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ADVANCES IN Cancer IMMUNOTHERAPY™

Basic Principles of Cancer Immunotherapy

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Dana-Farber Cancer Institute

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

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- Novartis: Consulting and Contracted Research
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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.

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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

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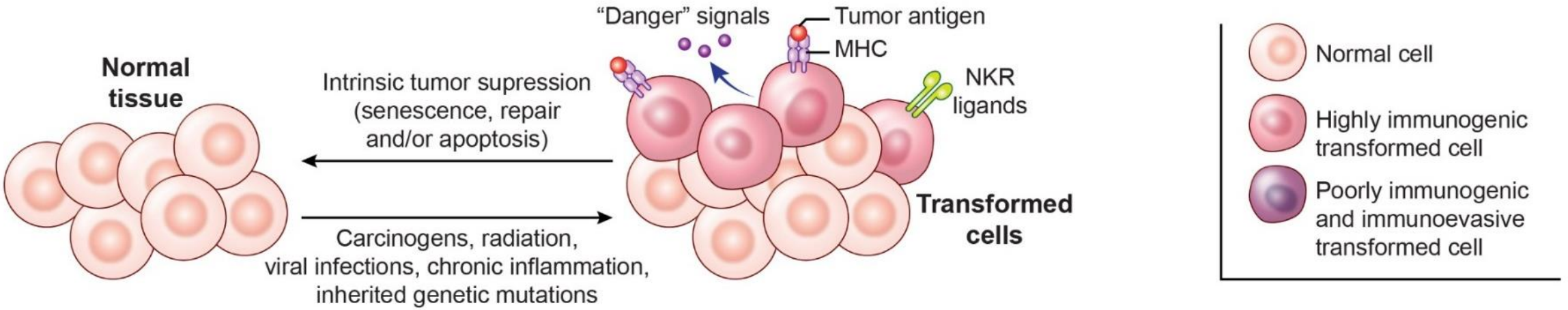
The 3 E's of Cancer Immunoediting



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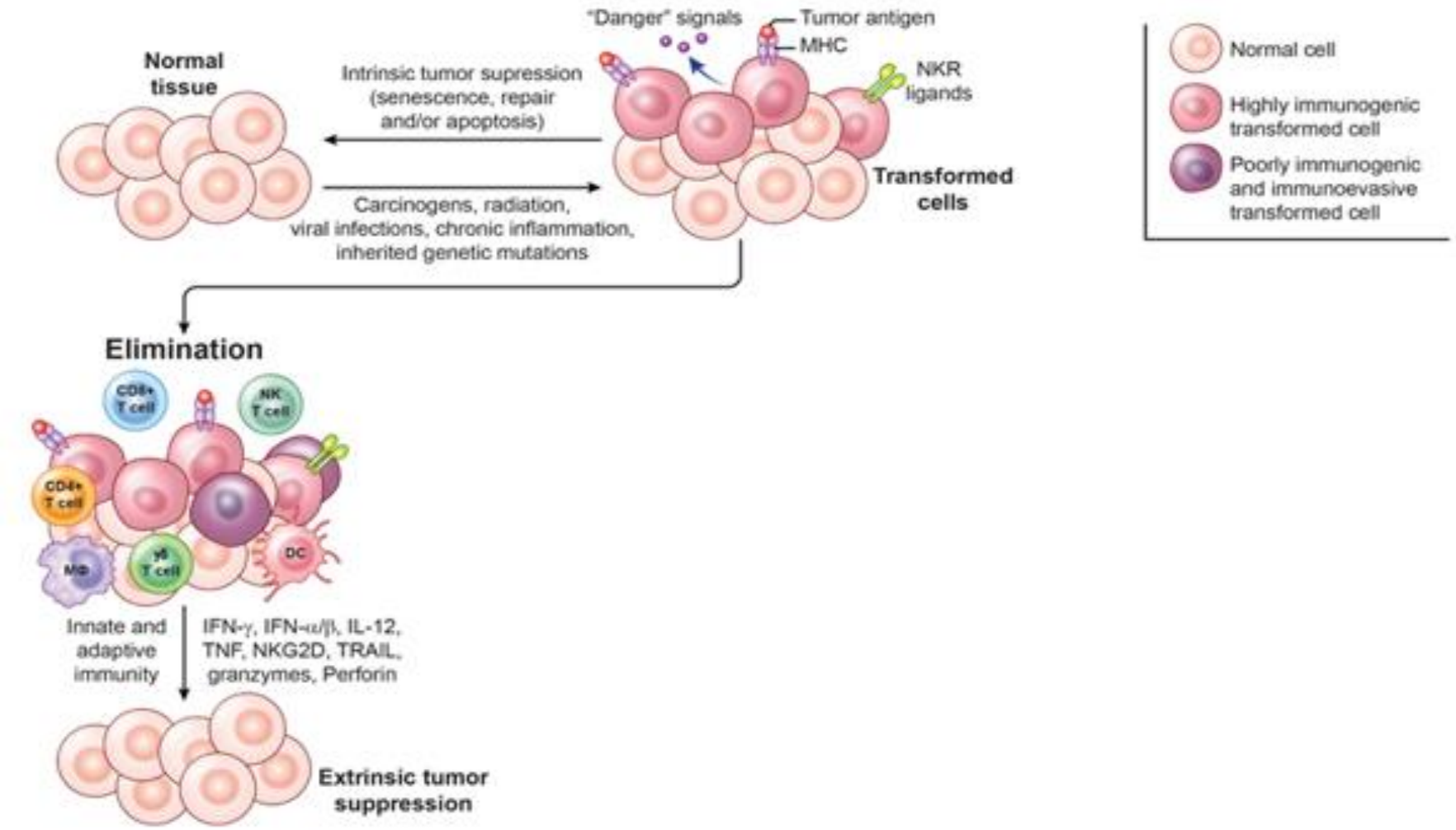
The 3 E's of Cancer Immunoediting



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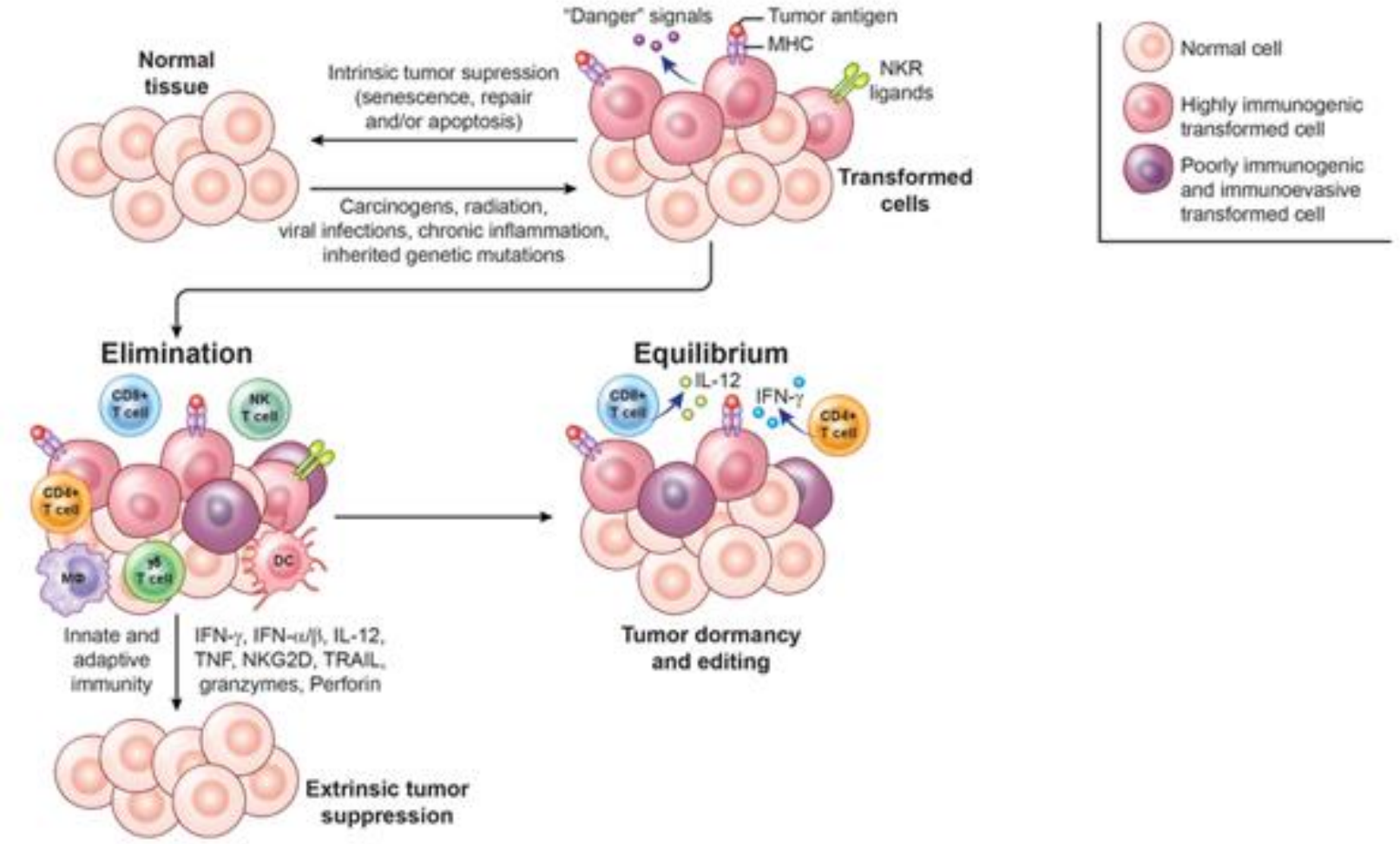

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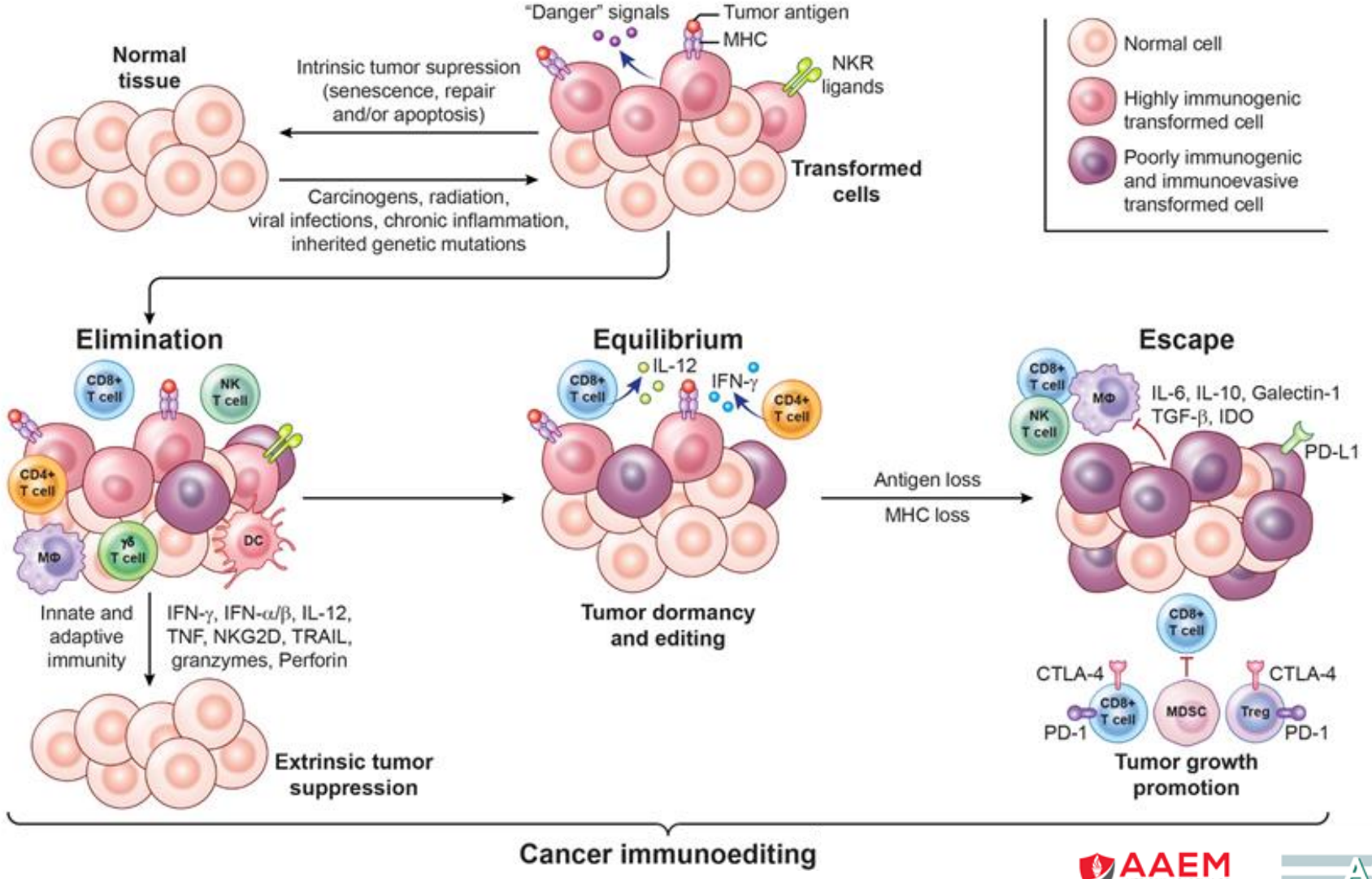

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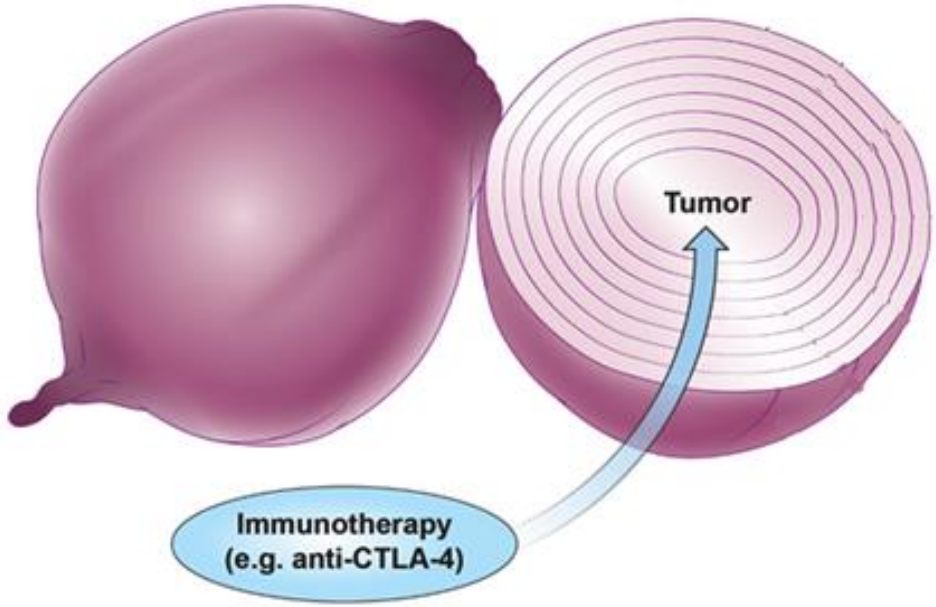
Multi-layered Immunosuppression

- 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



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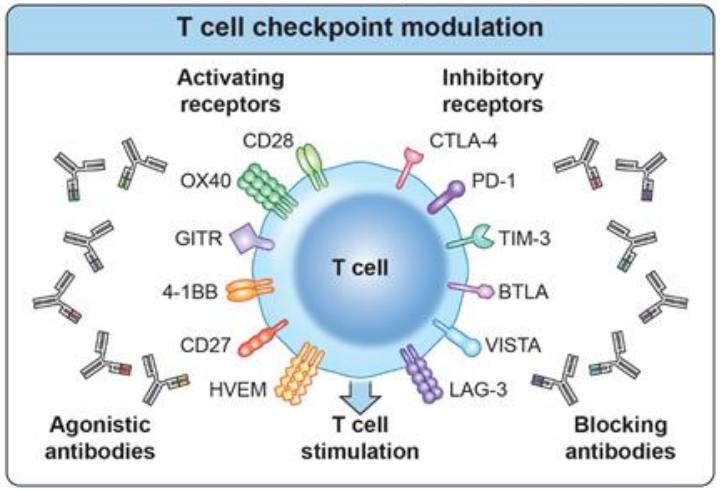
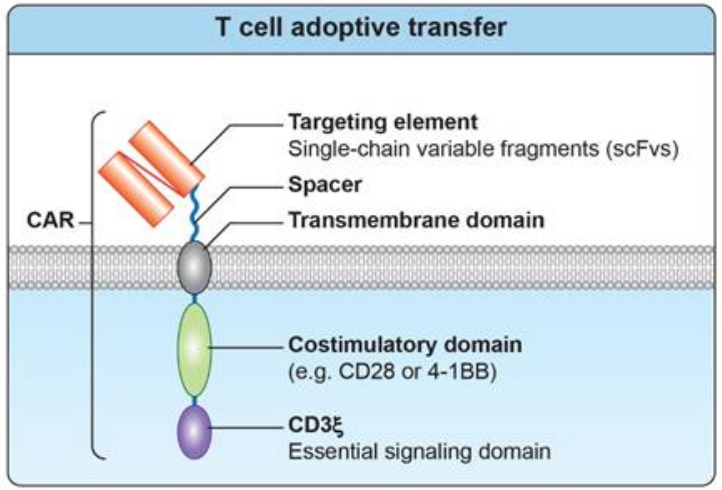
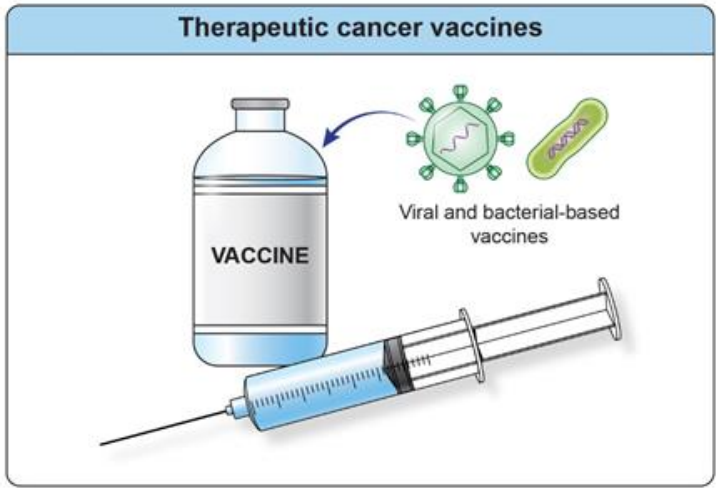
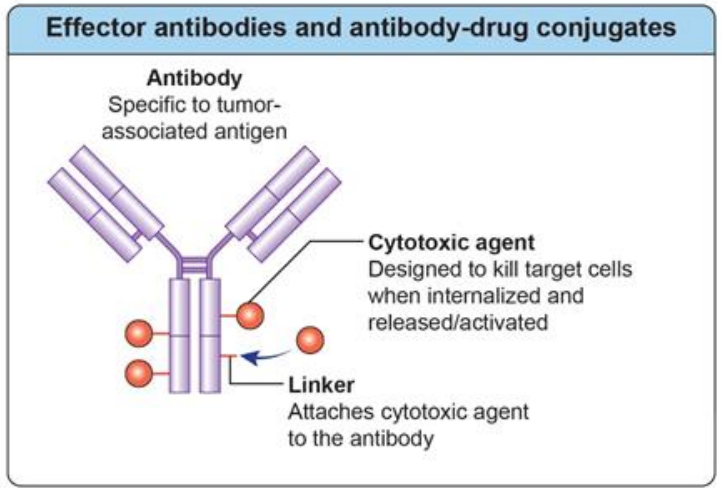
Types of Immunotherapy









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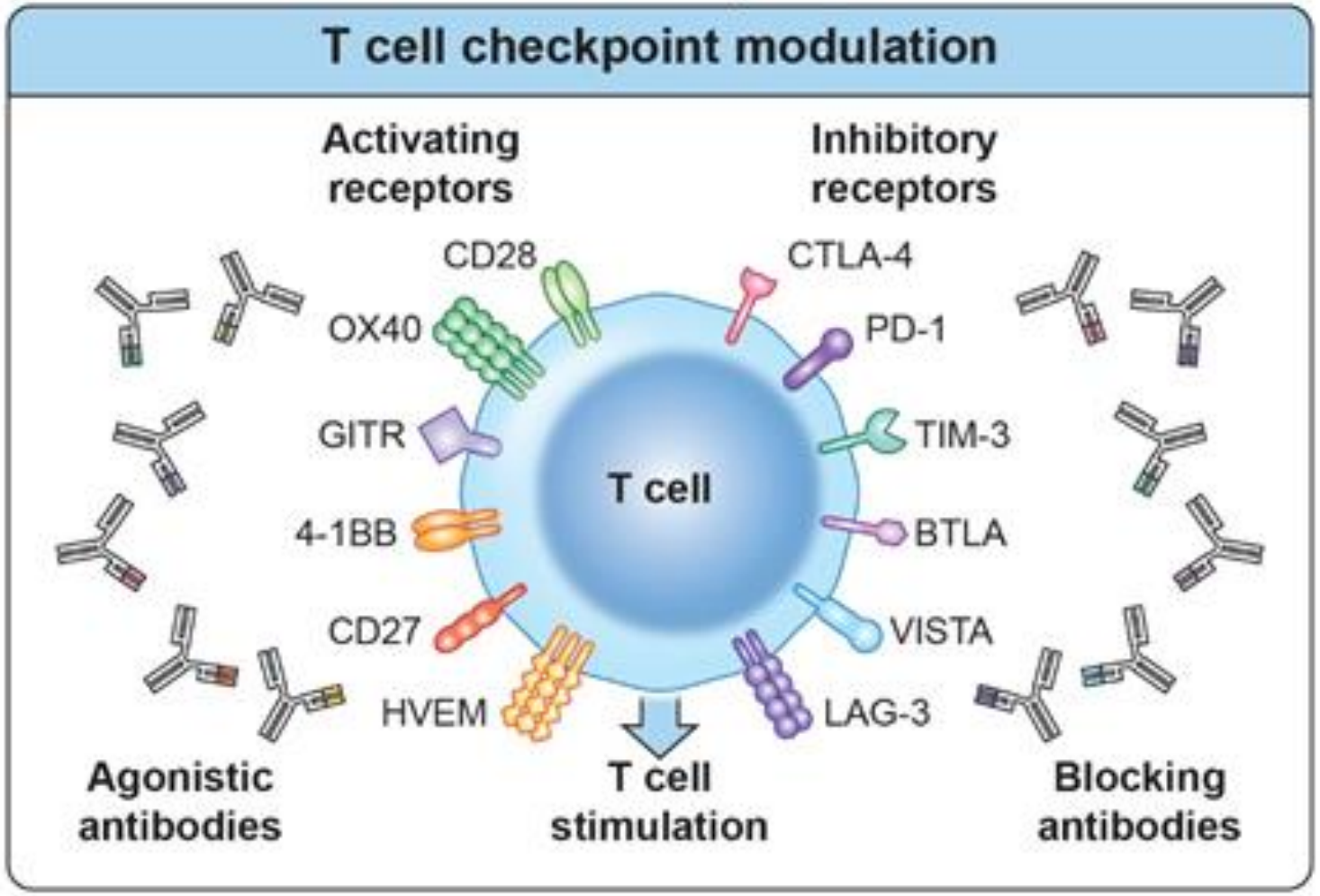
T cell Checkpoint Modulation



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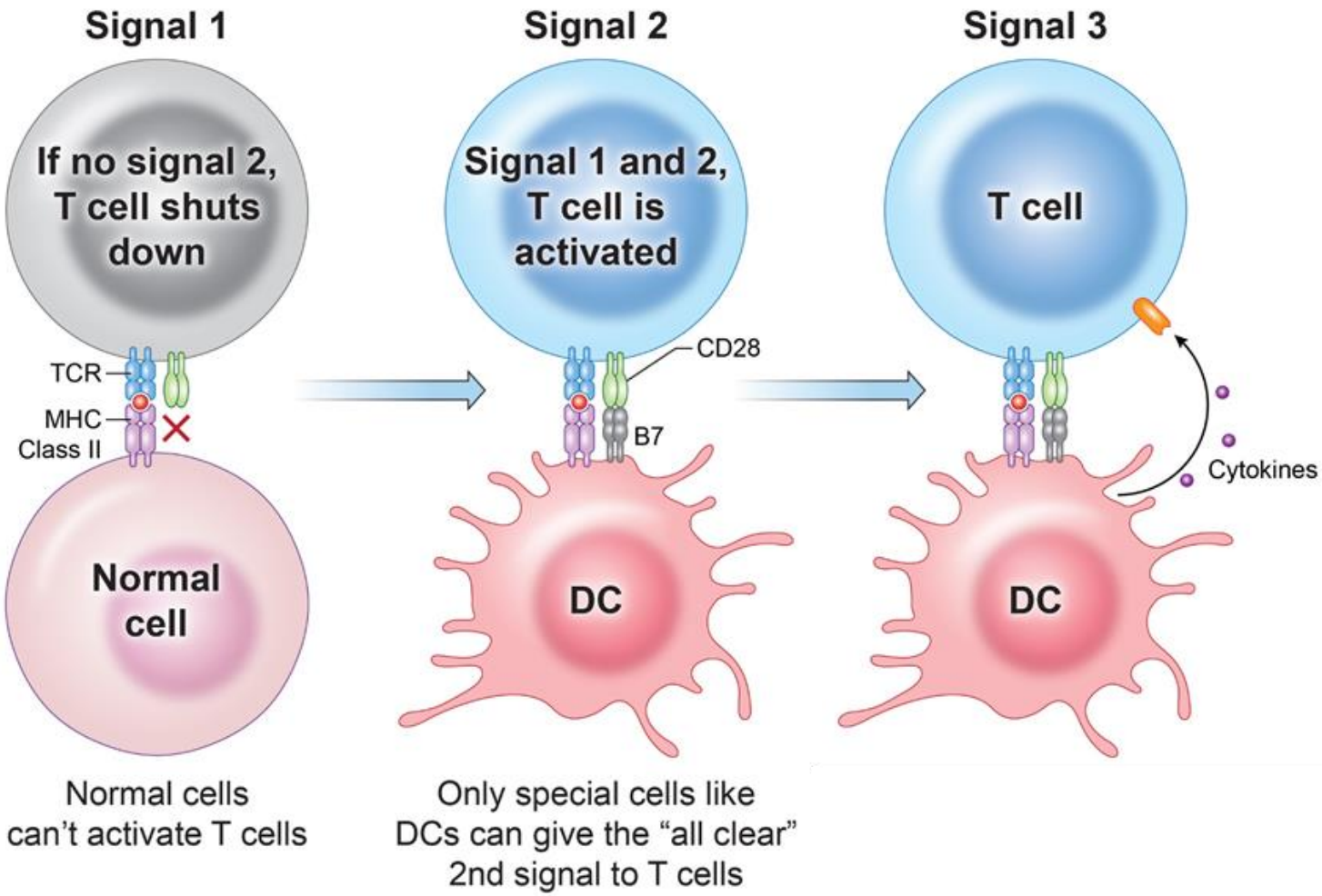
Antigen-specific T cell Activation



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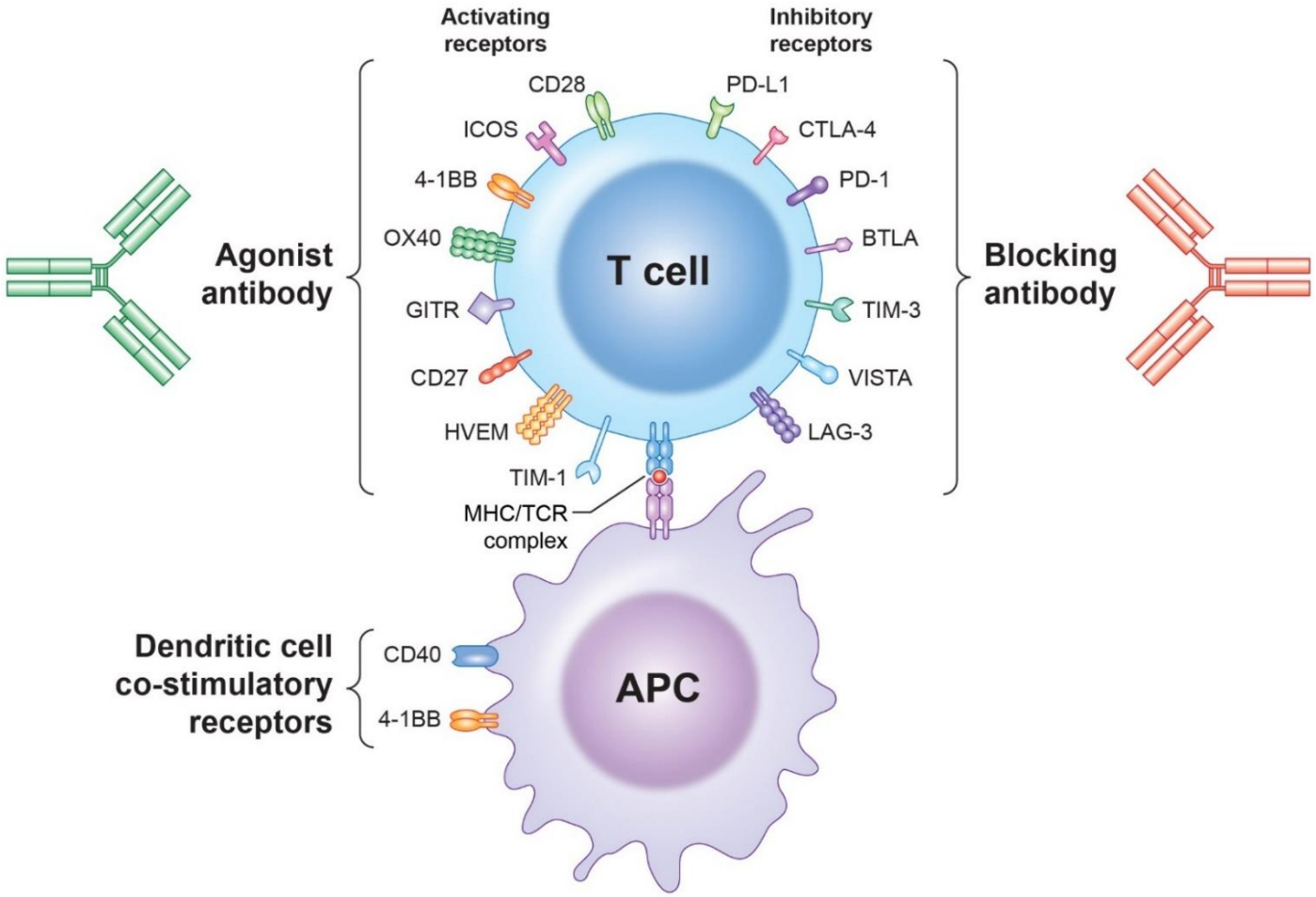
T Cell Checkpoint Modulation

- 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.



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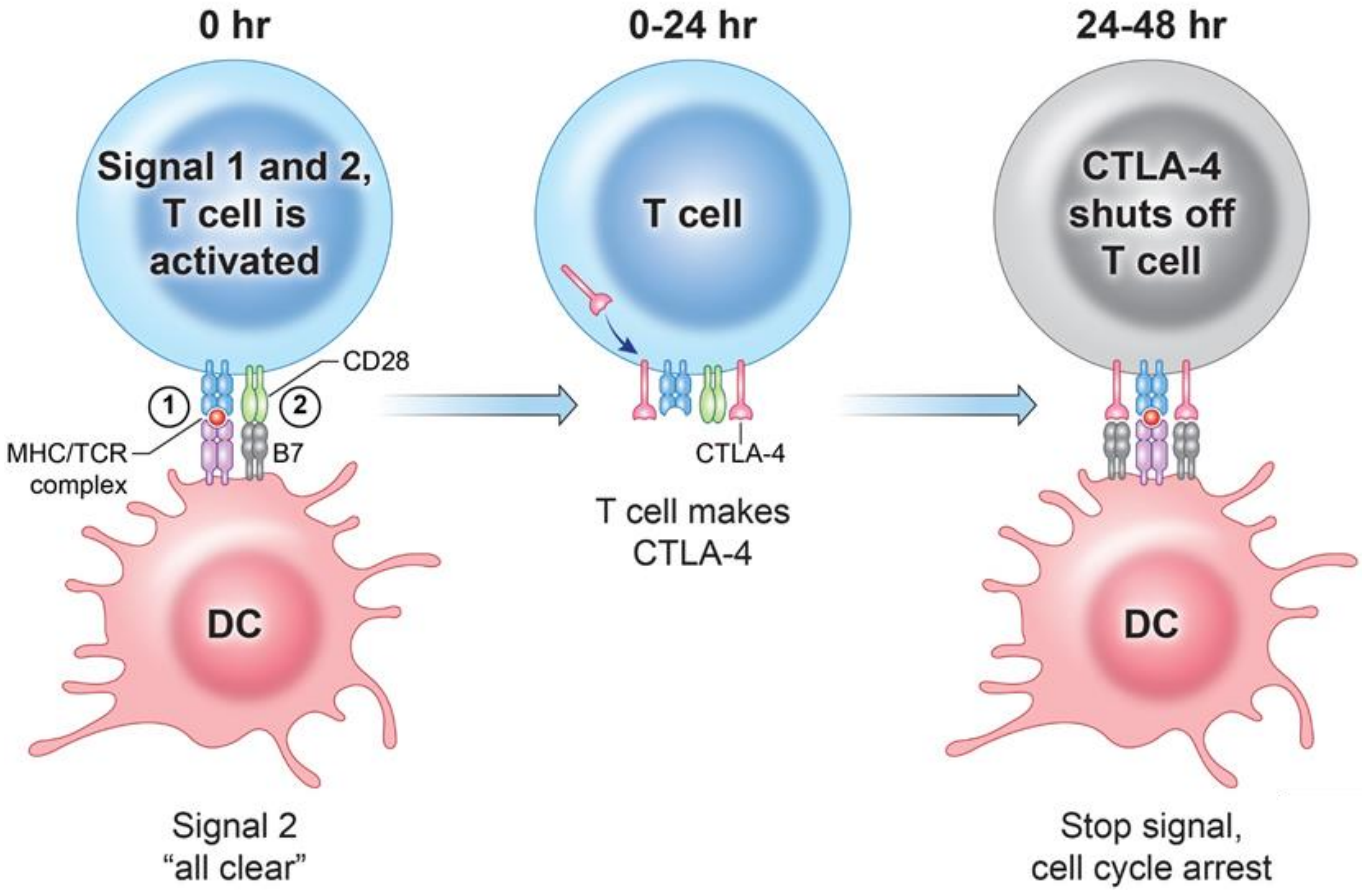
The CTLA-4 Checkpoint

- **C**ytotoxic **T**-**L**ymphocyte **A**ssociated Protein **4**
- Also known as CD152
- Negative regulator of T cell activation



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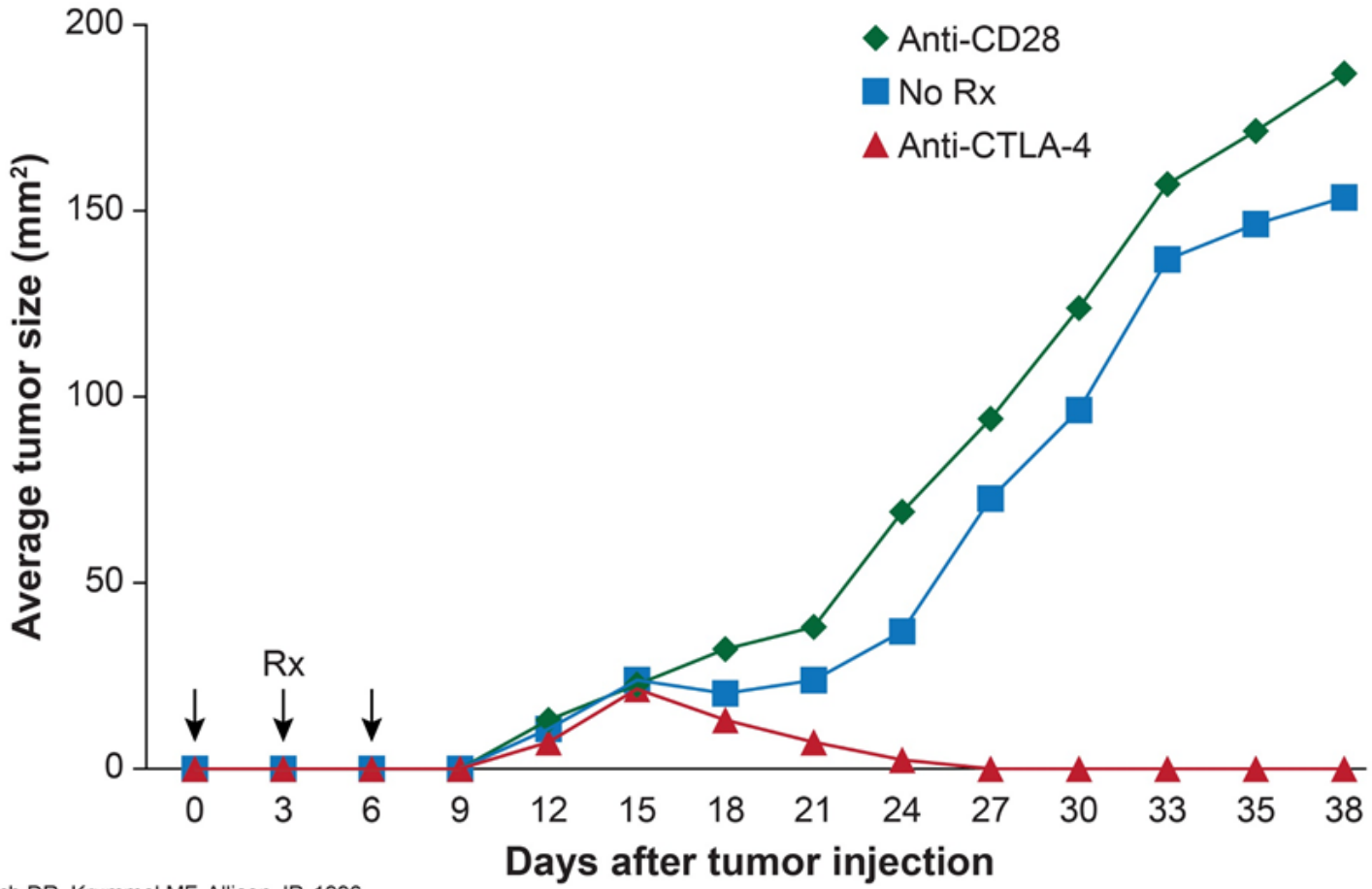
Anti-CTLA-4 induces regression of transplantable colon carcinoma



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

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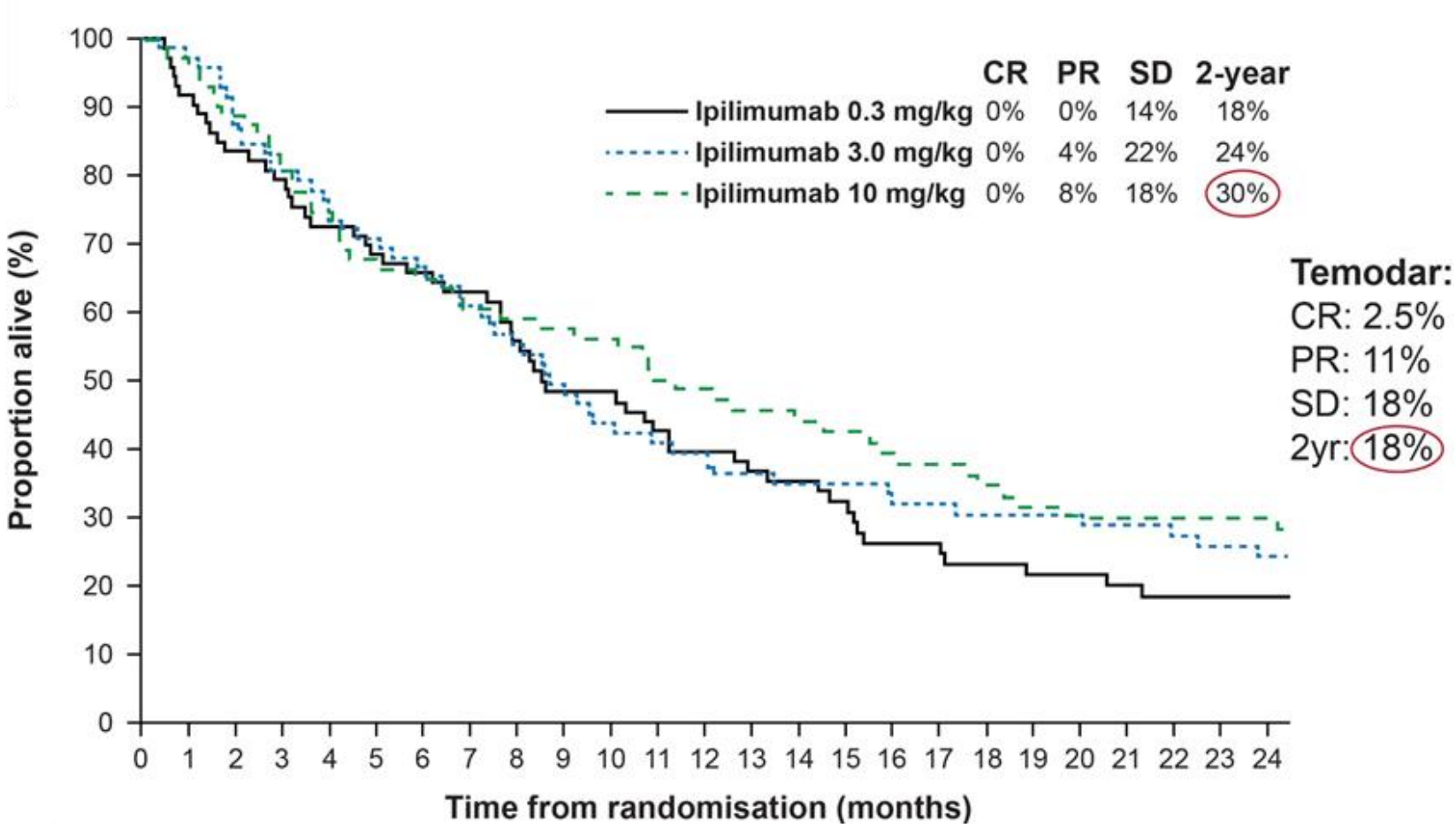
Ipilimumab (human anti CTLA-4)

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



Wolchok et al. Lancet Oncol 2010

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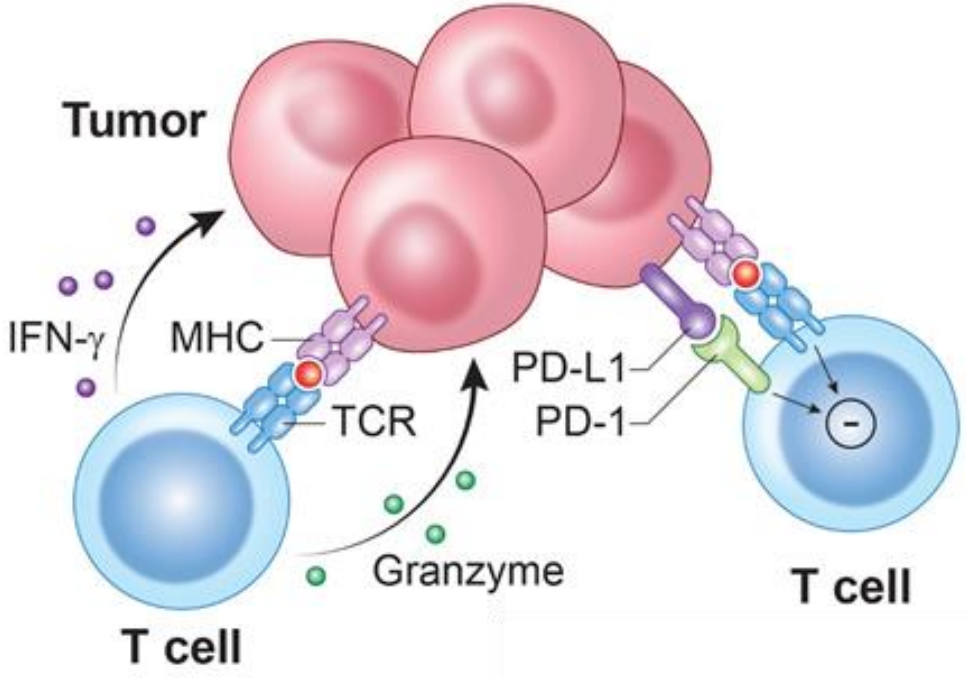
The PD-1/PD-L1 Checkpoint

- 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-γ
  - Oncogenic signaling pathways



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

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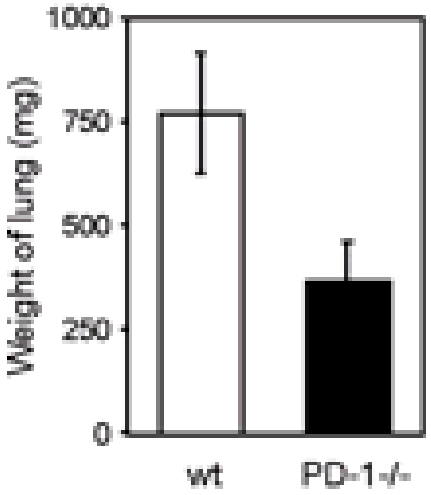
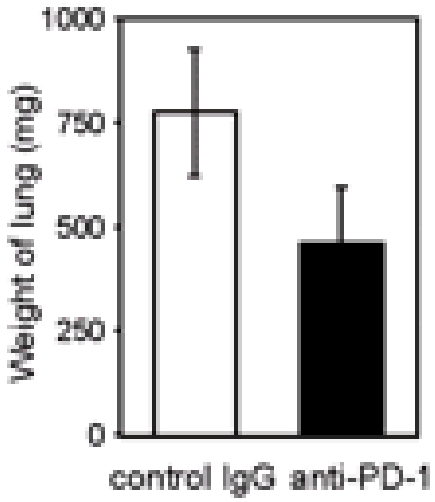
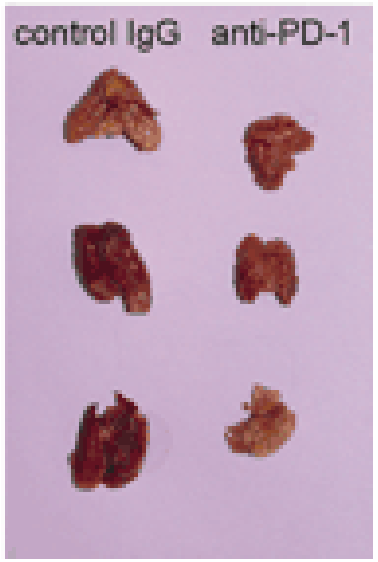
Anti-PD-1 Slows Tumor Growth in Pre-clinical Models

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







Iwai et al. Internat. Immunol 2004

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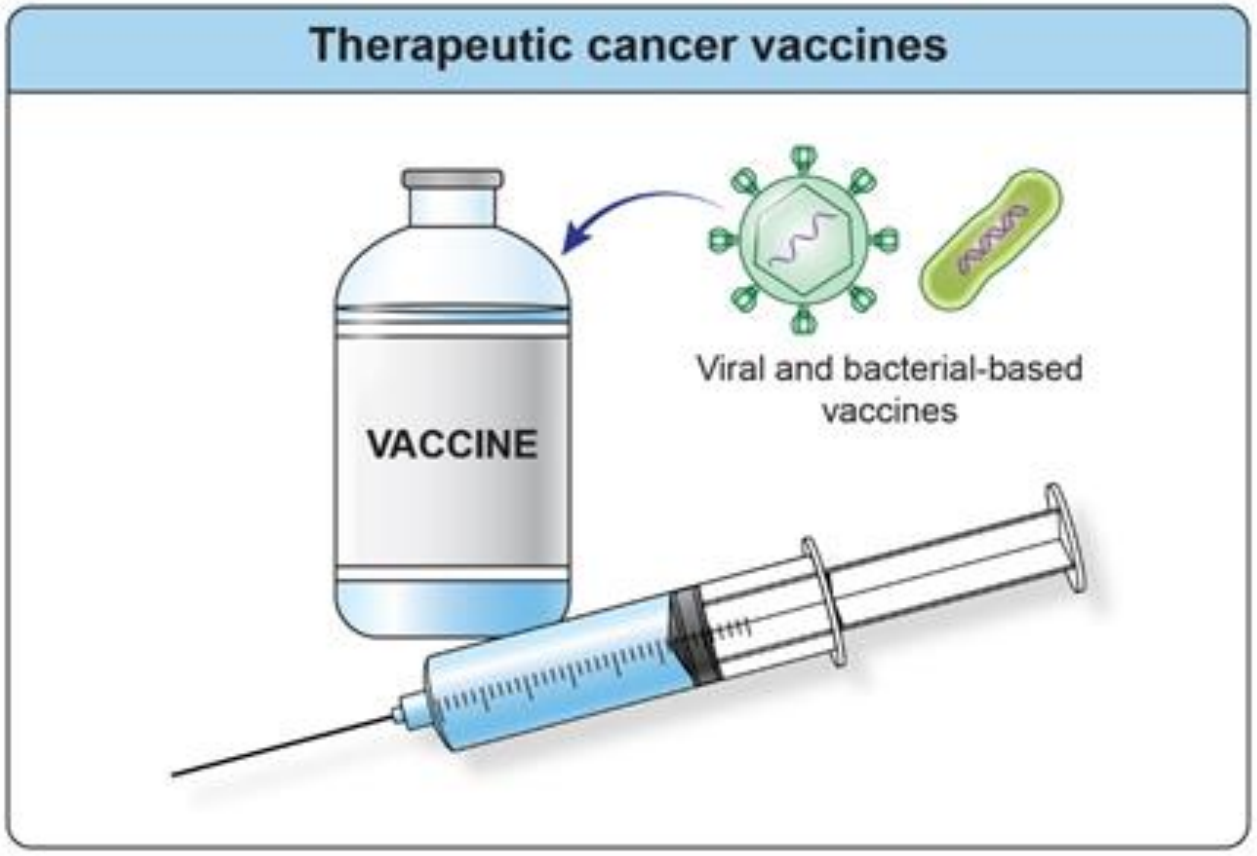
Therapeutic Cancer Vaccines

- 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.



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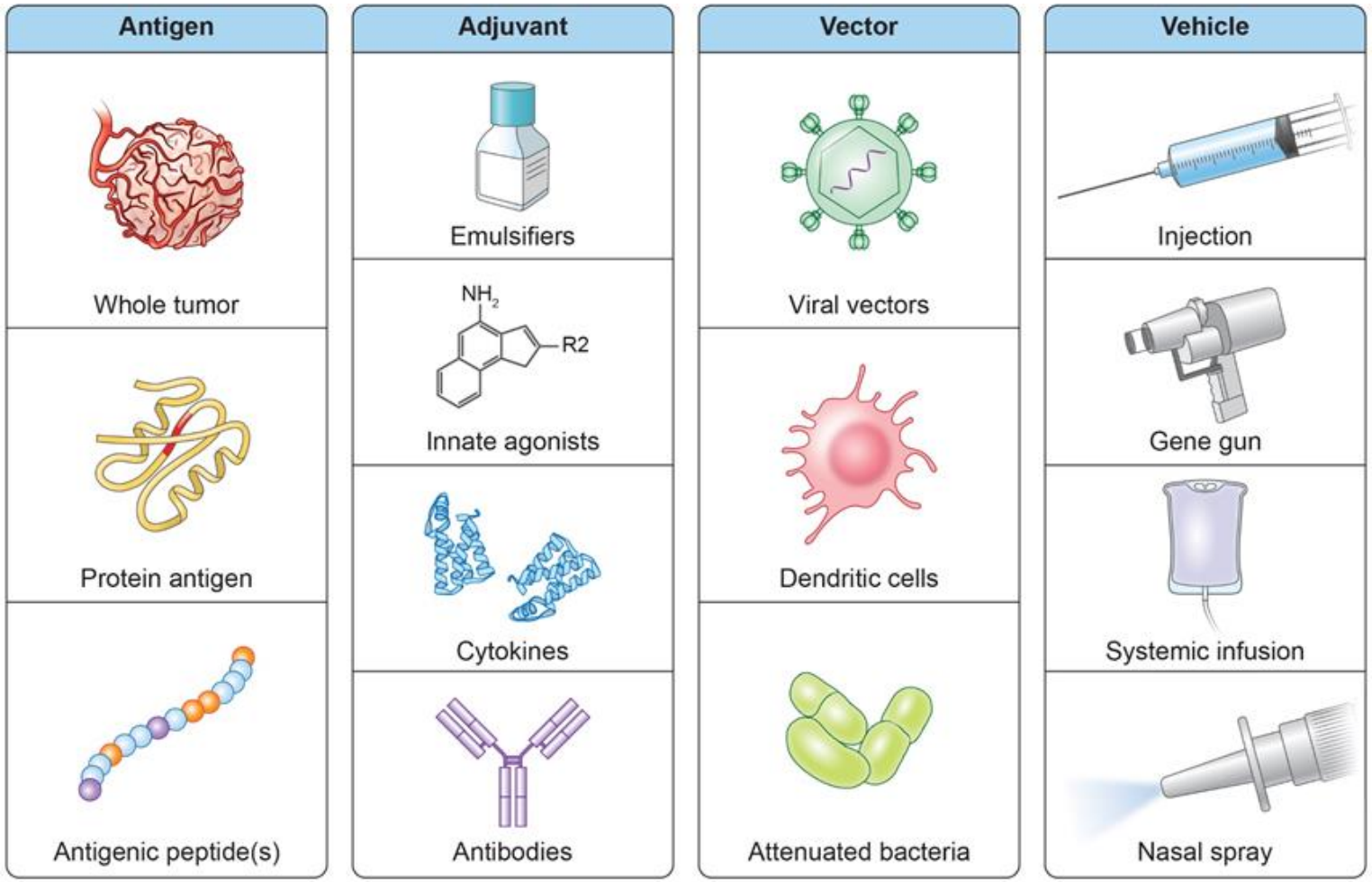
Components of a Cancer Vaccine



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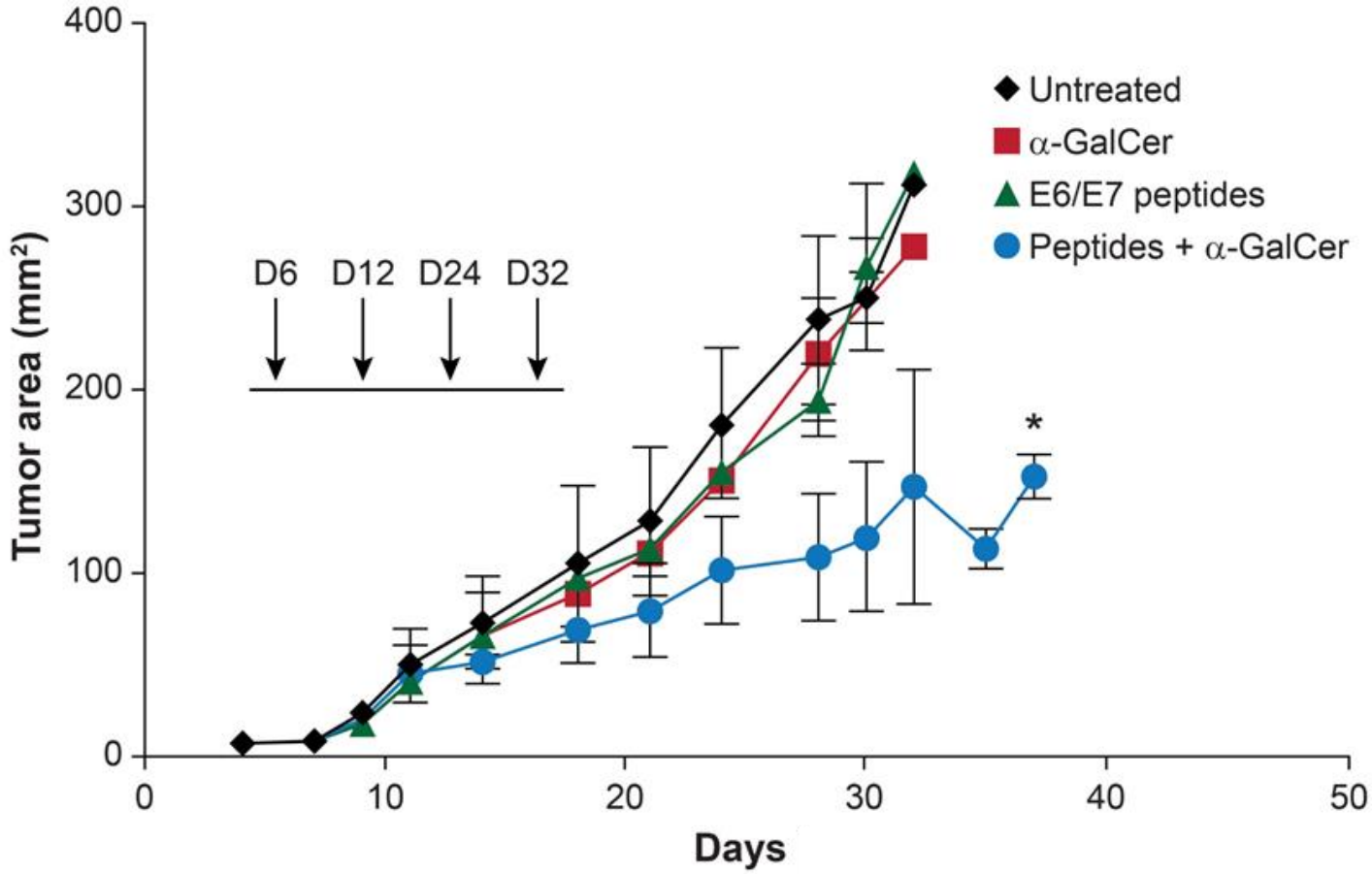
An intra-nasal HPV E6/E7: α-GalCer vaccine slows growth of TC-1 tumors



Shailbala Singh

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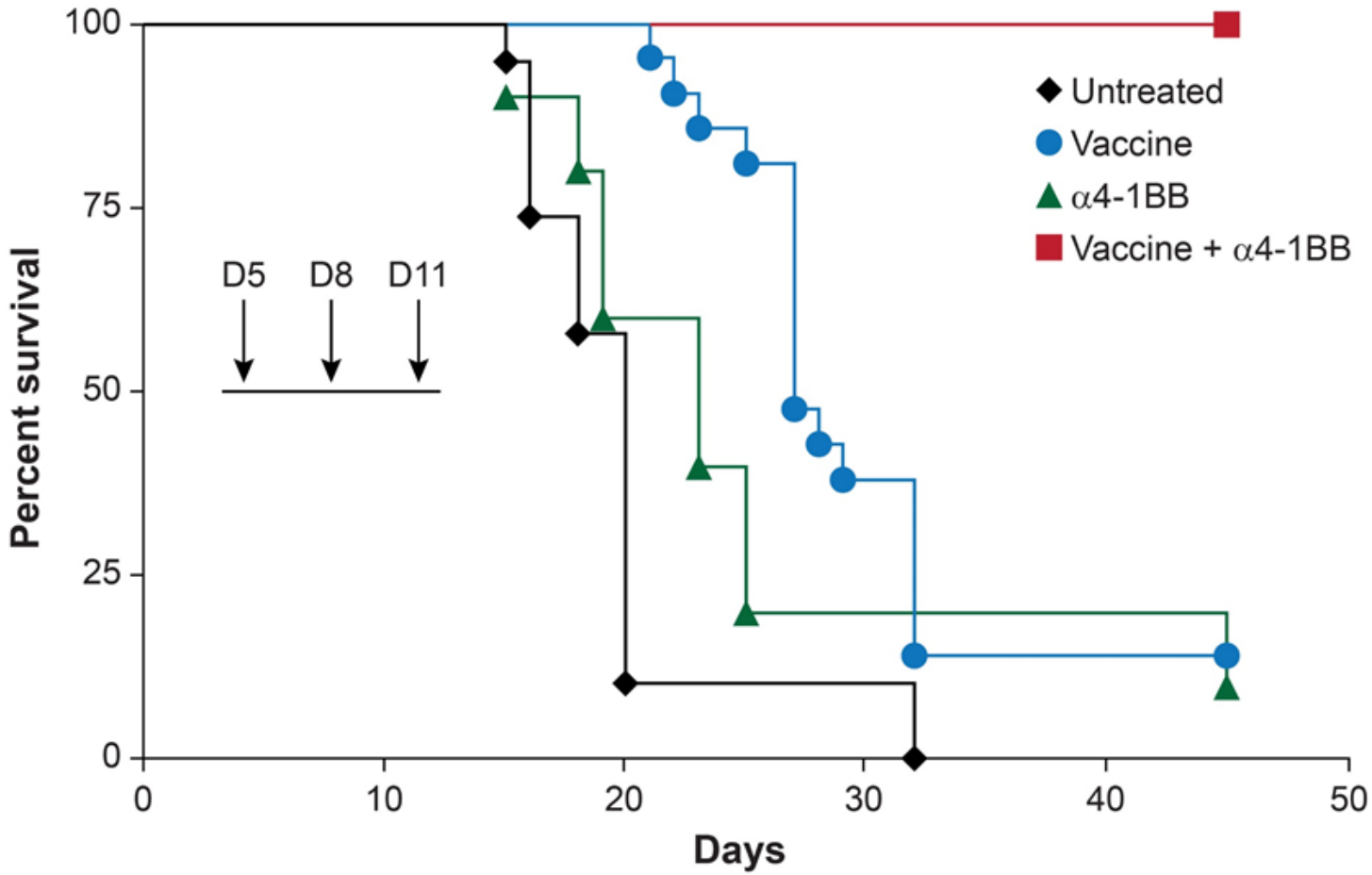
4-1BB agonist antibody and HPV E6/E7 vaccine synergize in curing TC-1 Tumors



Todd Bartkowiak, M.S.

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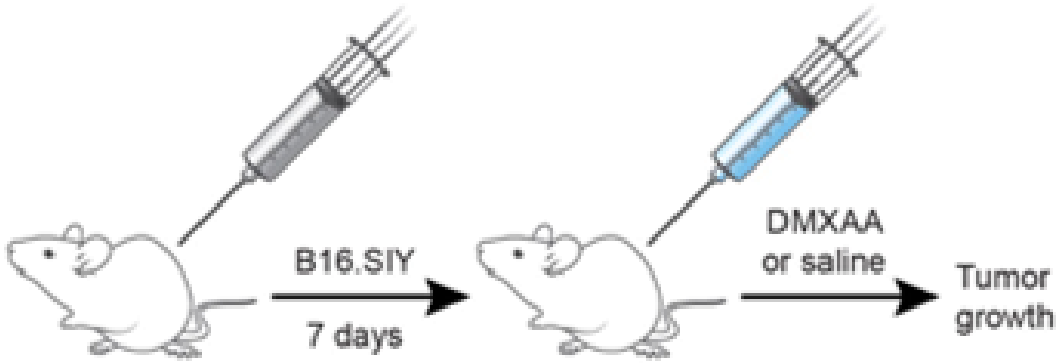
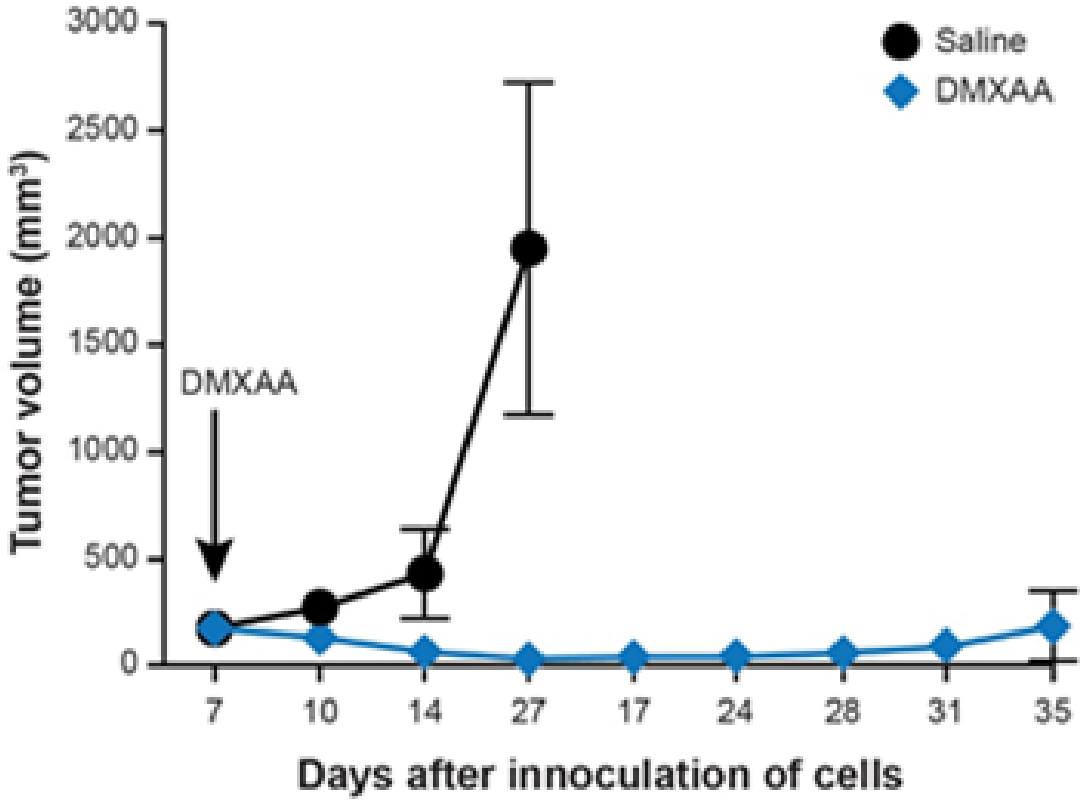
Intratumoral Injection of Innate Immune Agonists:
The Direct Vaccination Approach

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





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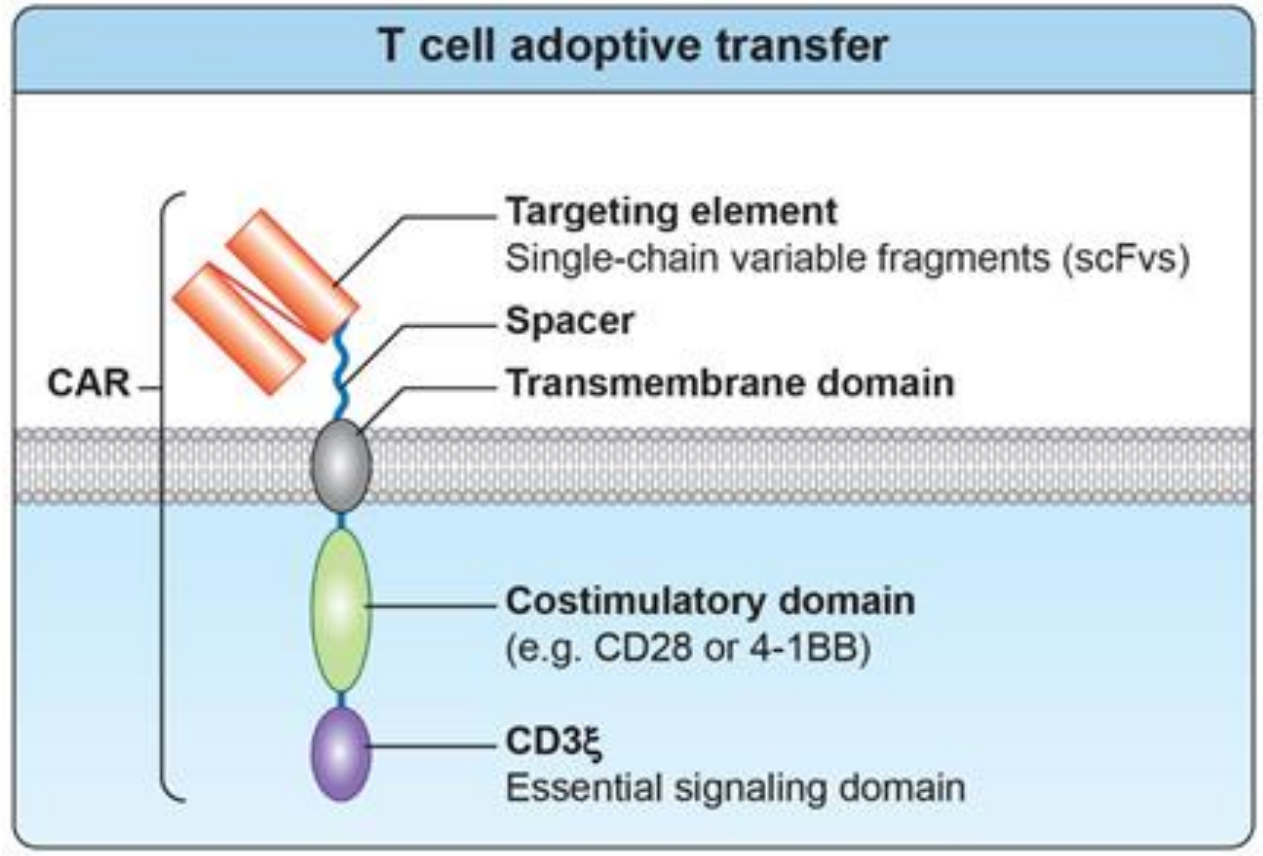
Adoptive Cell Transfer

- 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



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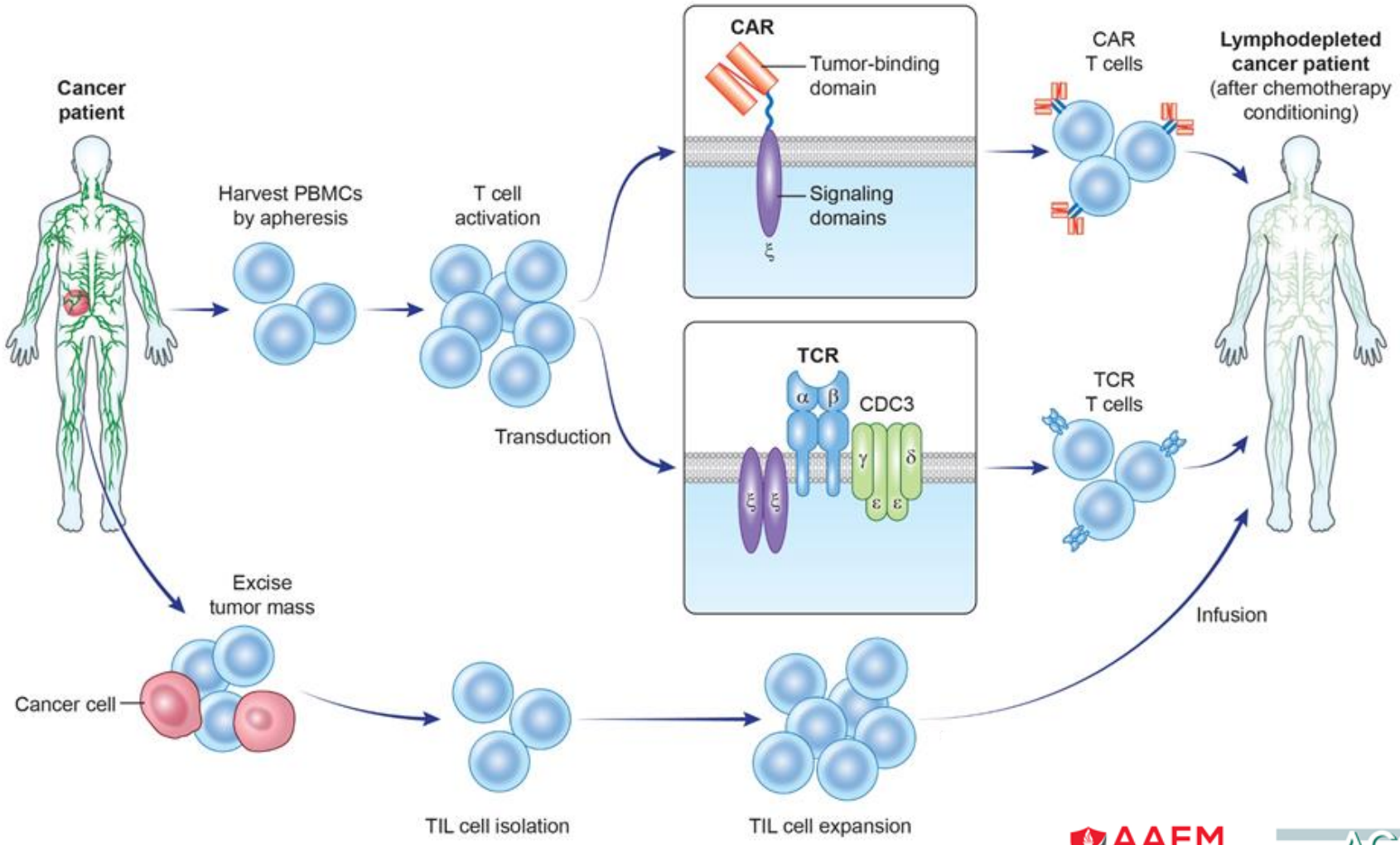
Adoptive Cell Therapy Process



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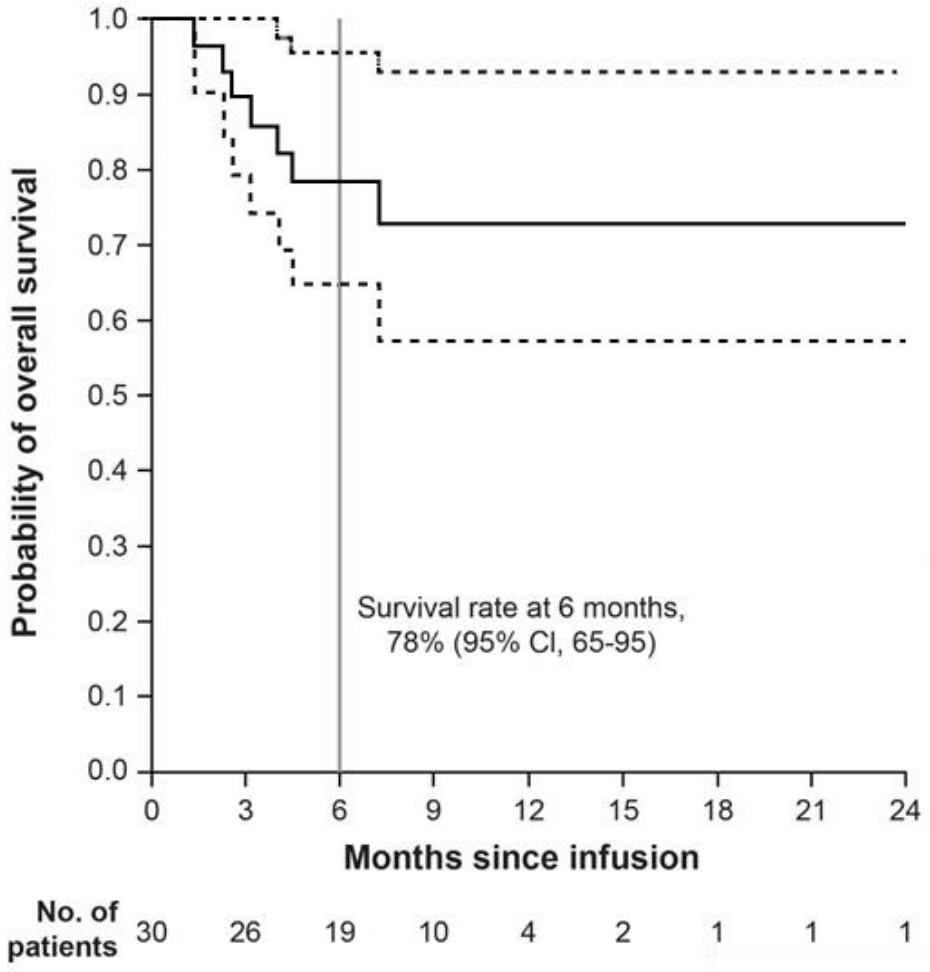
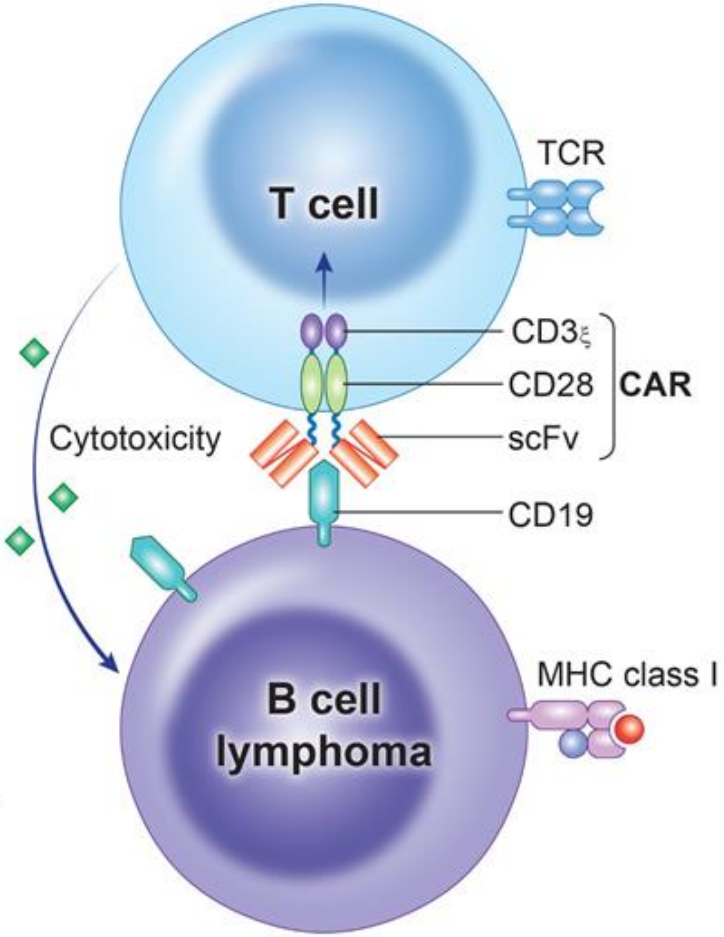
CD19 CAR T Cell Therapy for Relapsed B Cell ALL



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.



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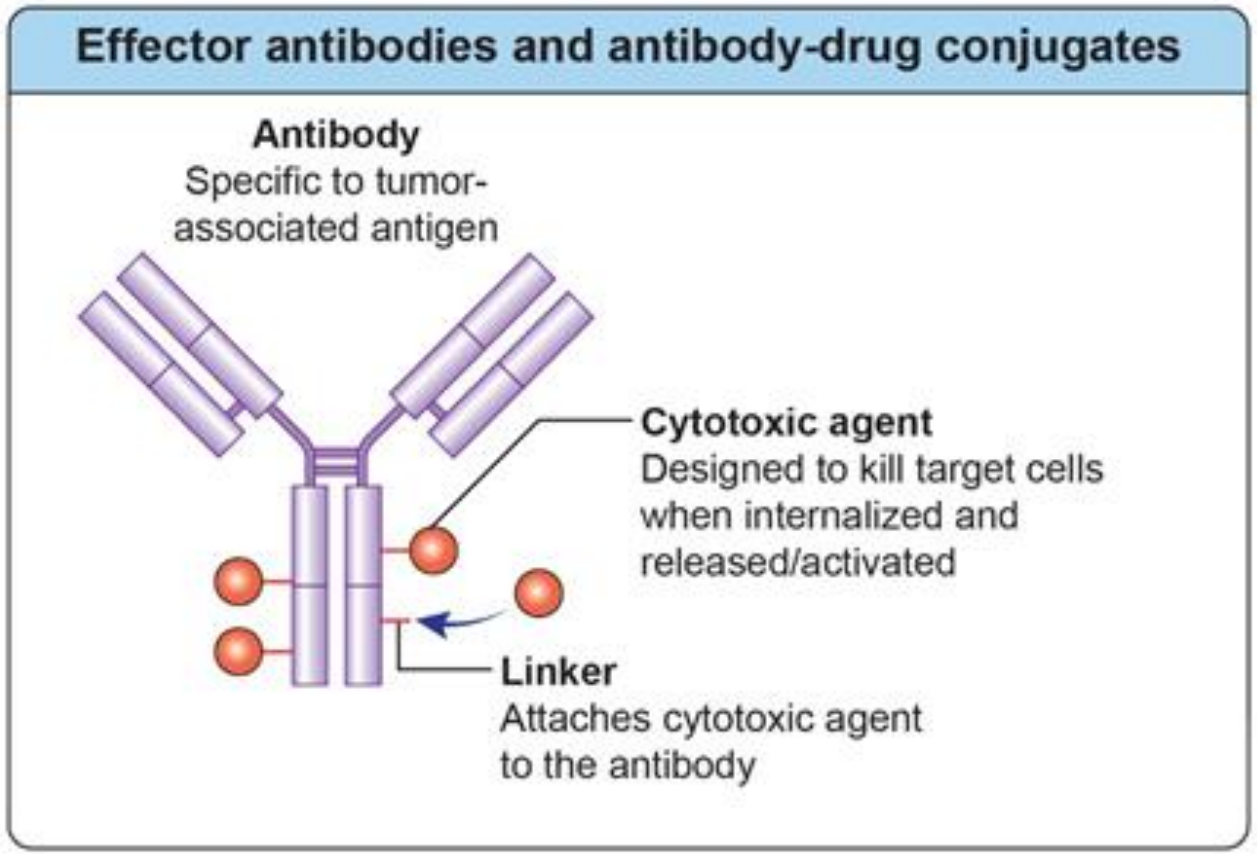
Effector Antibodies and Antibody-drug Conjugates (ADCs)

- 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



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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

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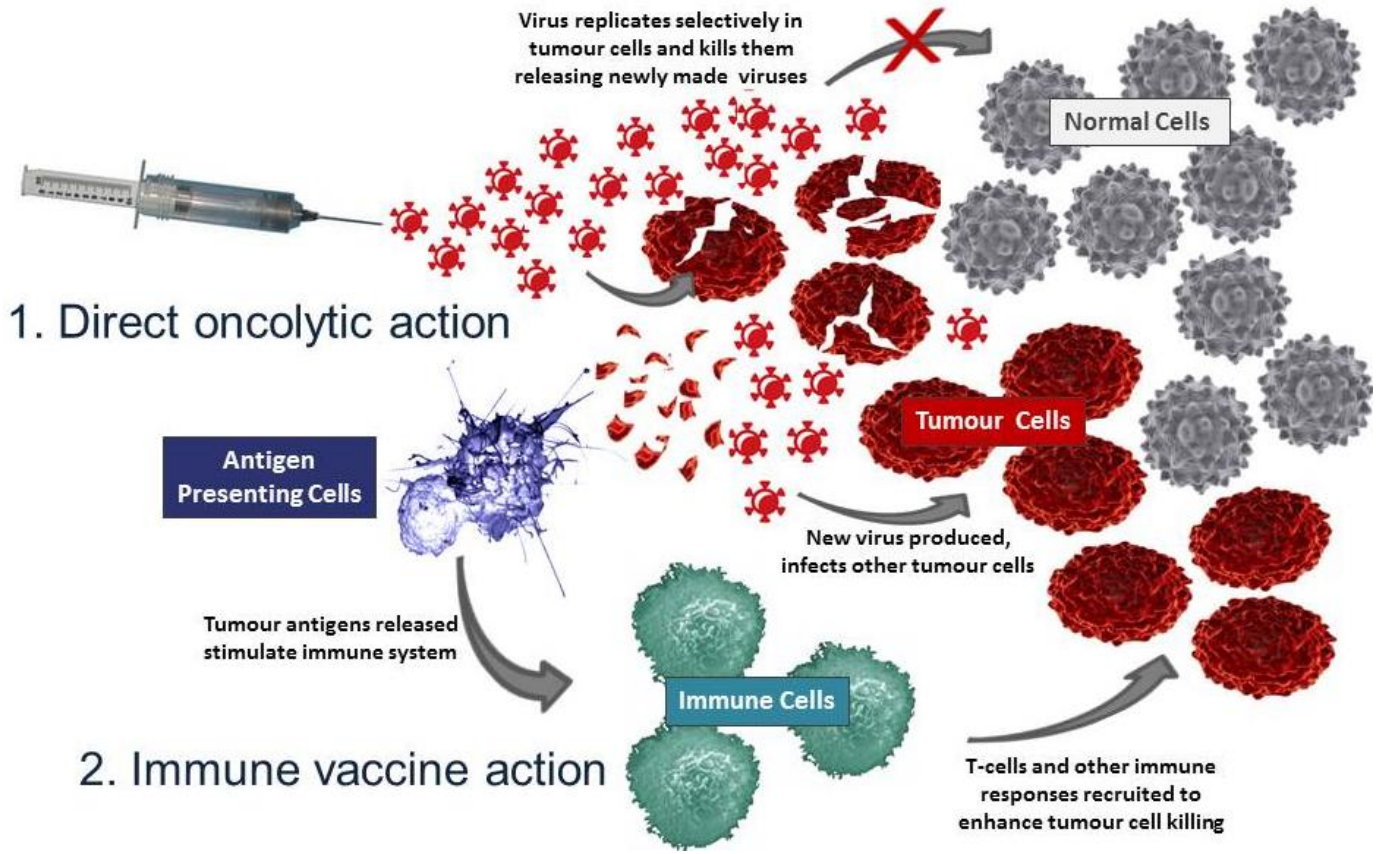
Oncolytic Viruses

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



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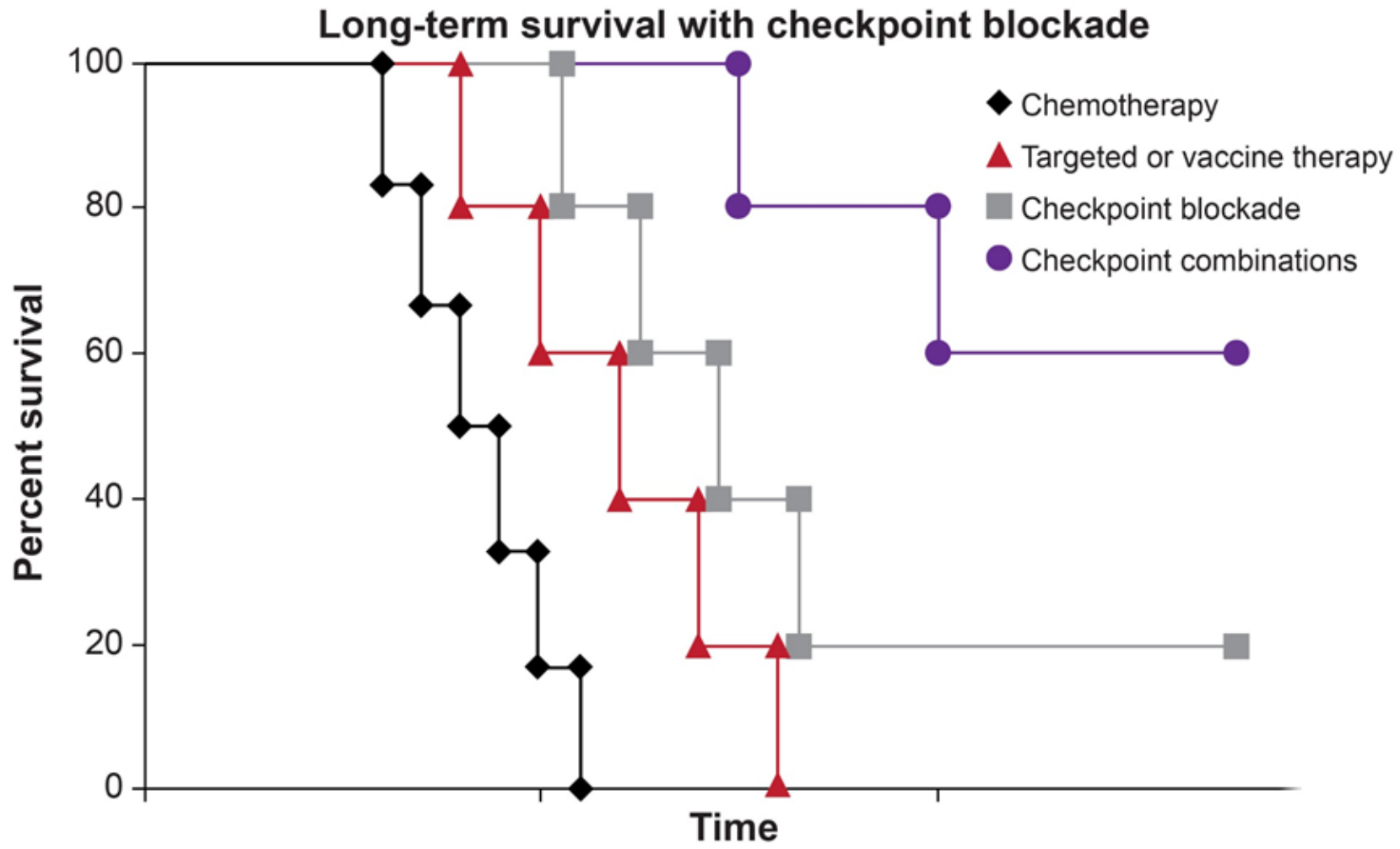
Combination Immunotherapies



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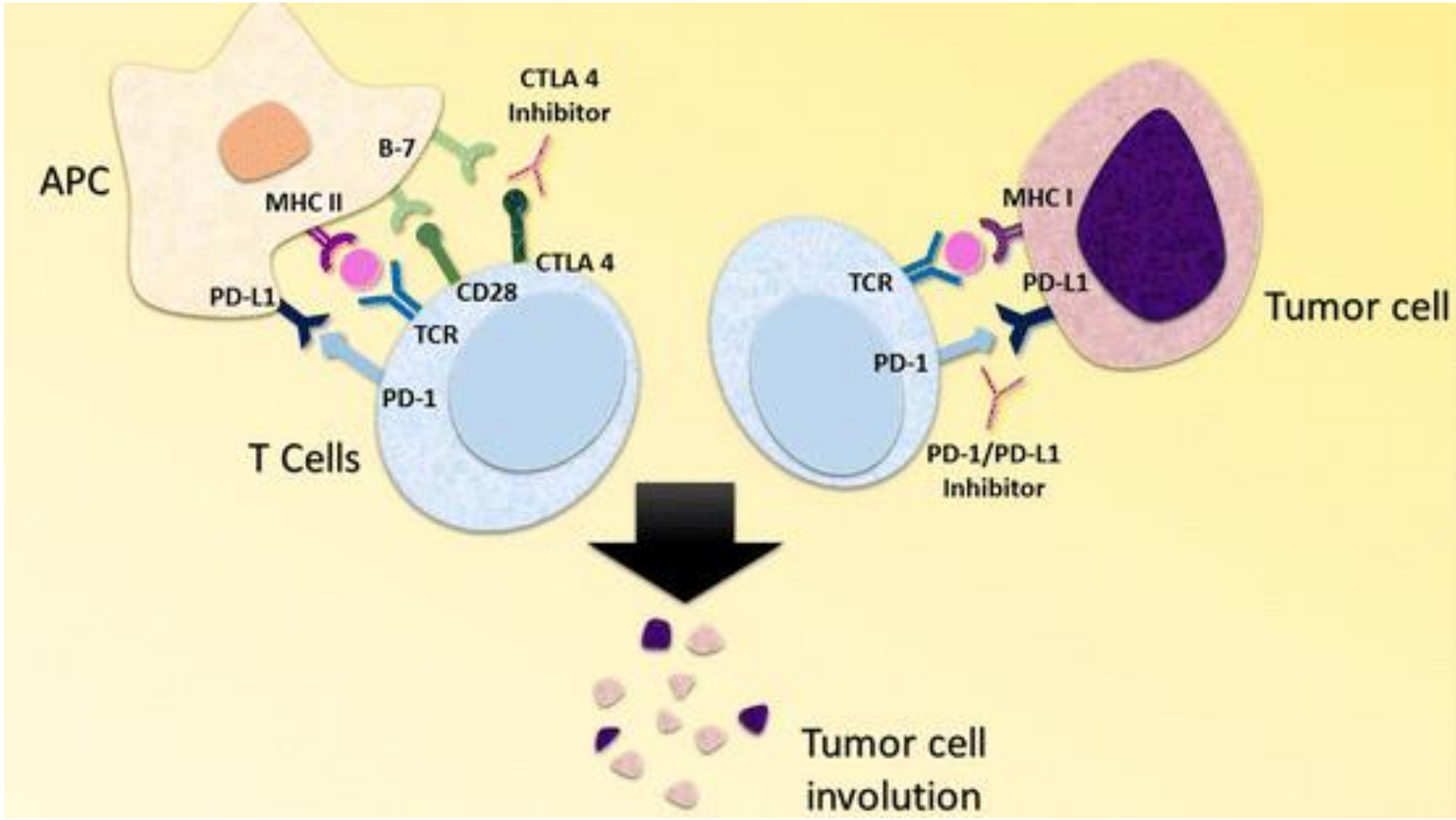
Combination Immunotherapies

Dual CTLA-4 and PD-1 inhibition



Chae et al. JITC 2018

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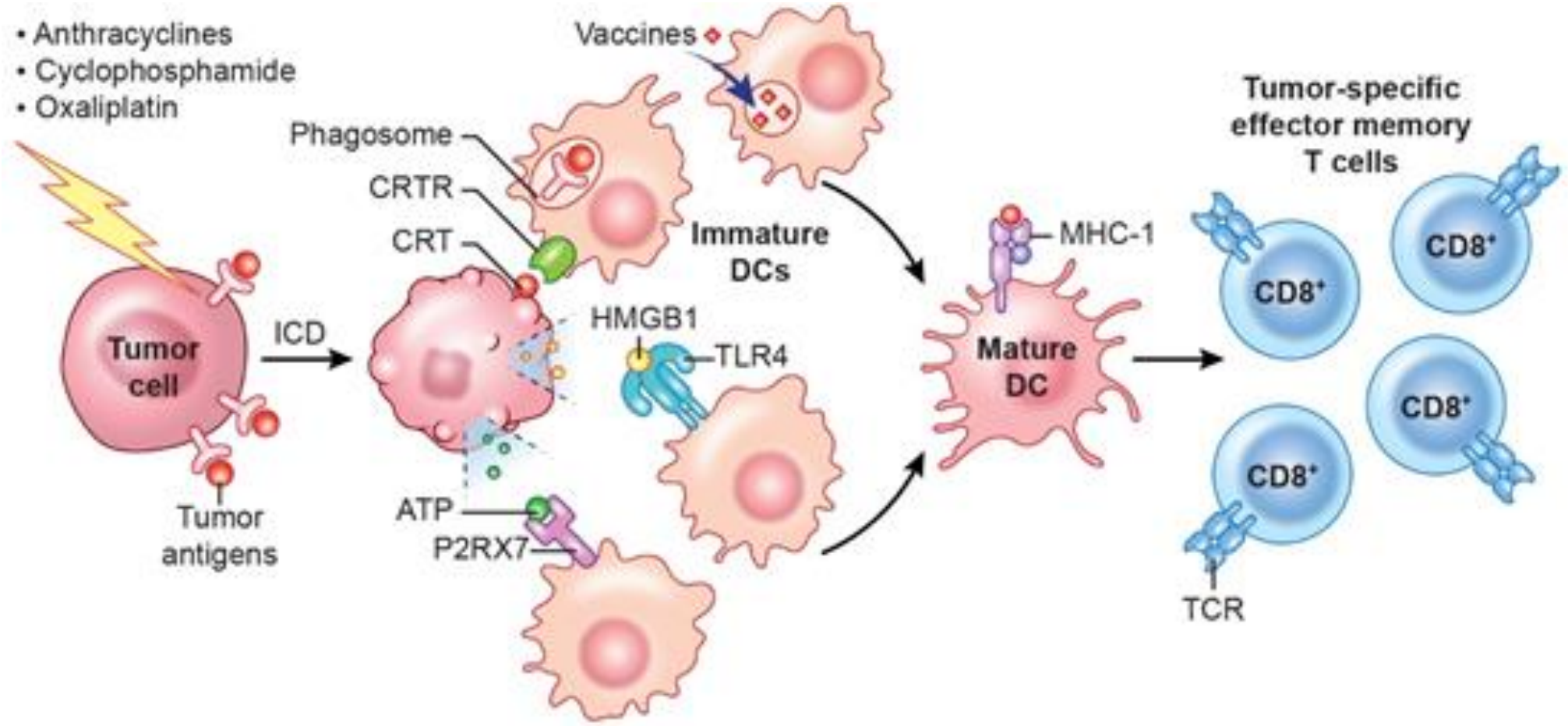
Combination Immunotherapies

Chemotherapy can induce an immune response



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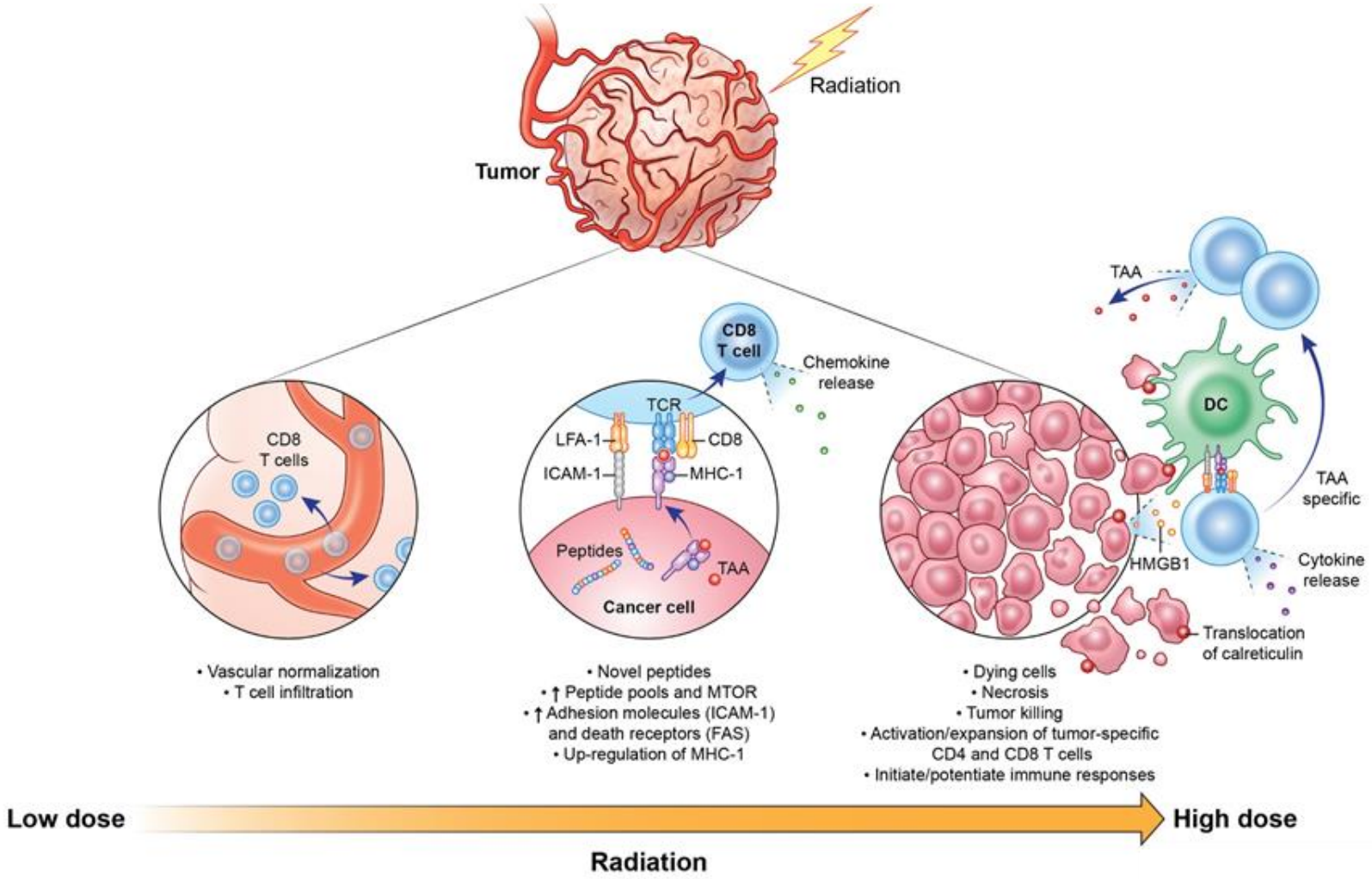
Combination Immunotherapies

Radiotherapy can induce an immune response



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

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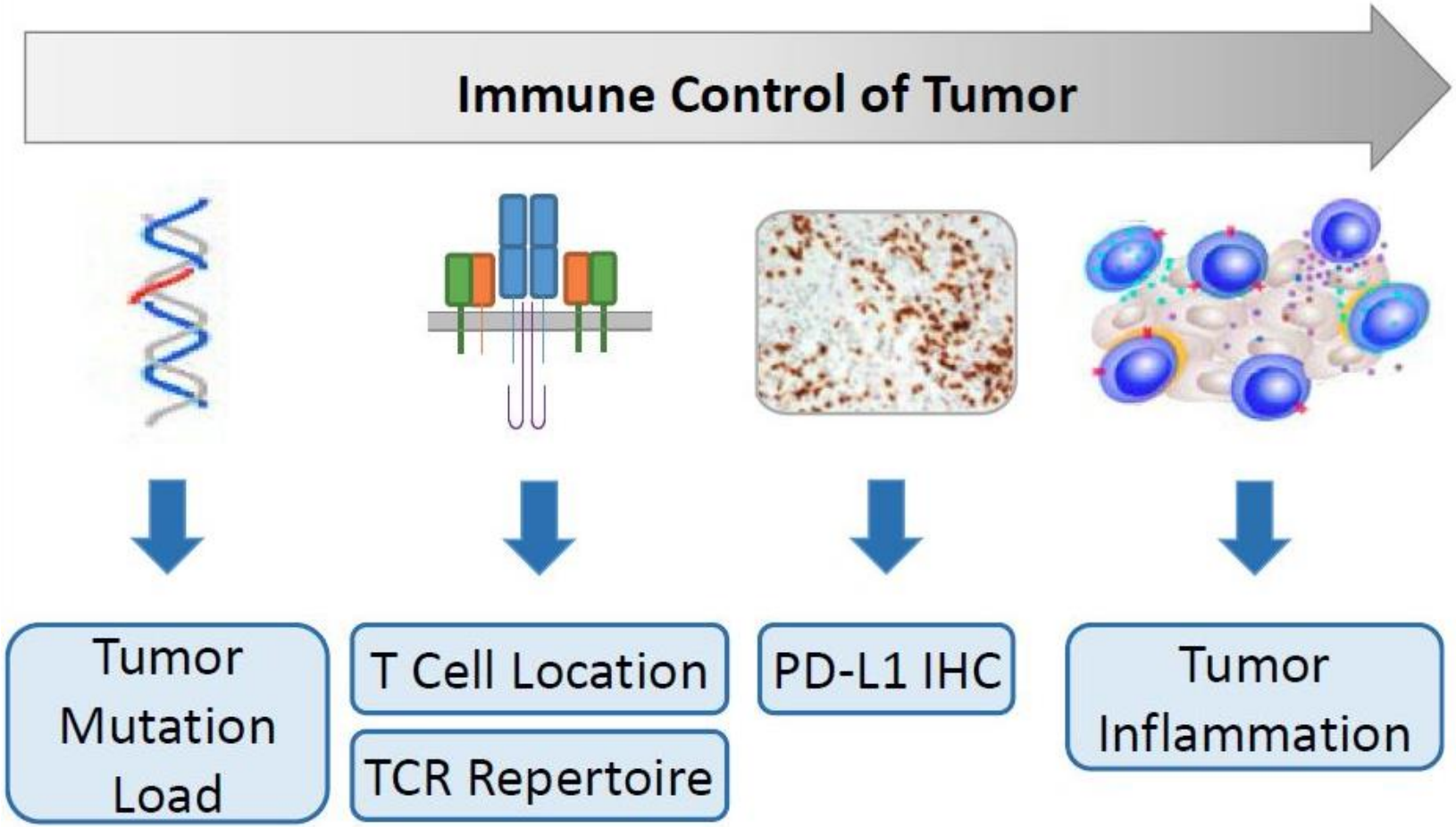
Immunotherapy Biomarkers



Cesano et al. Biomedicines 2018

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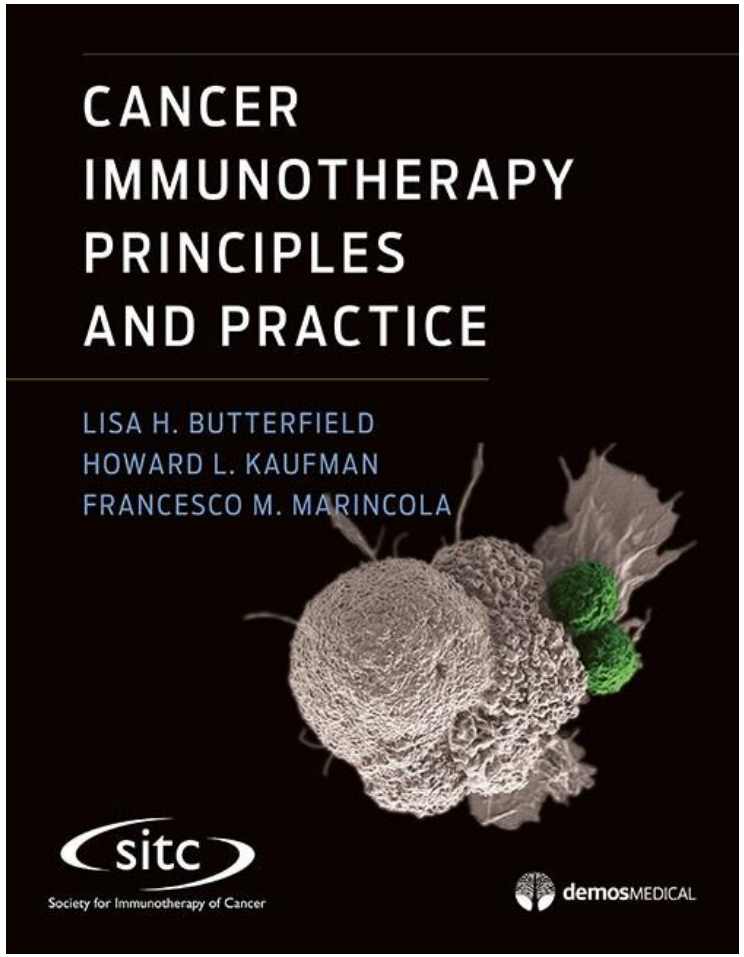
Further Resources



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Cancer Immunotherapy CONNECT

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