

ADVANCES IN  
**Cancer**  
IMMUNOTHERAPY™



# Basic Principles of Cancer Immunotherapy-part I

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Society for Immunotherapy of Cancer

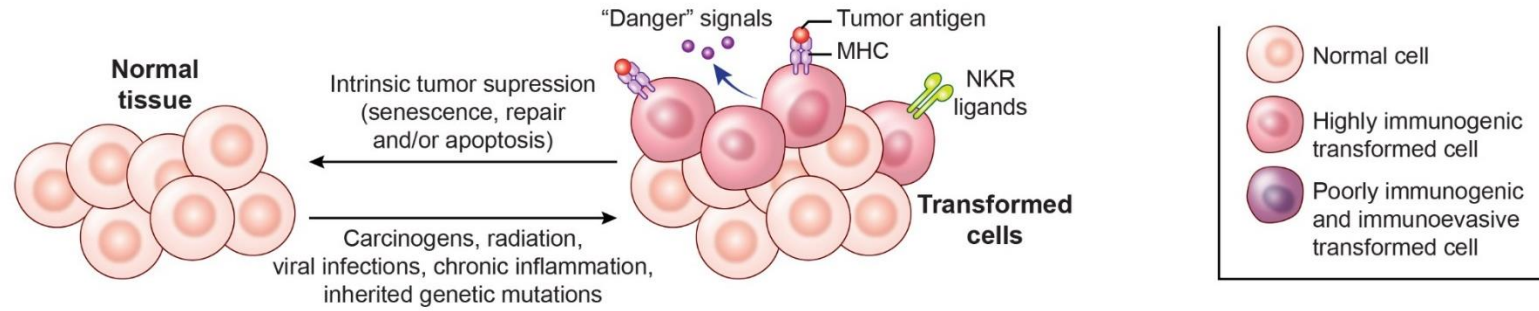
# Disclosures

- Verastem, 2016, Immune Design, 2016, Kite Pharma 2016, Shire 2017
- Simpatica, Scientific Advisory Board Member, 2017-present
- StemImmune Scientific and Medical Advisory Board, April 6, 2017-present
- None of these are relevant to the topic of basic immunology
- I may be discussing non-FDA approved indications during my presentation.

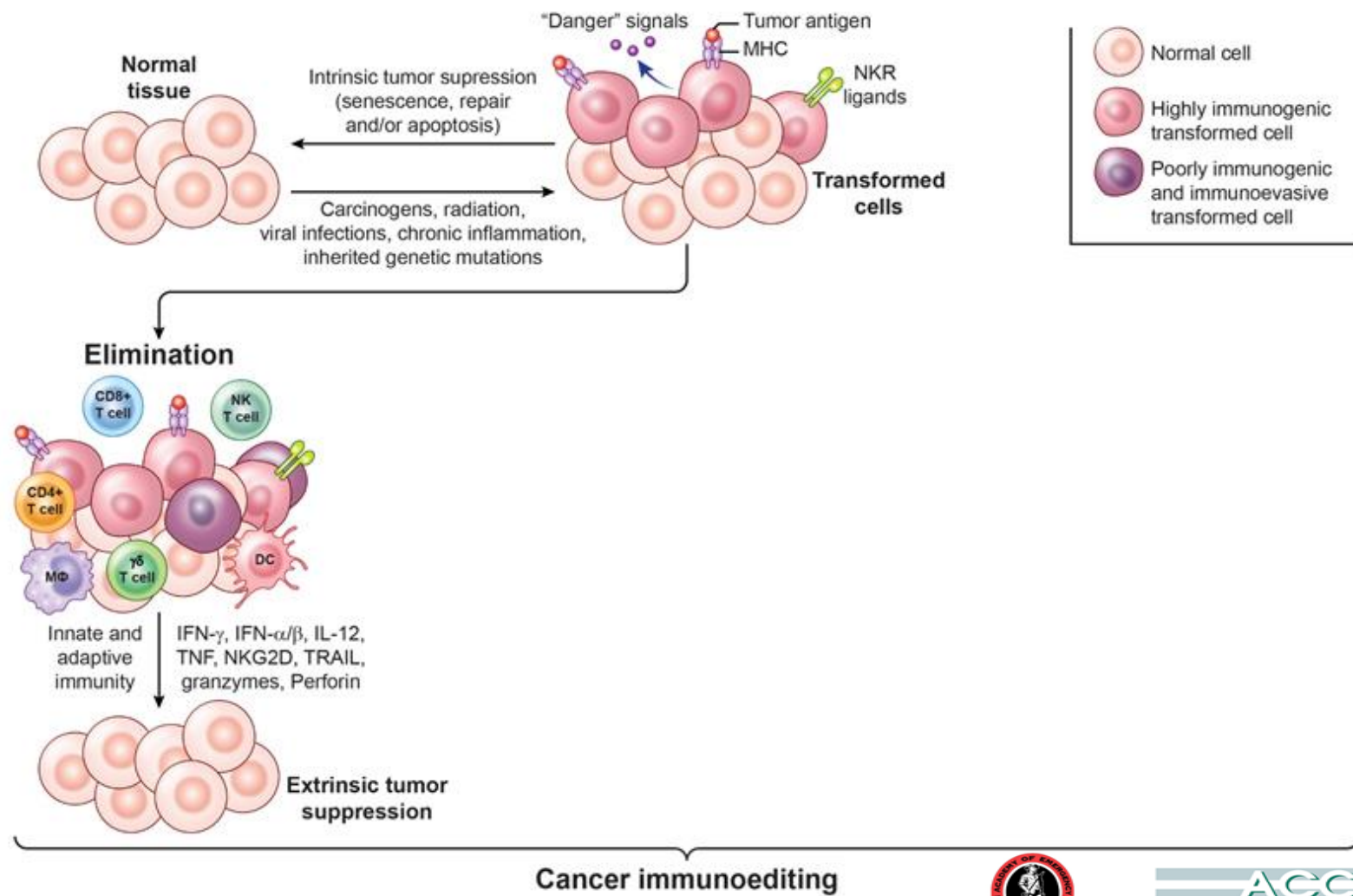
Why does the immune system fail to  
eliminate cancer?

Cancer cells grow progressively  
in immunocompetent hosts without evidence of  
T cell exhaustion or systemic anergy.

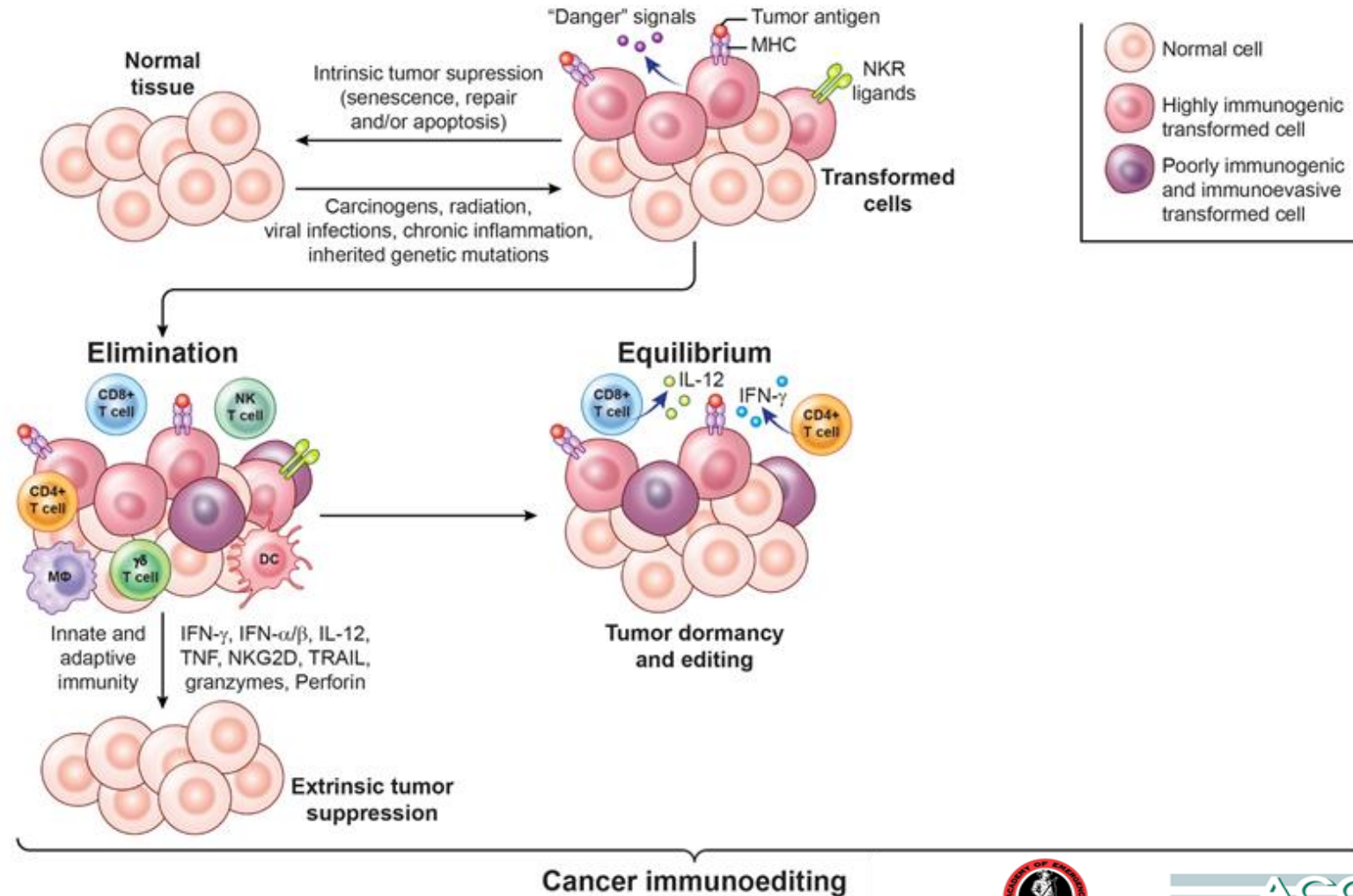
# The 3 Es of cancer immunoediting



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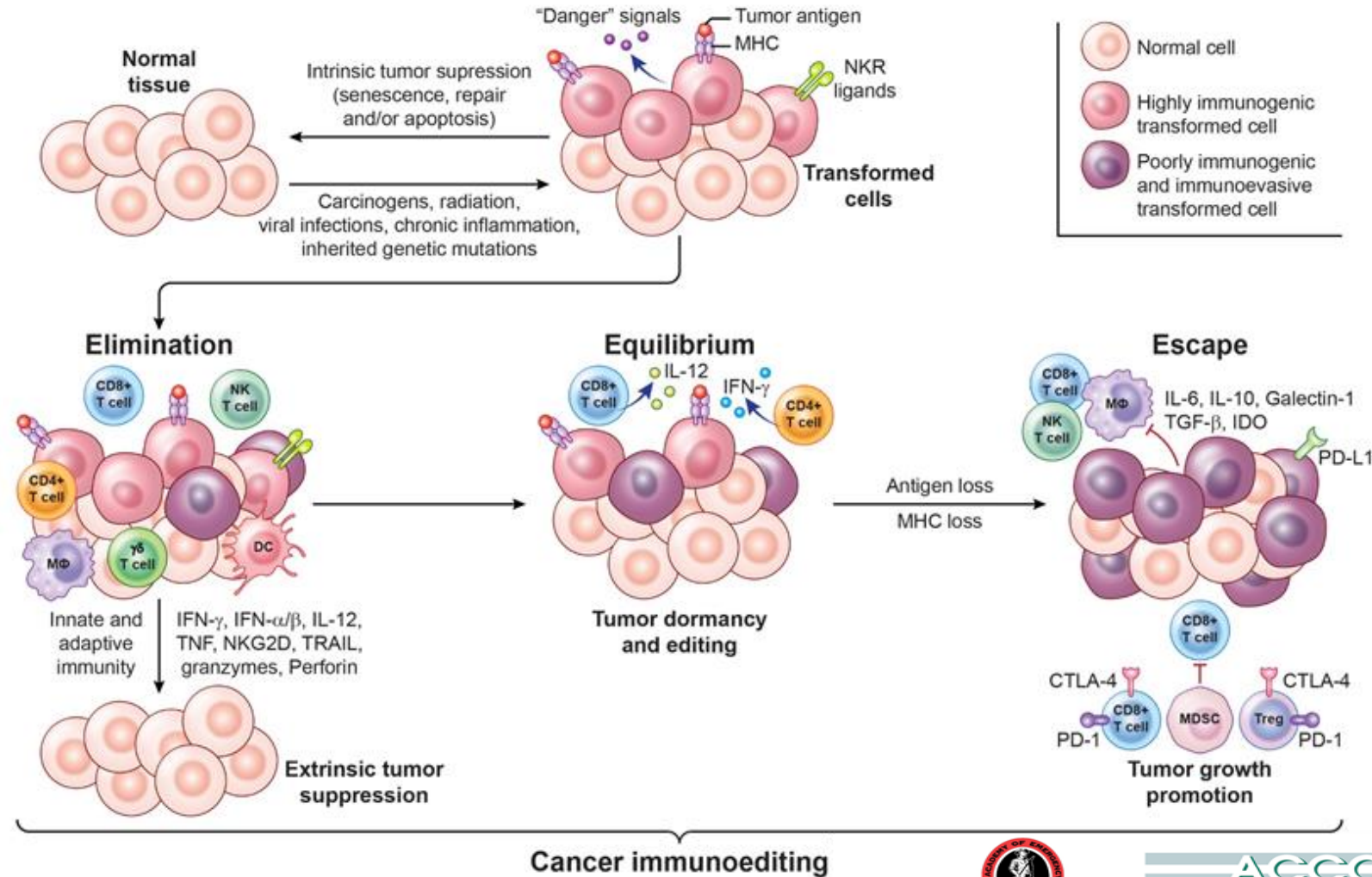


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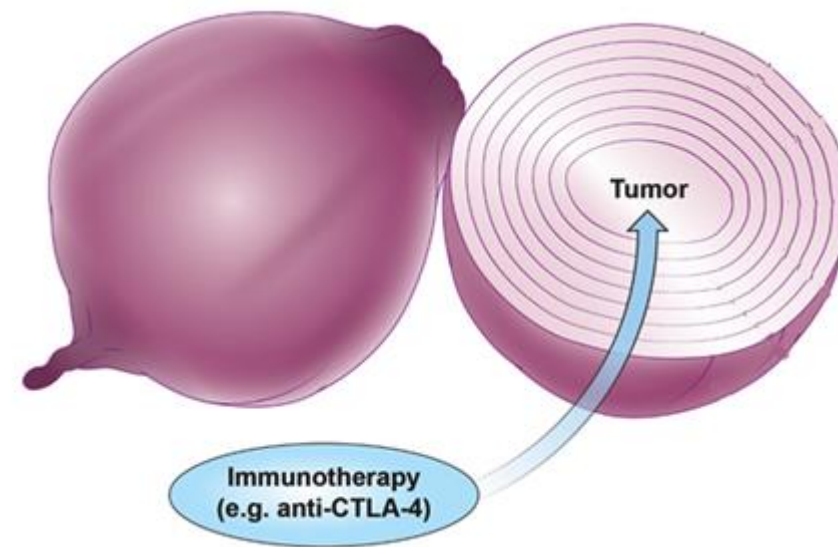
To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

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

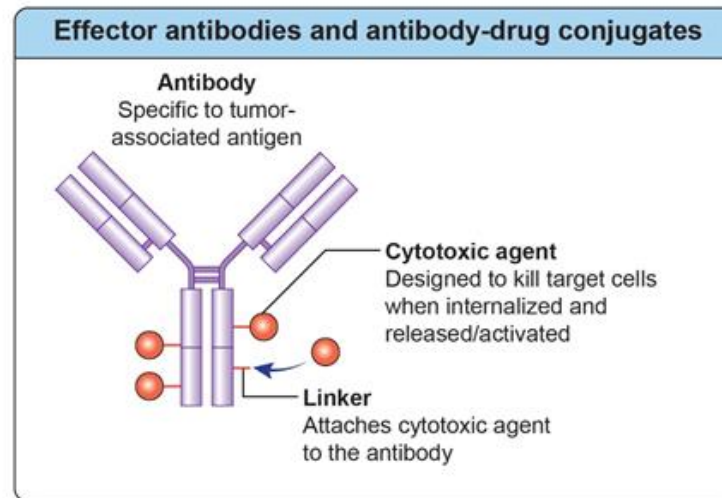
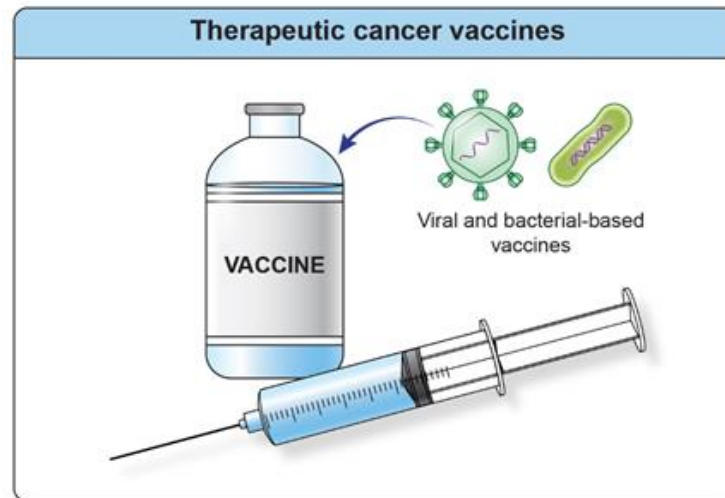
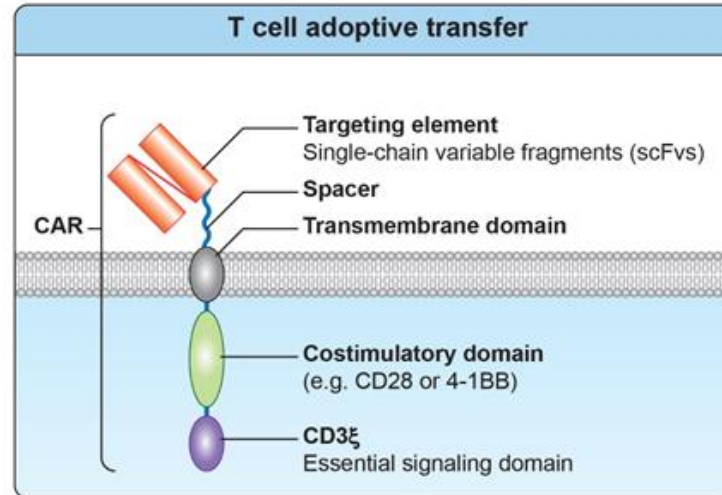
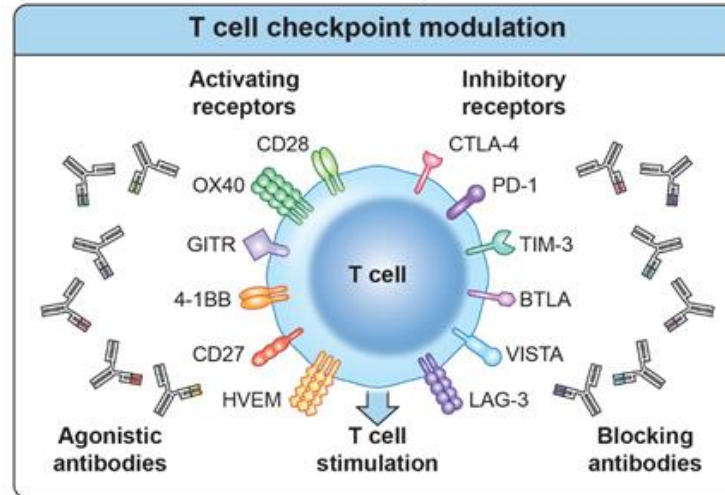


## Multi-layered immunosuppression

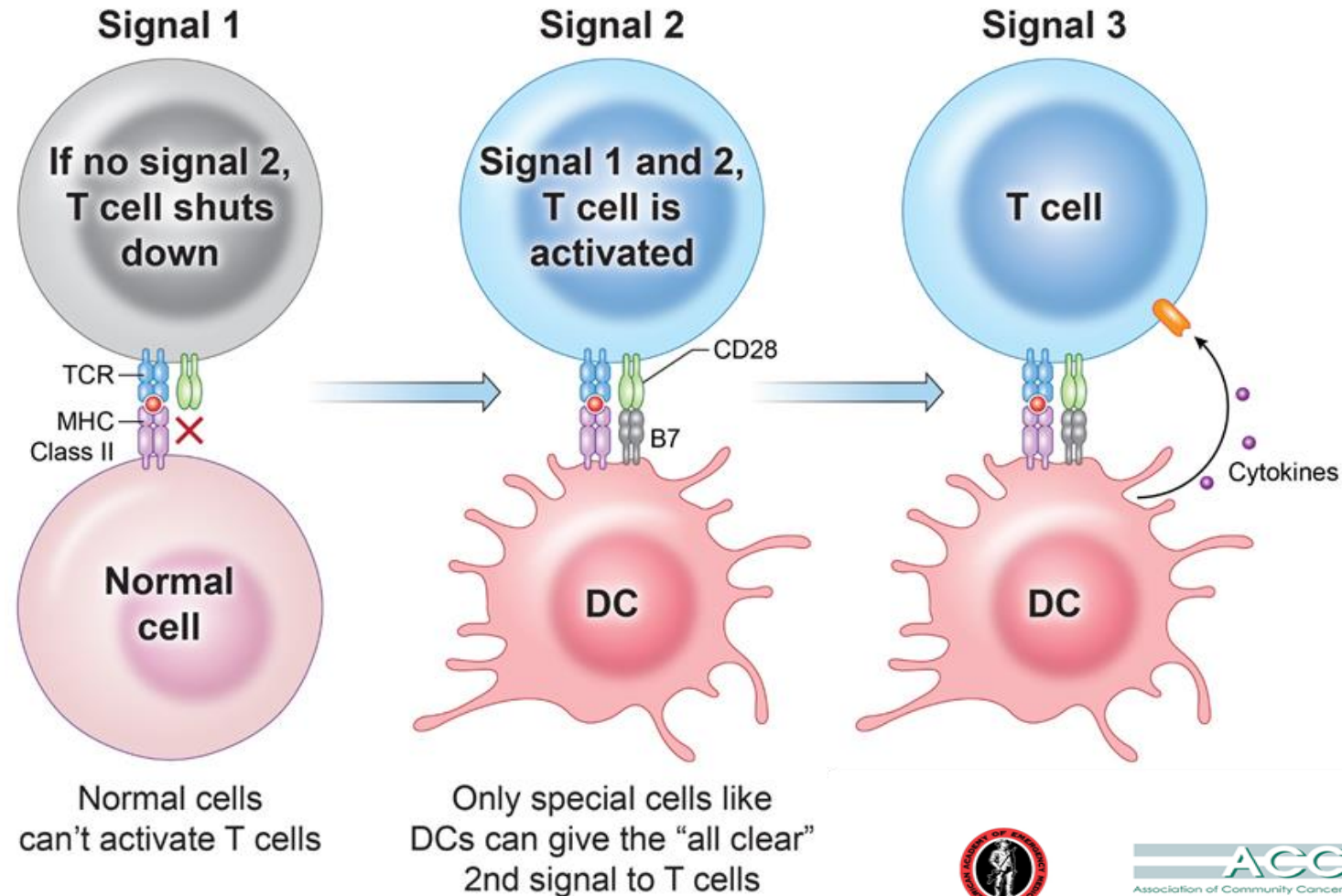
- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune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



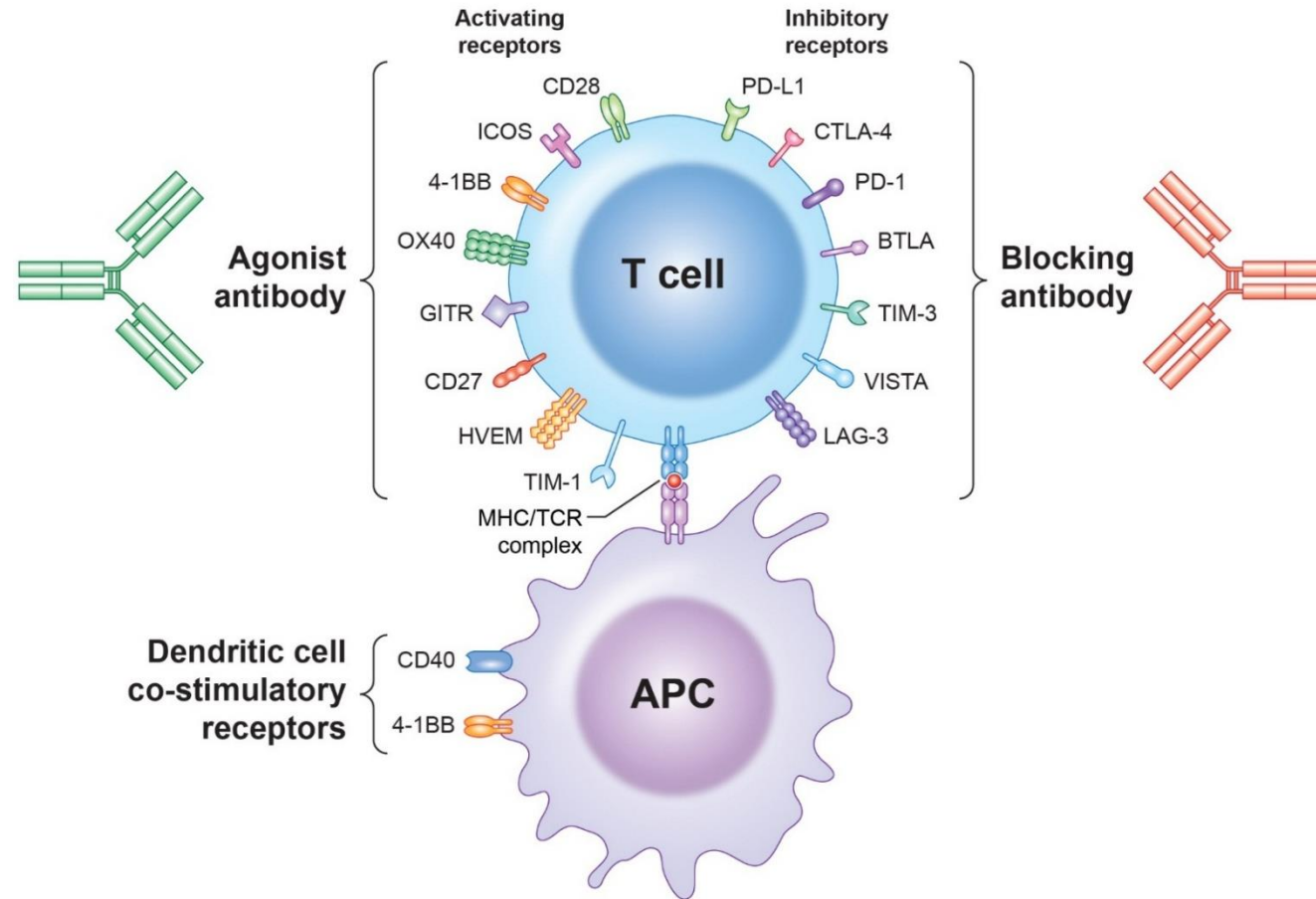
# Types of immunotherapy



# Three signals for antigen-specific T cell activation

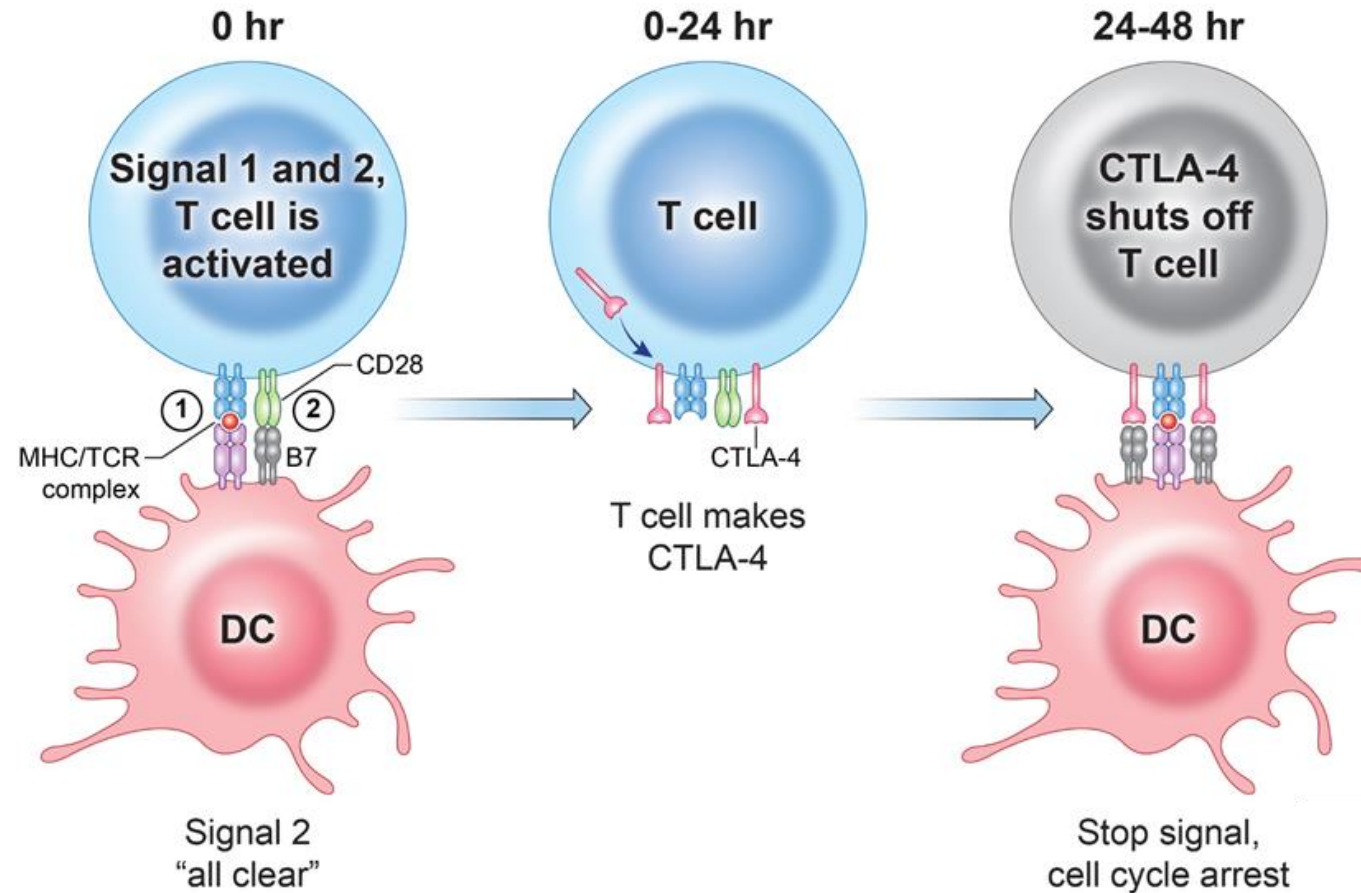


# T cell checkpoint modulation

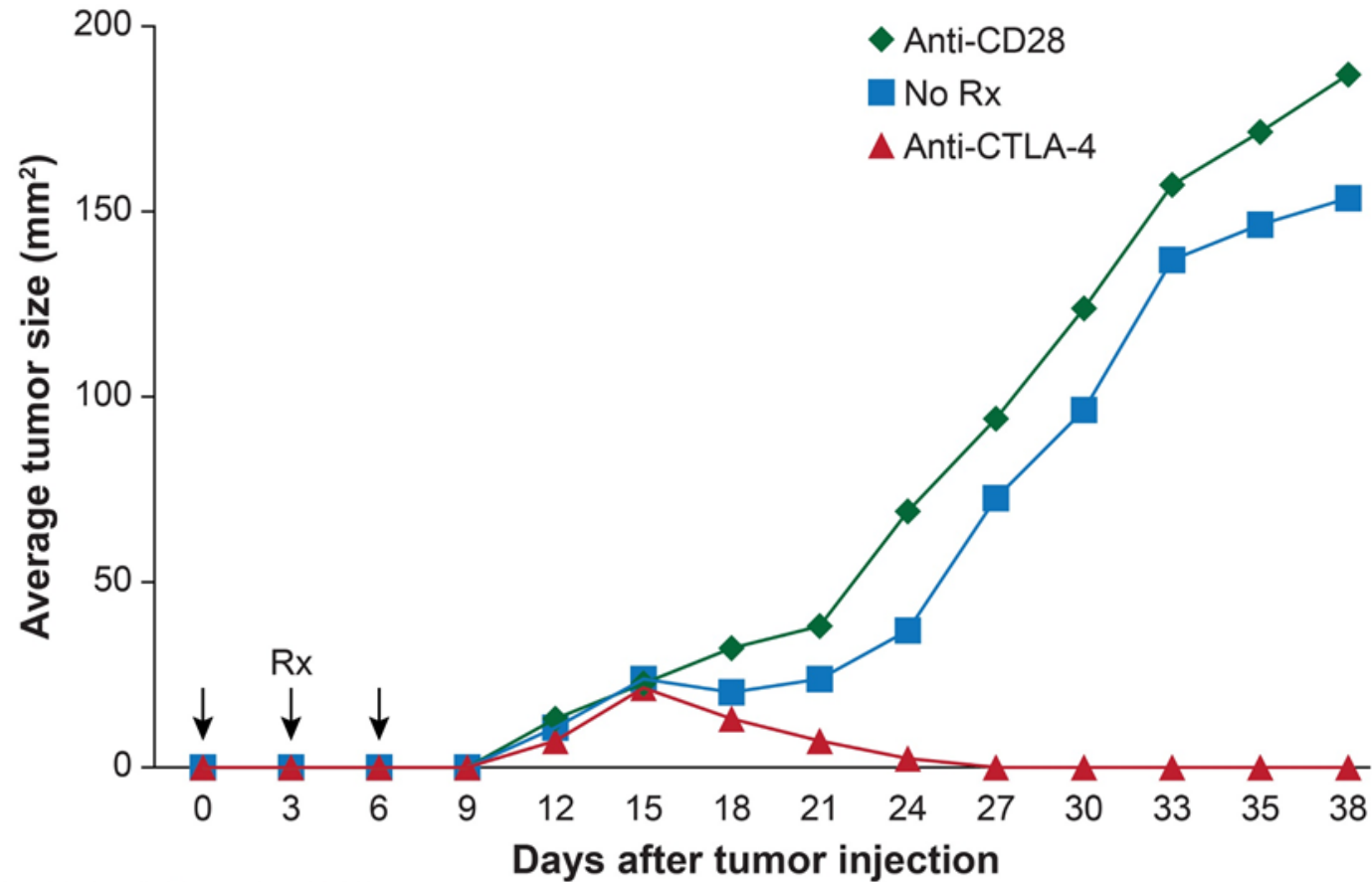




# CTLA-4, a negative regulator of T cell activity limits the responsiveness of activated T cells



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

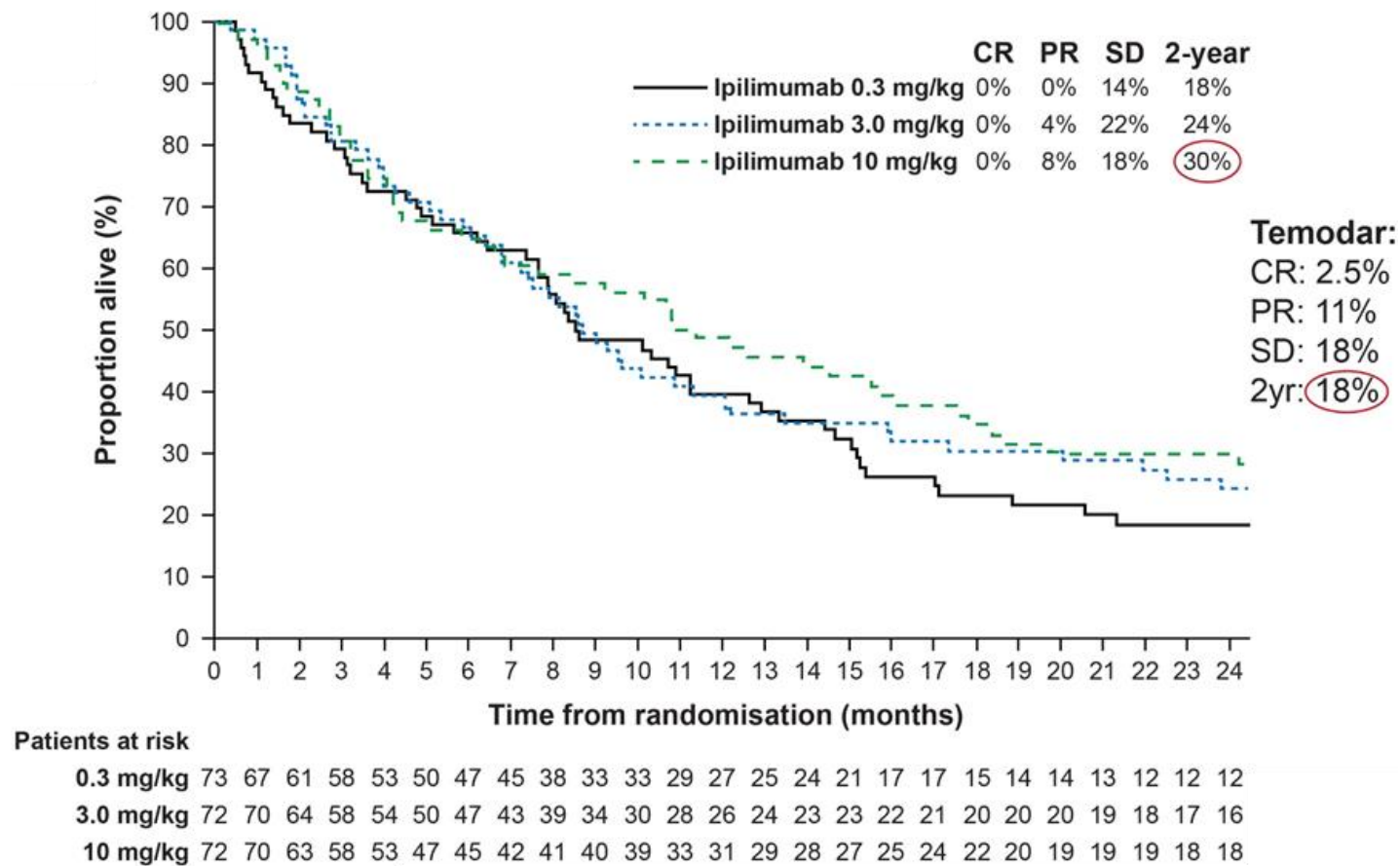


Leach DR, Krummel MF, Allison JP. 1996.  
Enhancement of antitumor immunity by CTLA-4 blockade.  
Science. 217(5256): 1734-6.





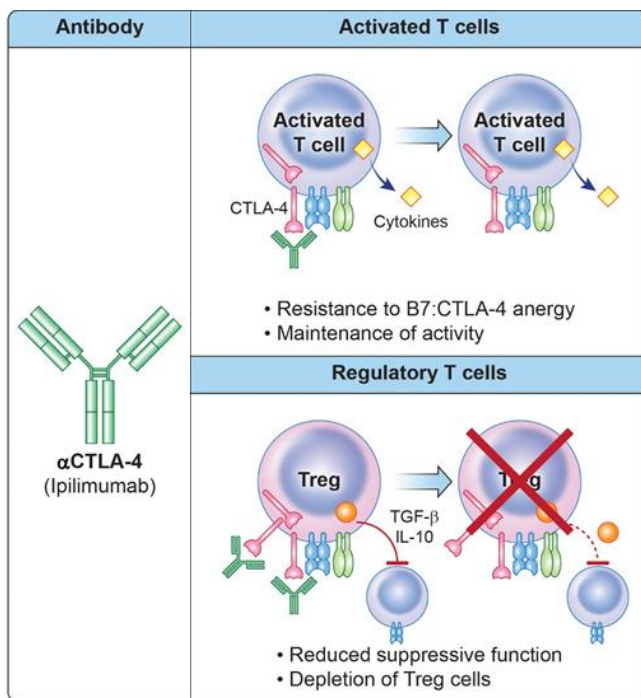
# Ipilimumab (human anti-CTLA-4) was approved for the treatment of metastatic melanoma by FDA in 2010



Wolchok et al. 2010. Lancet Oncol.



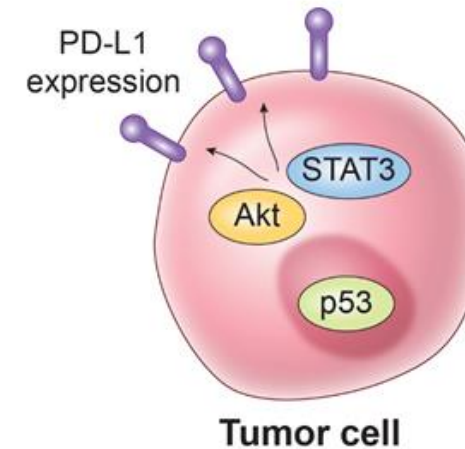
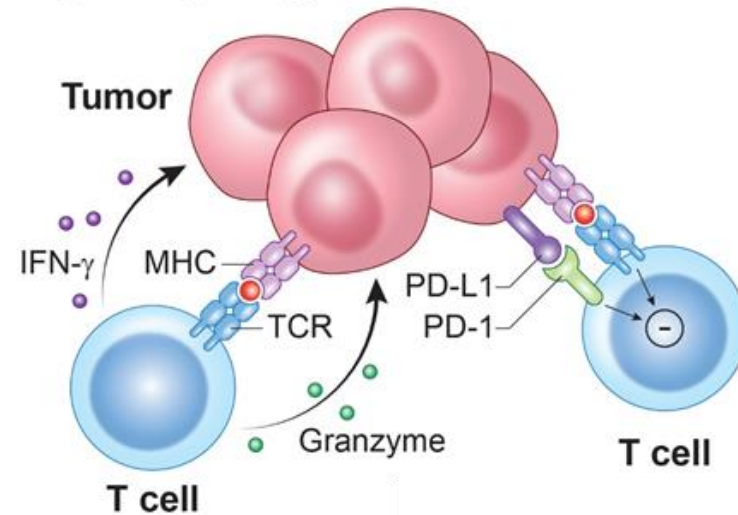
## Which T cells are affected by ipilimumab ( $\alpha$ CTLA-4)?



The efficacy and selectivity of anti-CTLA-4 therapy increase in patients who have higher percentages of activated tumor-specific T cells at the time of treatment

## PD-1: PD-L1 inhibitory pathway

- PD-1 signaling promotes T cell tolerization by inhibiting downstream activation signals
- PD-1 expression is upregulated by activated and exhausted T cell populations
- T cell surface PD-1 receptor binds to and is activated by PD-L1 and PD-L2
- Many cells within the tumor microenvironment express PD-L1/PD-L2 allowing for the suppression of T cell activation
- Tumor PD-L1 expression is regulated via two general mechanisms:
  1. TIL production of IFN- $\gamma$
  2. Oncogenic signaling pathways

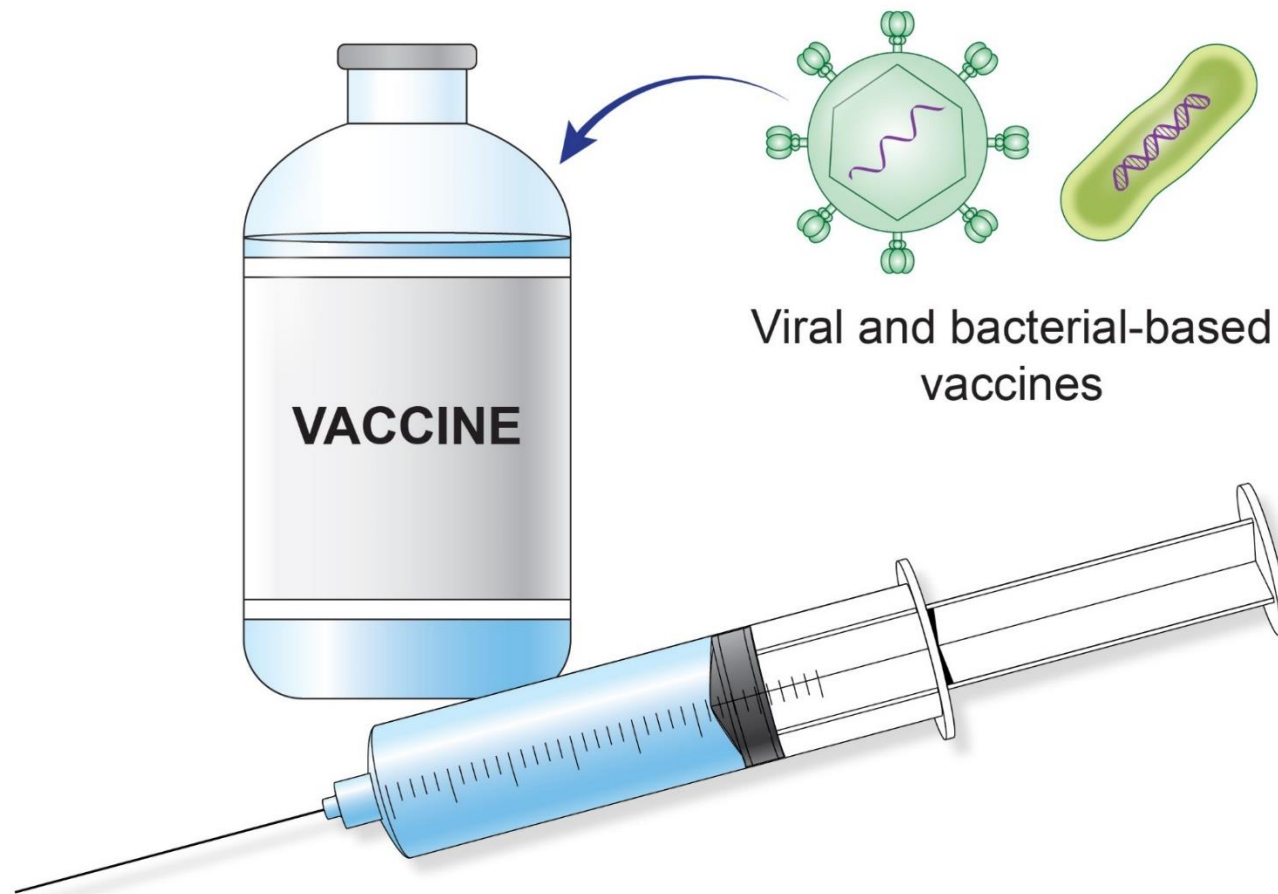


Francisco, L. et al. *Immunol Rev.* 2010. 236: 219.  
Pardoll, D.M. *Nat Rev Cancer.* 2012. 12: 252.

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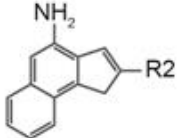
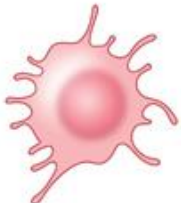
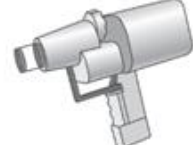
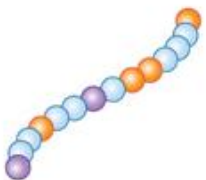
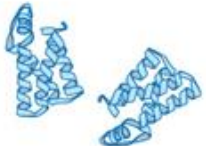
The goal of T cell checkpoint blockade is to make T cell “off-switches” inaccessible to tumor cells, thus restoring tumor-specific immunity.

# Therapeutic cancer vaccines





# Components of a cancer vaccine

| Antigen                                                                                                    | Adjuvant                                                                                              | Vector                                                                                                       | Mode of Administration                                                                                   |
|------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| <br>Whole tumor           | <br>Emulsifiers    | <br>Viral vectors         | <br>Injection         |
| <br>Protein antigen       | <br>Innate agonists | <br>Dendritic cells       | <br>Gene gun          |
| <br>Antigenic peptide(s) | <br>Cytokines       | <br>Attenuated bacteria | <br>Systemic infusion |
|                                                                                                            | <br>Antibodies    |                                                                                                              | <br>Nasal spray     |

# Basic Principles of Cancer Immunotherapy-Part II

**Hassane M. Zarour, MD**

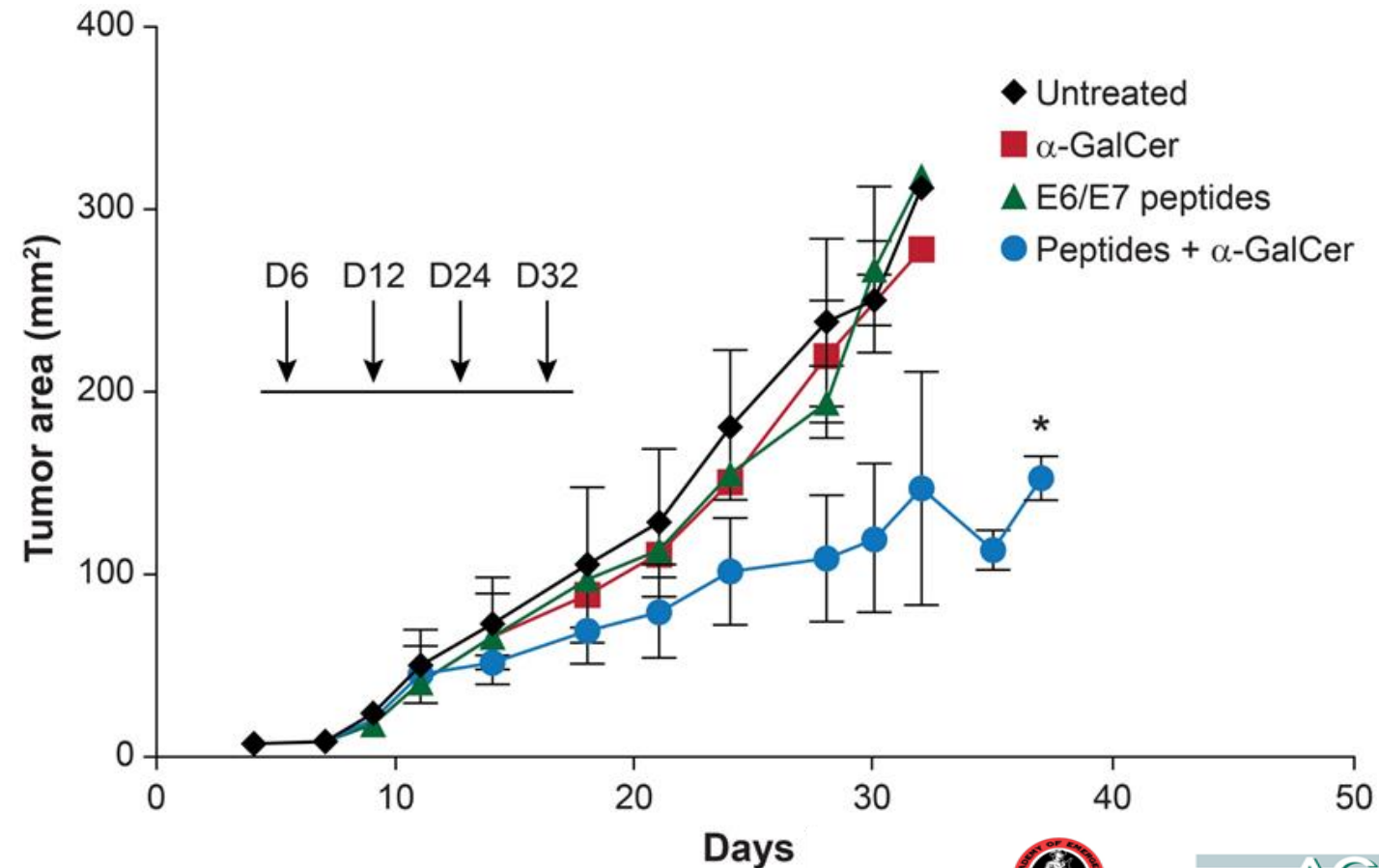
Professor of Medicine, Immunology and Dermatology  
UPMC Hillman Cancer Center



# Disclosures

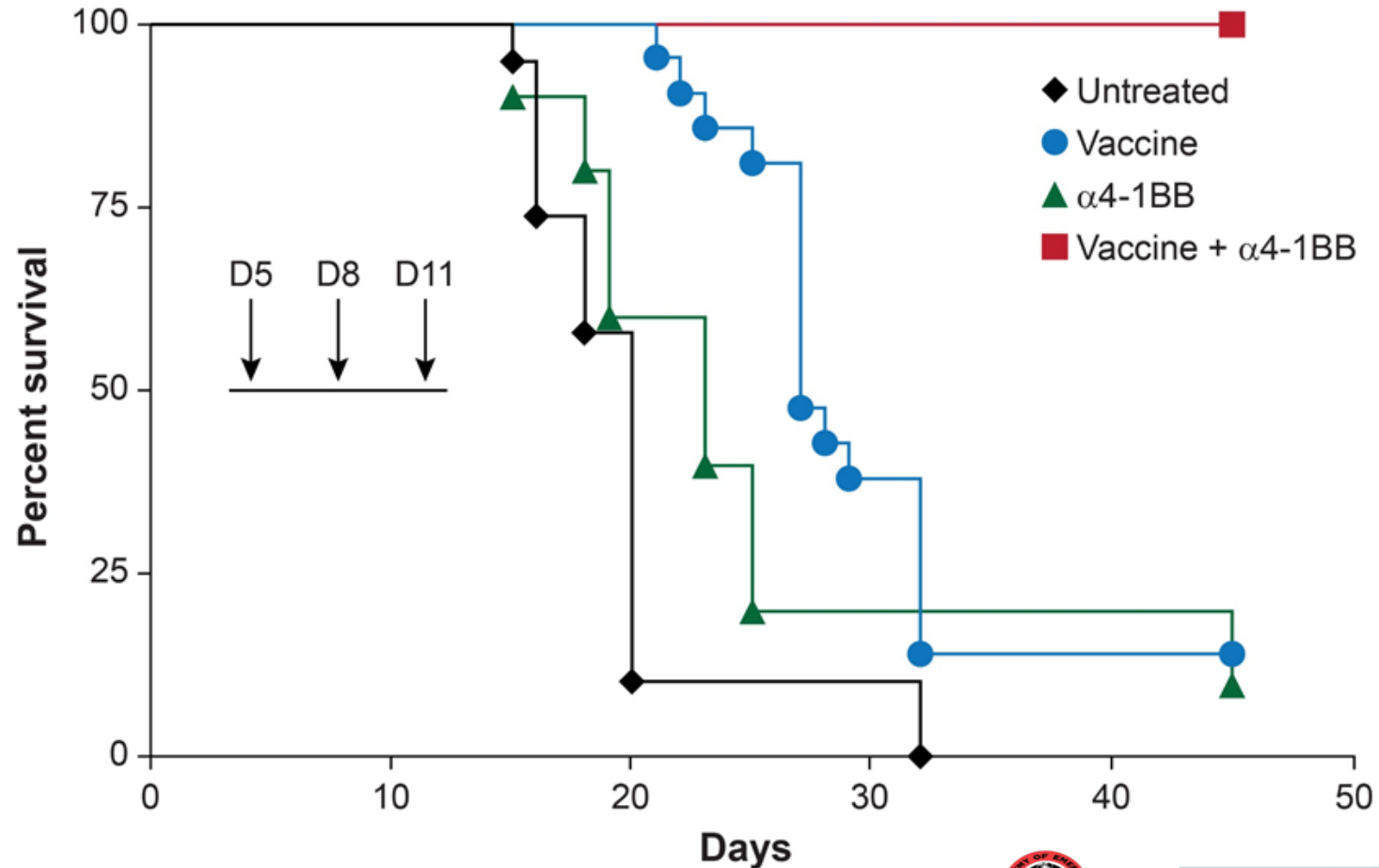
- Pierre Fabre Laboratories, Consulting Fees
- Bristol-Myers Squibb, TESARO, Inc., Contracted Research
- I may be discussing non-FDA approved indications during my presentation.

## 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

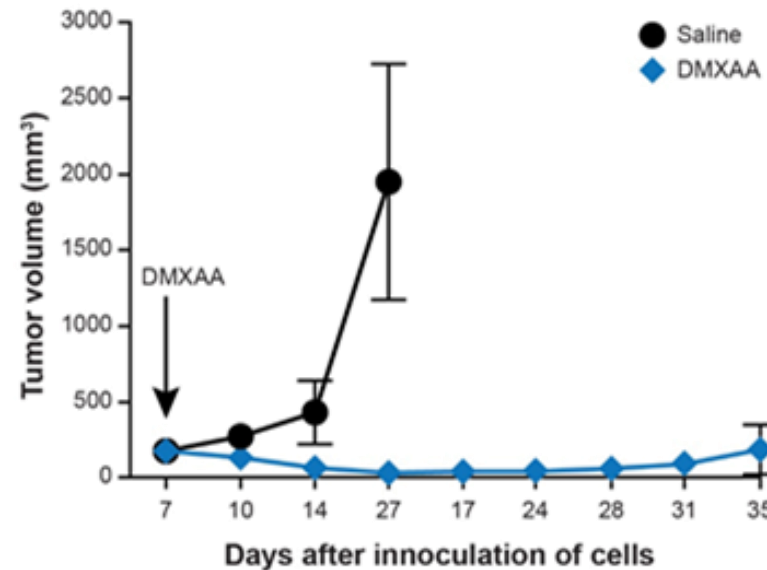


Todd Bartkowiak, M.S.



# Intratumoral injection of innate immune agonists: The direct vaccination approach

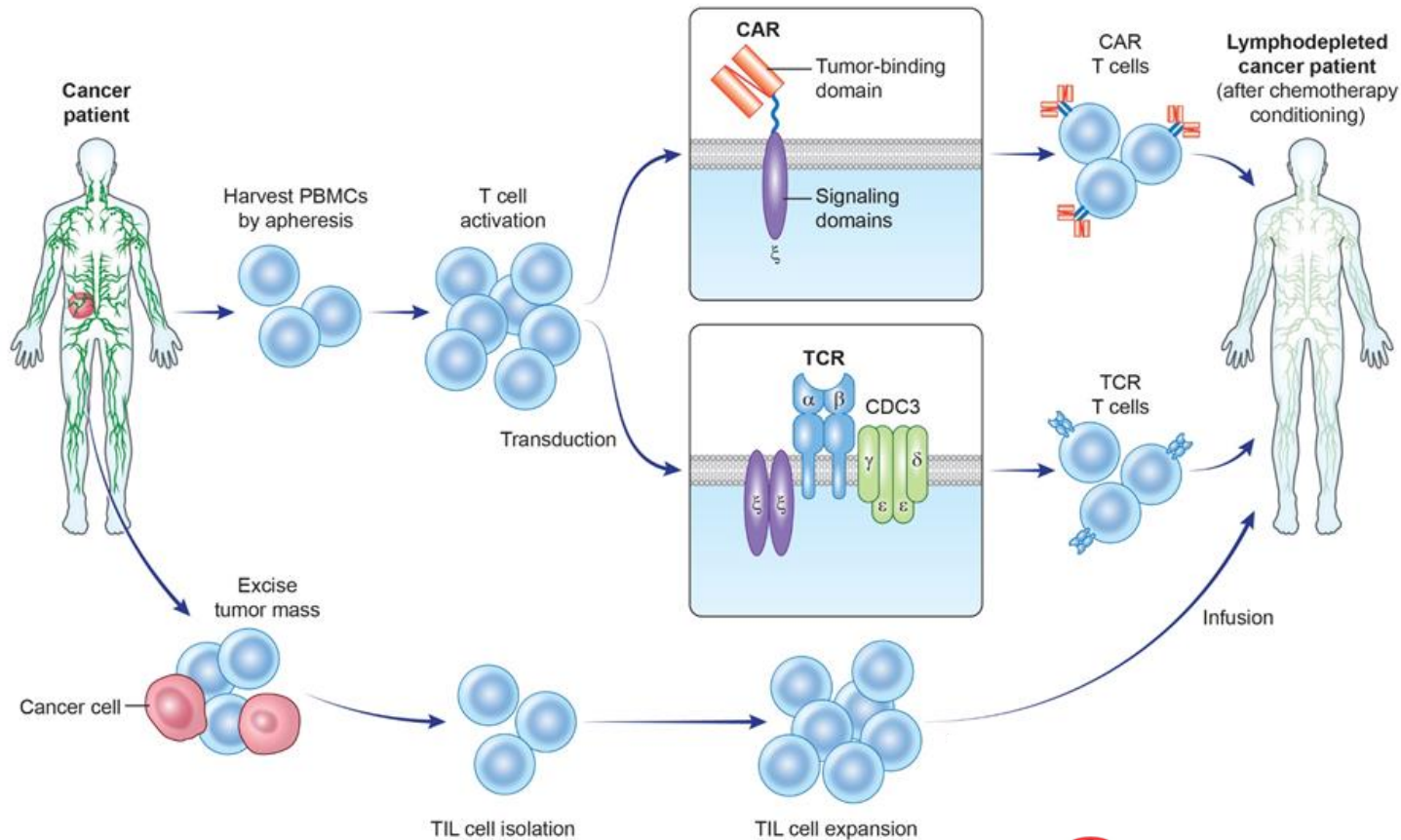
**Intratumoral DMXAA (mouse STING agonist) triggers rejection of B16 melanoma**



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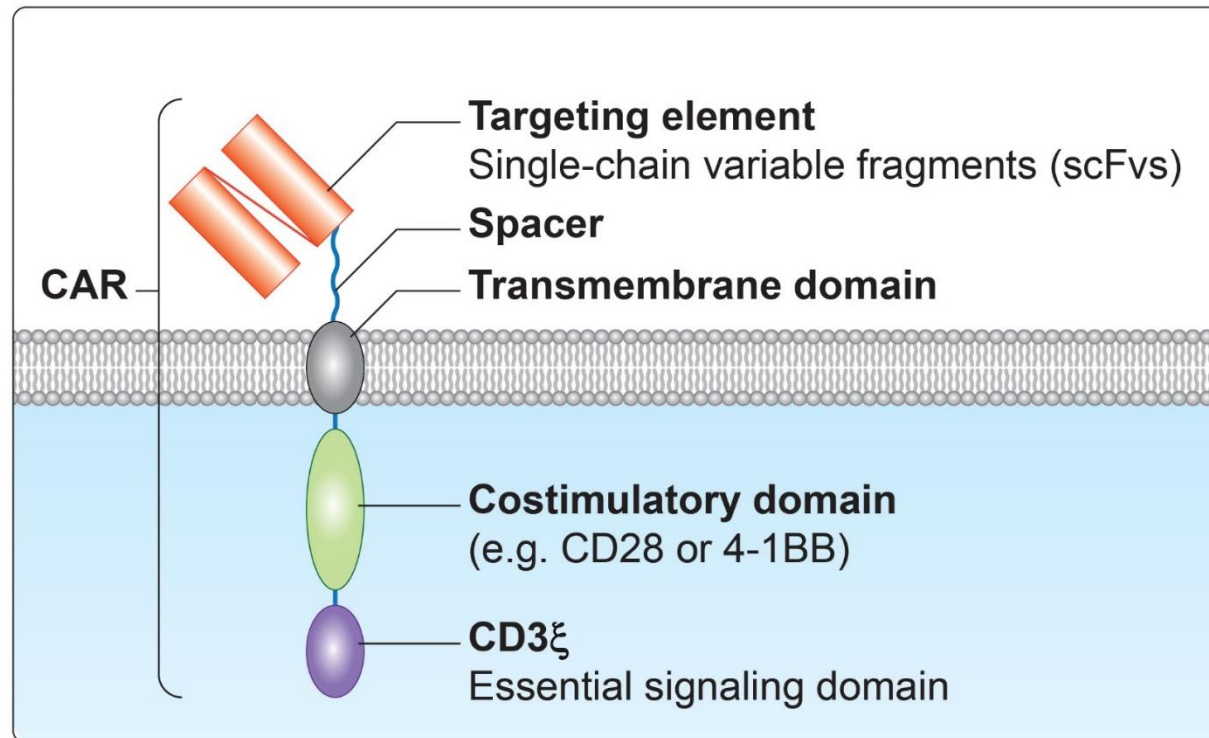
The goal of therapeutic cancer vaccination is to increase the immunogenicity of tumor antigens which are poorly presented by the tumor in order to generate a high frequency of tumor-specific T cells.

# Adoptive T cell therapy can involve engineered (CAR, TCR) or patient-derived (TIL, PBMC) T cells





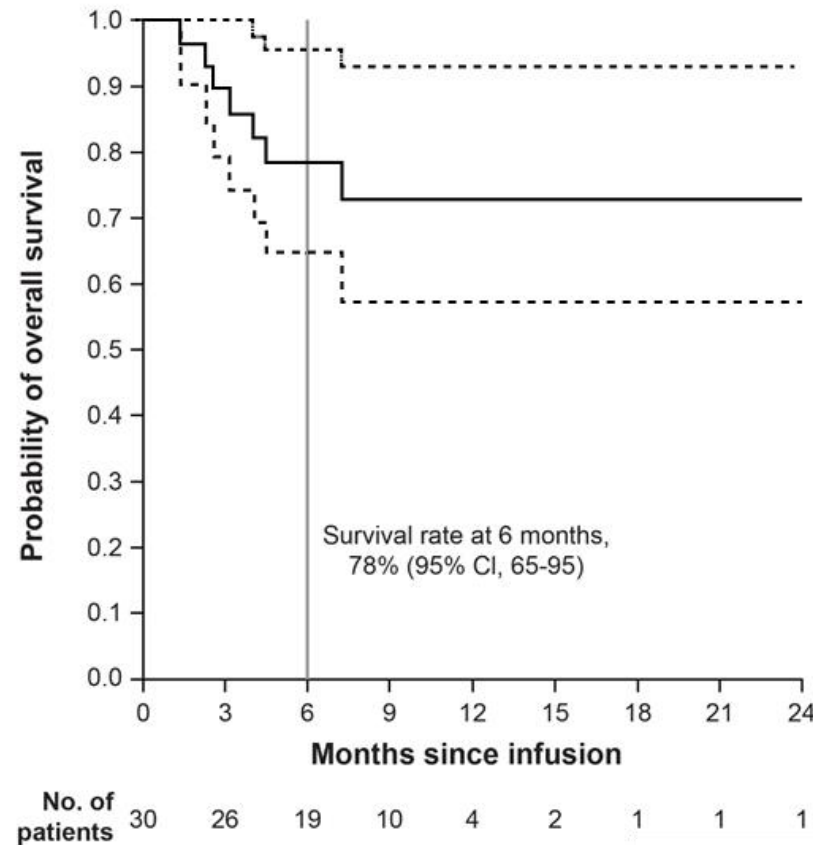
## T cell adoptive transfer



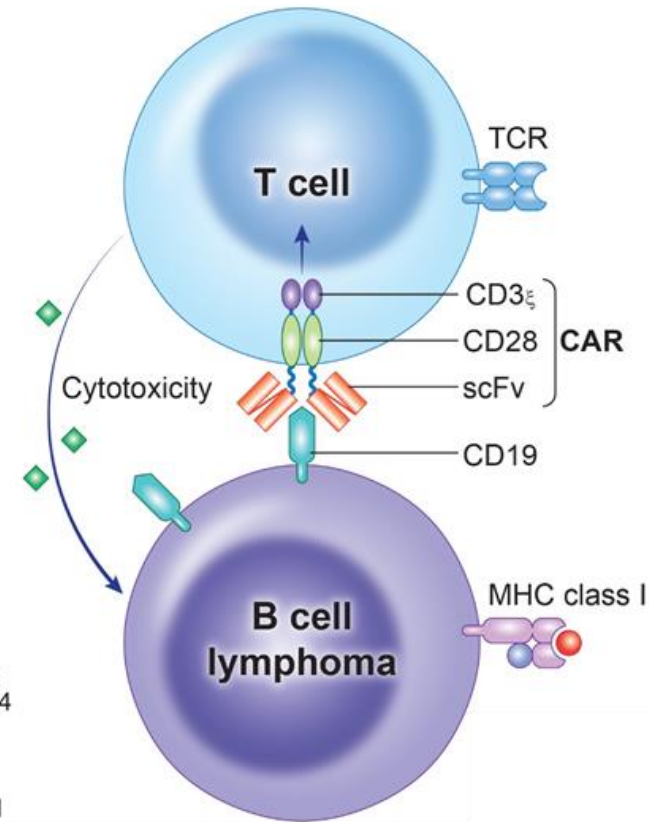
CARs, TIL, TCR, PBMCS



# Effective treatment of relapsed B cell ALL with CD19 CAR T cell therapy



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.



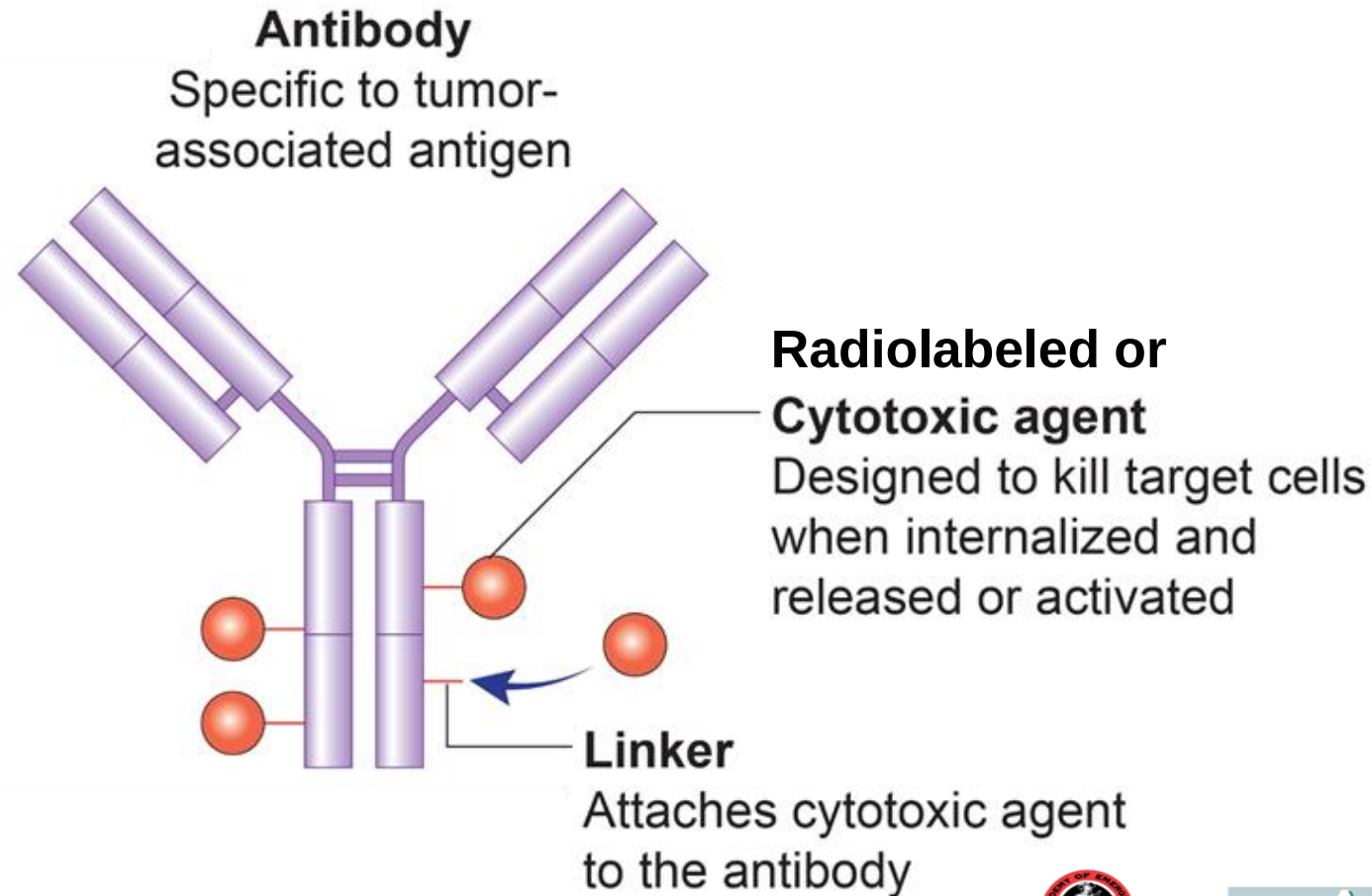


To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of T cell adoptive transfer is to win the numbers game and overwhelm the tumor with a higher frequency of tumor-specific T cells than it is capable of suppressing.



# Effector antibodies and antibody-drug conjugates (ADCs)



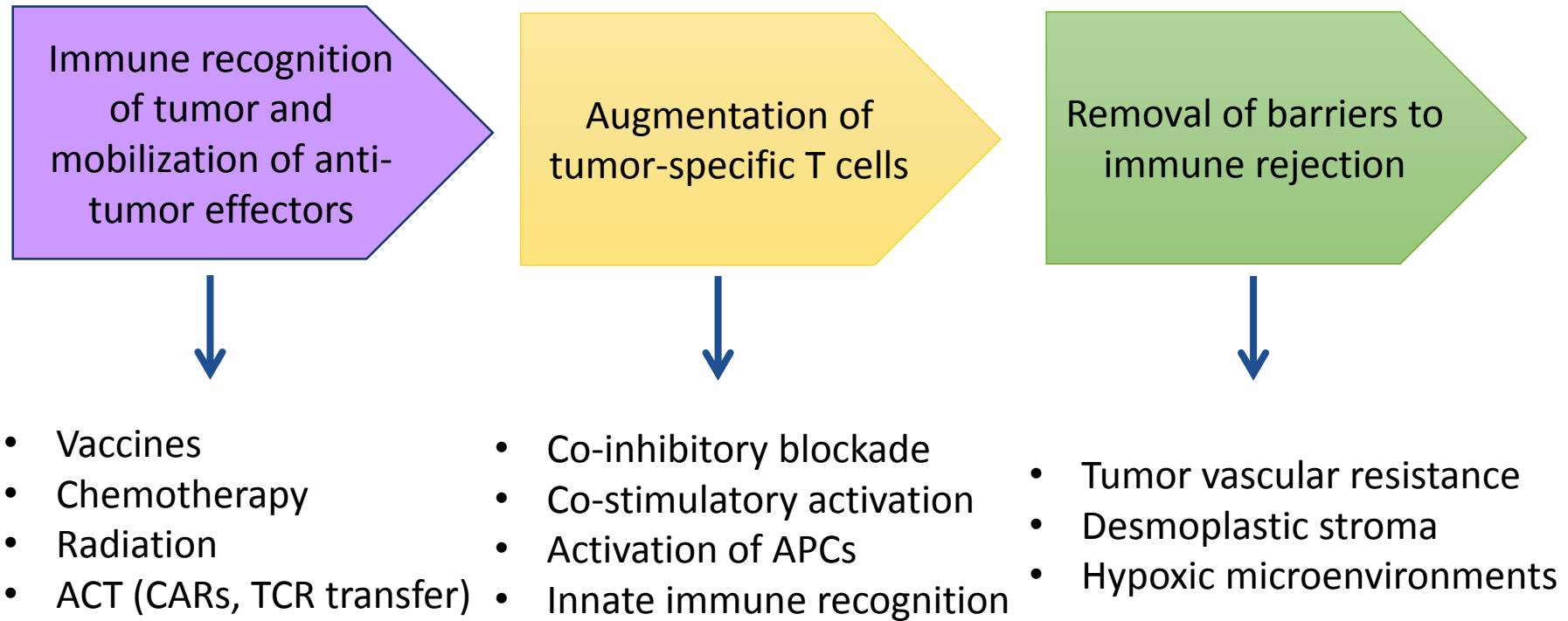
## Key ADC / antibody principles

- **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.



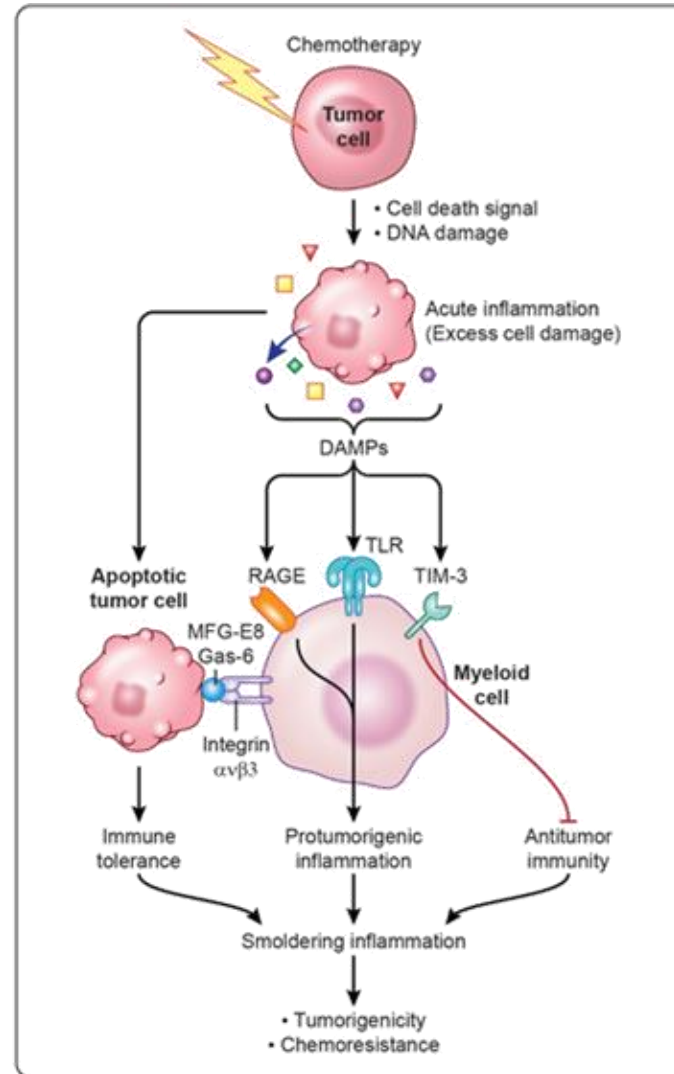
To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of effector antibodies is to utilize the exquisite sensitivity of antibodies to specifically target and kill tumor cells using mechanisms which are difficult to evade or suppress.



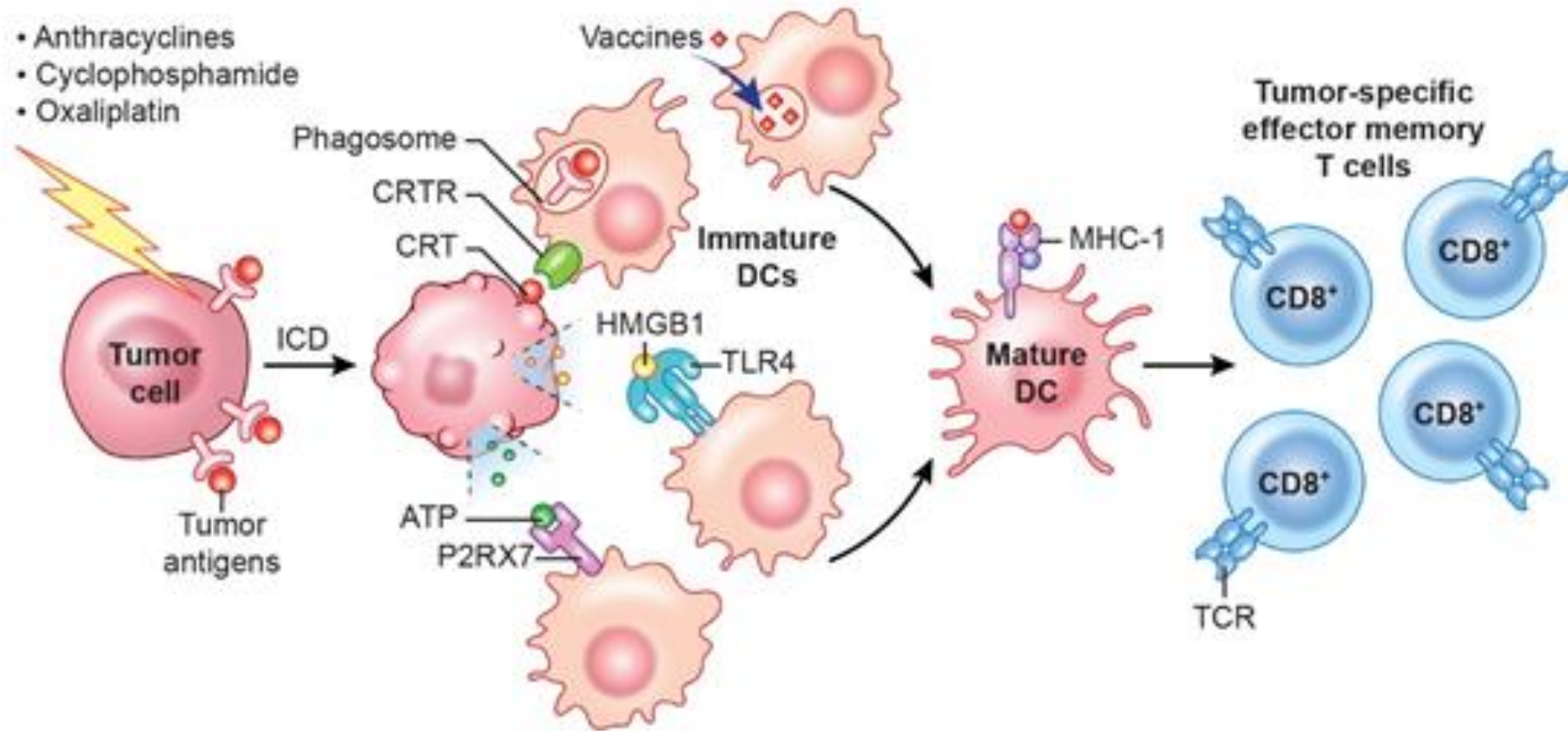
# A different perspective on chemotherapy

## Immunogenic versus non-immunogenic cell death



# A different perspective on chemotherapy

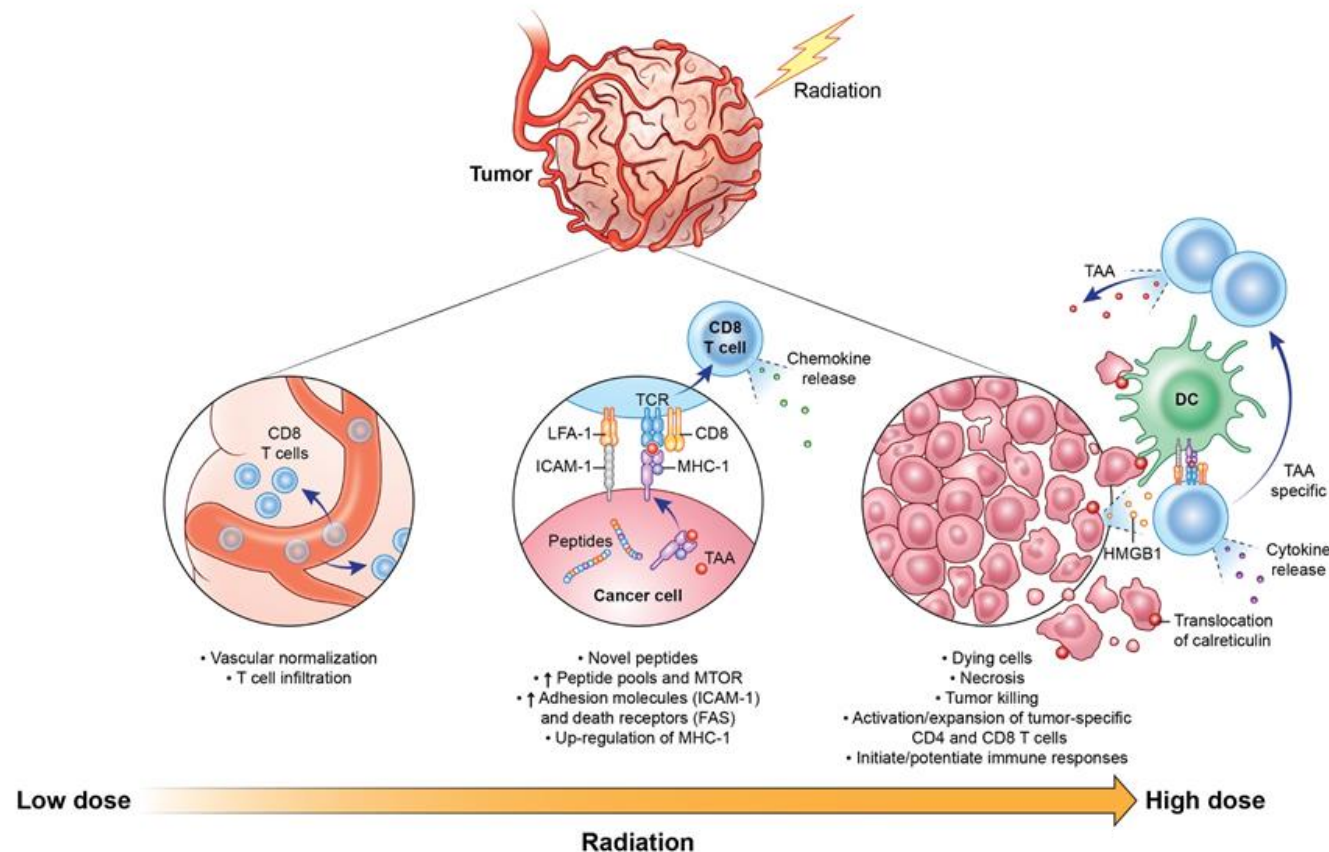
## Immunogenic versus non-immunogenic cell death





# Radiation Therapy:

A potent adjuvant for tumor immunity



Exploiting the untapped potential of immunogenic modulation by radiation  
in combination with immunotherapy for the treatment of cancer

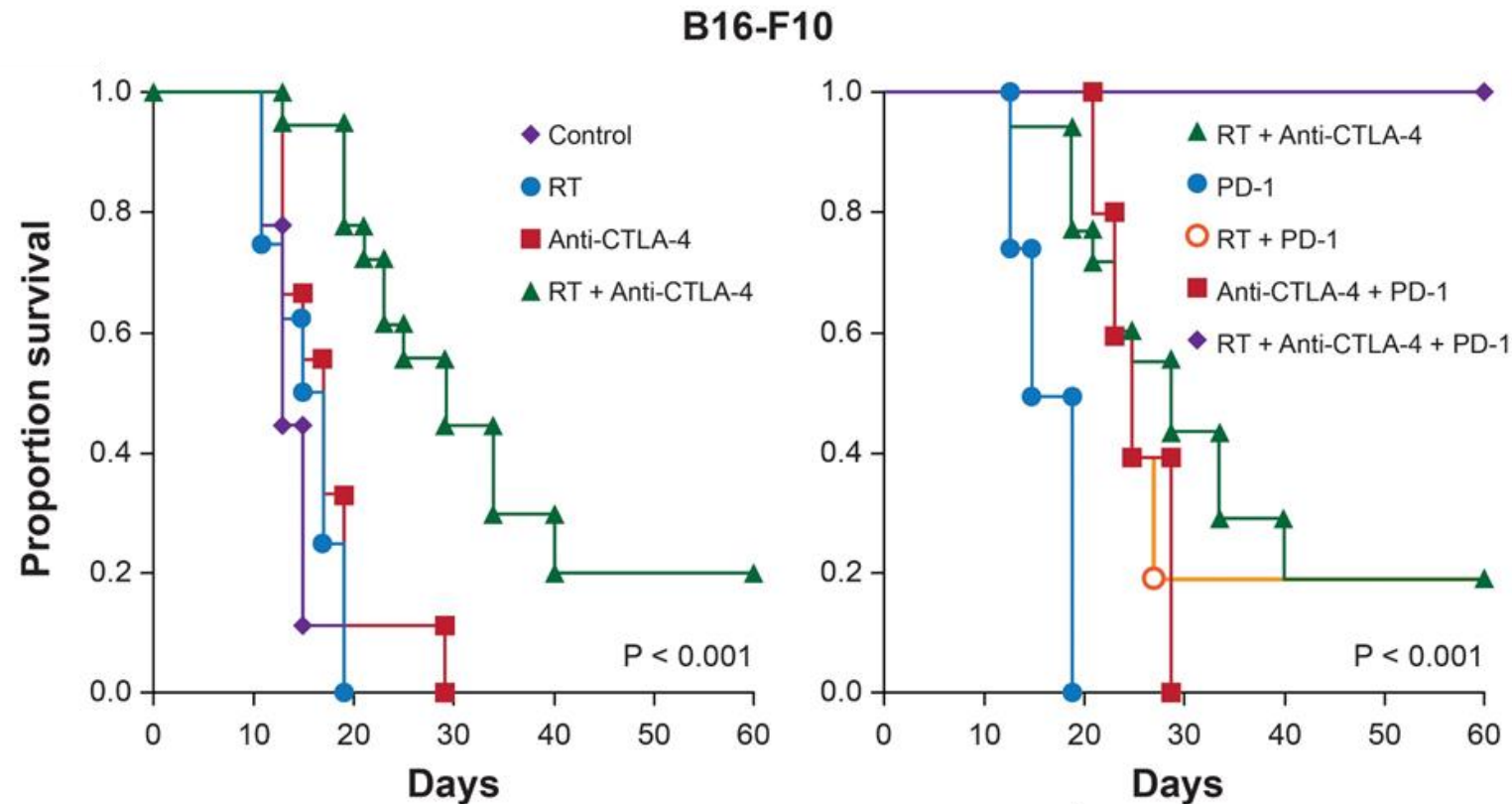
<http://www.ncbi.nlm.nih.gov/pubmed/18777956>



## Abscopal effect

- Localized treatment of a tumor causes/evokes reduction of distant ones
- Immunotherapy + radiotherapy with targeted immunomodulators and immune checkpoint blockade is intended to elicit the abscopal effect.

# Radiotherapy synergizes with blockade of CTLA-4 and PD-1 to cure melanoma lung metastases



Victor CT, Rech A, Maity A, Rengan R, Pauken K, Stelekati E, Benci J, Xu B, Dada H, Odorizzi P, et al. 2015.  
Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer.  
Nature. 520: 373-377.



# Why combination immunotherapy is the future?

More consistent benefit for a larger percentage of patients  
with a wide range of cancer types

