

ADVANCES IN
Cancer
IMMUNOTHERAPY™



Basic Principles of Cancer Immunotherapy



Society for Immunotherapy of Cancer

Disclosures

- OncoSec Medical Incorporated, Salary (ended 6/2016); OncoSec Medical Incorporated, Receipt of Intellectual Property Rights/Patent Holder
- Calithera BioSciences, Inc., Immunogenics LLC, OncoSec Medical Incorporated, Orphagen Pharmaceuticals, Inc., Spectrum Pharmaceuticals, Consulting Fees
- Immunogenics LLC, OncoSec Medical Incorporated, Orphagen Pharmaceuticals, Inc., Ownership Interest
- I *will not* 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.

Types of tumor antigens

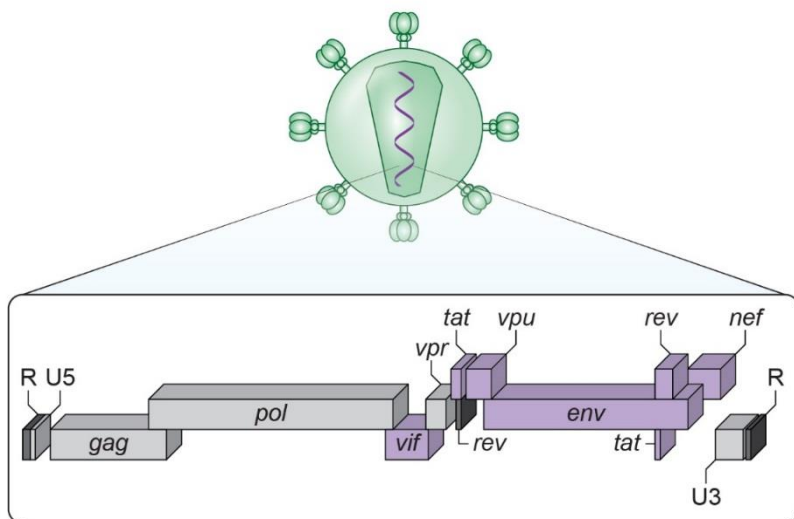


Tumor Associated Antigens (TAAs):

- Cancer-testis (CT) Antigens: MAGE, NY-ESO-1, SSX, [...] → Not normally expressed in somatic tissue (restricted to testes, sometimes, ovary or trophoblast); ectopically expressed by some tumors.
- Differentiation Antigens: GP-100, Melan-A/Mart-1, Tyrosinase, PSA, CEA, [...] → Normal expression restricted to specific cell lineages.
- Overexpressed Antigens: HER-2, p53, CSPG4, survivin, [...] → Broad expression, but low-level normal expression; increased in some tumors.
- Virus-encoded “neo”-antigens: HPV, MCPyV, EBV, etc.
- Mutation-derived neoantigens

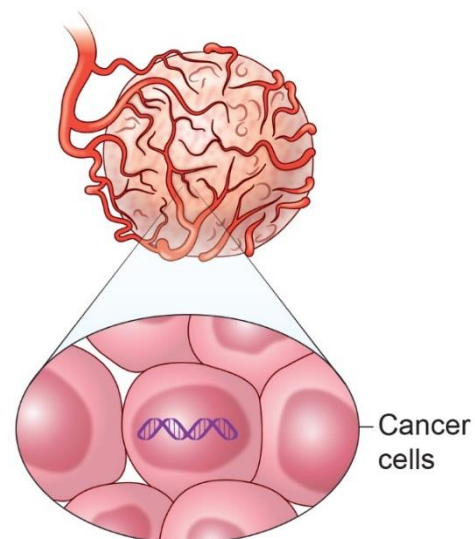
Like pathogens, tumors deploy multigenic immune evasion programs

The HIV-1 genome



With <9.8kB of genome space, HIV, like many other viruses, devotes a large percentage of its genome to immune evasion.

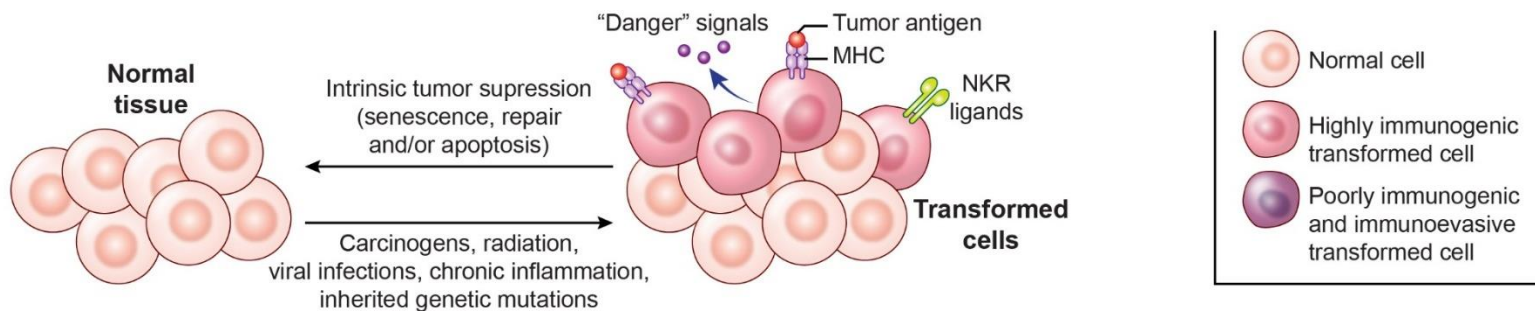
Tumor



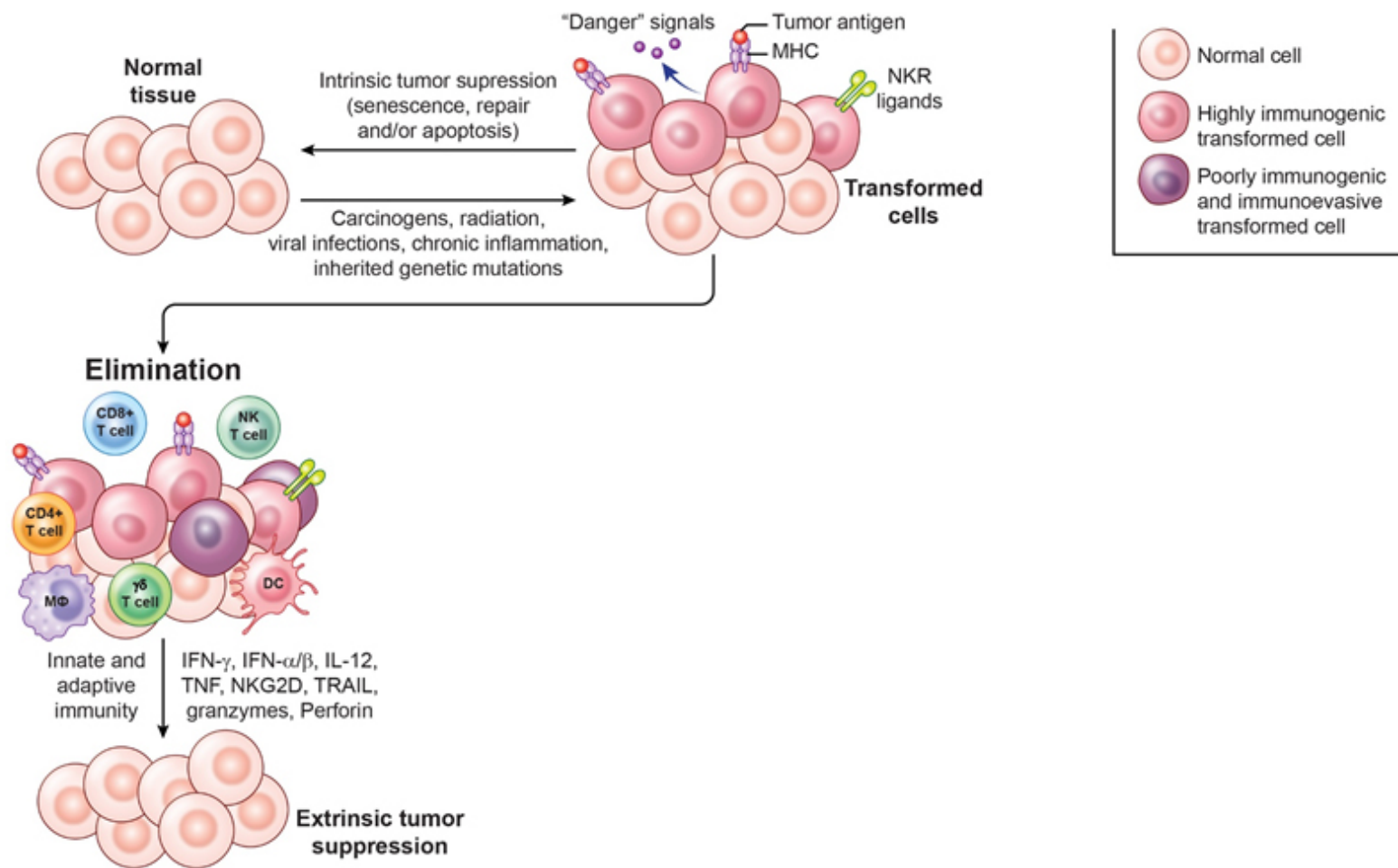
Can access the entire 3×10^9 base genome for evolutionary as well as adaptive immune evasion.



The 3 Es of cancer immunoediting



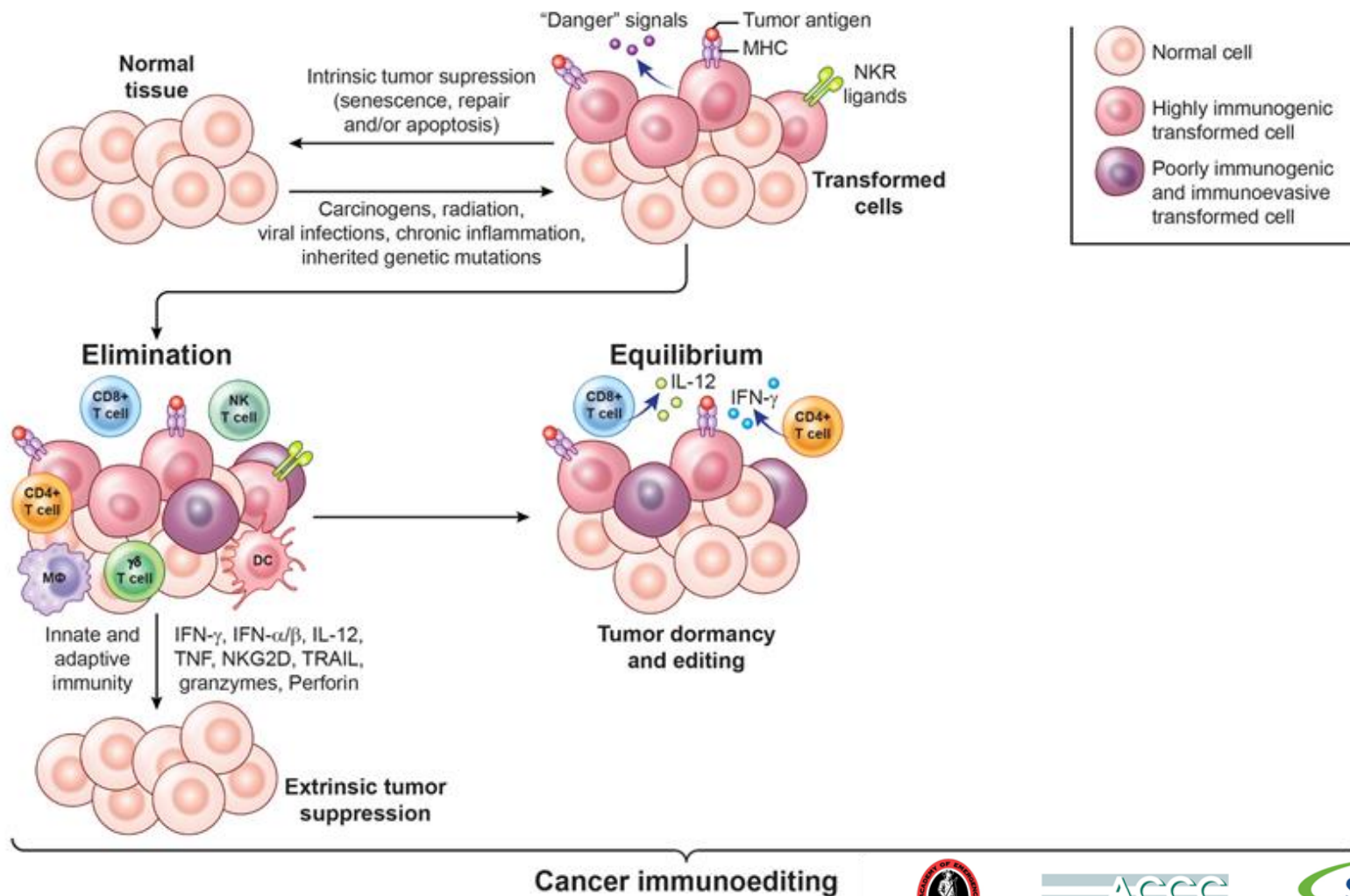
The 3 Es of cancer immunoediting



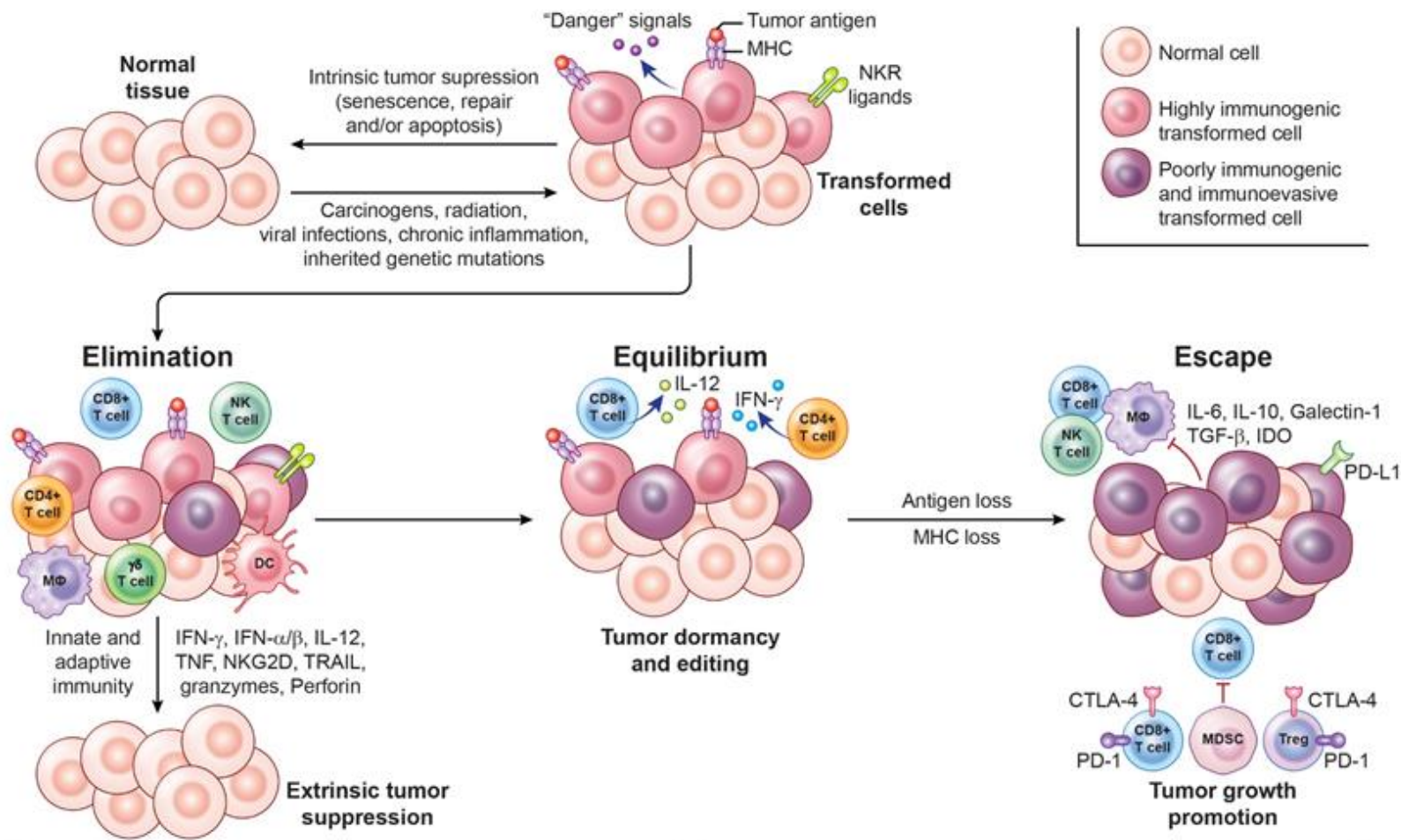
Cancer immunoediting



The 3 Es of cancer immunoediting



The 3 Es of cancer immunoediting

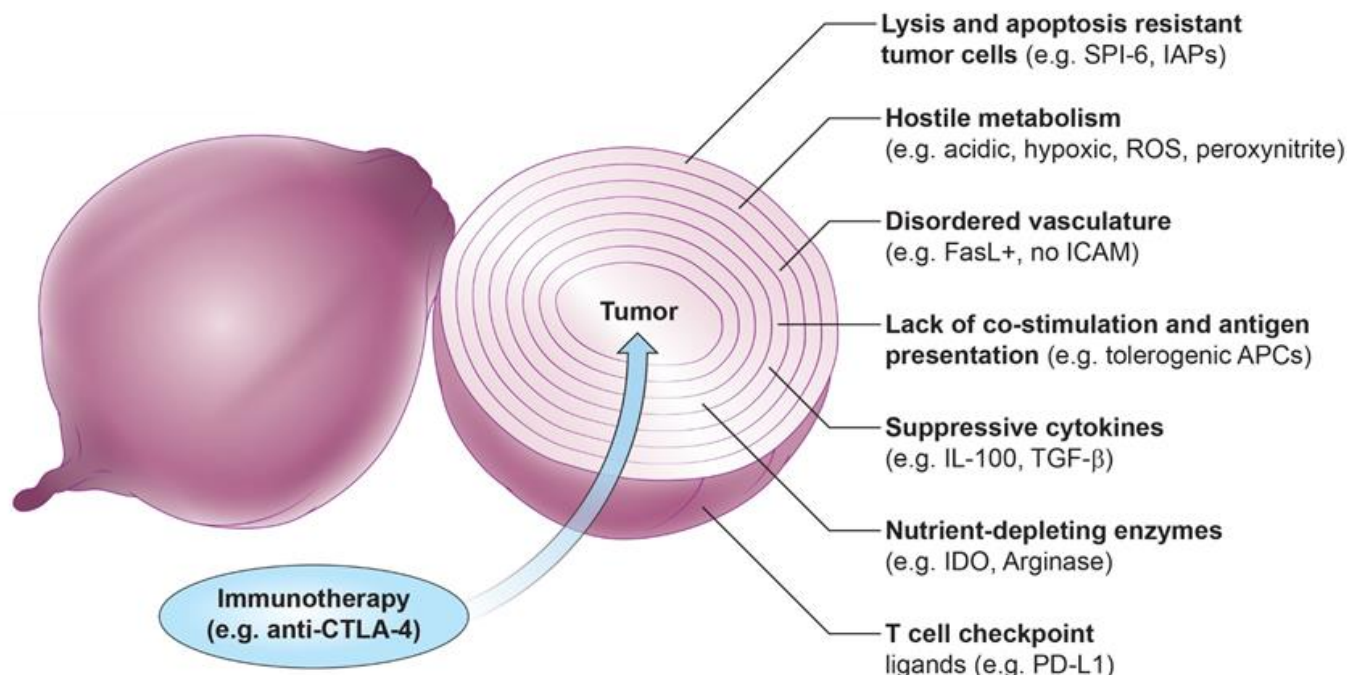


Cancer immunoediting





Multi-layered immunosuppression



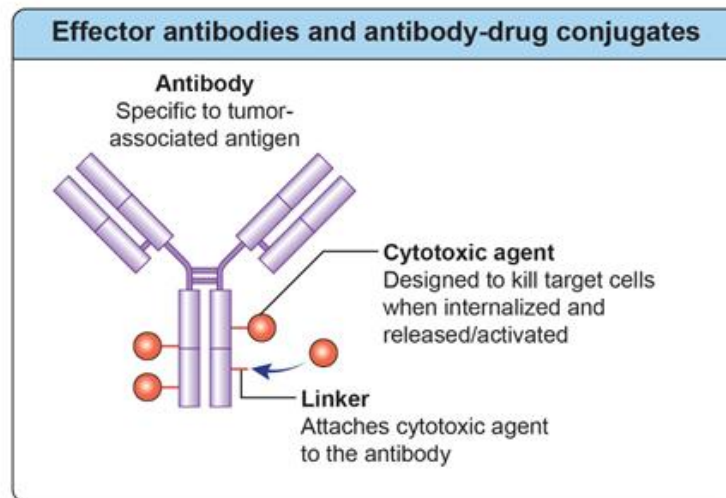
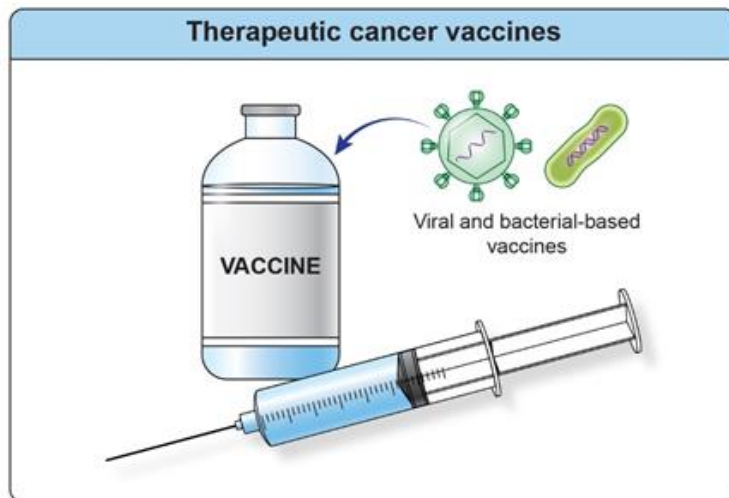
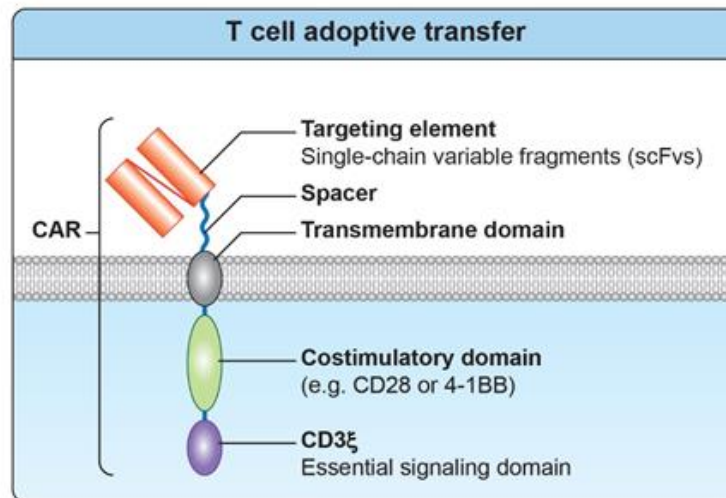
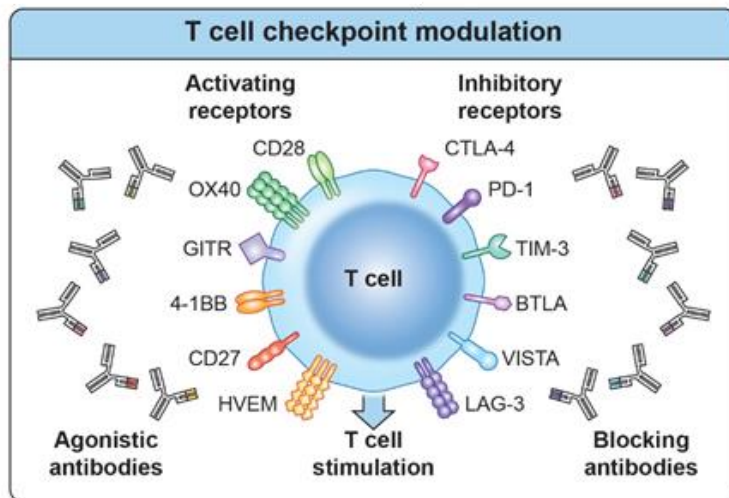
- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune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



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

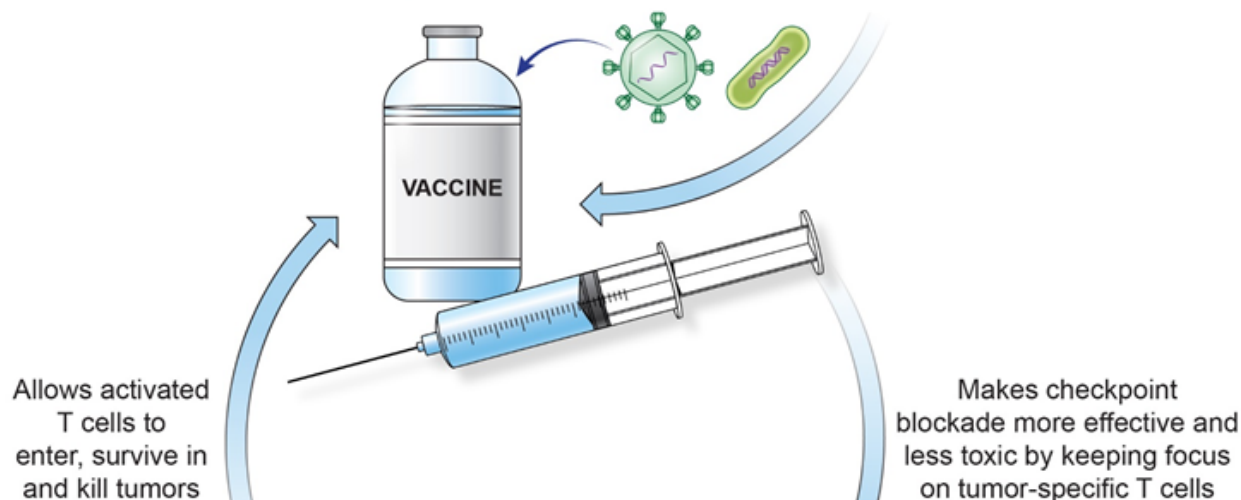
The goal of immunotherapy, then, is to restore the capacity of the immune system to recognize and reject cancer.

Types of immunotherapy

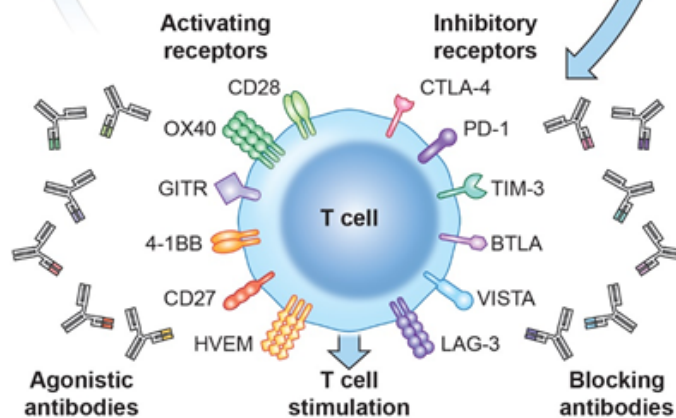


Order matters...

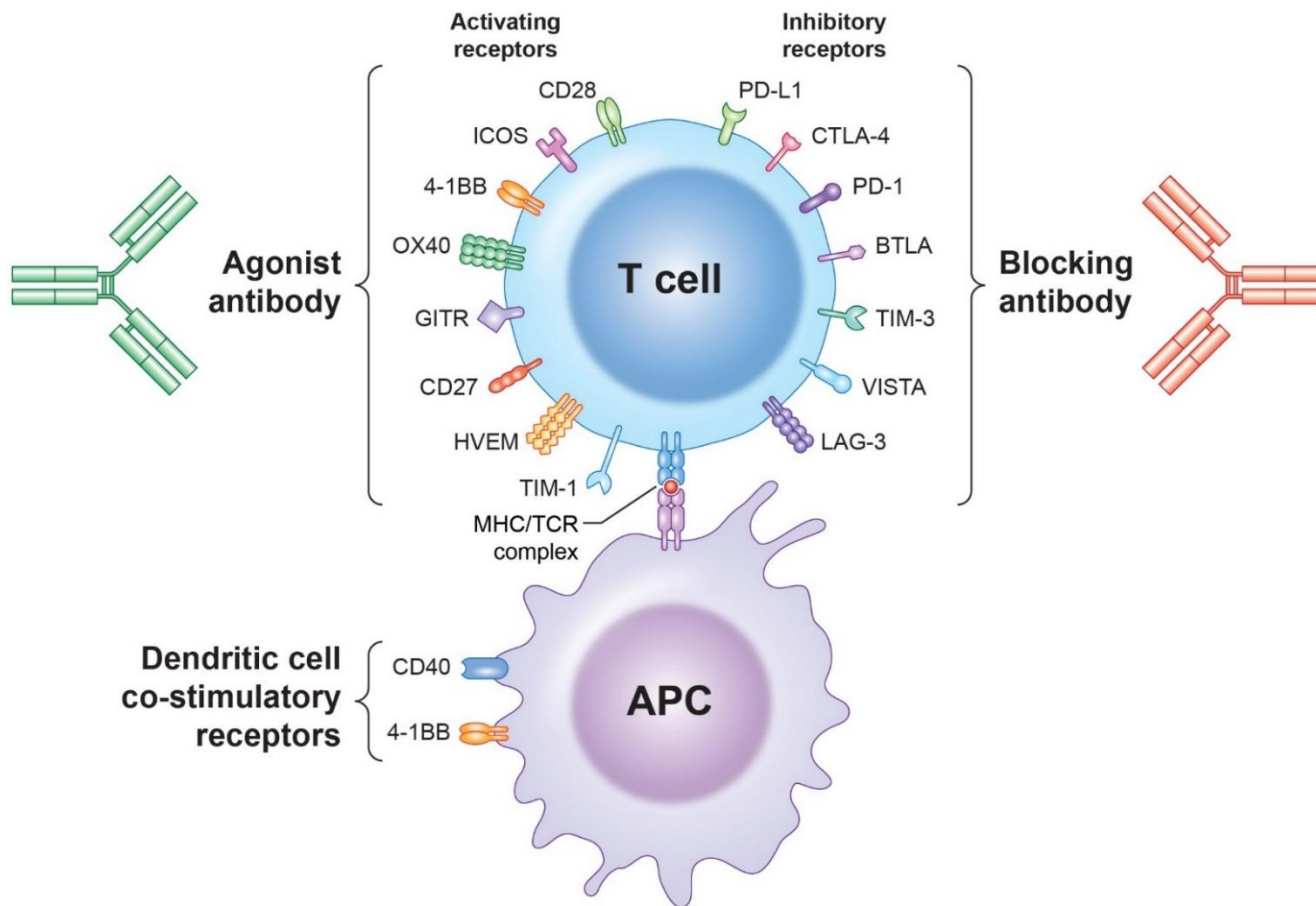
Therapeutic cancer vaccines



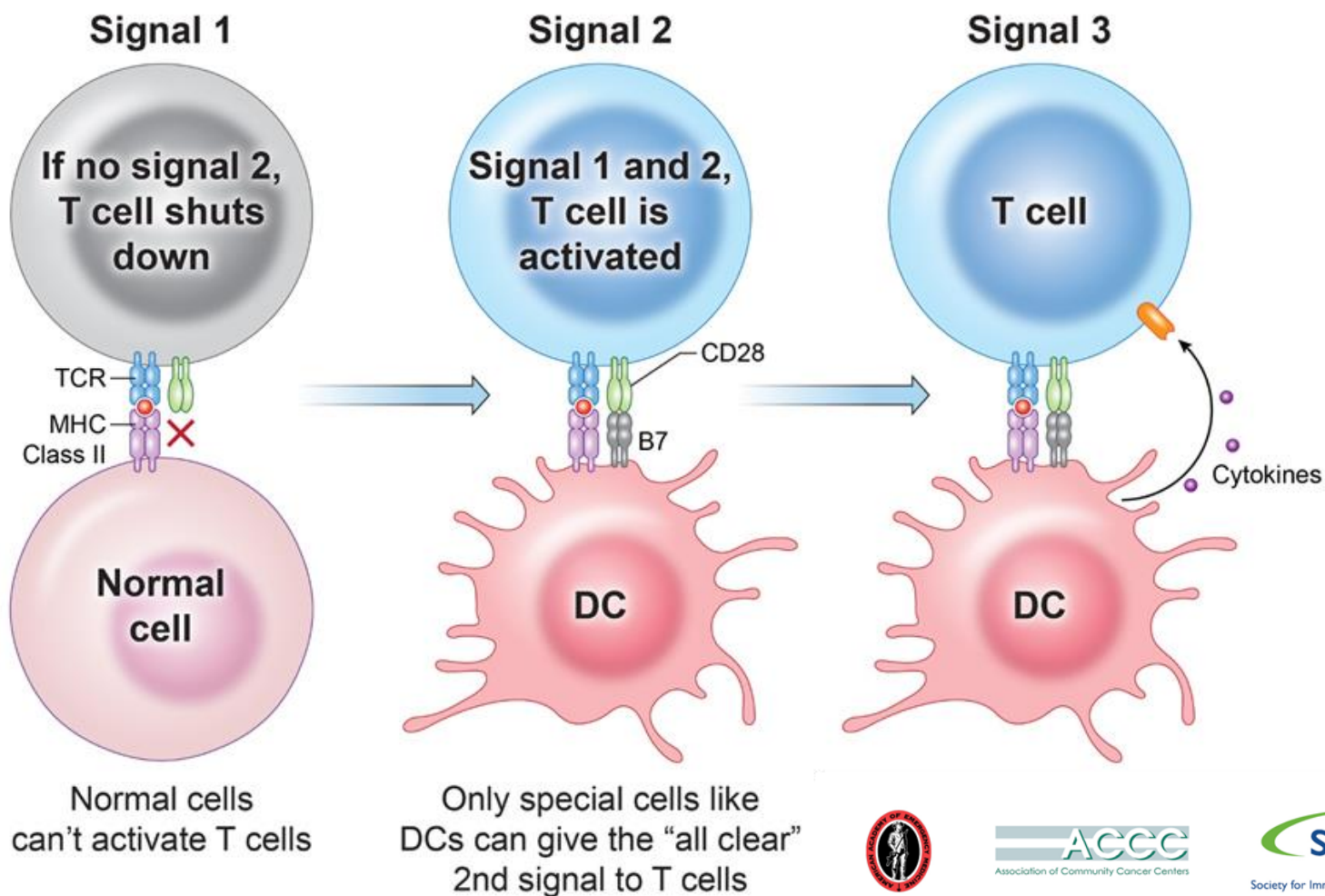
T cell checkpoint modulation



T cell checkpoint modulation

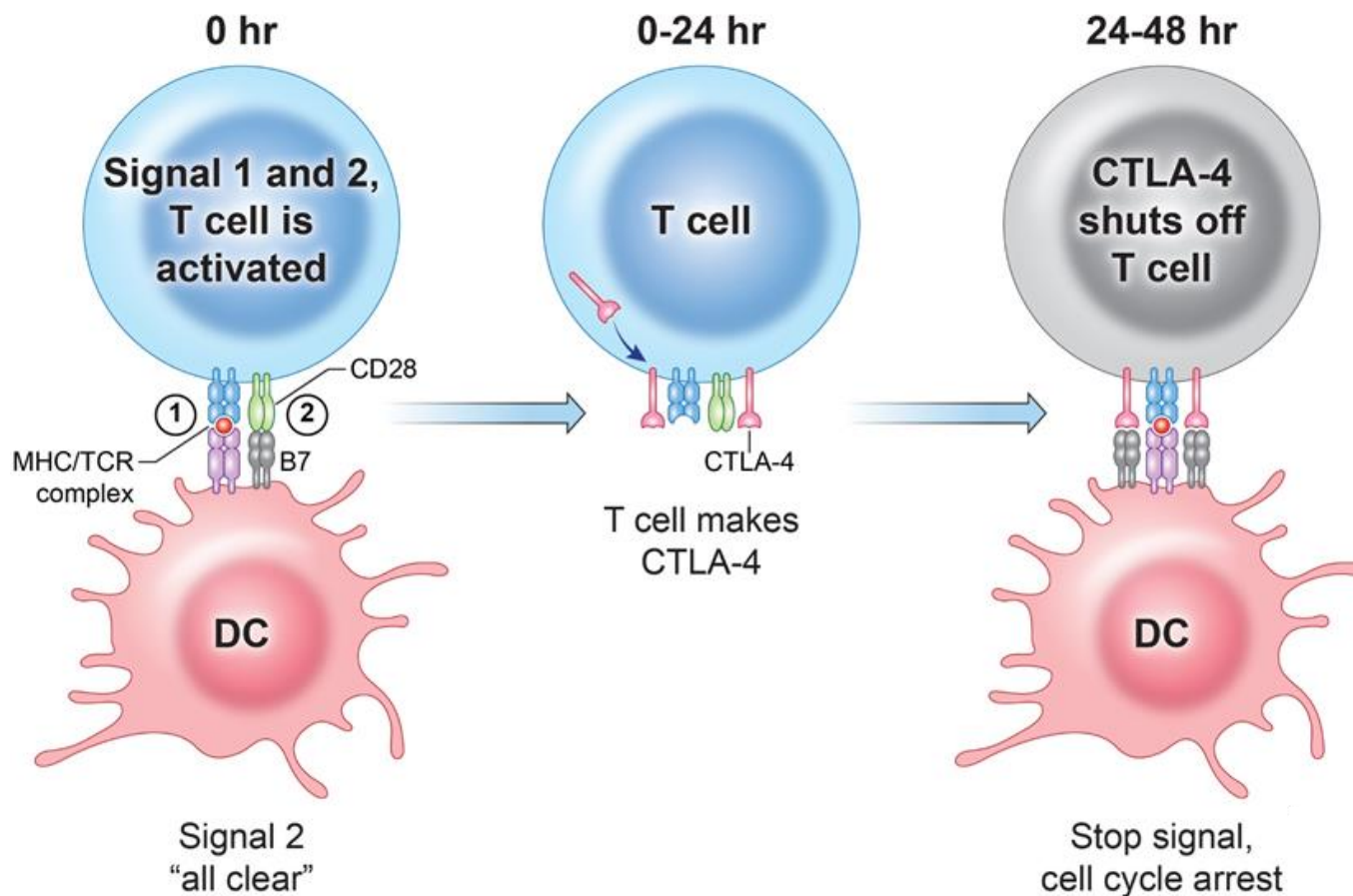


Three signals for antigen-specific T cell activation

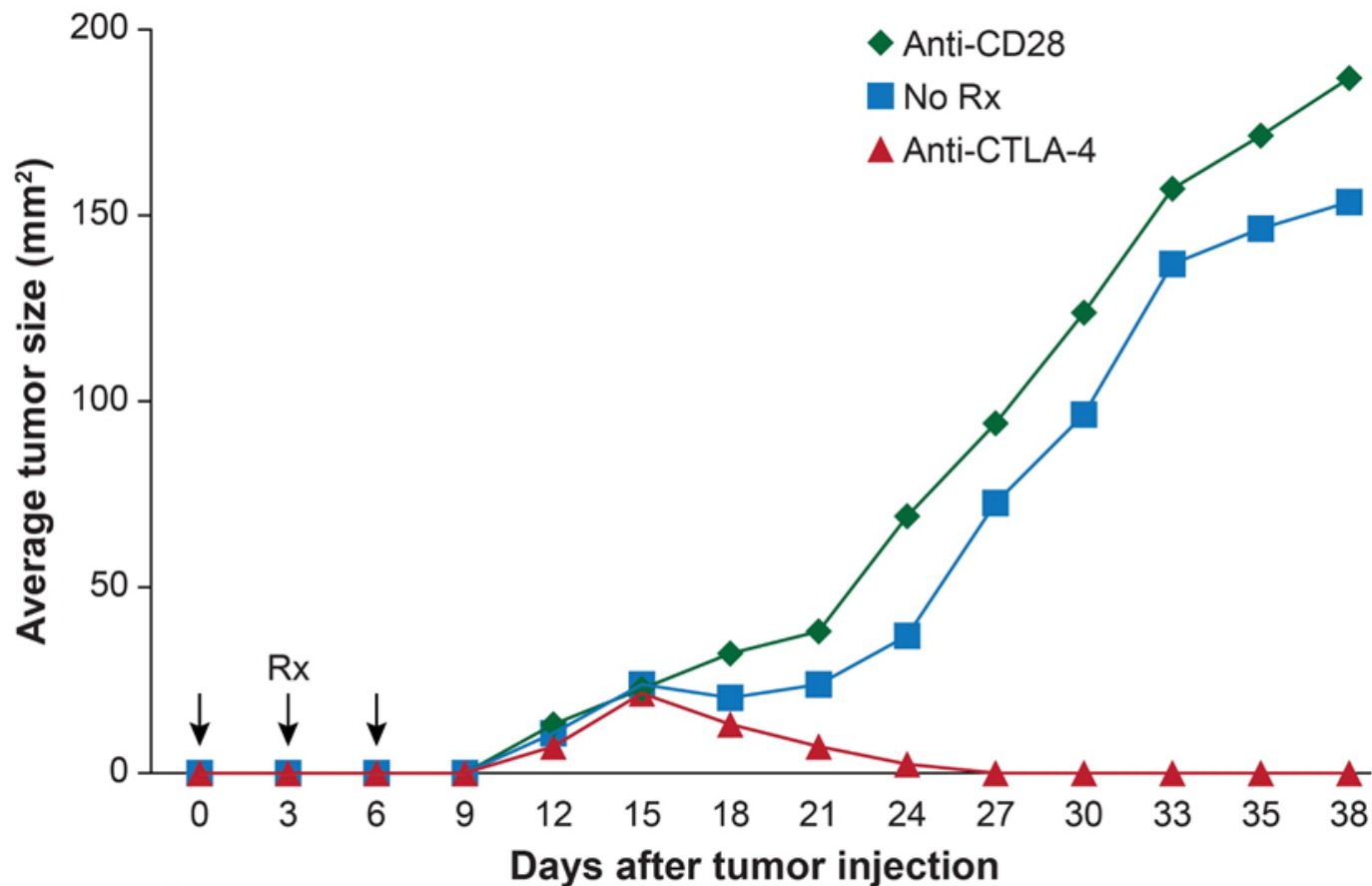




CTLA-4, a negative regulator of T cell activity, limits the responsiveness of activated T cells



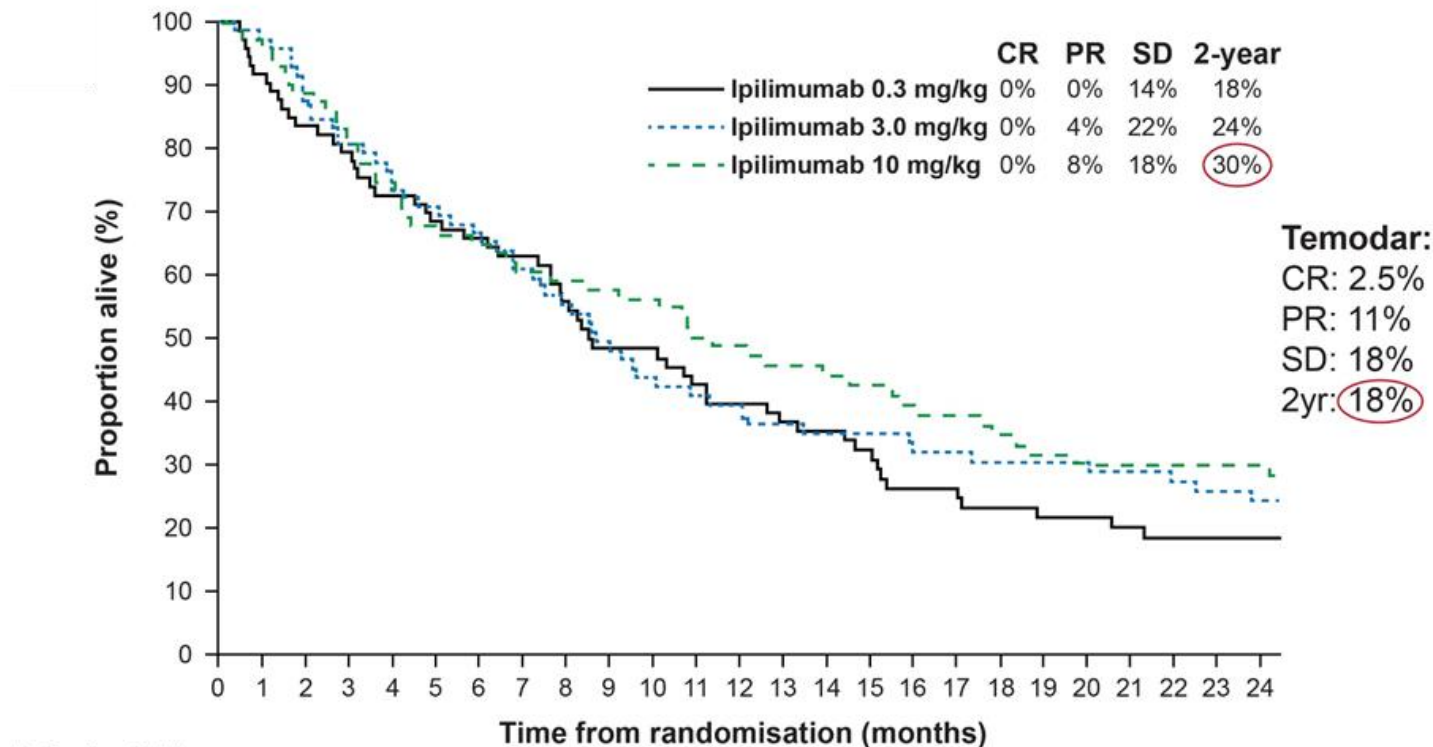
Anti-CTLA-4 induces regression of transplantable colon carcinoma



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



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



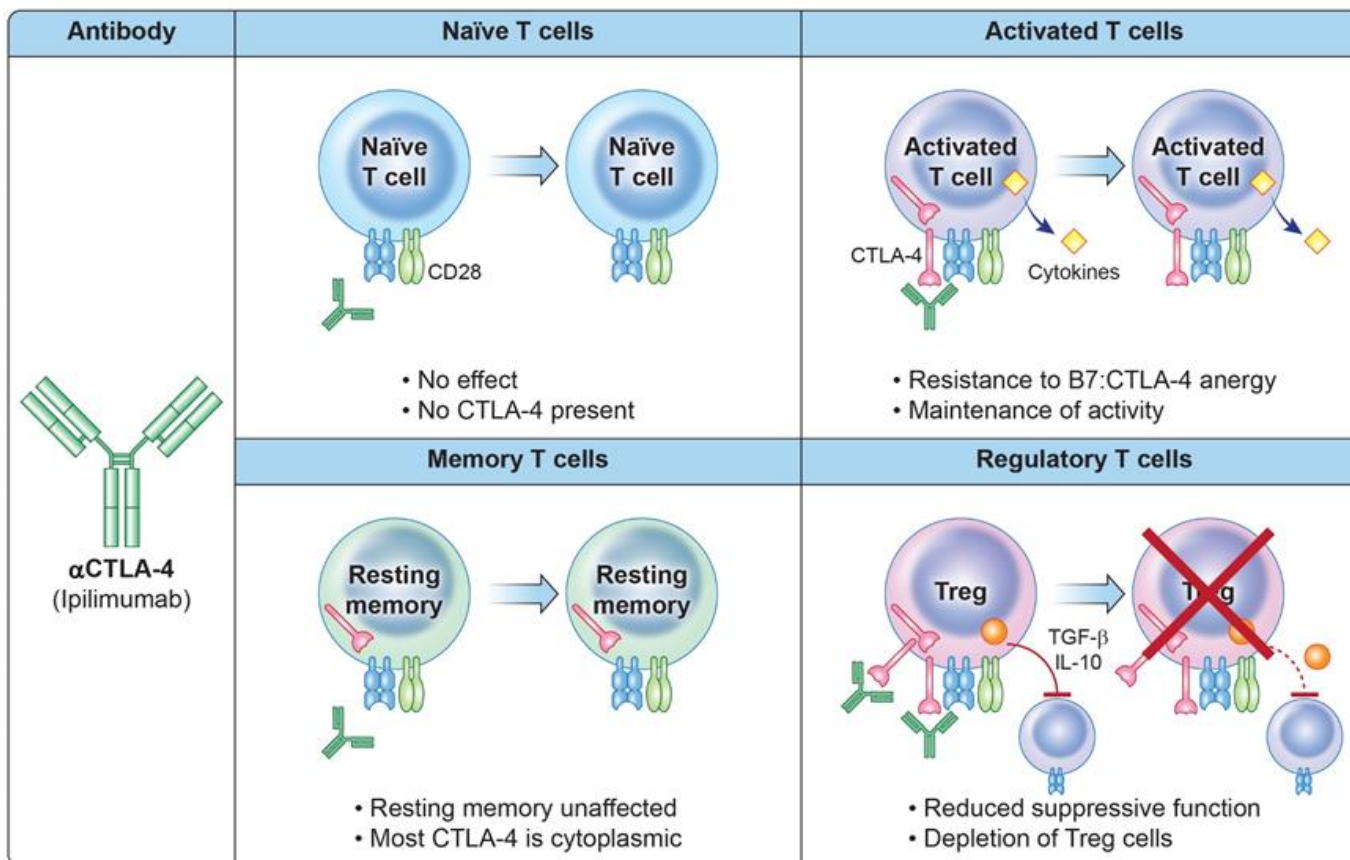
Patients at risk

0.3 mg/kg	73	67	61	58	53	50	47	45	38	33	33	29	27	25	24	21	17	17	15	14	14	13	12	12	12
3.0 mg/kg	72	70	64	58	54	50	47	43	39	34	30	28	26	24	23	23	22	21	20	20	20	19	18	17	16
10 mg/kg	72	70	63	58	53	47	45	42	41	40	39	33	31	29	28	27	25	24	22	20	19	19	19	18	18

Wolchok et al. 2010. Lancet Oncol.



Which T cells are affected by Ipilimumab (α CTLA-4)?

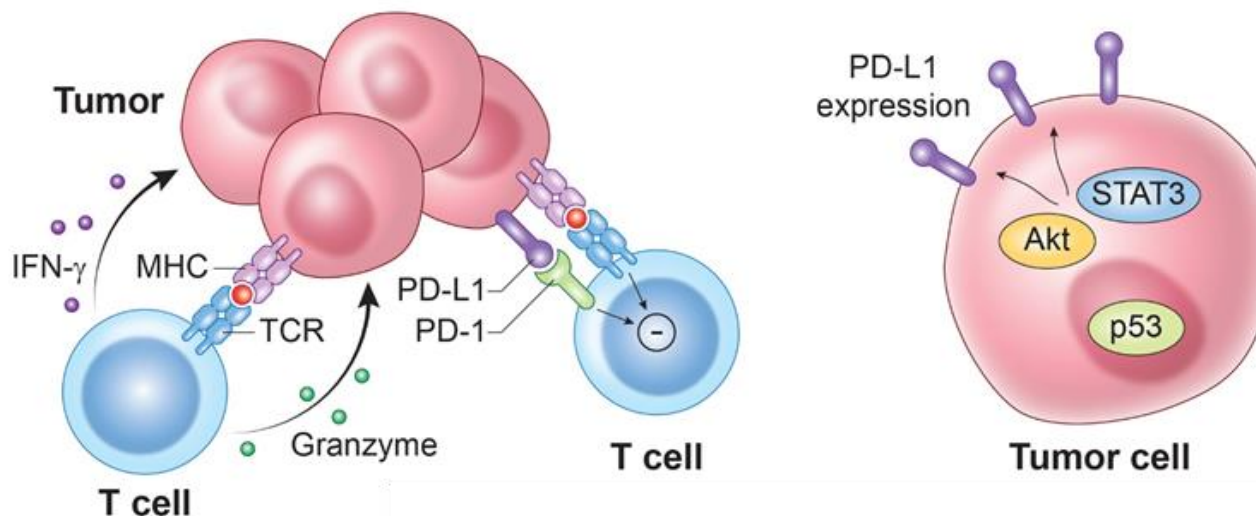


The efficacy and selectivity of anti-CTLA-4 therapy increase in patients who have higher percentages of activated tumor-specific T cells at the time of treatment.



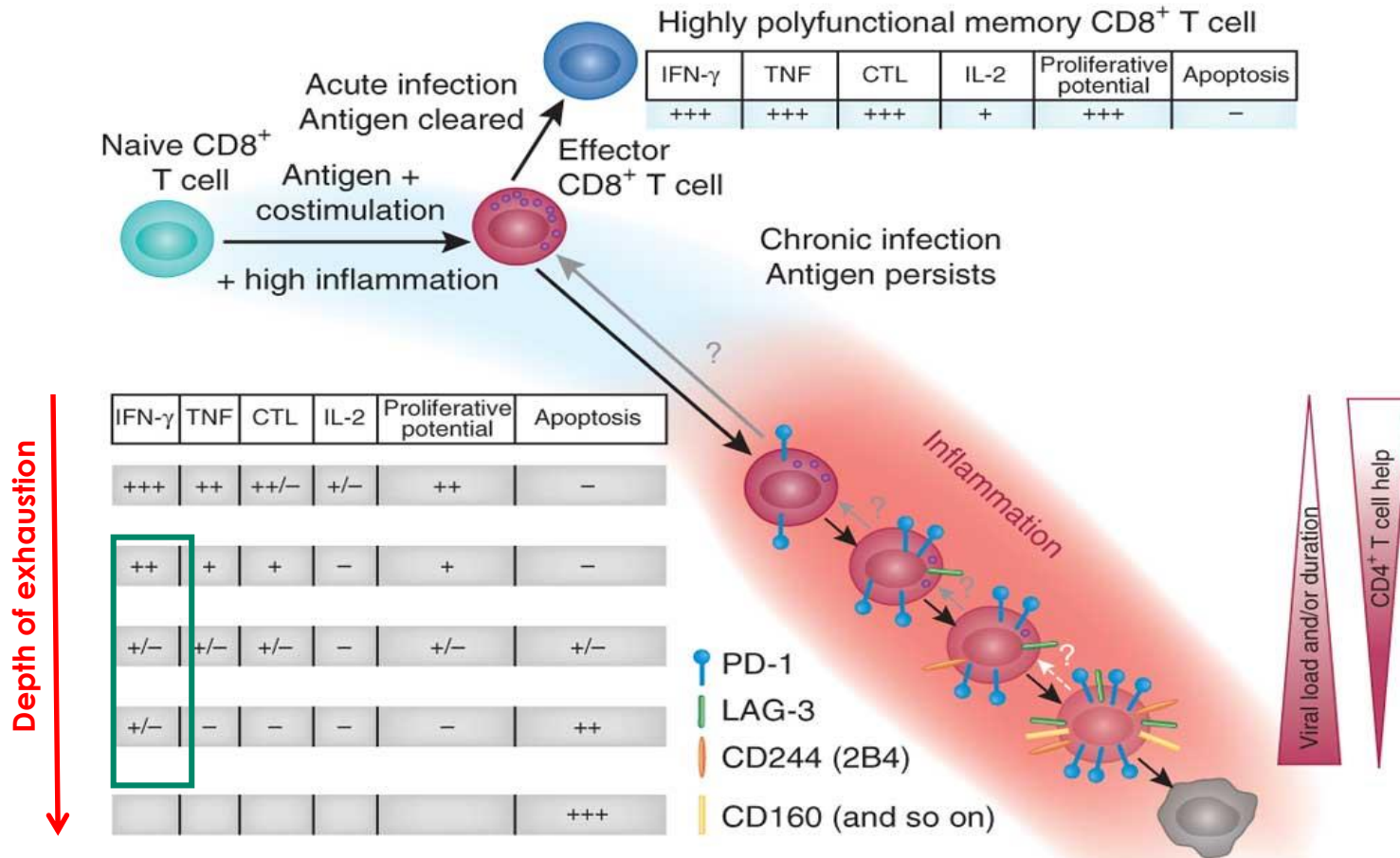
PD-1: PD-L inhibitory pathway

- 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- γ
 2. Oncogenic signaling pathways



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

Hierarchical model of CD8 T cell exhaustion due to chronic antigen exposure

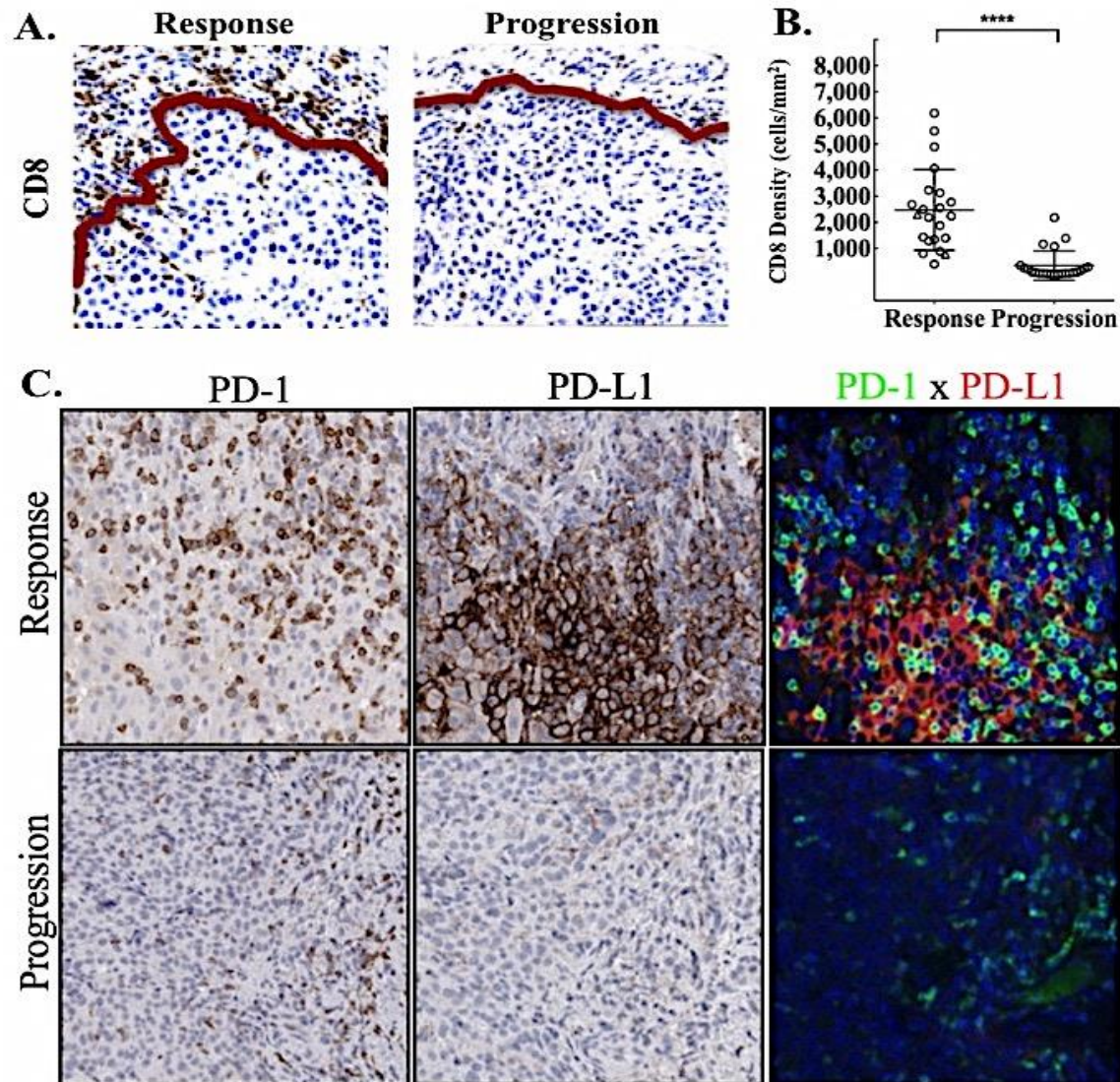


Adapted from Wherry-EJ, *Nature Immunology* 12, 492–499 (2011)

In melanoma, Rosenberg had demonstrated that PD-1^{hi} CTLA-4⁺ CD8s represented a broad group of tumor-antigen-specific CD8 clones.

Gros-A, et al, *JCI* 2014 May;124(5):2246-5

'Adaptive Immune Resistance' predicts response to anti-PD-1 in melanoma

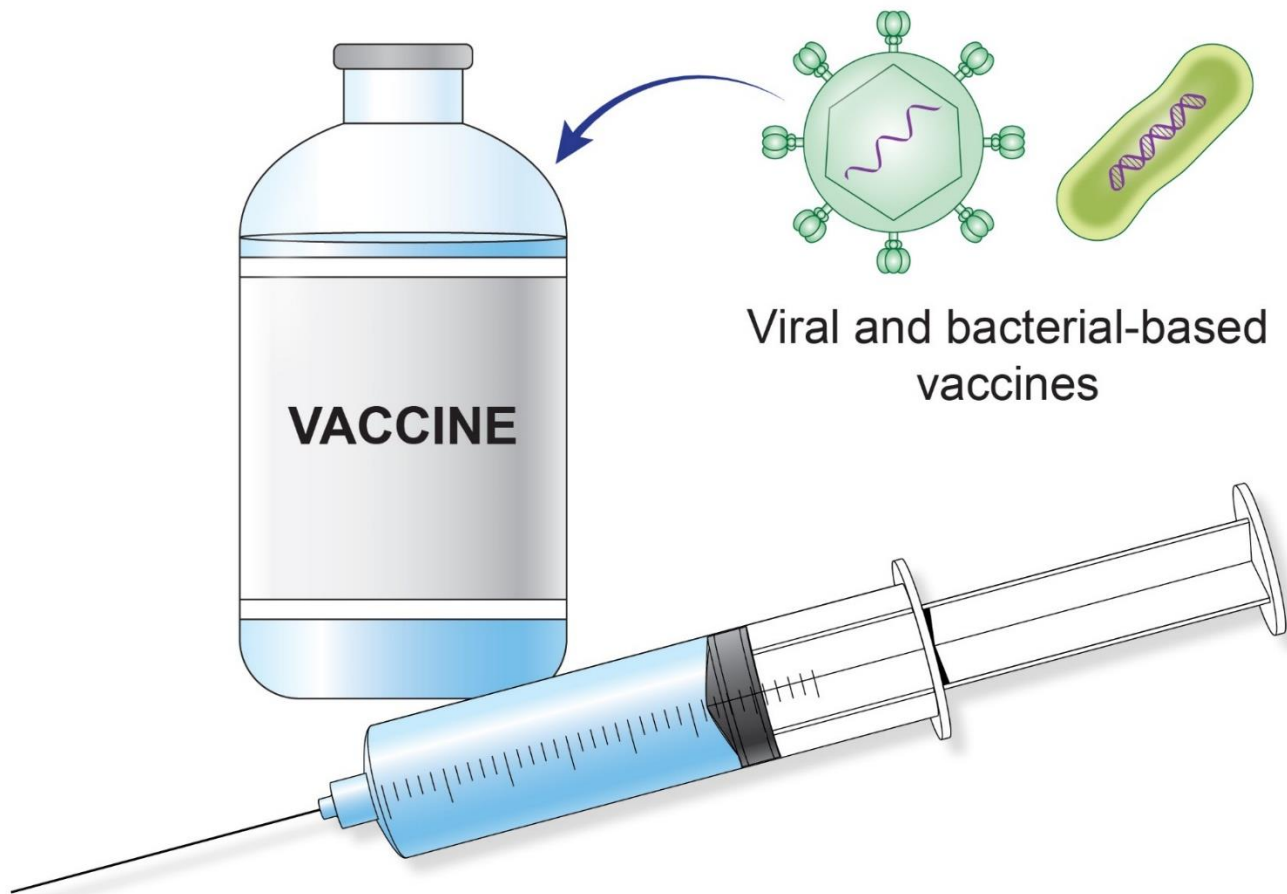


Tumeh-PC, *Nature*. 2014 Nov 26; 515(7528): PD-1 blockade induces responses by inhibiting adaptive immune resistance

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






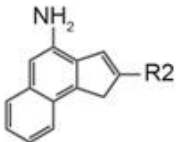
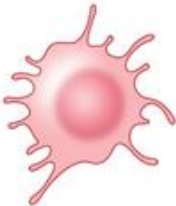
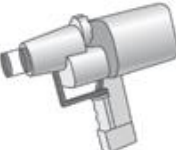
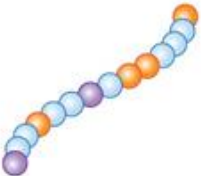

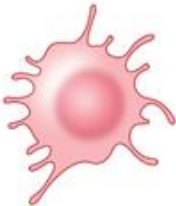

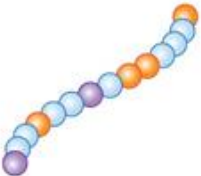



The goal of T cell checkpoint blockade is to make T cell “off-switches” inaccessible to tumor cells, thus restoring tumor-specific immunity.

Therapeutic cancer vaccines



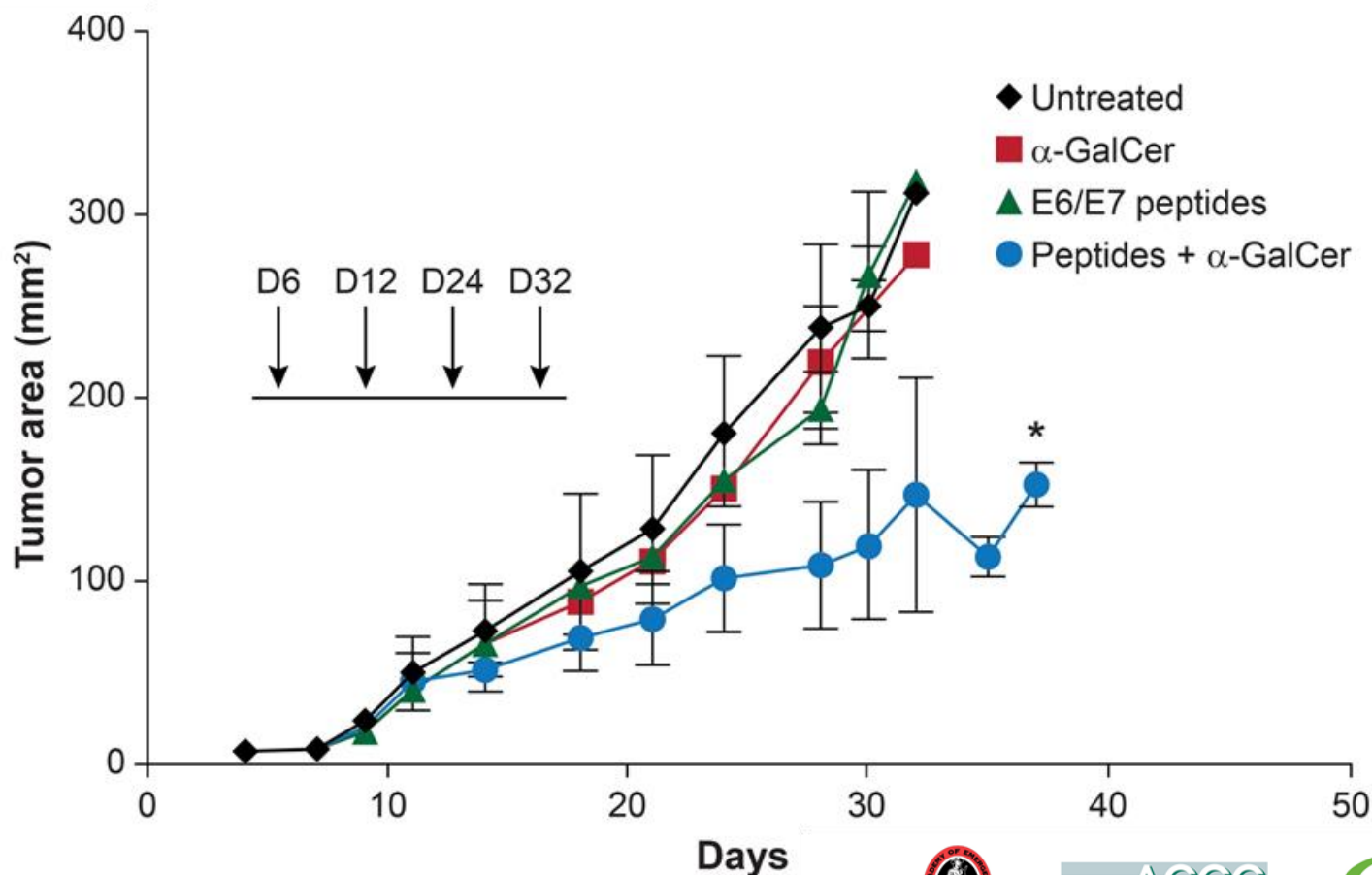


Components of a cancer vaccine

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



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



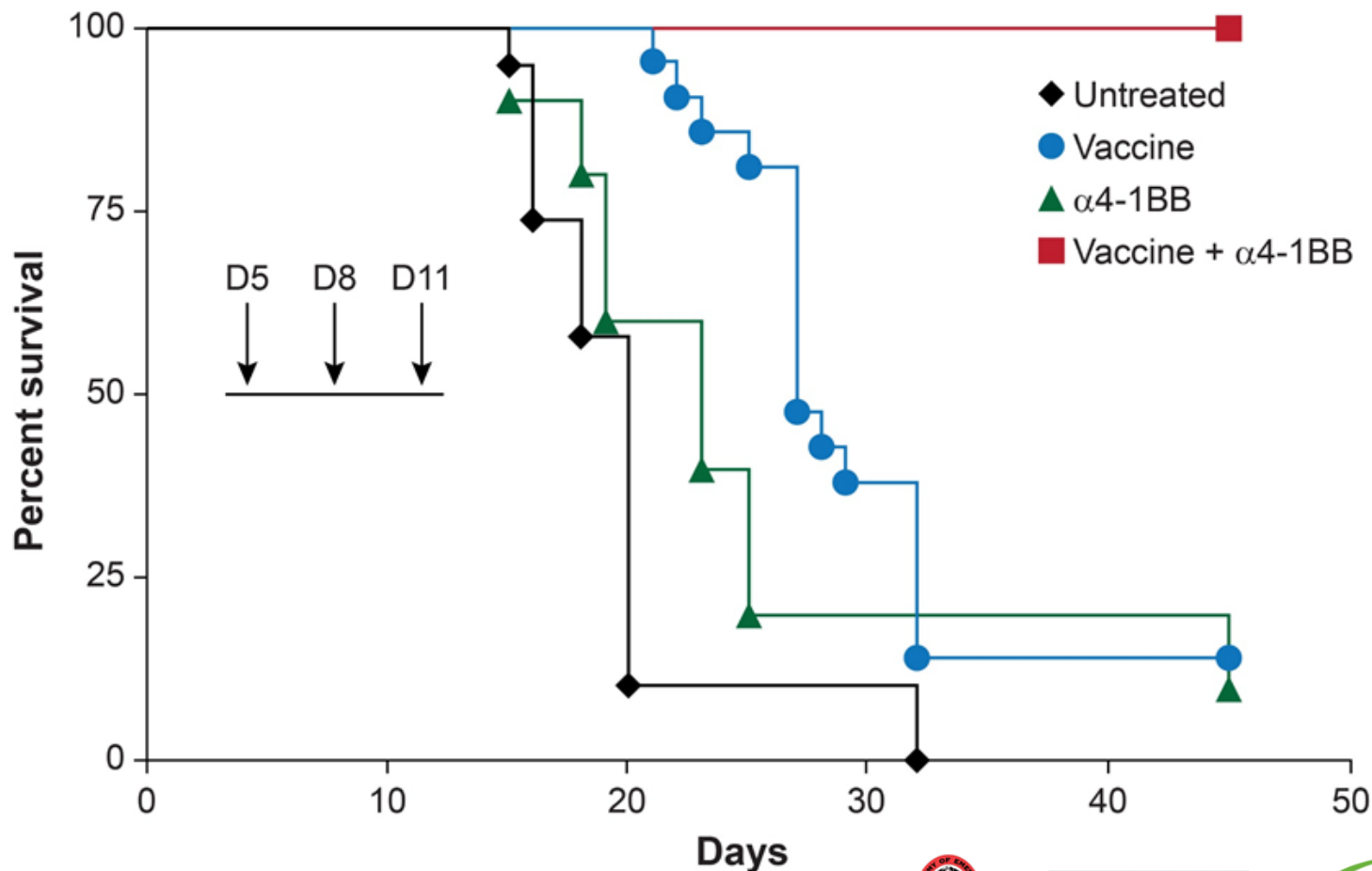
Shailbala Singh

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



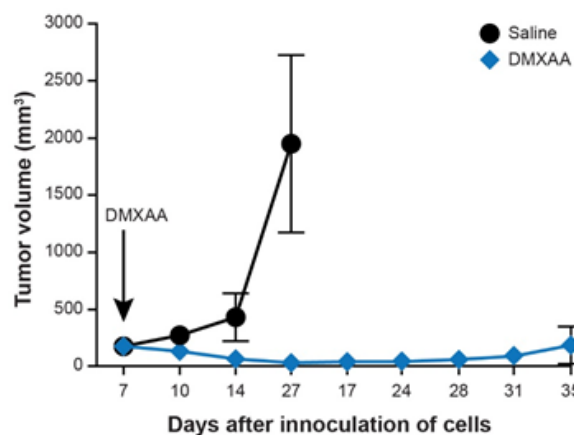
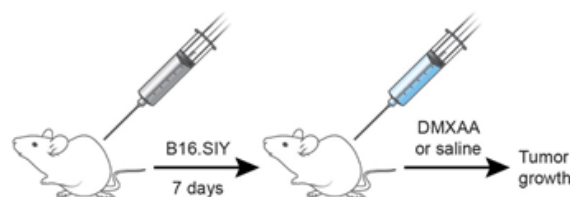
Todd Bartkowiak, M.S.





Intratumoral injection of innate immune agonists: The direct vaccination approach

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



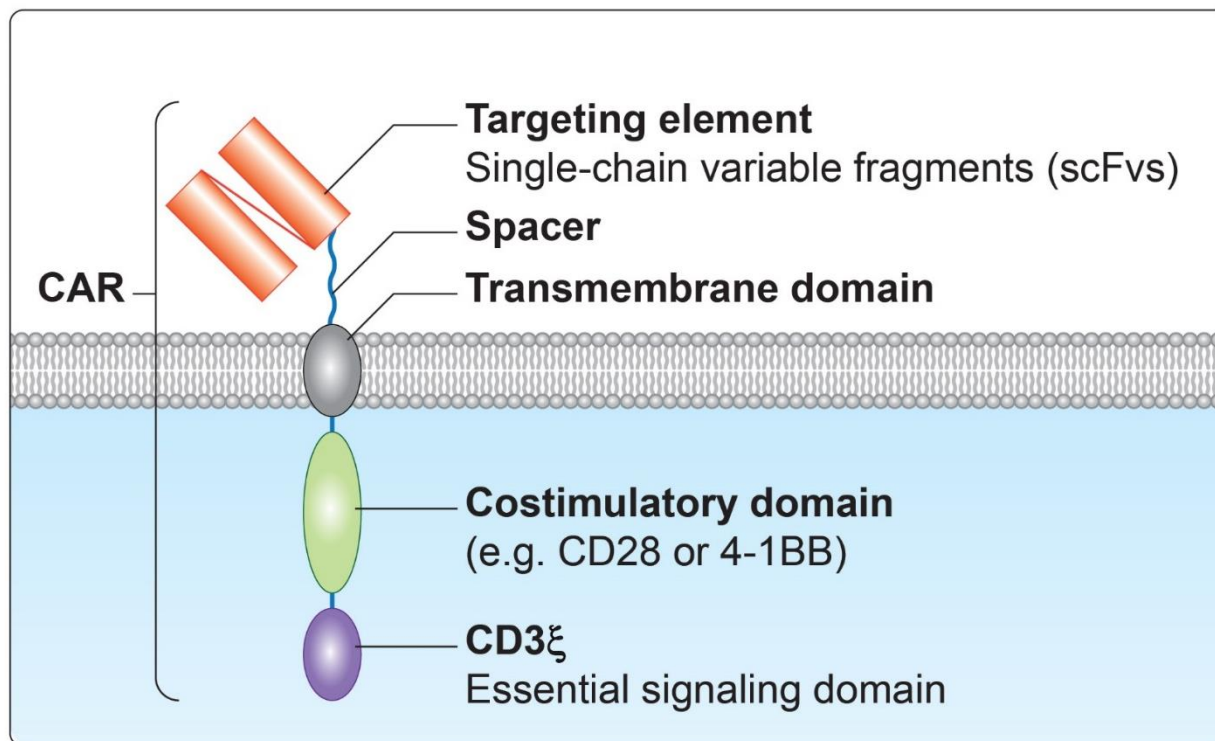
Current question: Can local injection of one lesion evoke rejection of distant ones?
This is known as the abscopal effect.

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

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.



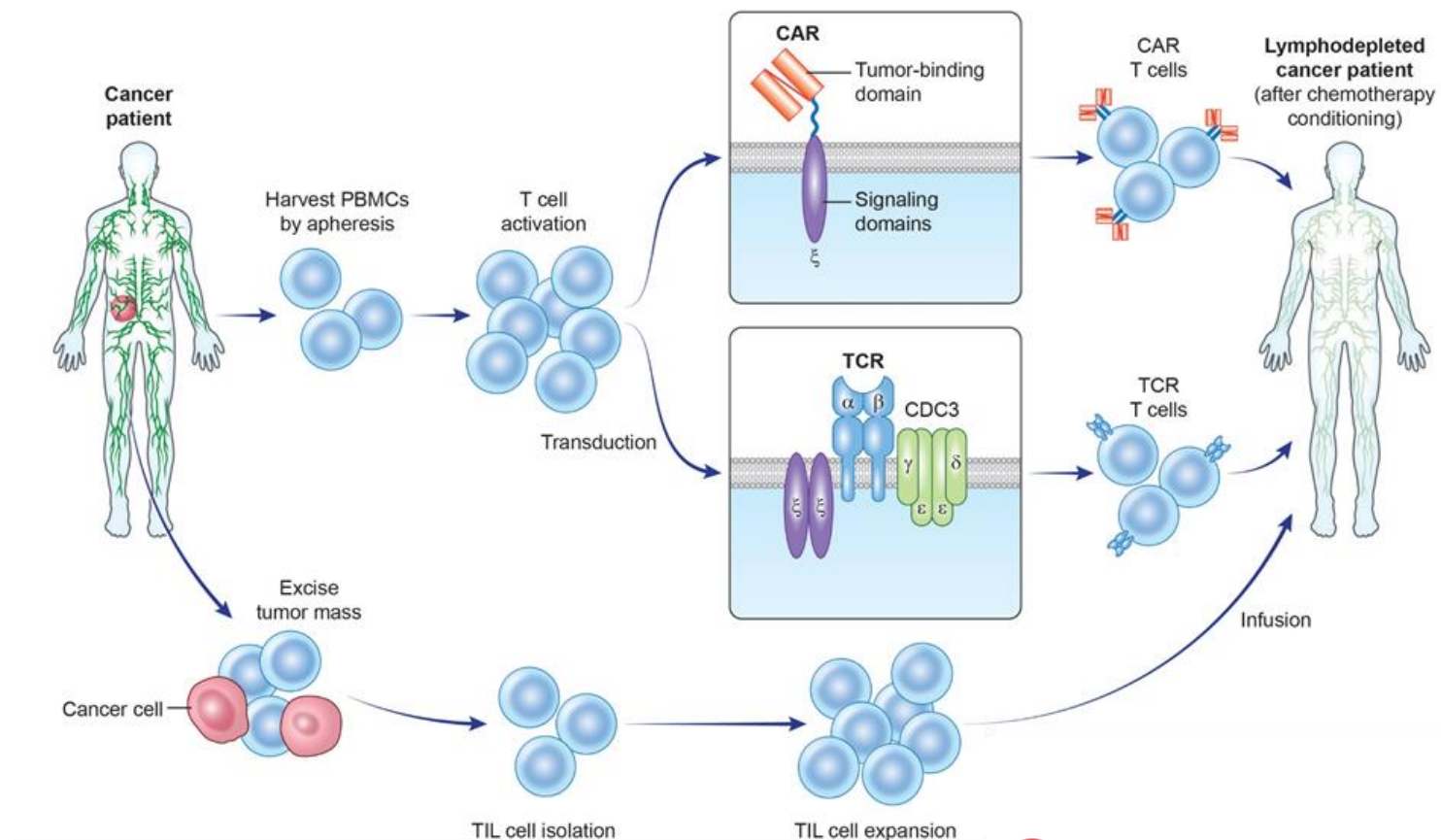
T cell adoptive transfer



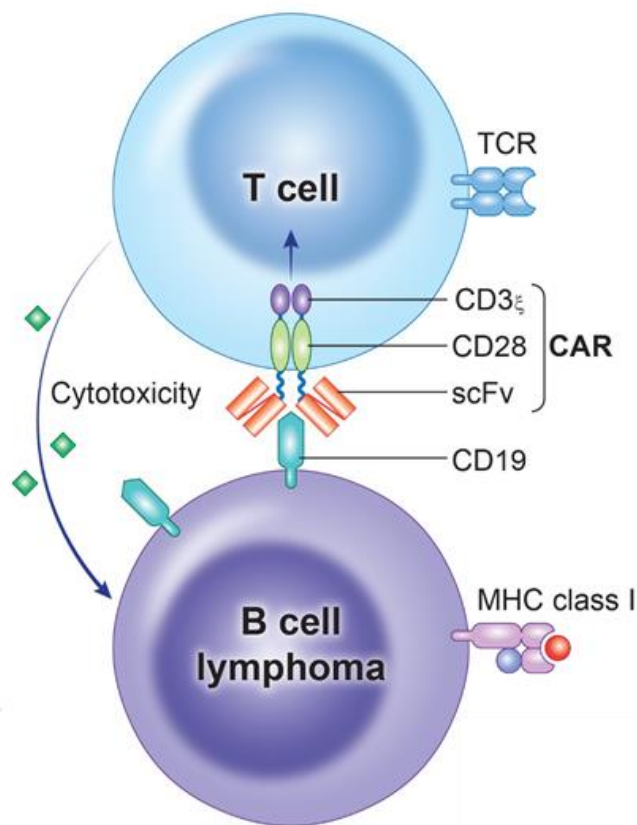
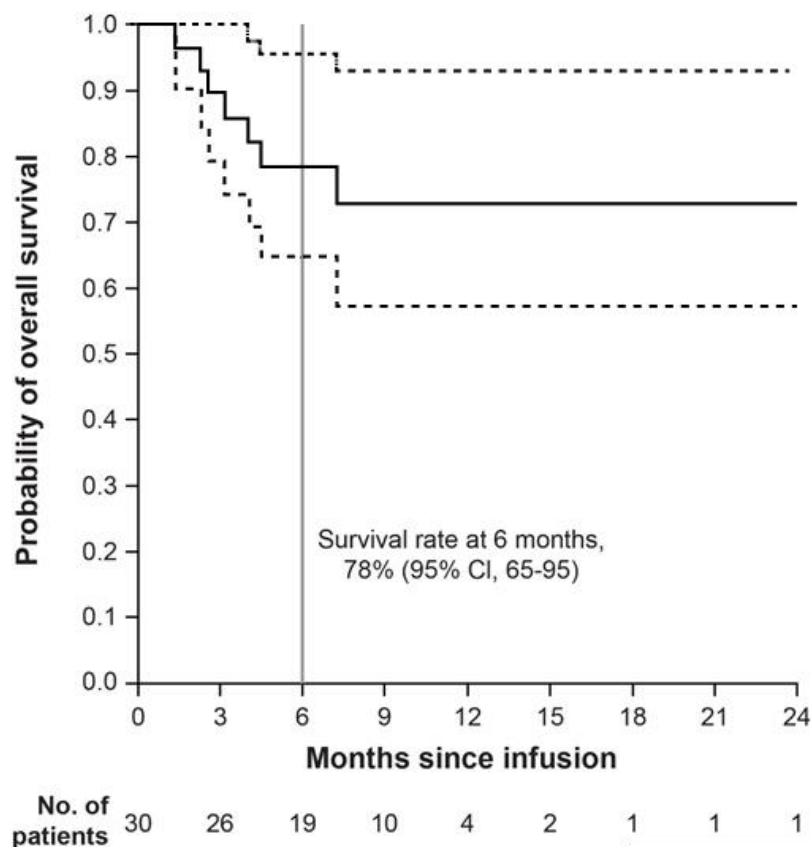
CARs, TIL, engineered PBMC, etc...



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



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.

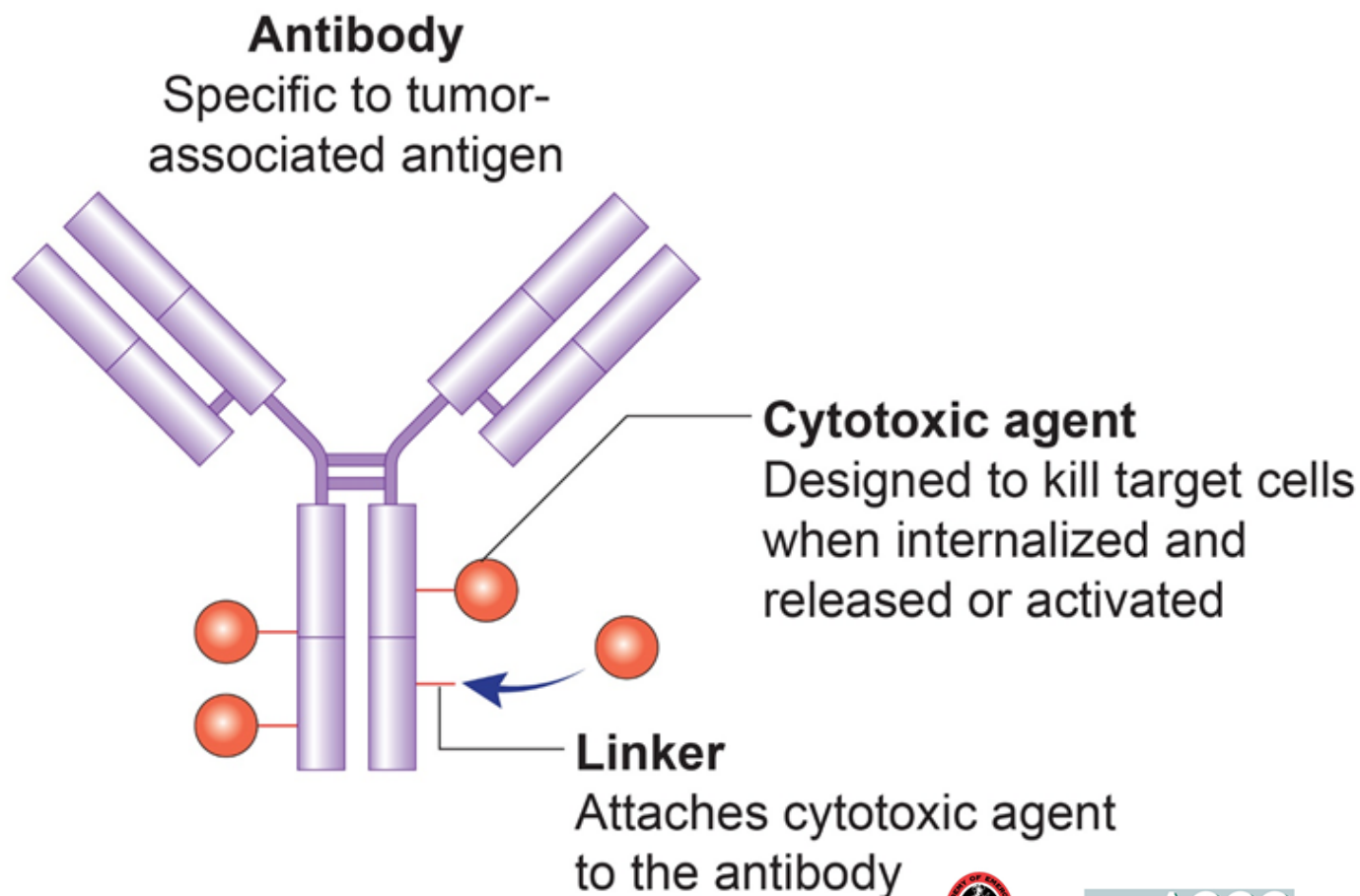


To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

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)

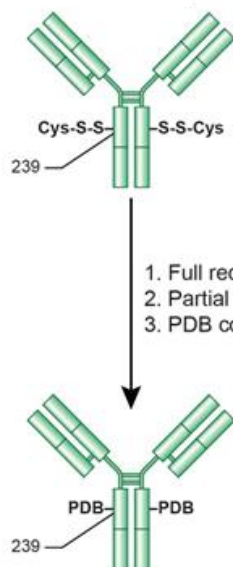


Key ADC/antibody principles

- **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.

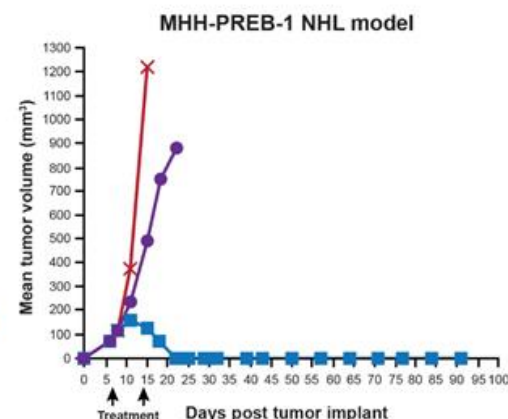
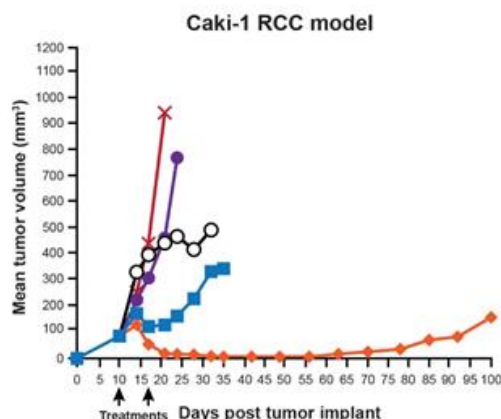
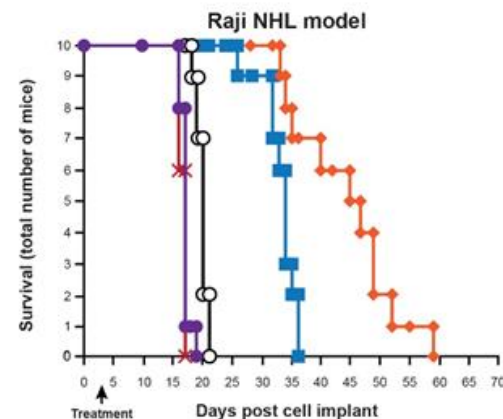
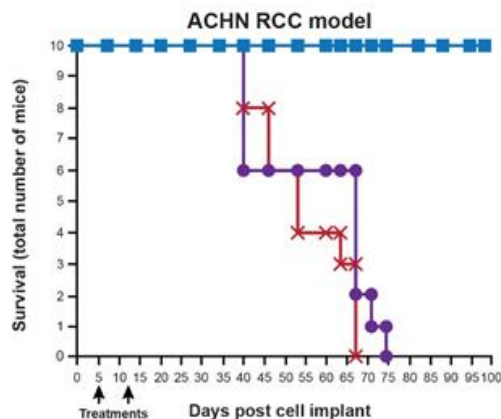


SGN-70A in the clinic for NHL and RCC



1. Full reduction
2. Partial re-oxidation
3. PDB conjugation

Conjugation process for the 239C antibody format. The engineered antibody, expressed in CHO cells, was isolated as the cysteine disulfide at position 239. The antibody was fully reduced with TCEP and partially reoxidized with dehydroascorbic acid. The resulting free cysteines at position 239 were conjugated to the PDB-linker to give the PDB ADC with nominally 2 drugs/mAb.



× Untreated
 ◆ h1F6239C-PDB 0.3 mg/kg
 ■ h1F6239C-PDB 0.1 mg/kg

○ hlgG239C-PDB 0.3 mg/kg
 ● hlgG239C-PDB 0.1 mg/kg

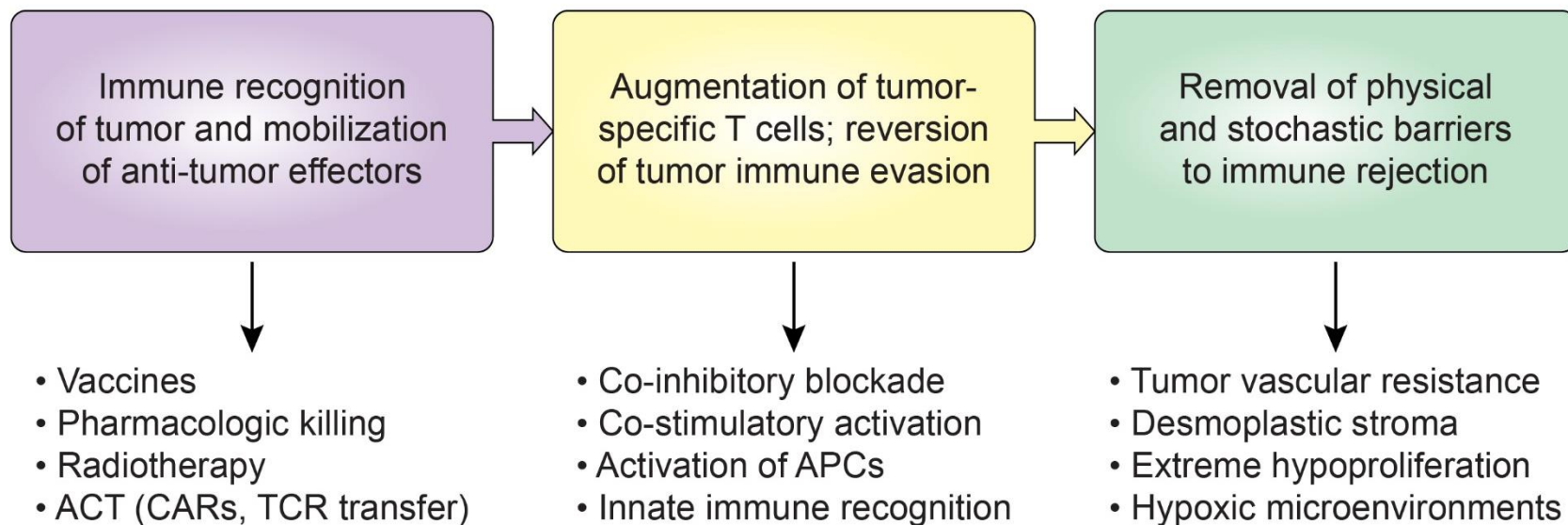
Jeffrey SC, Burke PJ, Lyon RP, Meyer DW, Sussman D, Anderson M, Hunter JH, Leiske CI, Miyamoto JB, Nocholas ND, et al. 2013. A potent anti-CD70 antibody-drug conjugate combining a dimeric pyrrolobenzodiazepine drug with site-specific conjugation technology. *Bioconjug Chem*. 24(7): 1256-63.



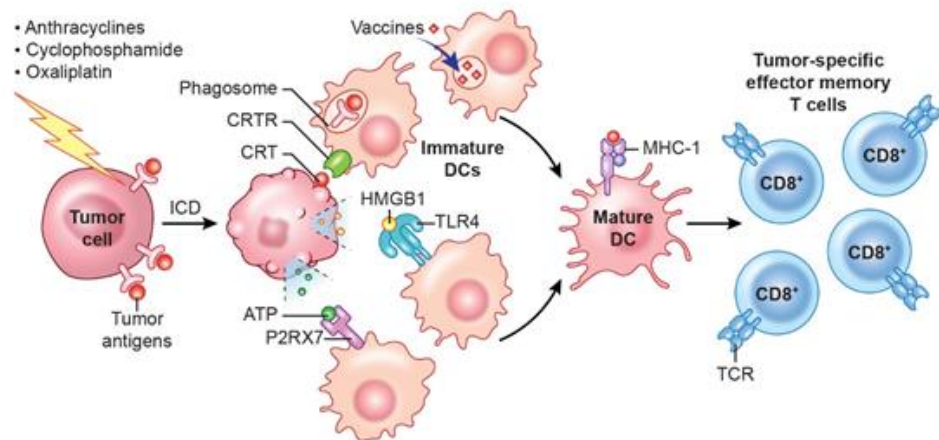
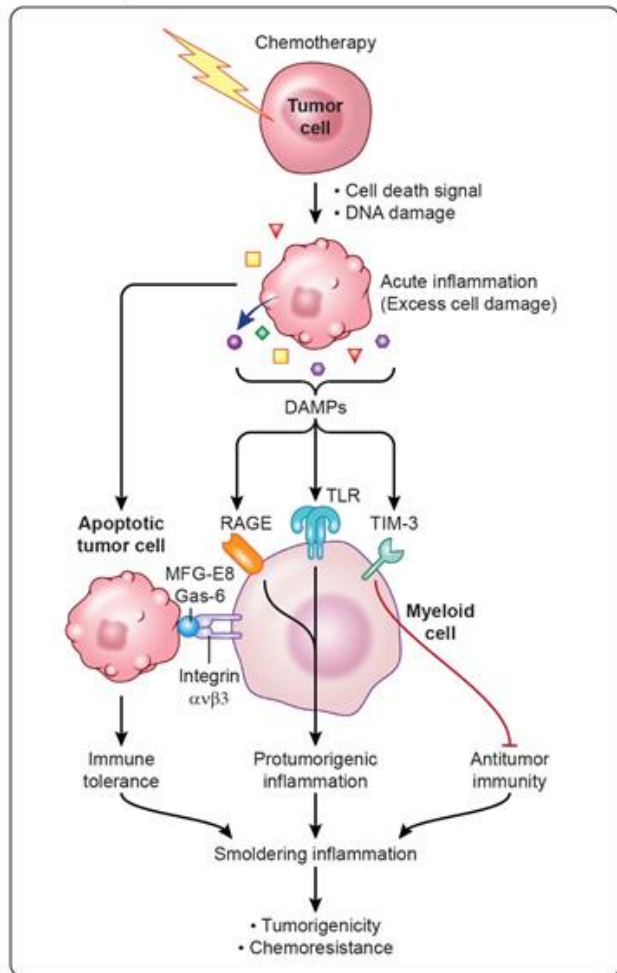
To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

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.

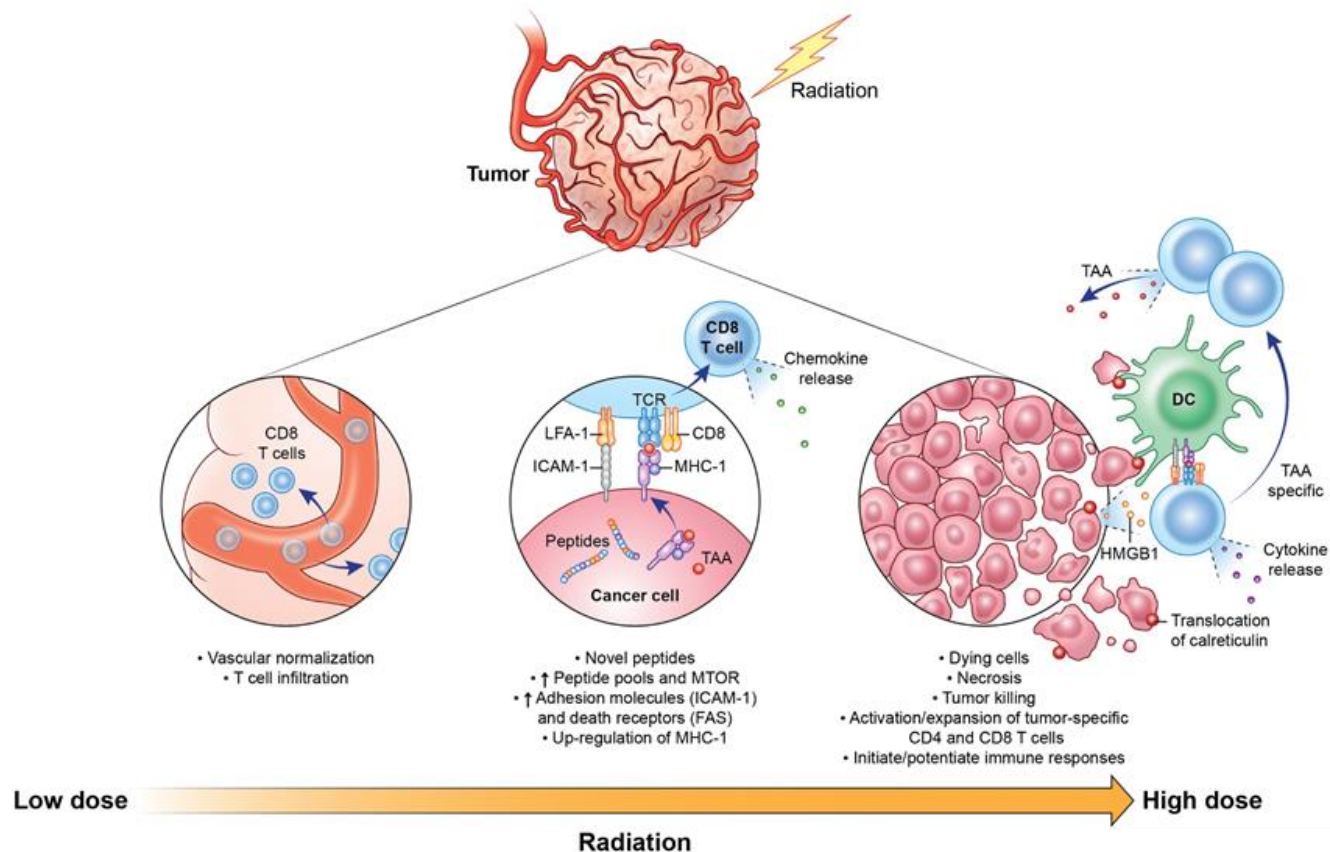
Seeking combinations outside of T cell checkpoint immunotherapy



A different perspective on chemotherapy: Immunogenic versus non-immunogenic cell death



Radiation therapy: A potent adjuvant for tumor immunity

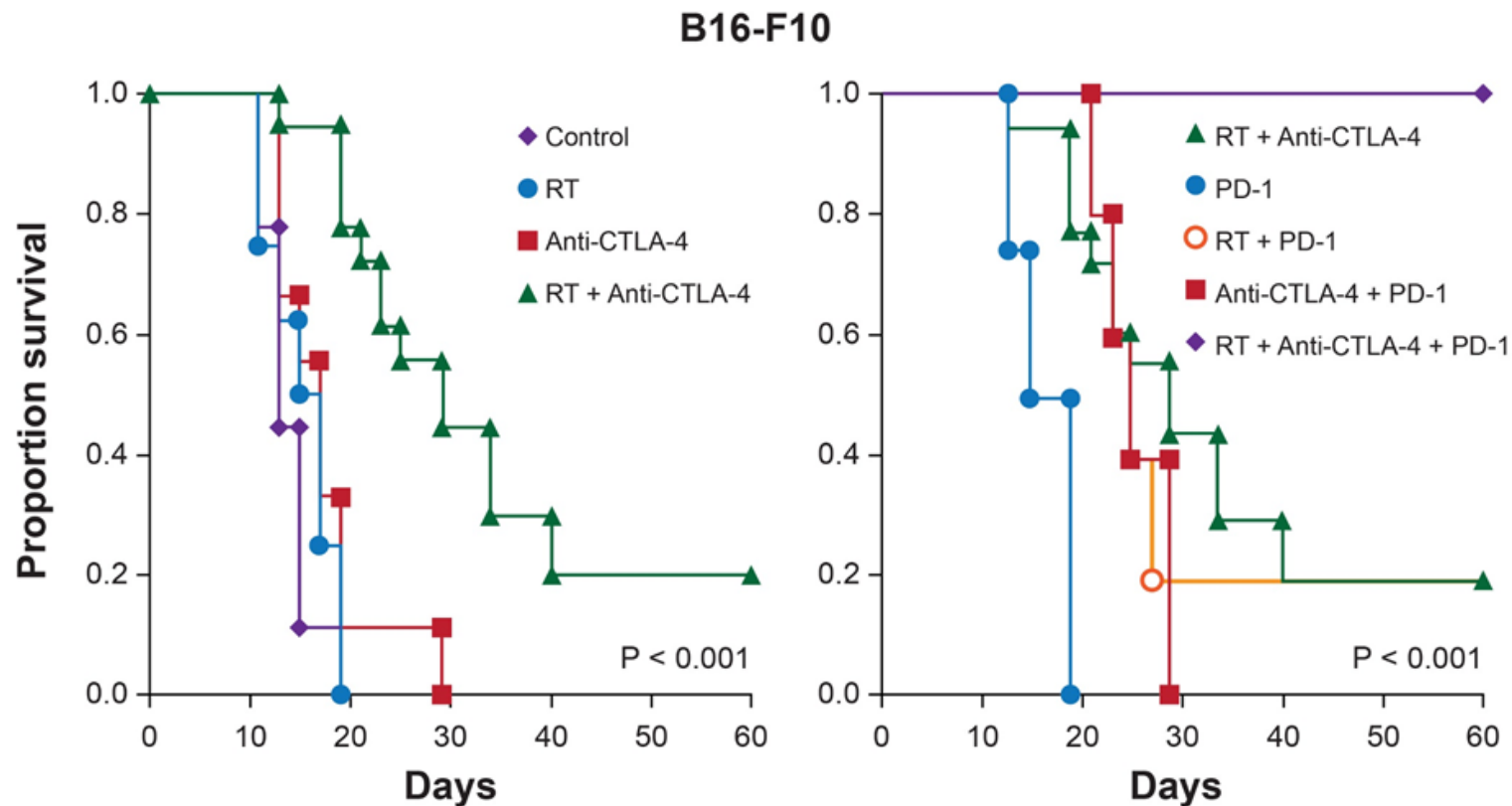


Exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer

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



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

