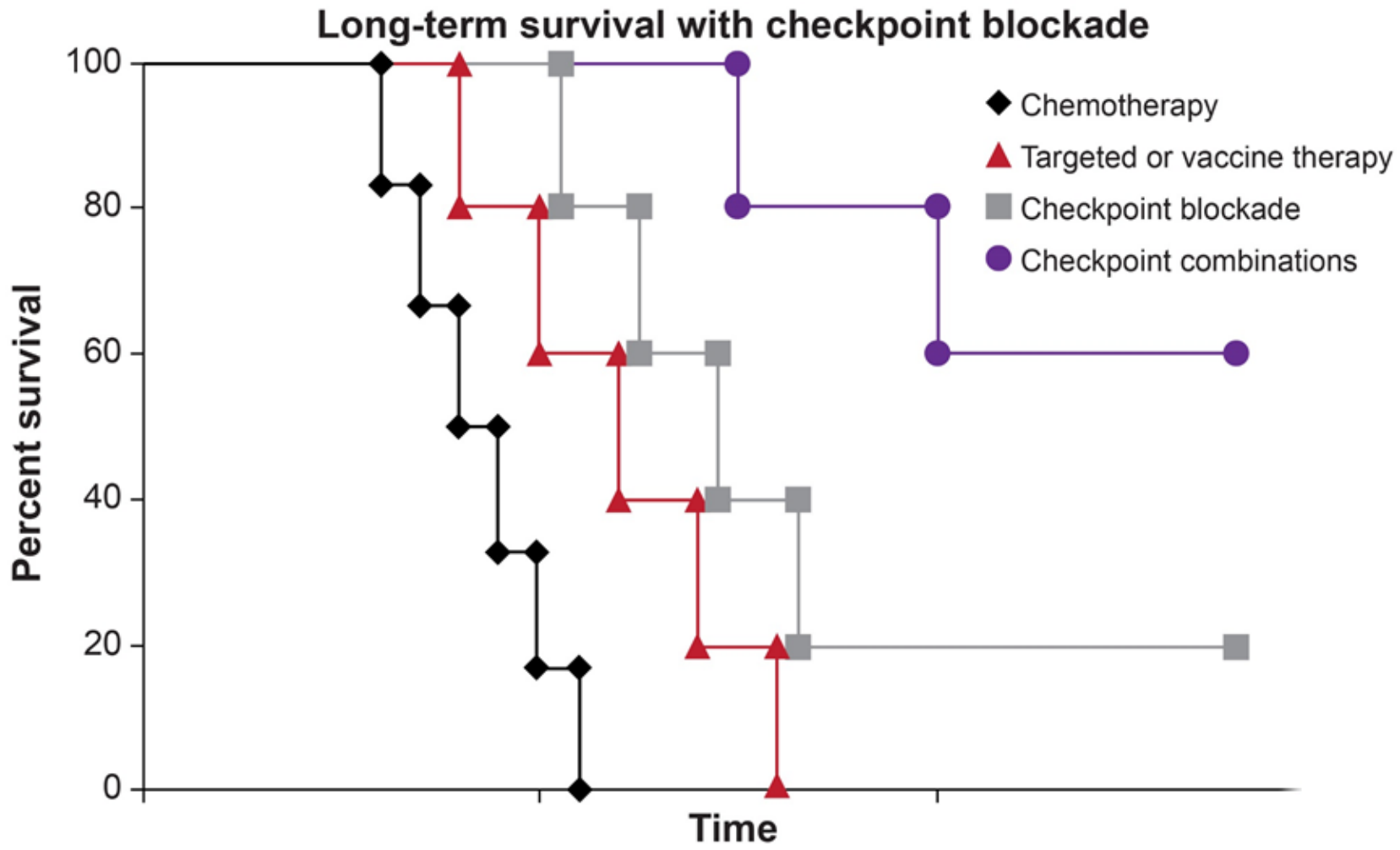
Oncolytic Viruses

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



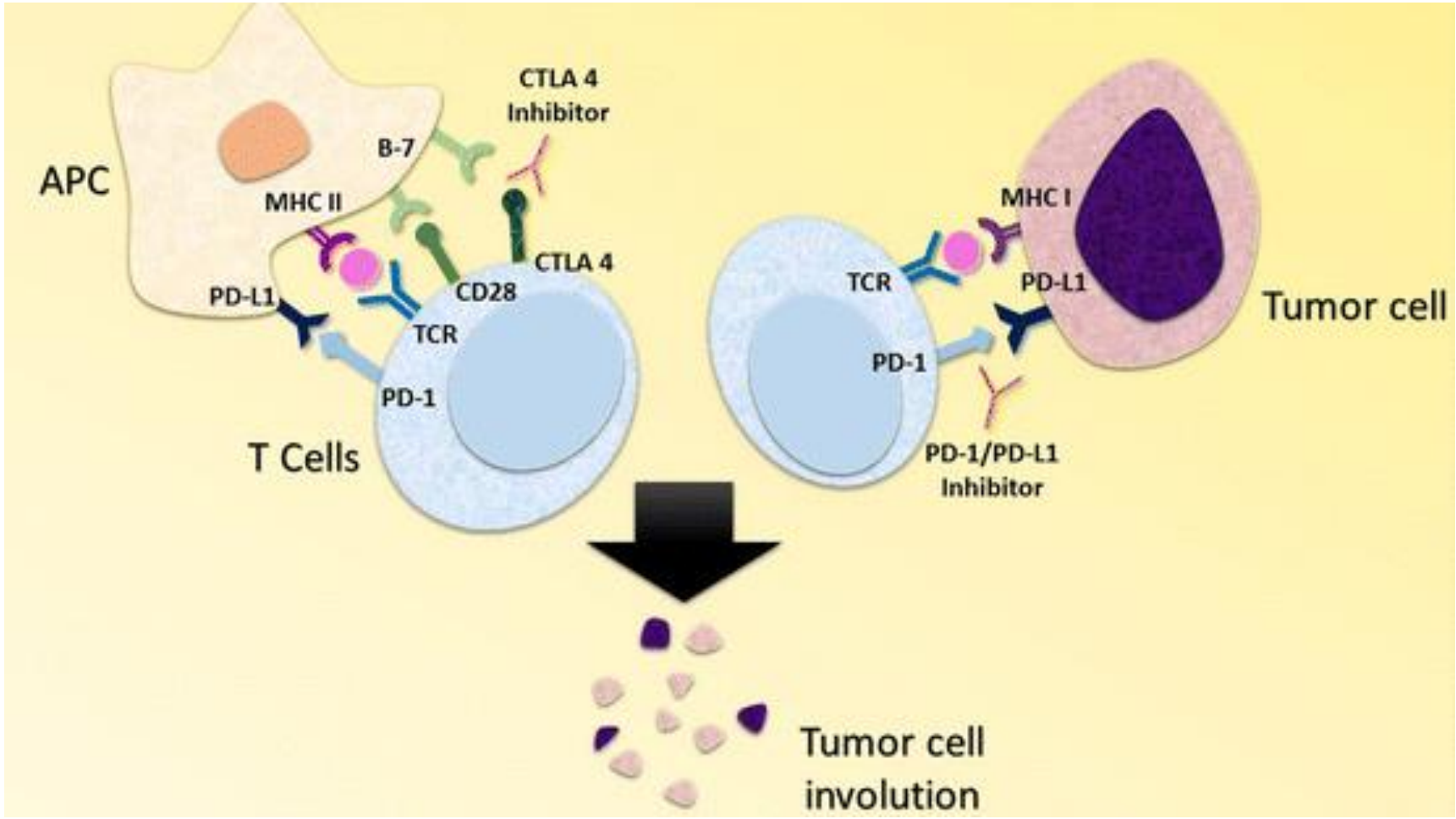
dddmag.com

Combination Immunotherapies



Combination Immunotherapies

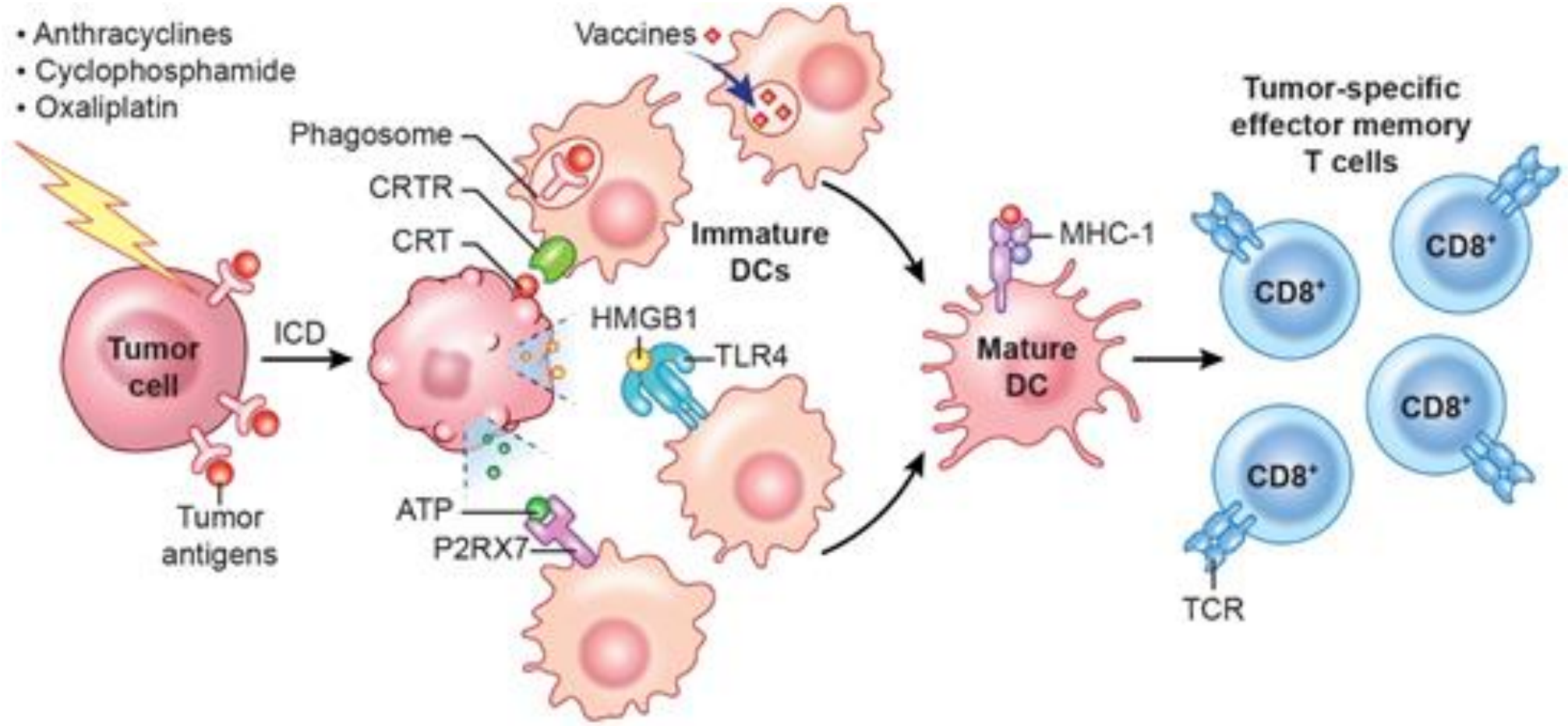
Dual CTLA-4 and PD-1 inhibition



Chae et al. JITC 2018

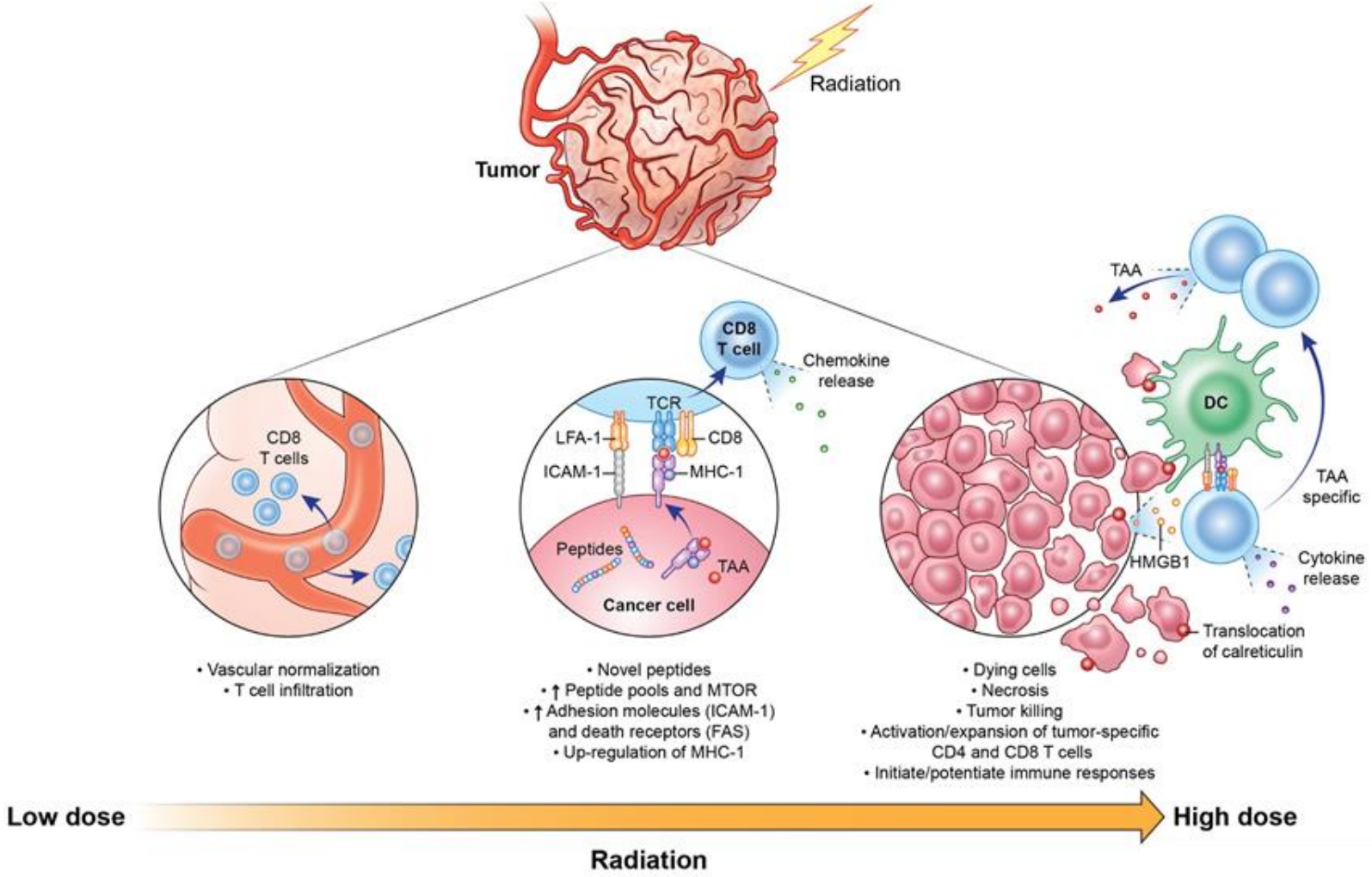
Combination Immunotherapies

Chemotherapy can induce an immune response



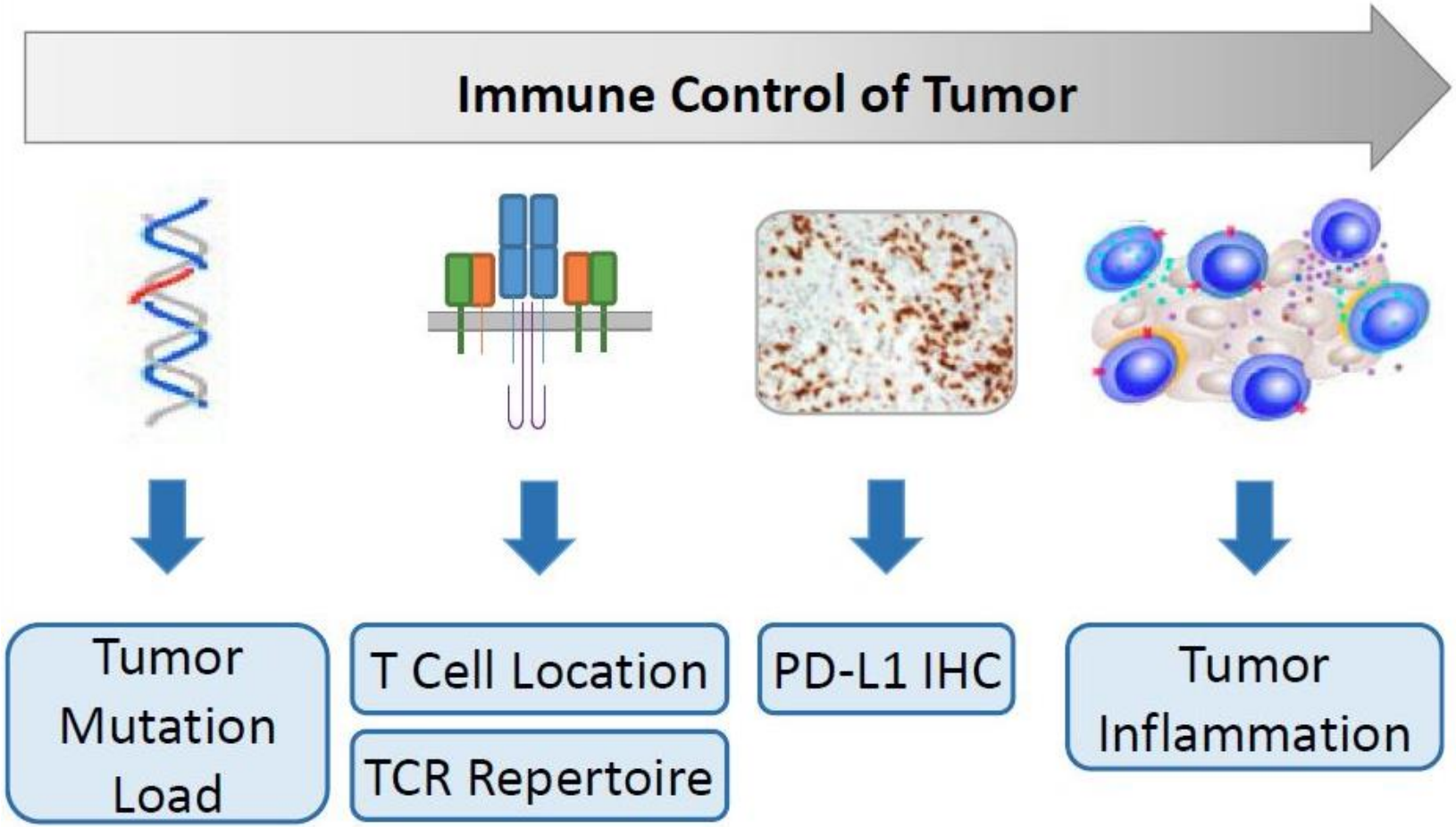
Combination Immunotherapies

Radiotherapy can induce an immune response



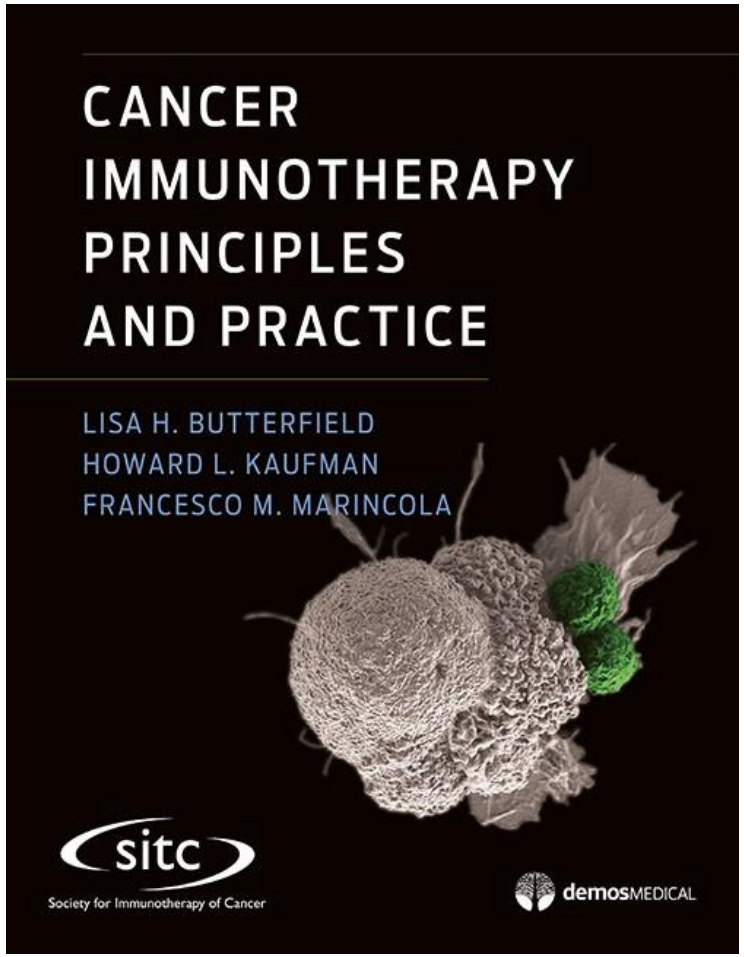
http://www.ncbi.nlm.nih.gov/pubmed/18777956

Immunotherapy Biomarkers



Cesano et al. Biomedicines 2018

Further Resources



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Cancer Immunotherapy CONNECT