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ADVANCES IN Cancer IMMUNOTHERAPY™

Basic Principles of Cancer Immunotherapy

Theodore F. Logan, MD

Associate Professor of Clinical Medicine

Indiana University Simon Cancer Center

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Disclosures

- Contracted Research:
  - Abbott Laboratories, Abraxis BioScience, Acceleron Pharma, Amgen, Argos Therapeutics, AstraZeneca, AVEO, BioVex, BMS, Eisai, Lilly, GlaxoSmithKline, Roche, Immatics, Merck, Novartis, Pfizer, Roche, Synta, Threshold Pharmaceuticals, Millennium, TRACON Pharma, Cerulean Pharma, EMD Serono, Prometheus Laboratories, Macrogenics, Peloton Therapeutics, Iovance Biotherapeutics, MedImmune, Dynavax
- 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.

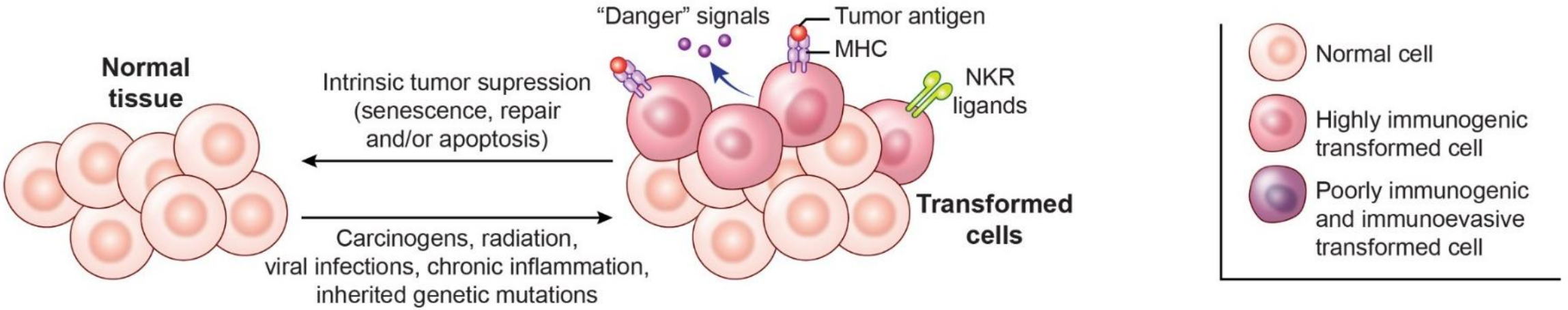
Why Does the Immune System Fail to Eliminate Cancer?

- 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

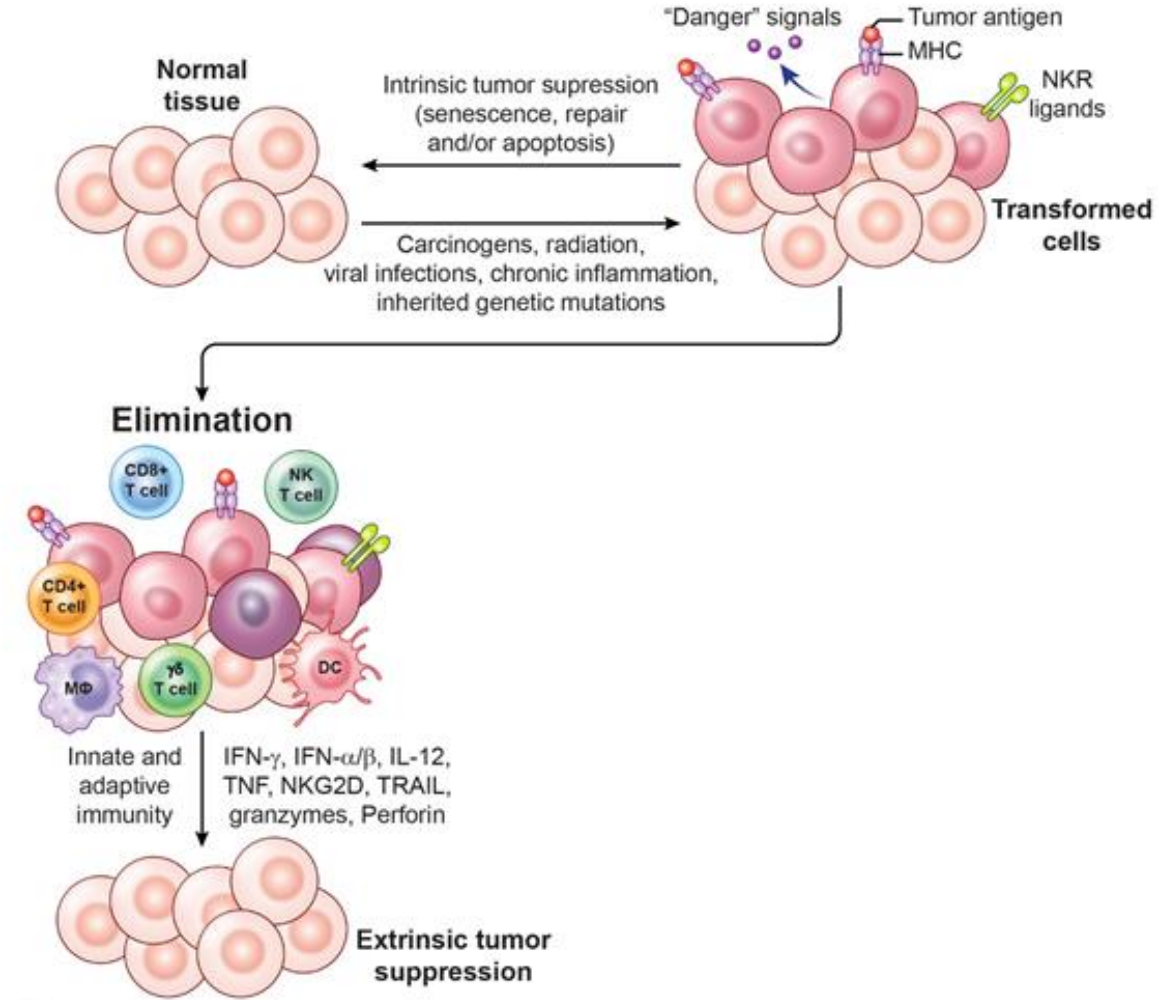
Development of Immunotherapy

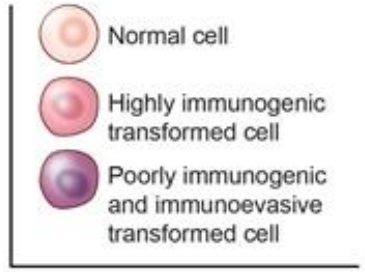
- Coley 1893 Coley's Toxin
- Shear 1941 Endotoxin
- Carswell/Old 1976 TNF
- Morgan/Gallo 1976 IL-2
- Berendt/North 1978 Endotoxin regression depends on T cells
- Rosenberg/others 1980s –beyond-clinical trials IL-2/cytokines etc.
- Ehrlich 1909 proposed immune system control of tumor
- Medawar 1950s allogeneic rejection
- Prehn/Main 1957 inbred mouse strains- MCA tumors differed from self-tumor Ag
- Burnet/Thomas 1957 Immunosurveillance disproved 1974, proved 2001
- Dunn 2002 Immune Editing hypothesis

The 3 E's of Cancer Immunoediting



The 3 E's of Cancer Immunoediting





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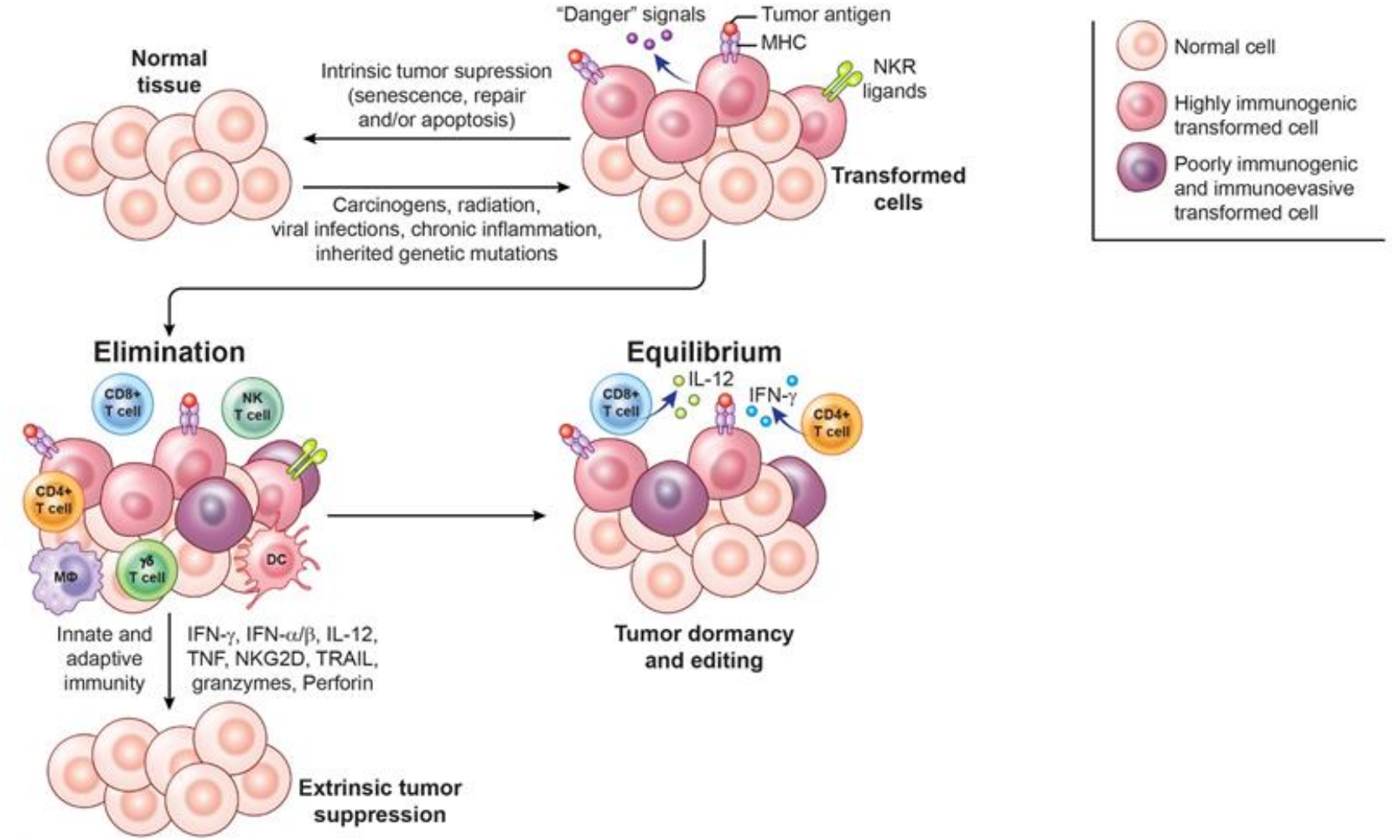

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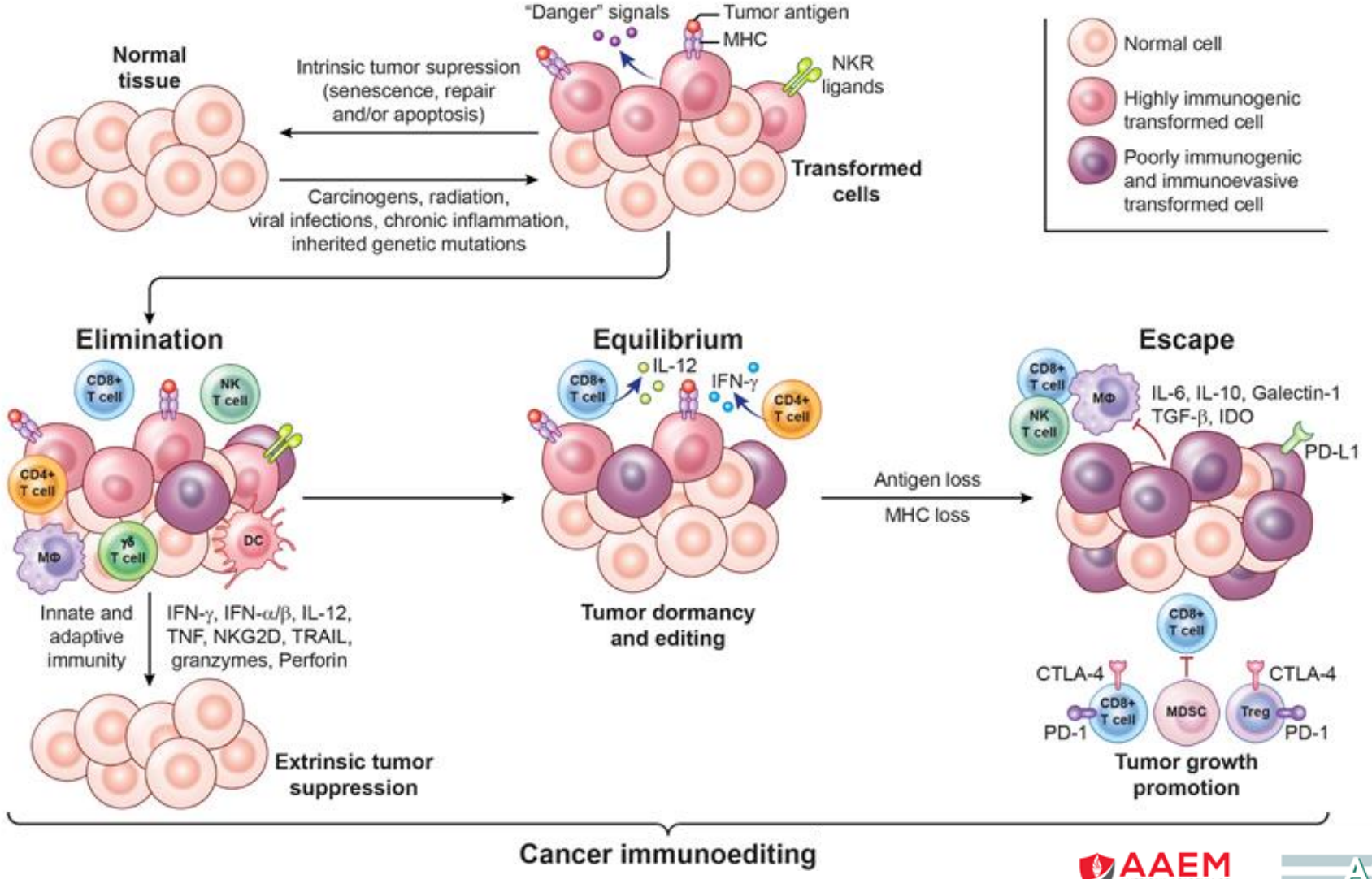
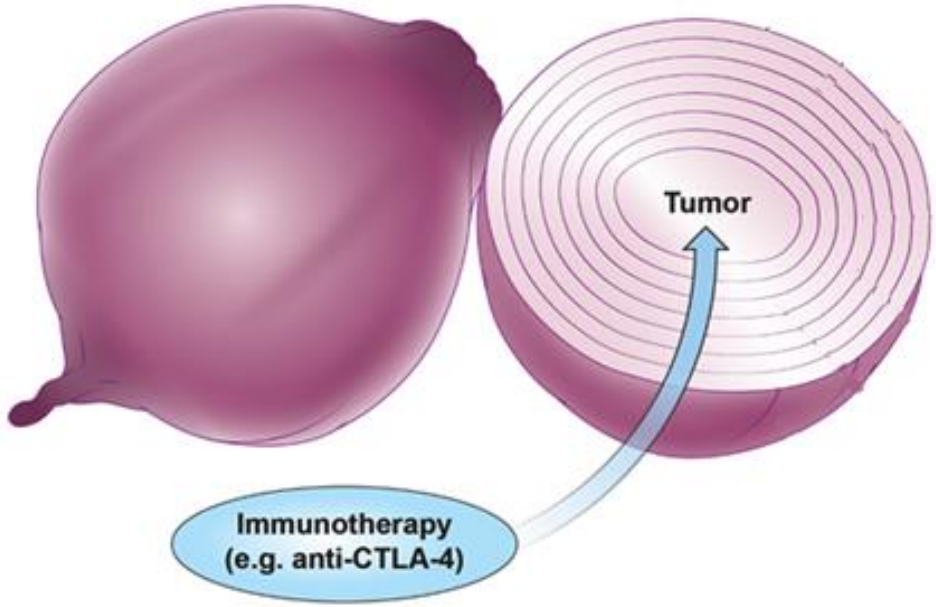
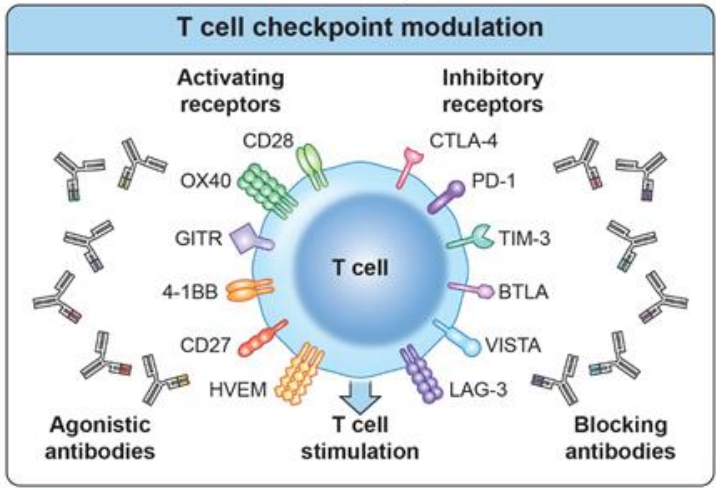


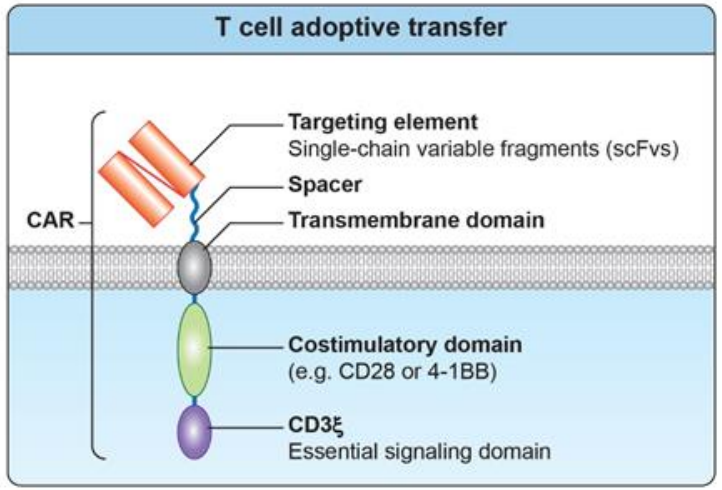
Multi-layered Immunosuppression

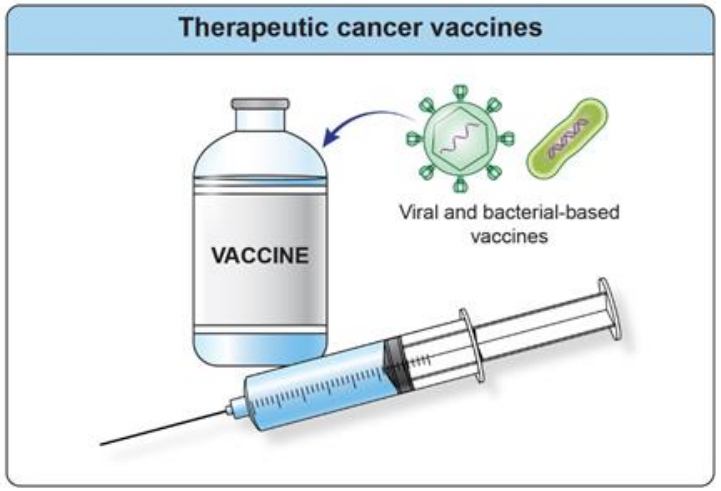
- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune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

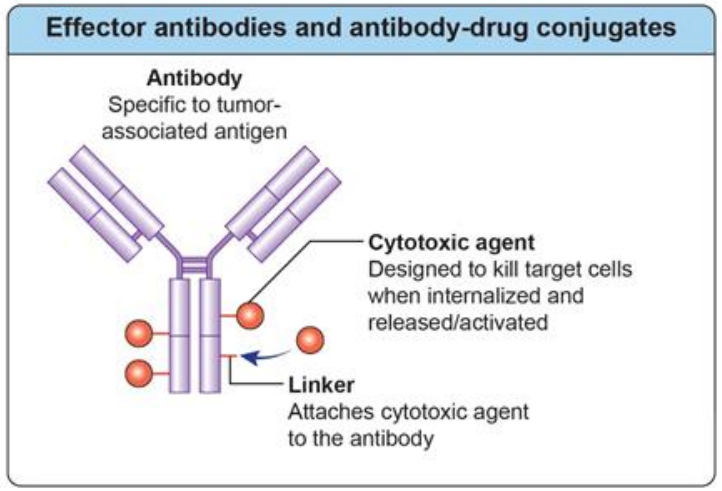


Types of Immunotherapy

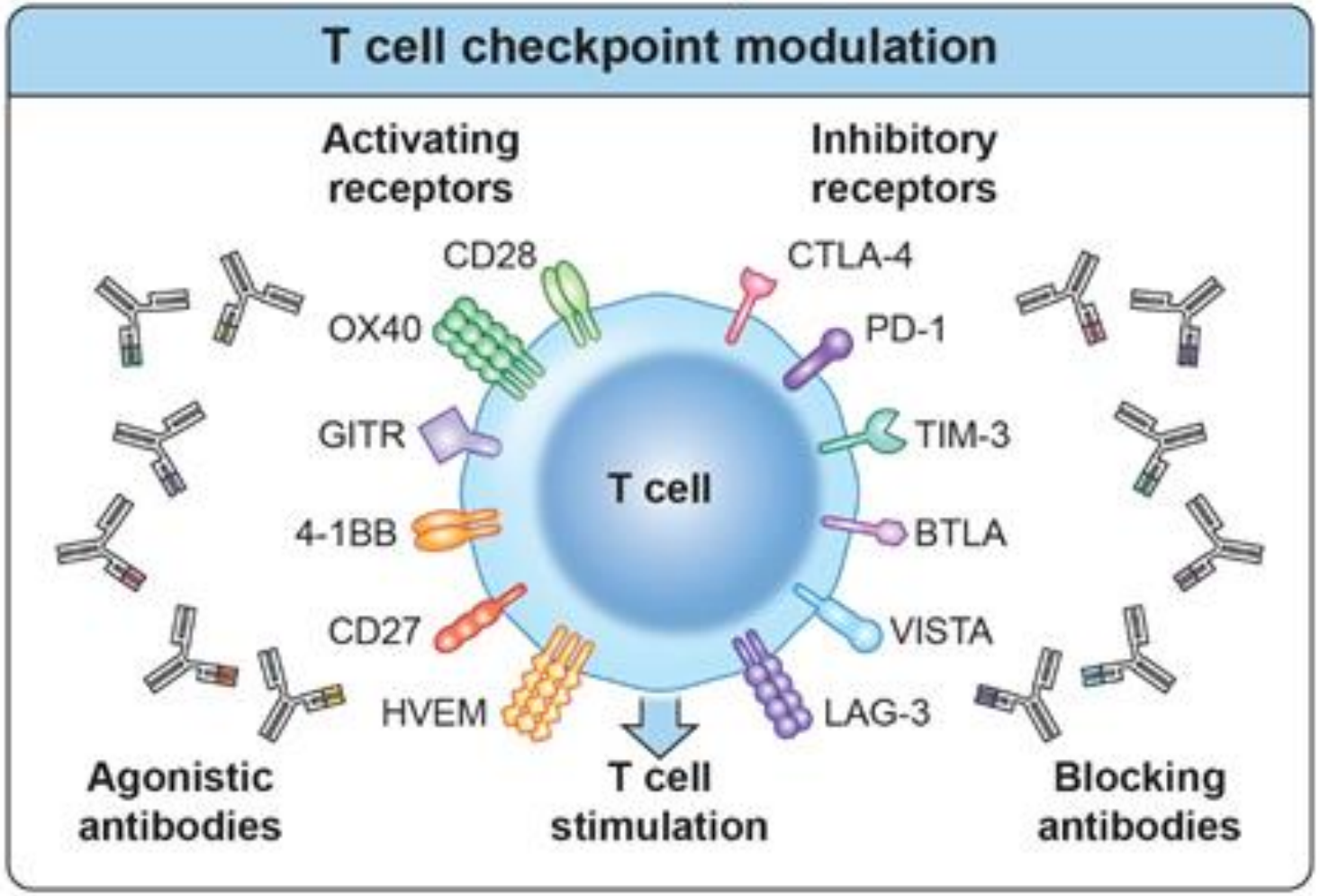




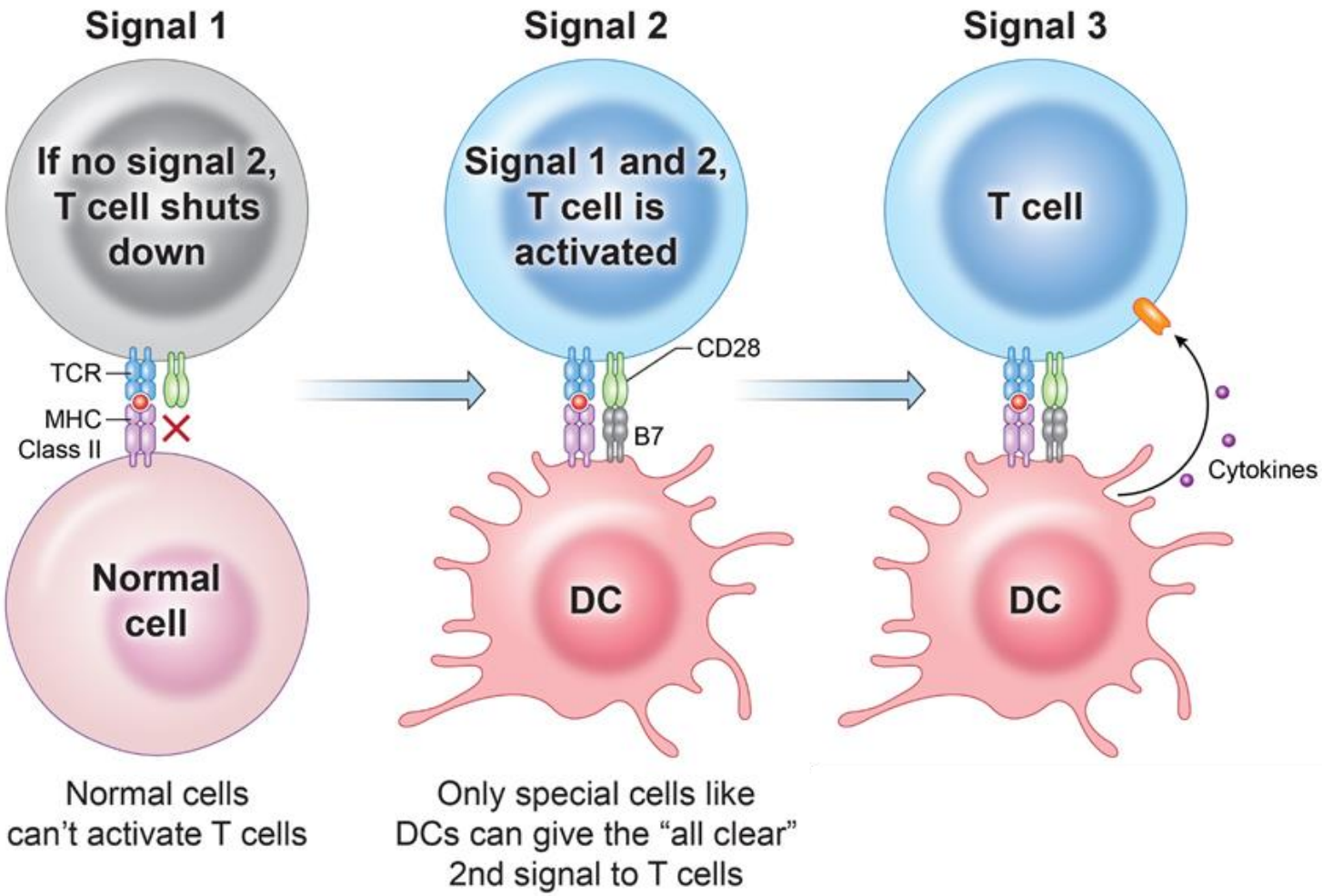




T cell Checkpoint Modulation

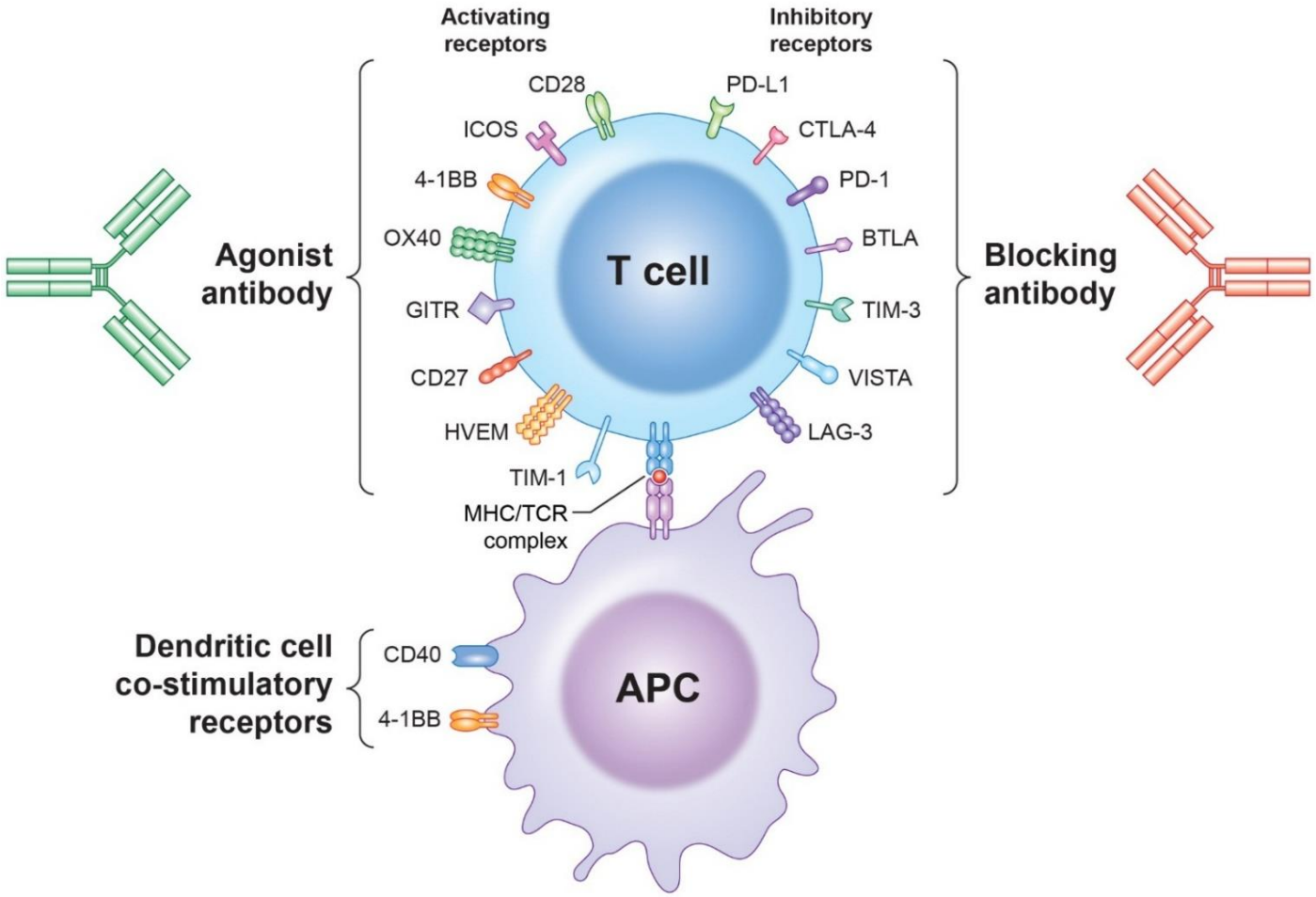


Antigen-specific T cell Activation



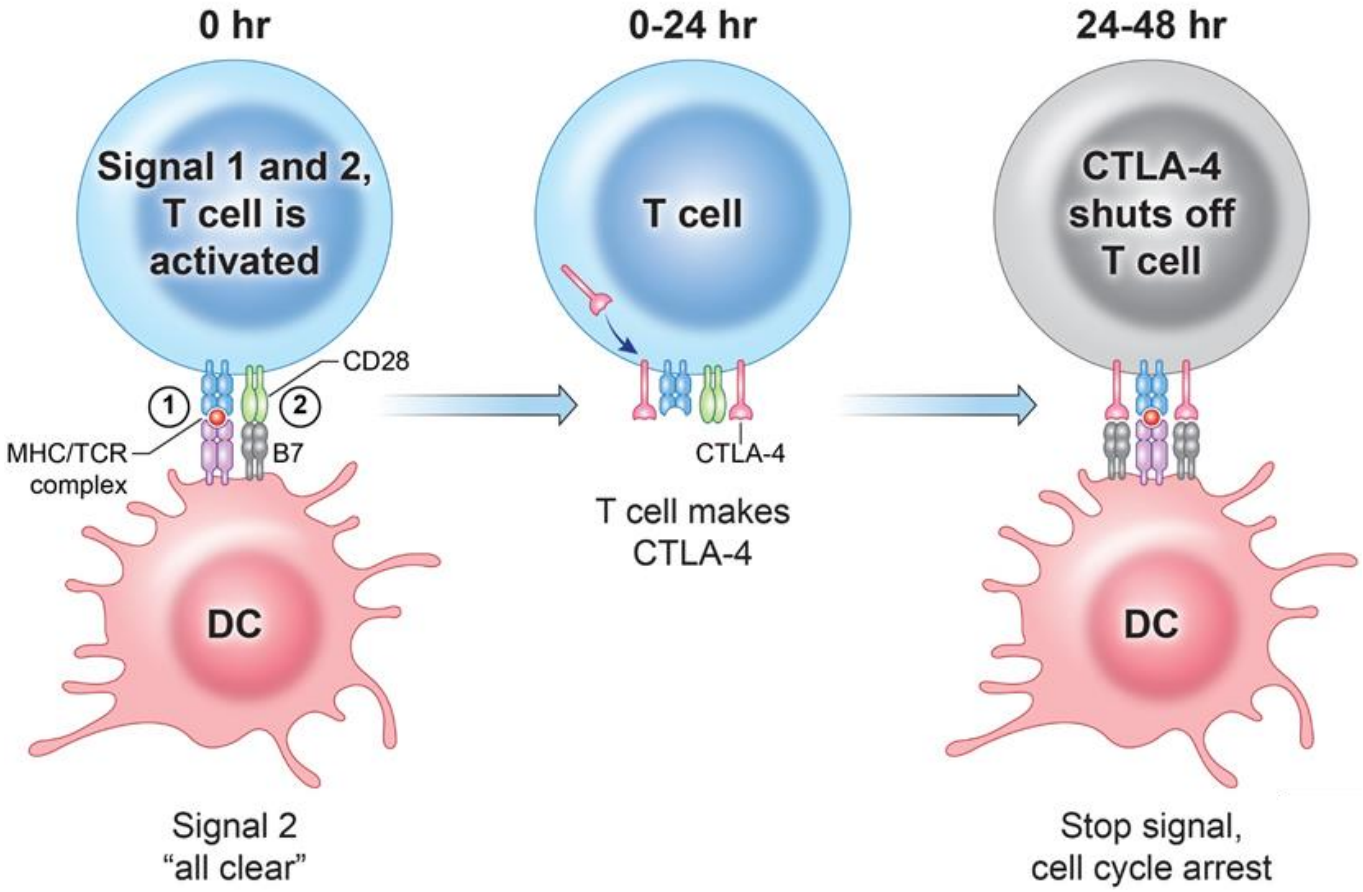
T Cell Checkpoint Modulation

- 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.

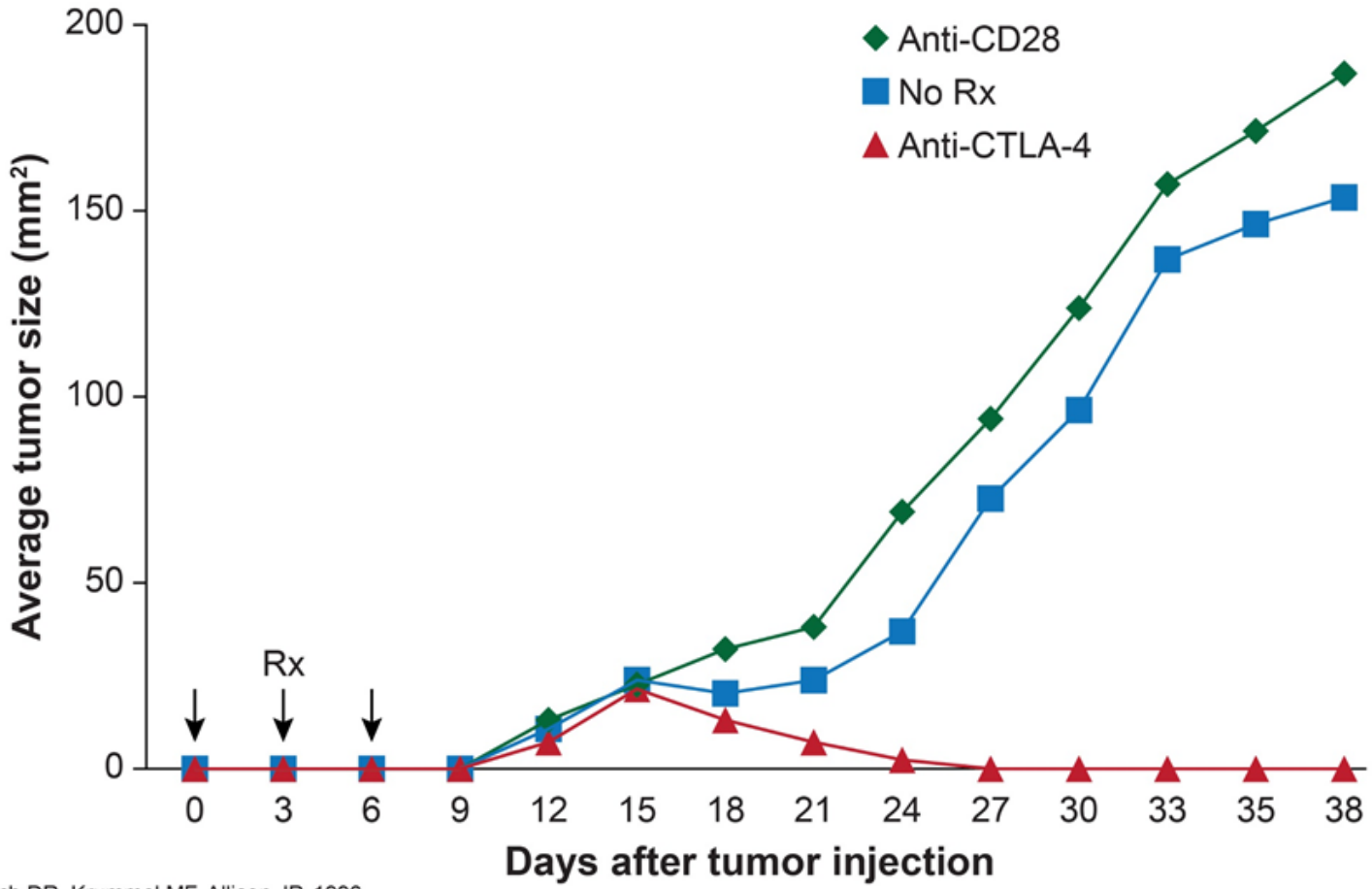


The CTLA-4 Checkpoint

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



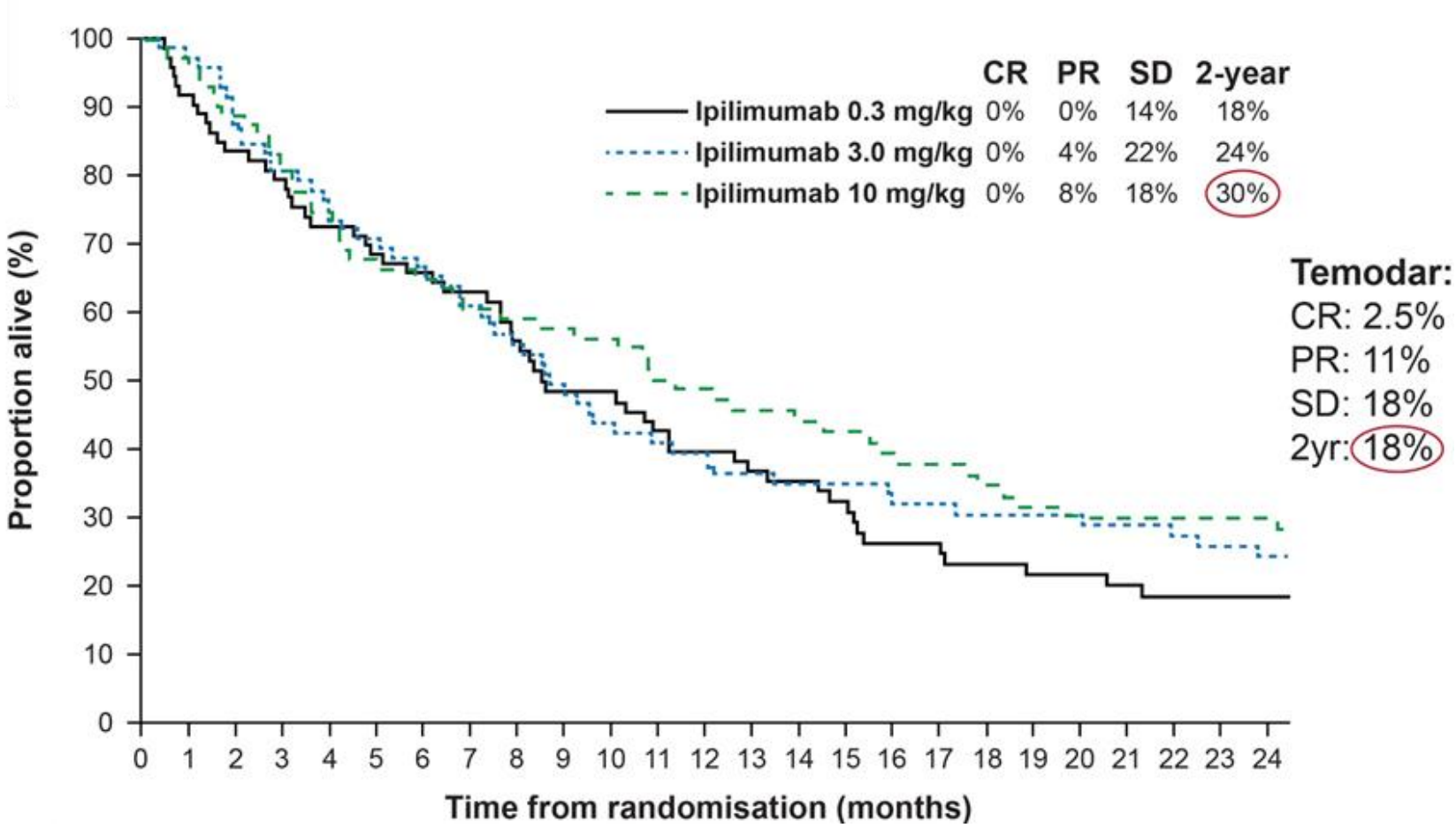
Anti-CTLA-4 induces regression of transplantable colon carcinoma



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

Ipilimumab (human anti CTLA-4)

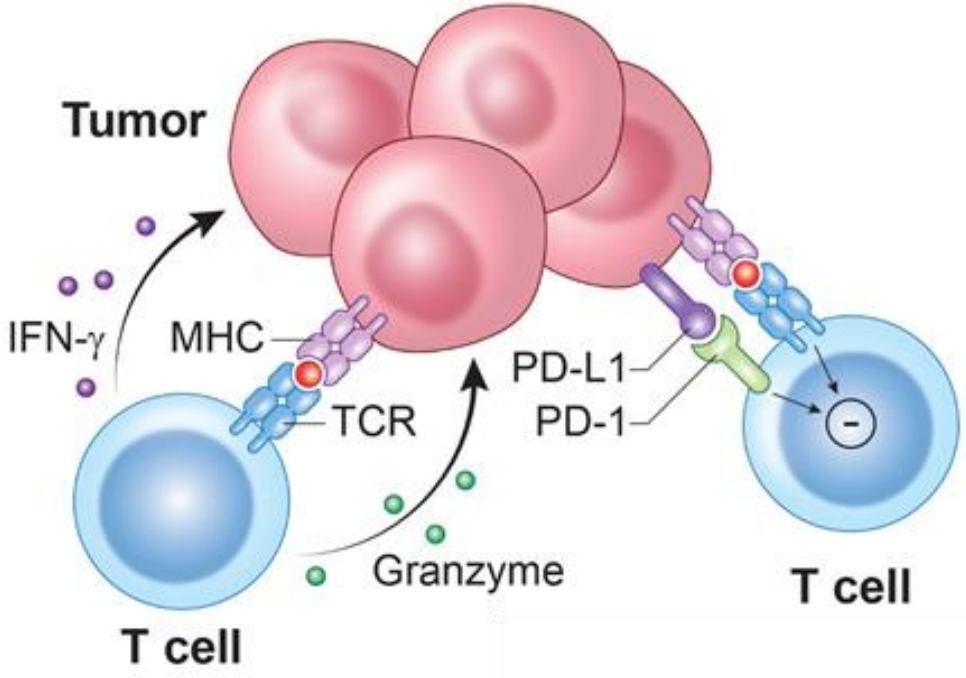
- Granted FDA approval for treatment of patients with metastatic melanoma in 2010



Wolchok et al. Lancet Oncol 2010

The PD-1/PD-L1 Checkpoint

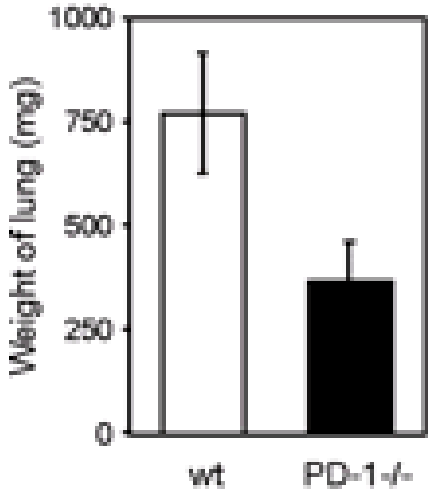
- Promotes T cell tolerization through inhibiting activation signaling
- T cell PD-1 interacts with PD-L1 and PD-L2
- Many cells express PD-L1/PD-L2 and can suppress T cell activation
- Tumors express PD-L1 through two primary mechanisms
  - TIL production of IFN-γ
  - Oncogenic signaling pathways

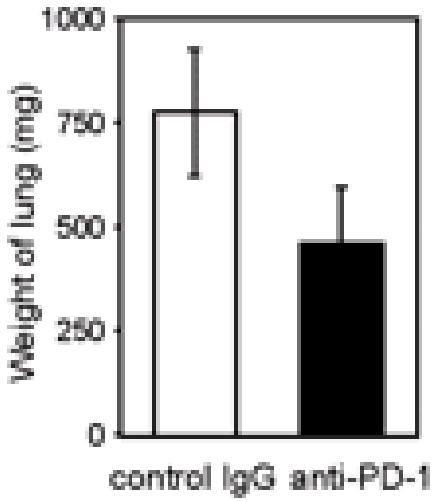


Francisco, L. et al. *Immunol Rev.* 2010. 236: 219.
Pardoll, D.M. *Nat Rev Cancer.* 2012. 12: 252.

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

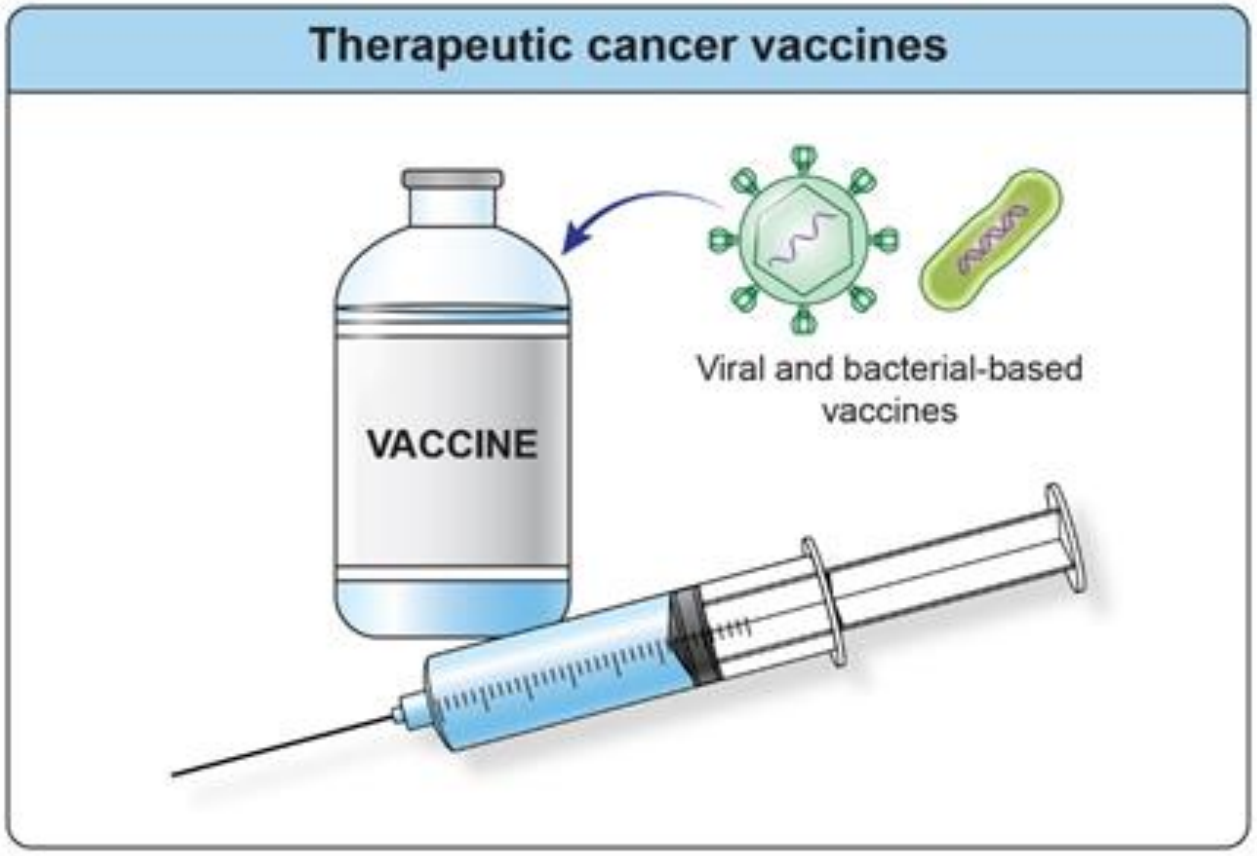




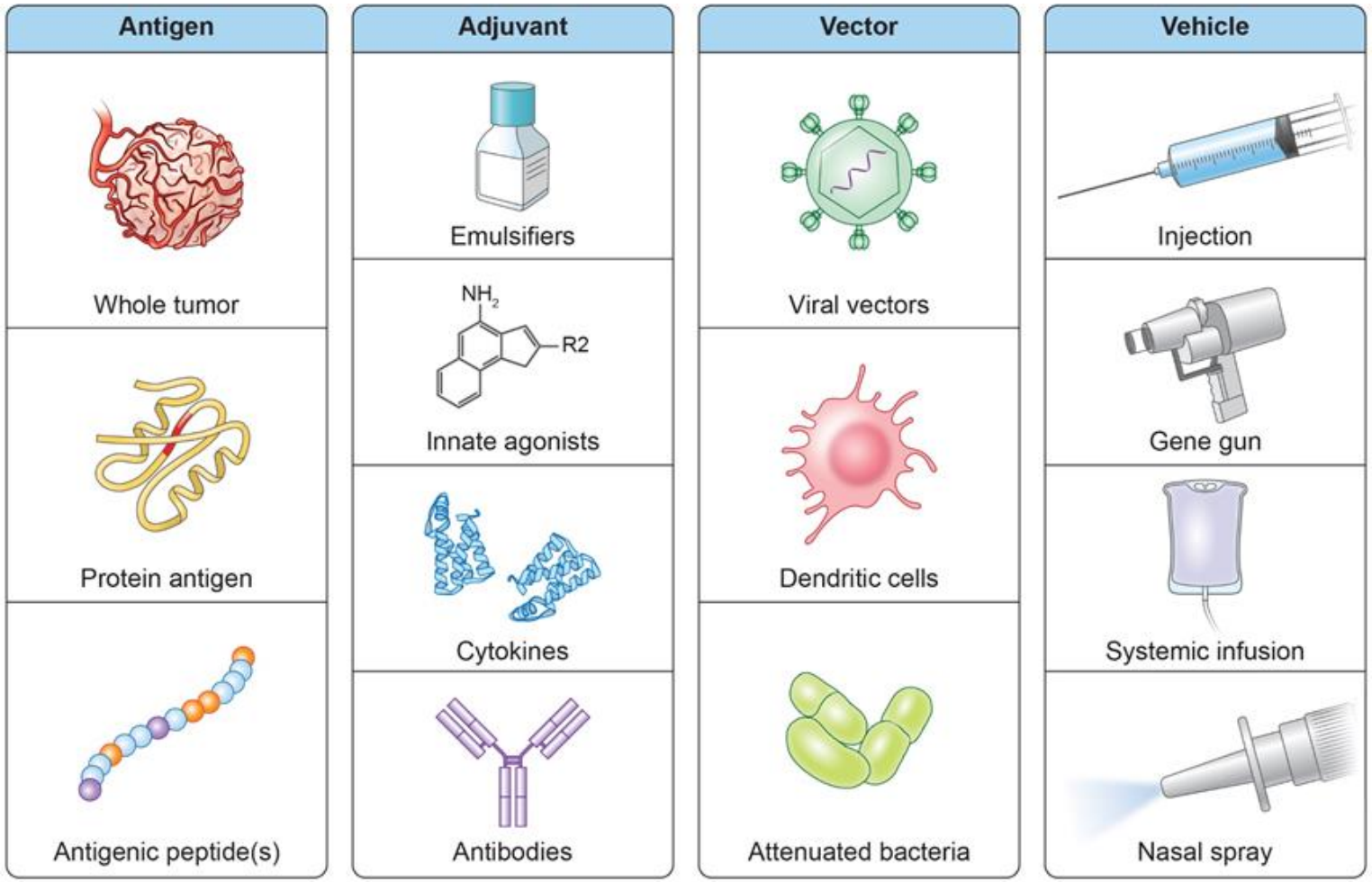
Iwai et al. Internat. Immunol 2004

Therapeutic Cancer Vaccines

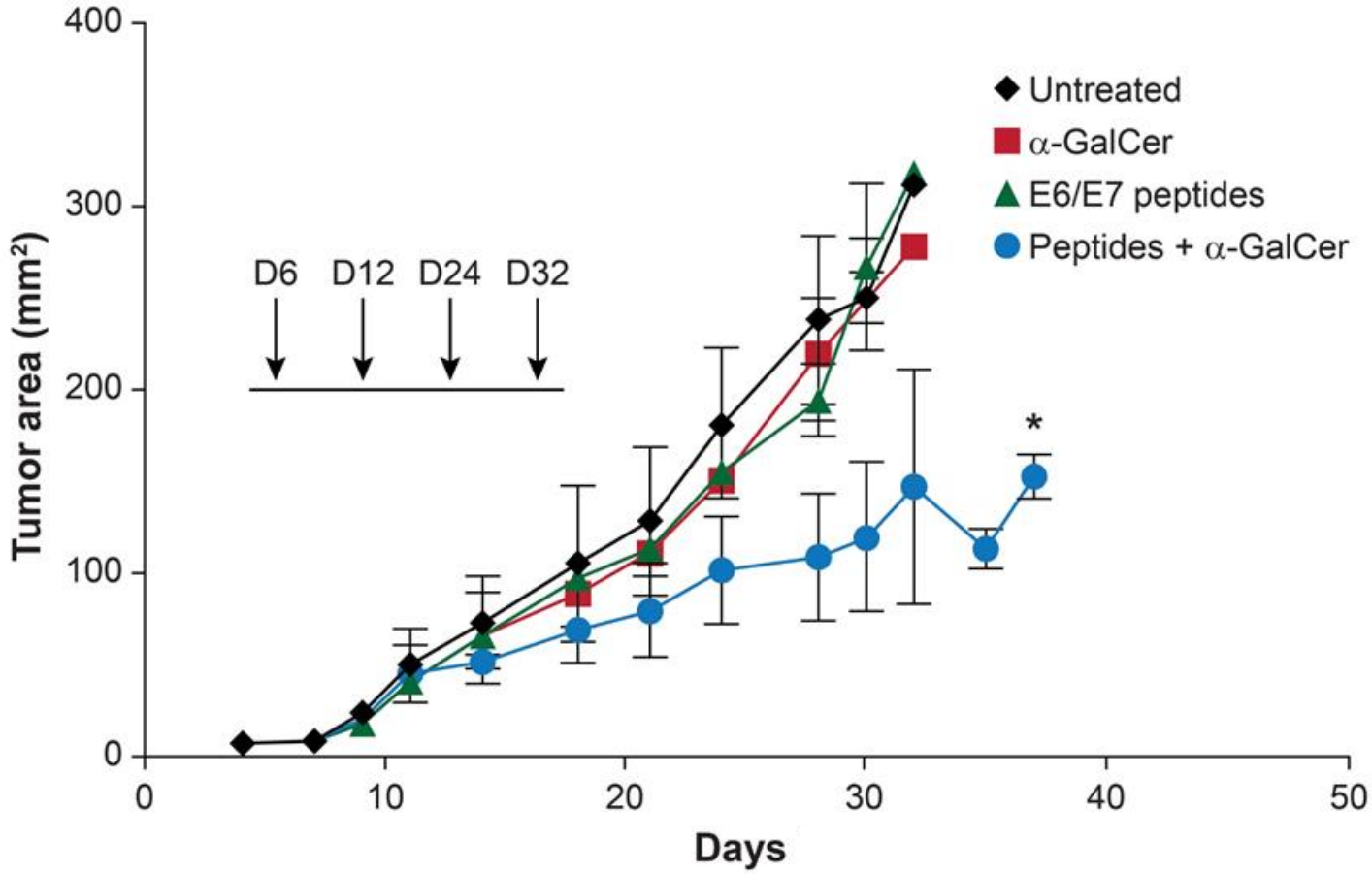
- The goal of therapeutic cancer vaccination is to increase the immunogenicity of tumor antigens in order to generate a high frequency of tumor-specific T cells.



Components of a Cancer Vaccine

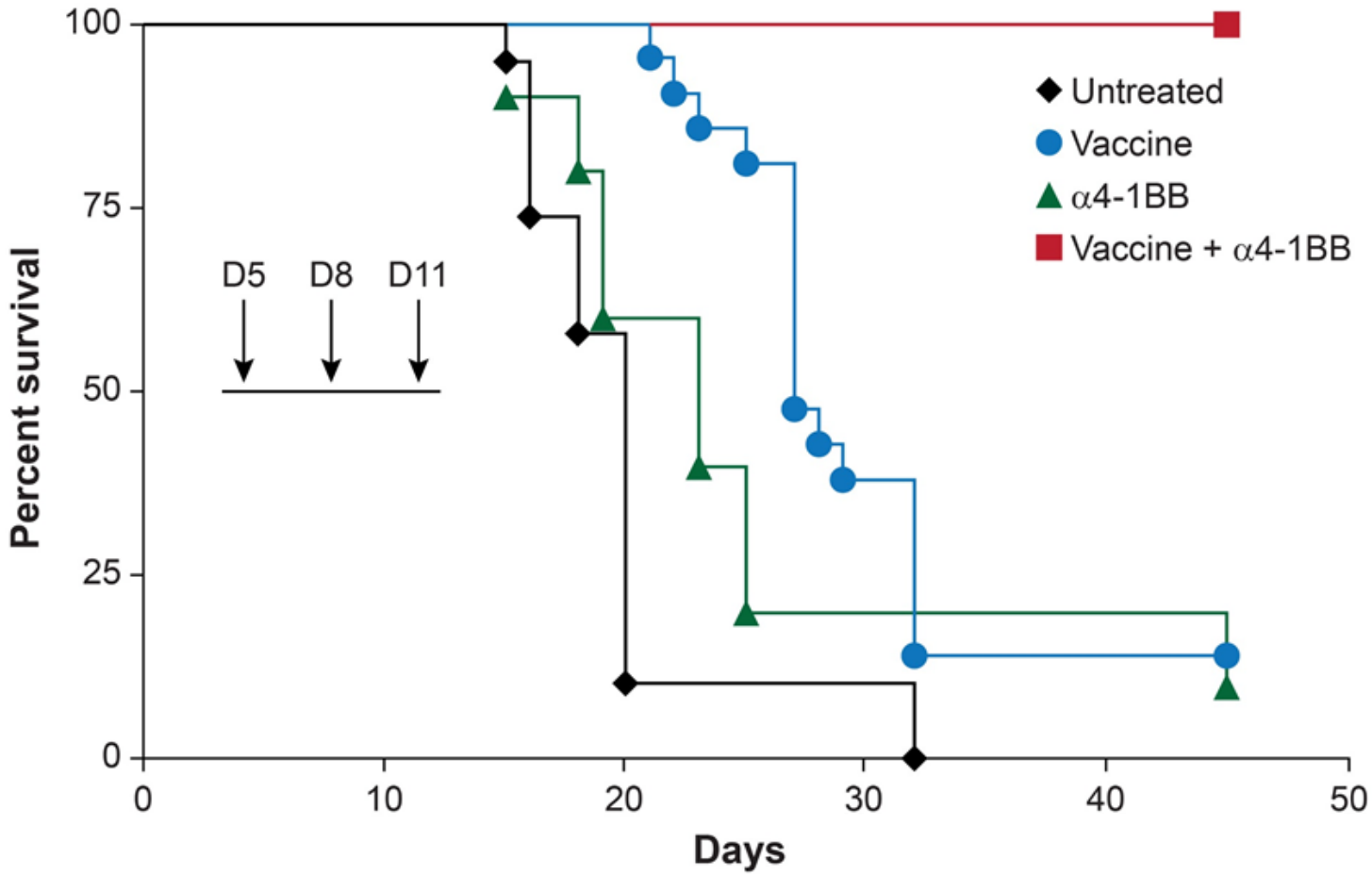


An intra-nasal HPV E6/E7: α-GalCer vaccine slows growth of TC-1 tumors



Shailbala Singh

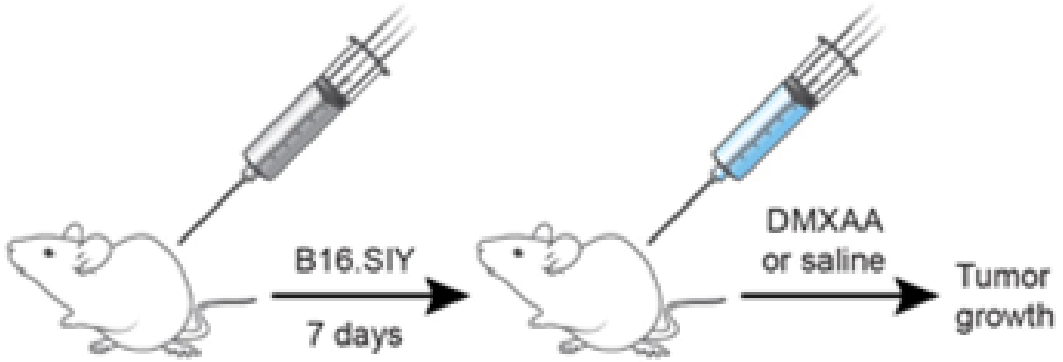
4-1BB agonist antibody and HPV E6/E7 vaccine synergize in curing TC-1 Tumors

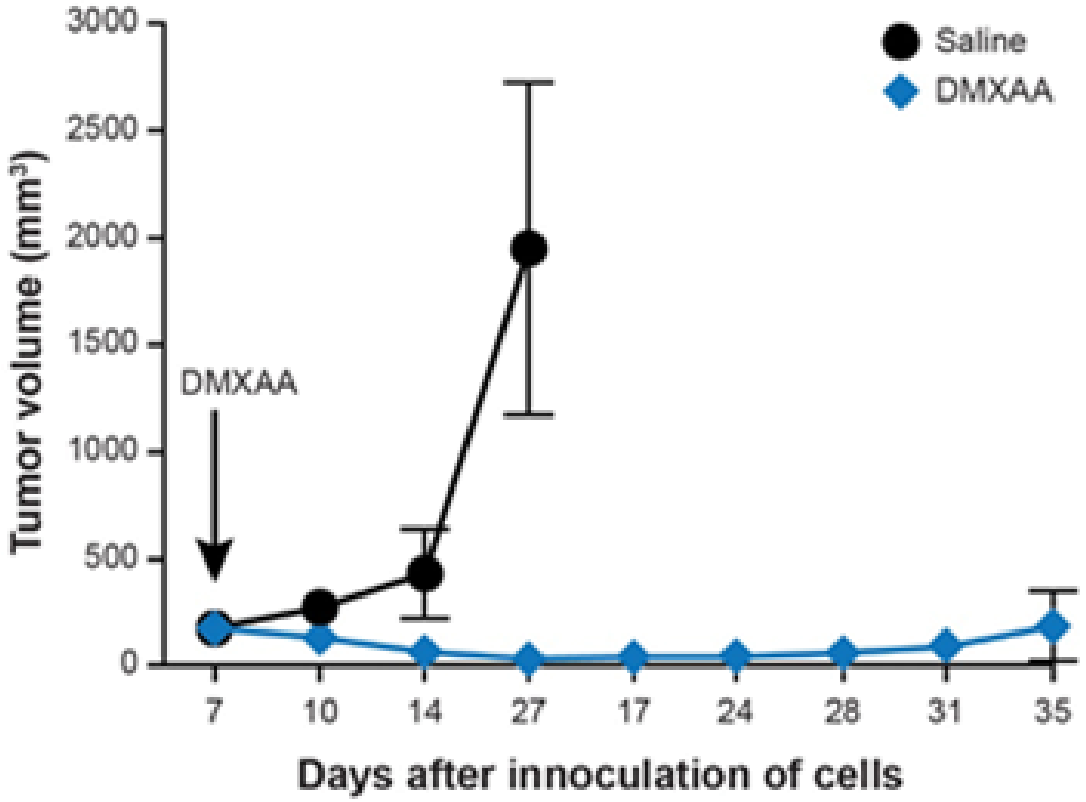


Todd Bartkowiak, M.S.

Intratumoral Injection of Innate Immune Agonists:
Direct Vaccination Approach

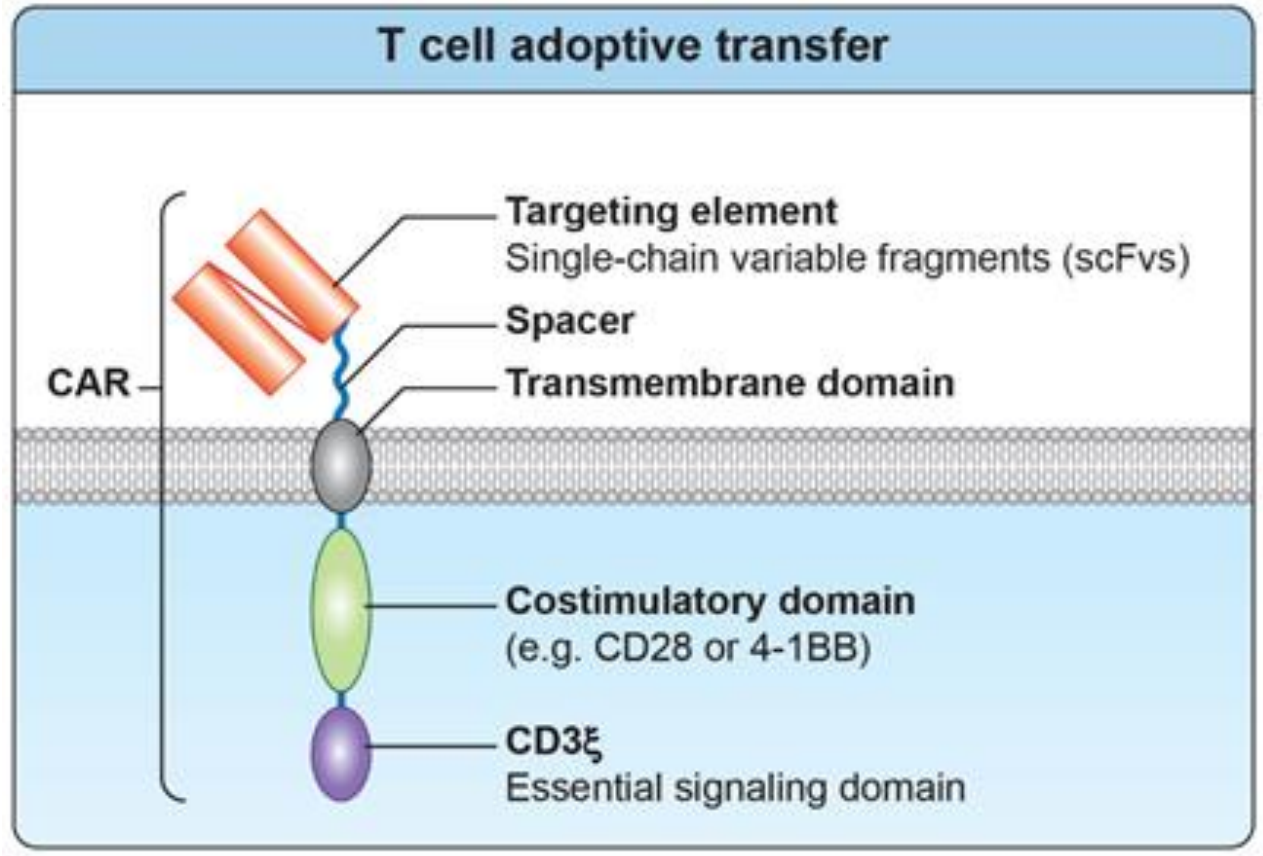
- Intratumoral DMXAA (mouse STING agonist) triggers rejection of B16 melanoma



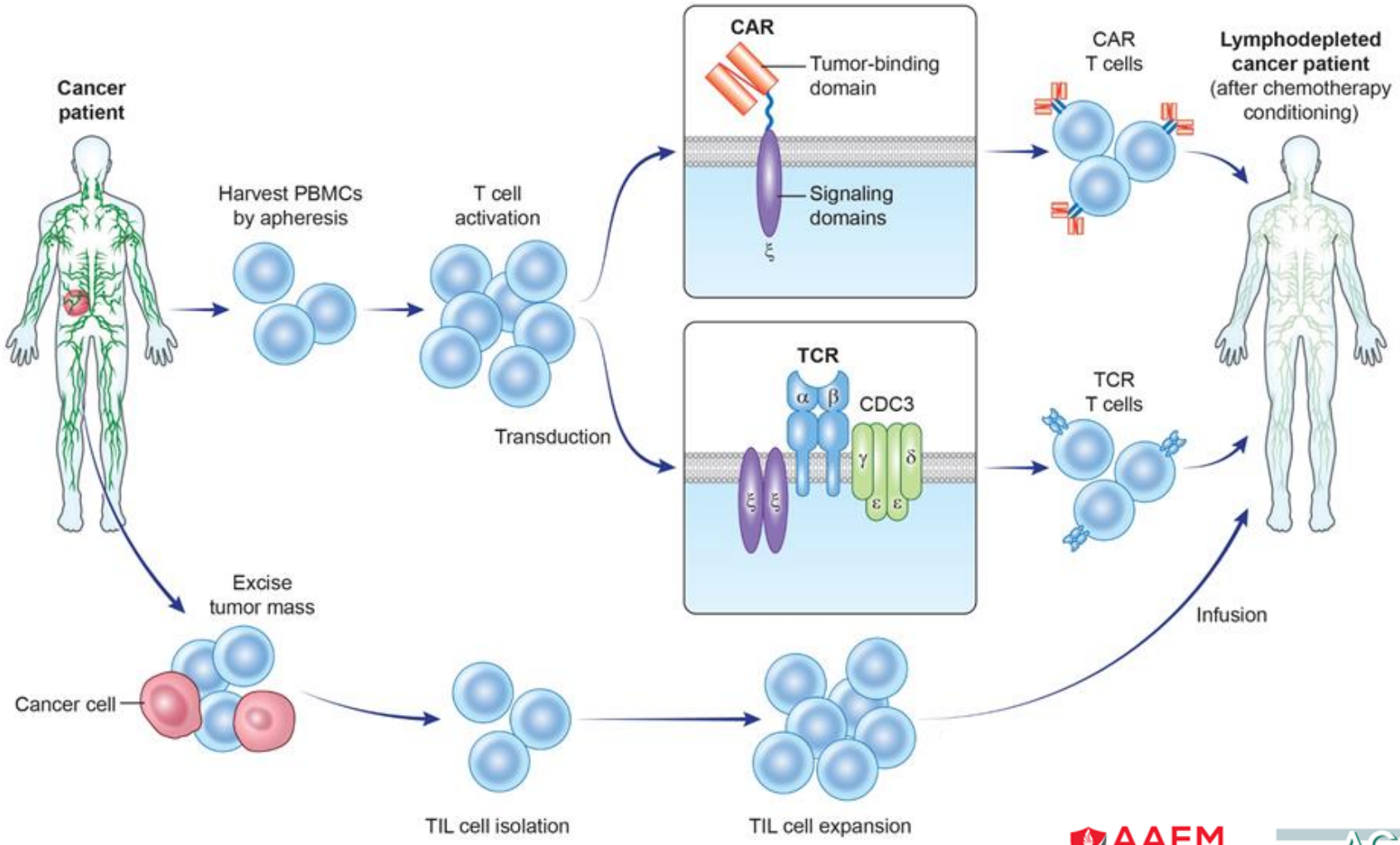


Adoptive Cell Transfer

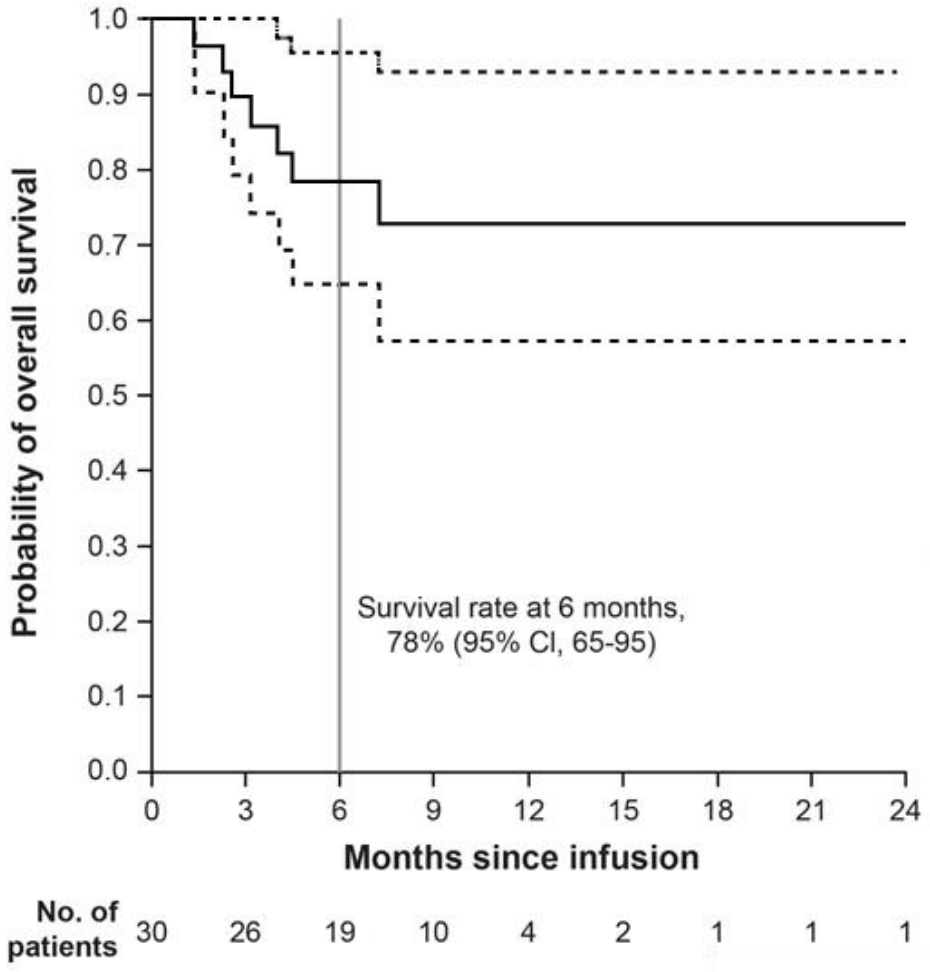
- The goal of adoptive cell transfer is to overwhelm the tumor with a higher frequency of tumor-specific immune cells and/or engineer immune cells to target cancer



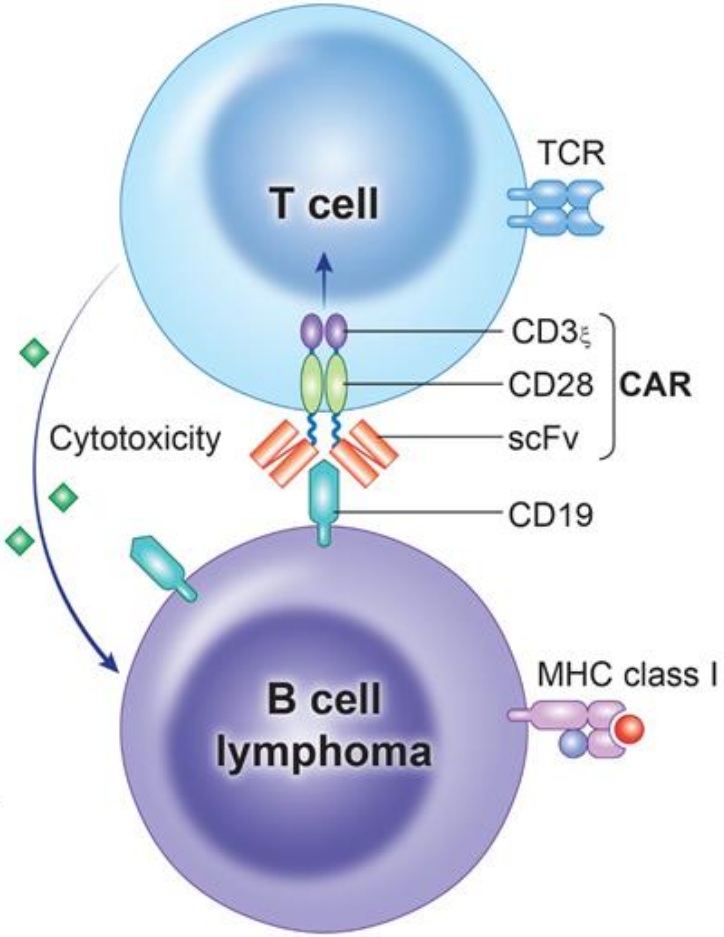
Adoptive Cell Therapy Process



CD19 CAR T Cell Therapy for Relapsed B Cell ALL

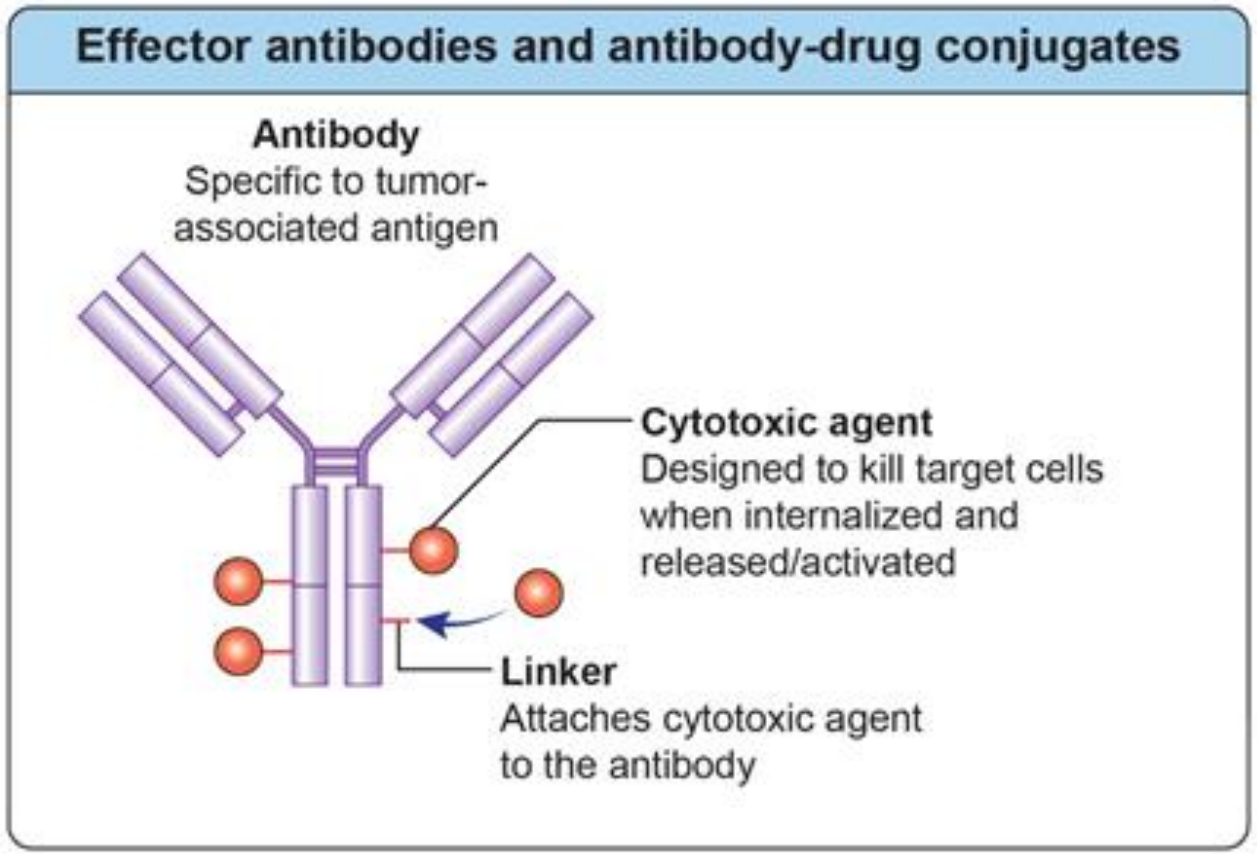


Maude S, Frey N, Shaw P, Aplenc R, Barrett D, Bunin N, Chew A, Gonzalez V, Zheng Z, Lacey S, et al. 2014. Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England Journal of Medicine. 374(10): 998.



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 of suppress and/or through delivery of cytotoxic agents

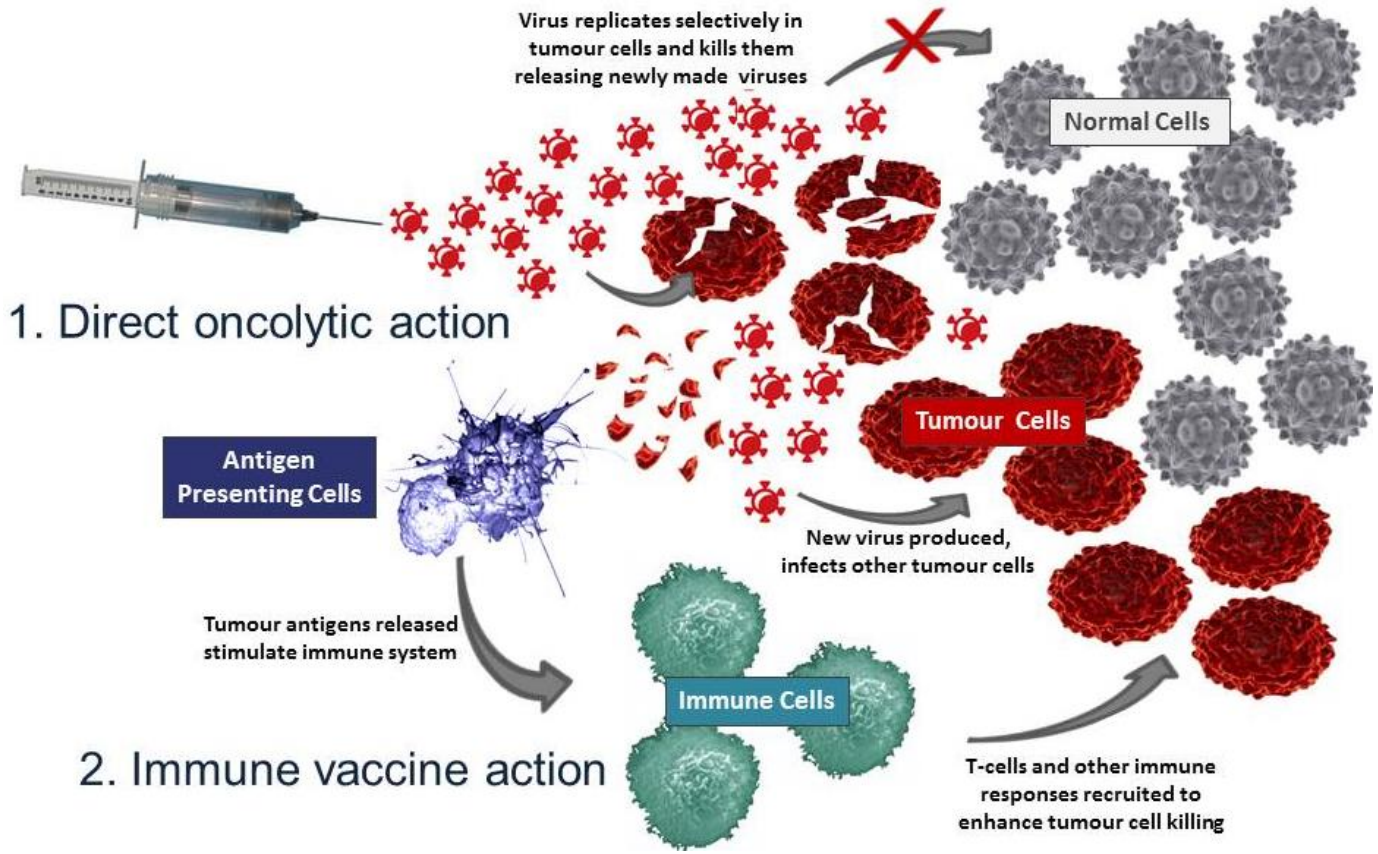


Key ADC/Antibody Principles

- **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

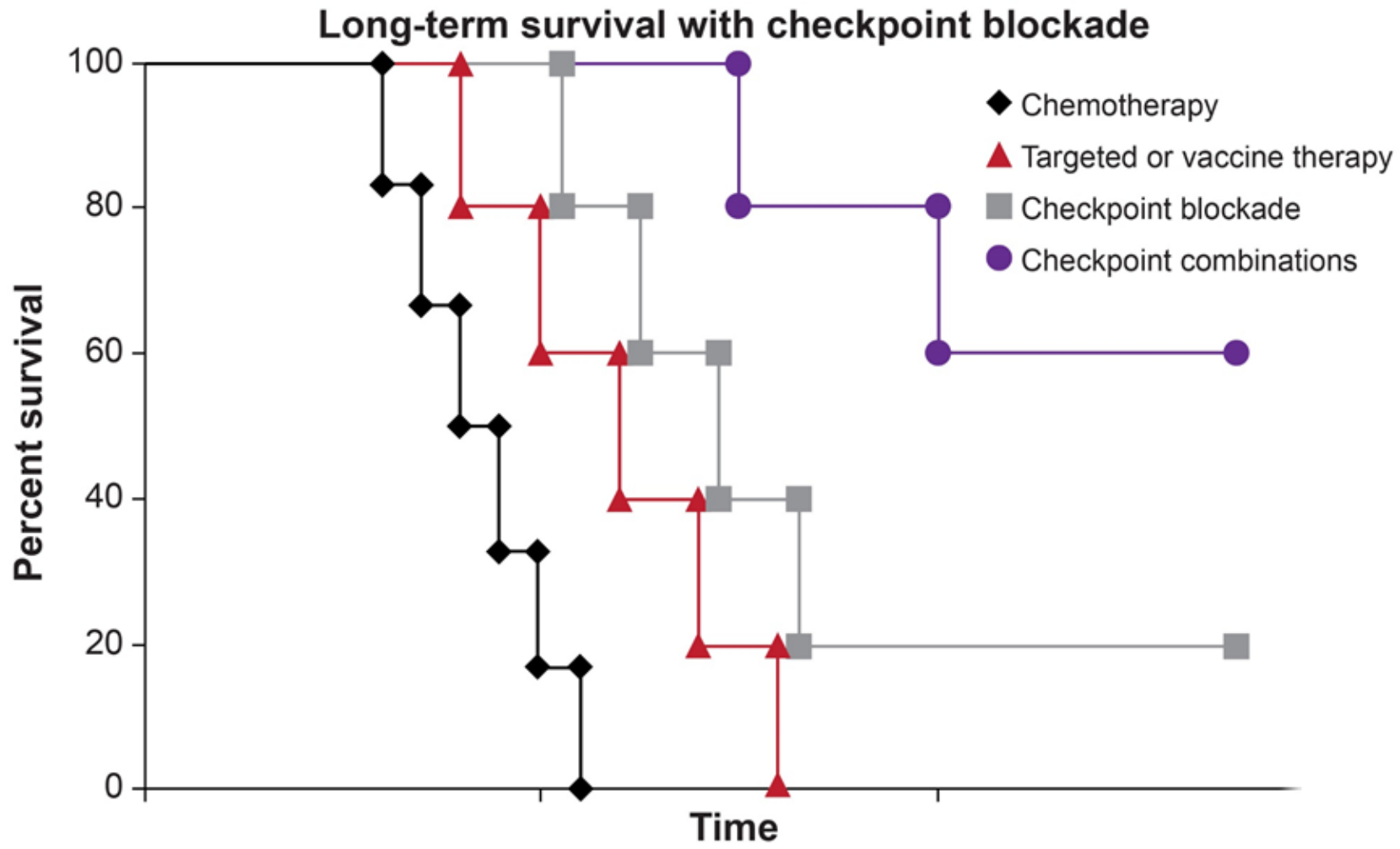
Oncolytic Viruses

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



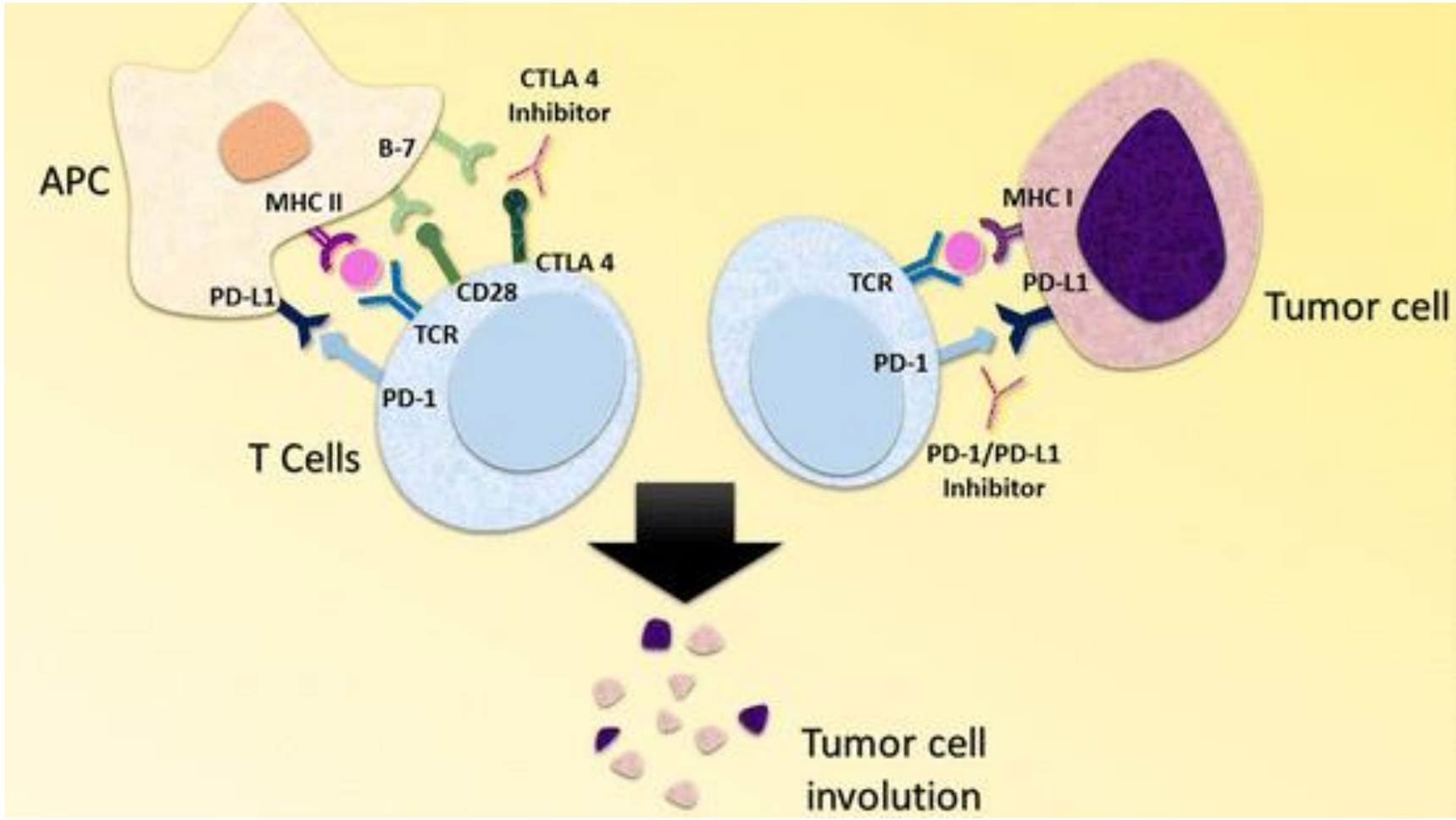
dddmag.com

Combination Immunotherapies



Combination Immunotherapies

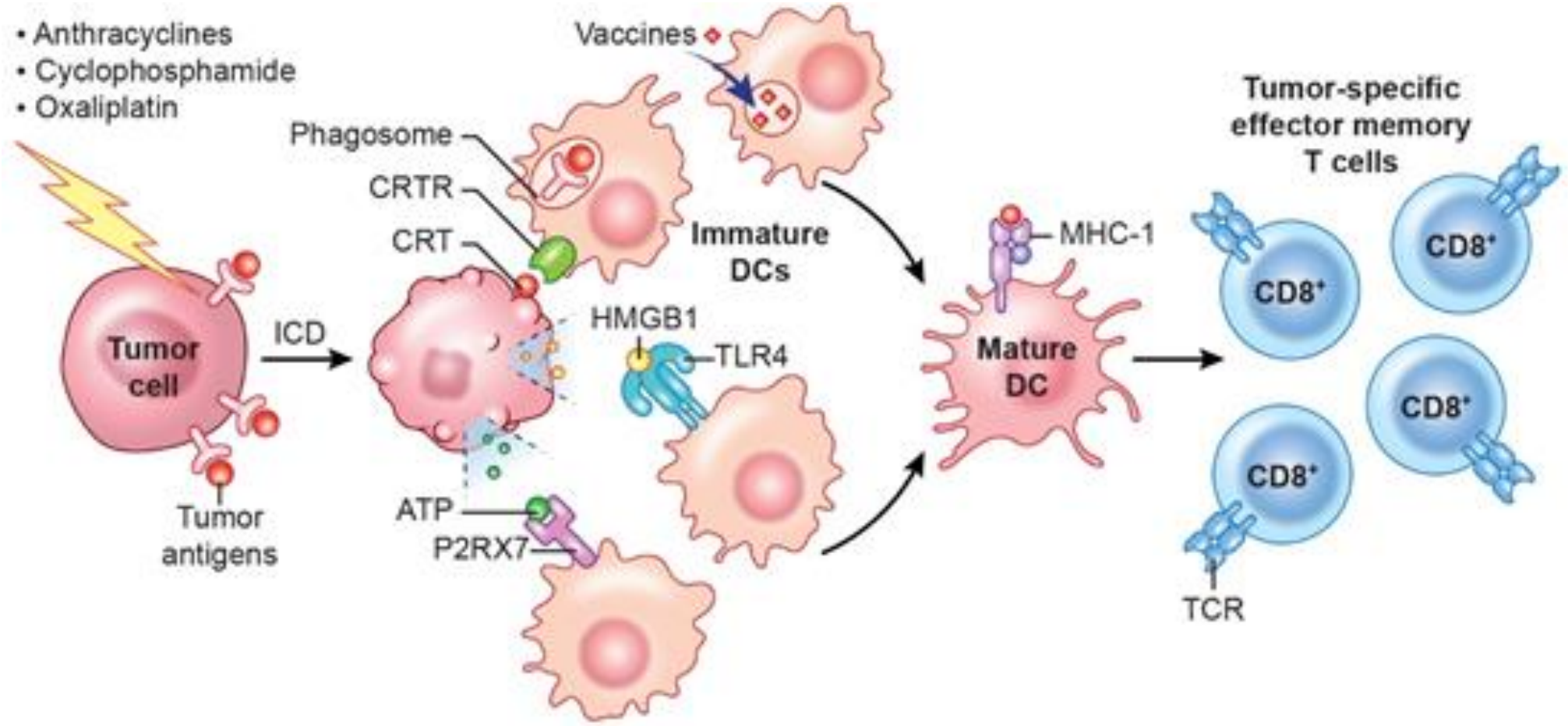
Dual CTLA-4 and PD-1 inhibition



Chae et al. JITC 2018

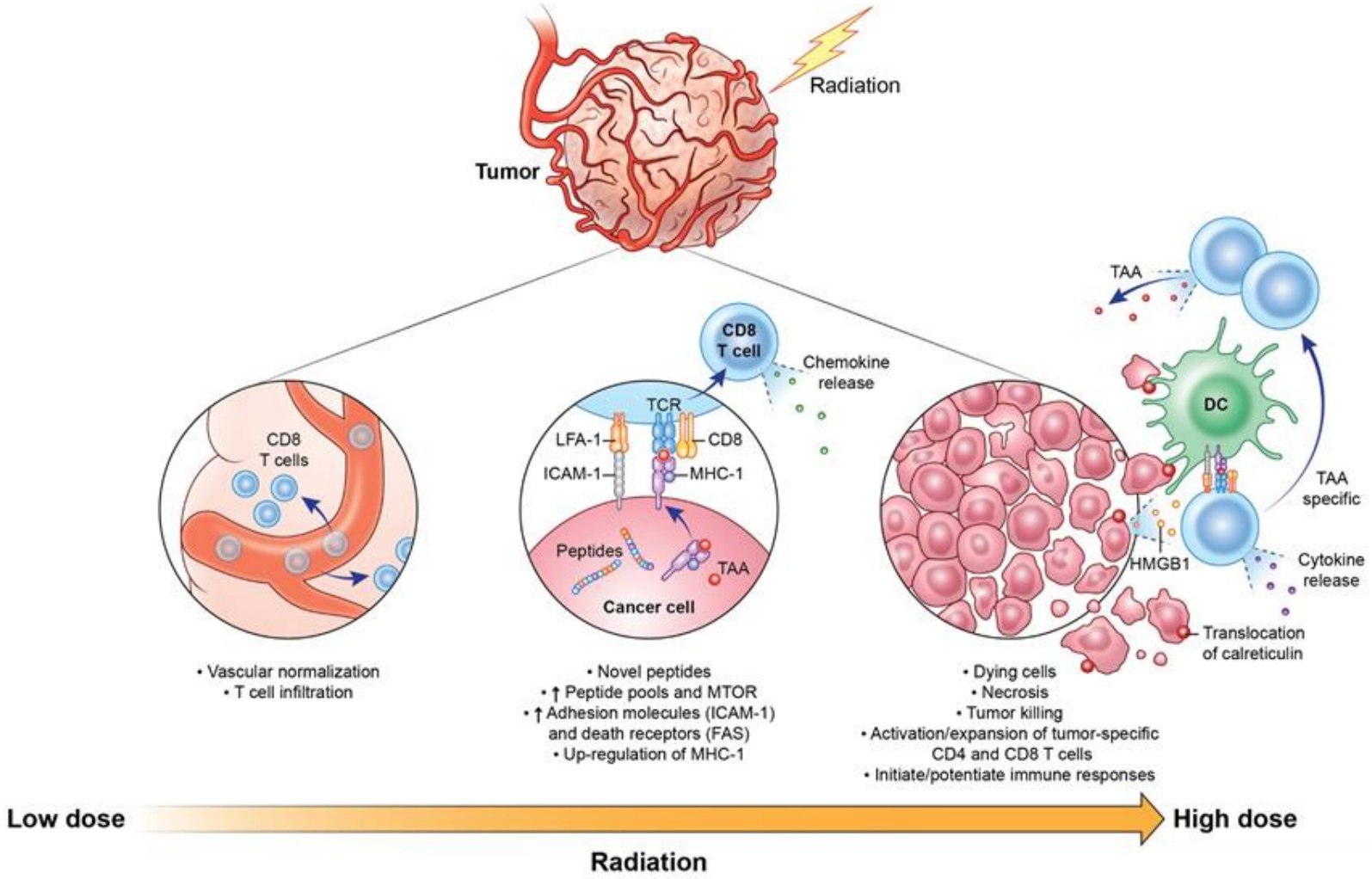
Combination Immunotherapies

Chemotherapy can induce an immune response



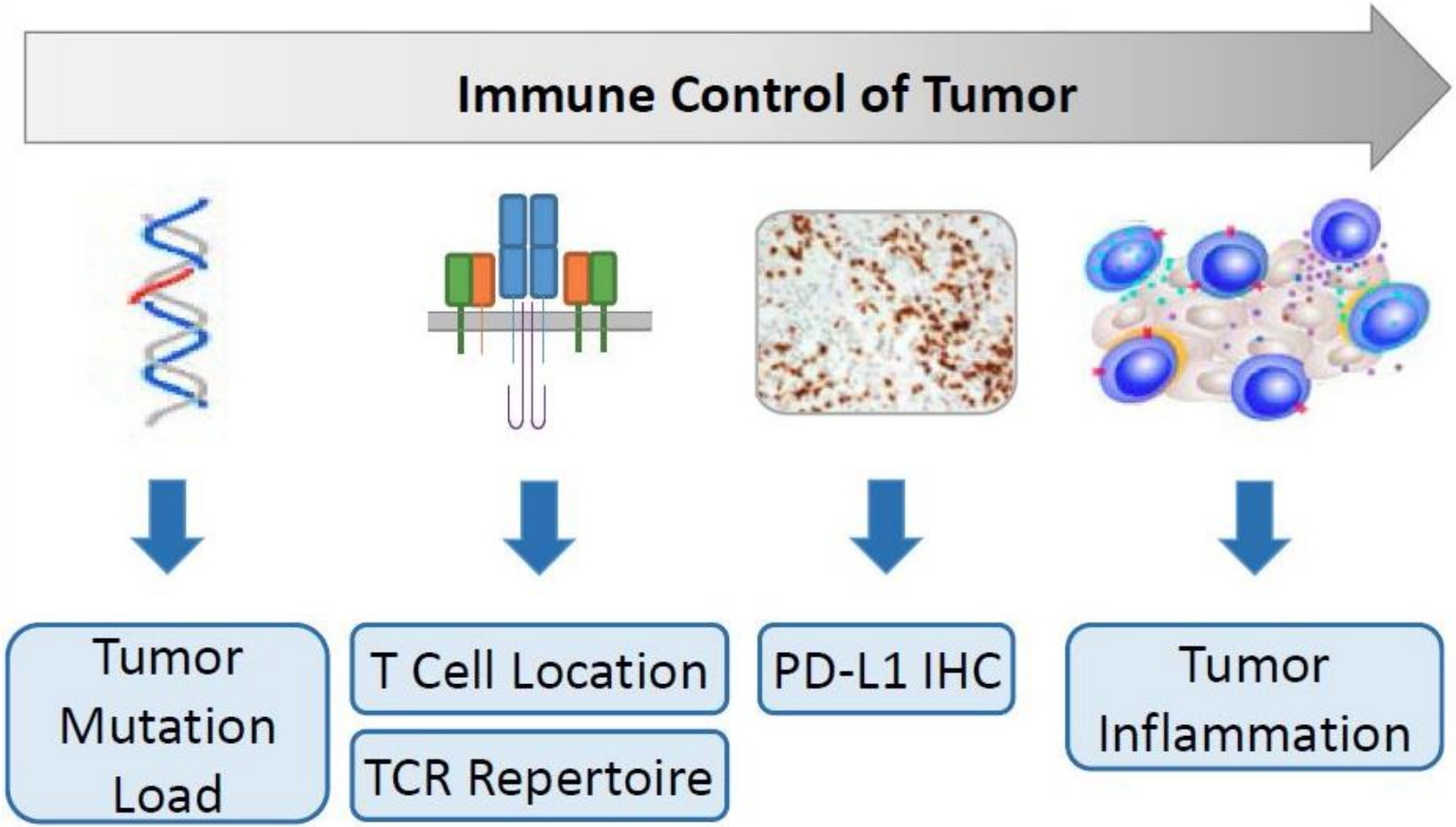
Combination Immunotherapies

Radiotherapy can induce an immune response



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

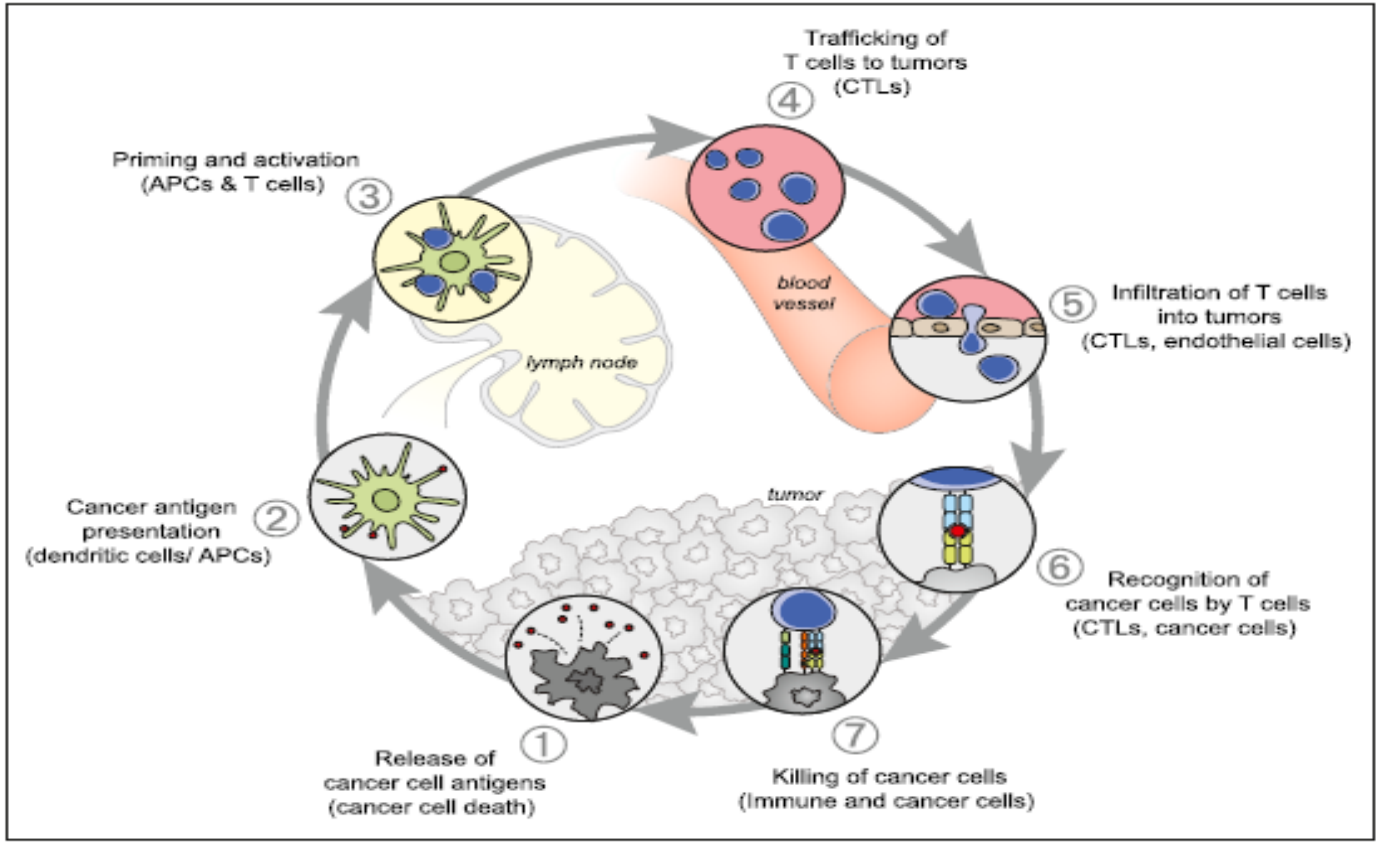
Immunotherapy Biomarkers



Cesano et al. Biomedicines 2018

Oncology Meets Immunology: The Cancer-Immunity Cycle

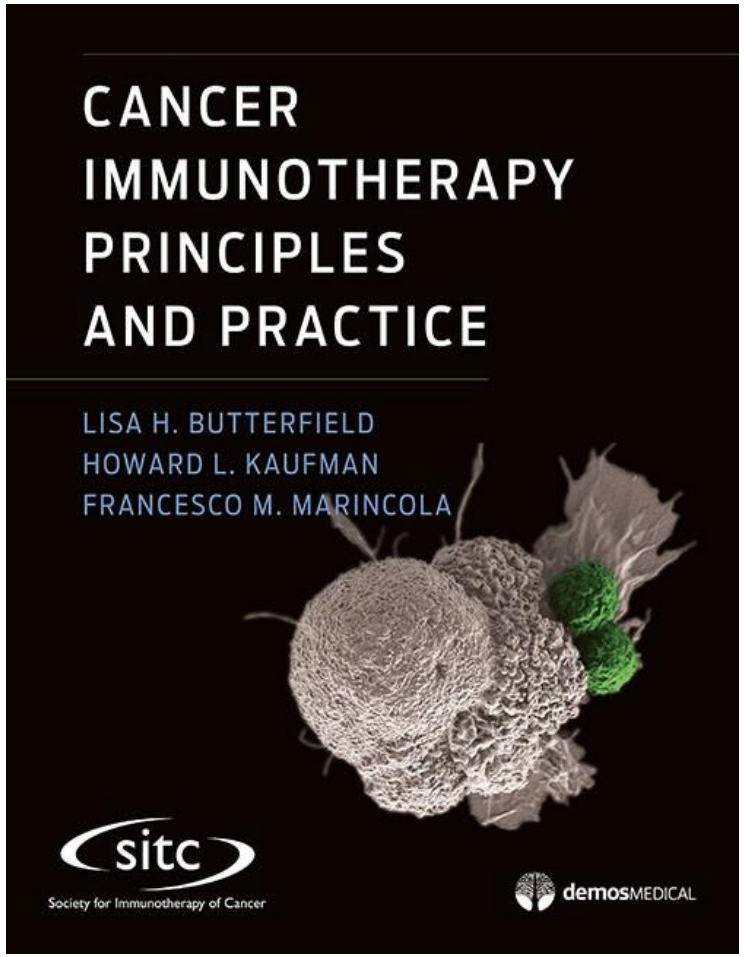
Daniel S. Chen[1,3] and Ira Mellman[2,3,*]
[1]Stanford Medical Oncology, Stanford University School of Medicine, Stanford, CA 94305, USA
[2]Department of Biochemistry & Biophysics, University of California, San Francisco School of Medicine, San Francisco, CA 94143, USA
[3]Genentech, 1 DNA Way, South San Francisco, CA 94080, USA
*Correspondence: mellman.ira@gene.com
http://dx.doi.org/10.1016/j.immuni.2013.07.012



- Immunity 2013 39:1-10

Figure 1. The Cancer-Immunity Cycle
The generation of immunity to cancer is a cyclic process that can be self propagating, leading to an accumulation of immune-stimulatory factors that in principle should amplify and broaden T cell responses. The cycle is also characterized by inhibitory factors that lead to immune regulatory feedback mechanisms, which can halt the development or limit the immunity. This cycle can be divided into seven major steps, starting with the release of antigens from the cancer cell and ending with the killing of cancer cells. Each step is described above, with the primary cell types involved and the anatomic location of the activity listed. Abbreviations are as follows: APCs, antigen presenting cells; CTLs, cytotoxic T lymphocytes.

Further Resources



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Cancer Immunotherapy CONNECT