ADVANCES IN Cancer IMMUNOTHERAPY™

Basic Principles of Cancer Immunotherapy

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

- **Research Funding: Merck, Pfizer**
- **Other Consulting: Agenus, Lilly, Janssen, Novartis**
- **I will be discussing non-FDA approved indications during my presentation.**

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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.

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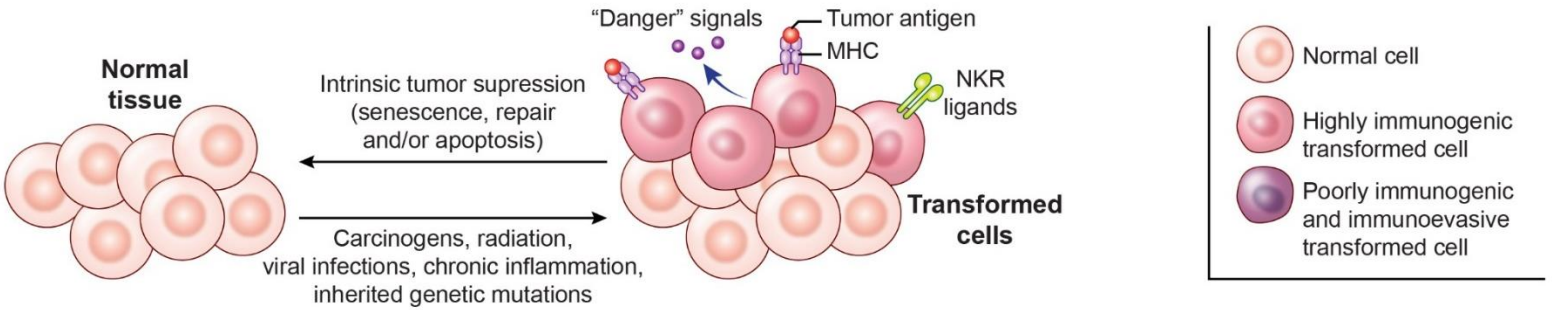
The 3 Es of cancer immunoediting



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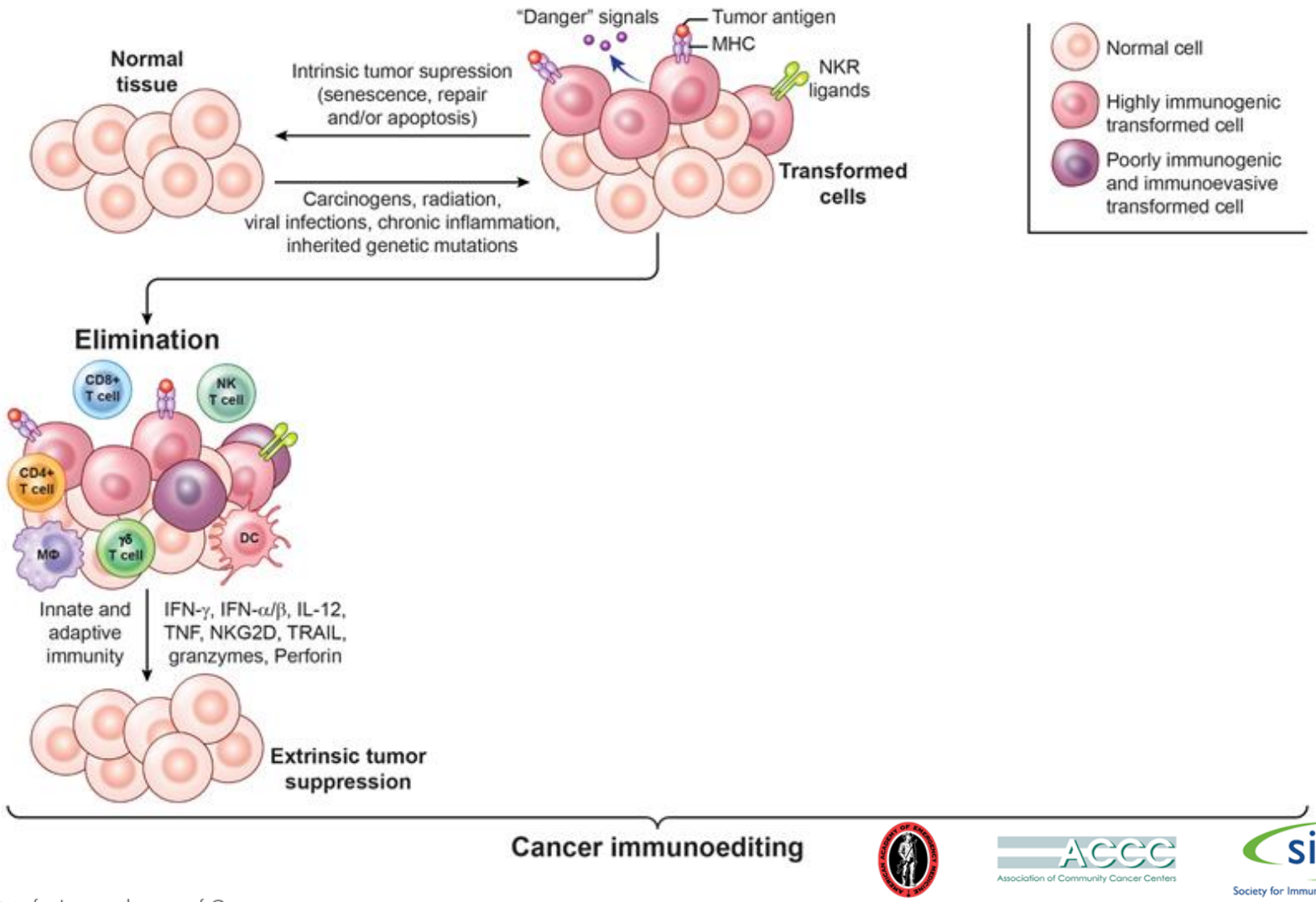
The 3 Es of cancer immunoediting



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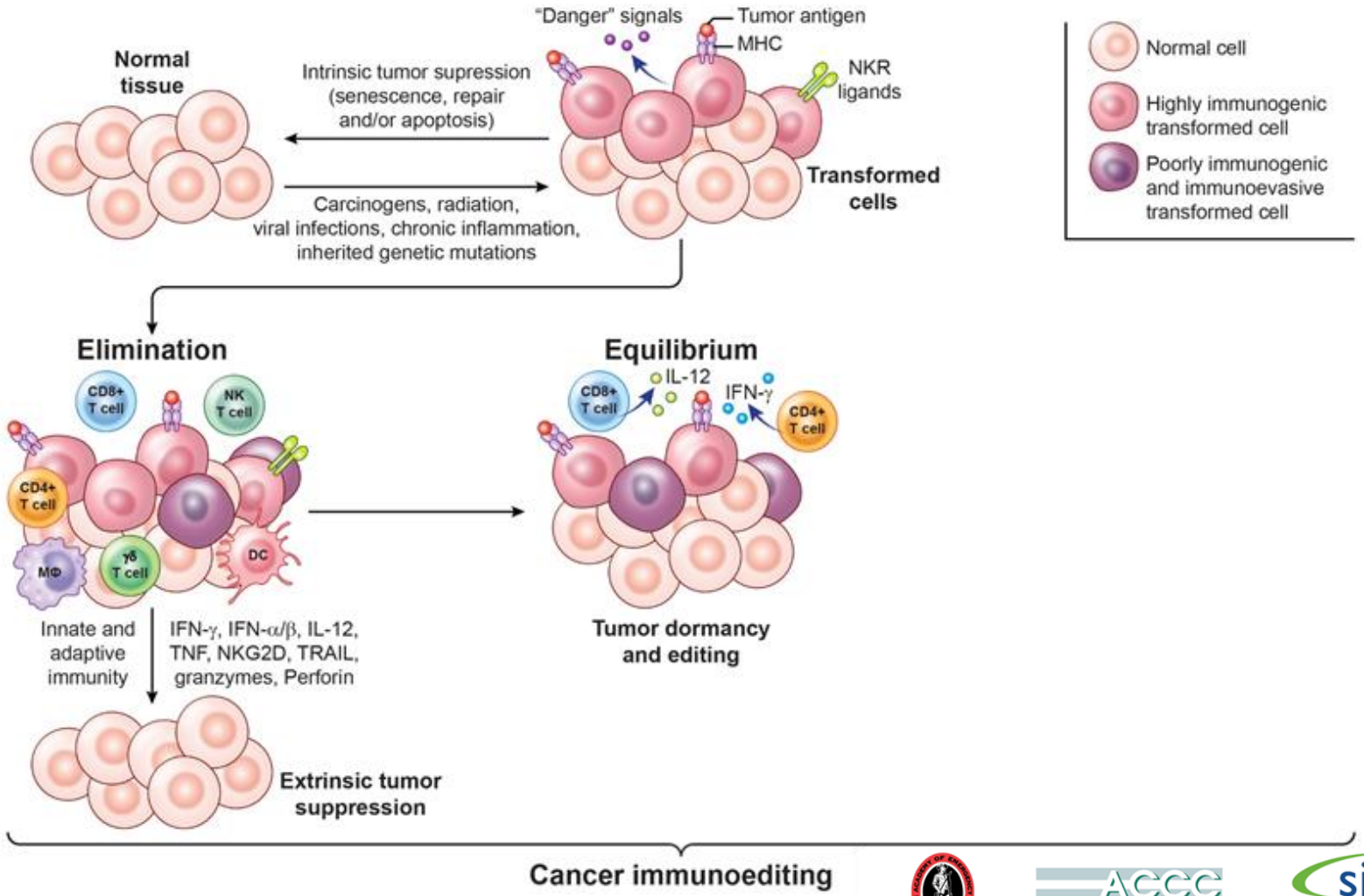

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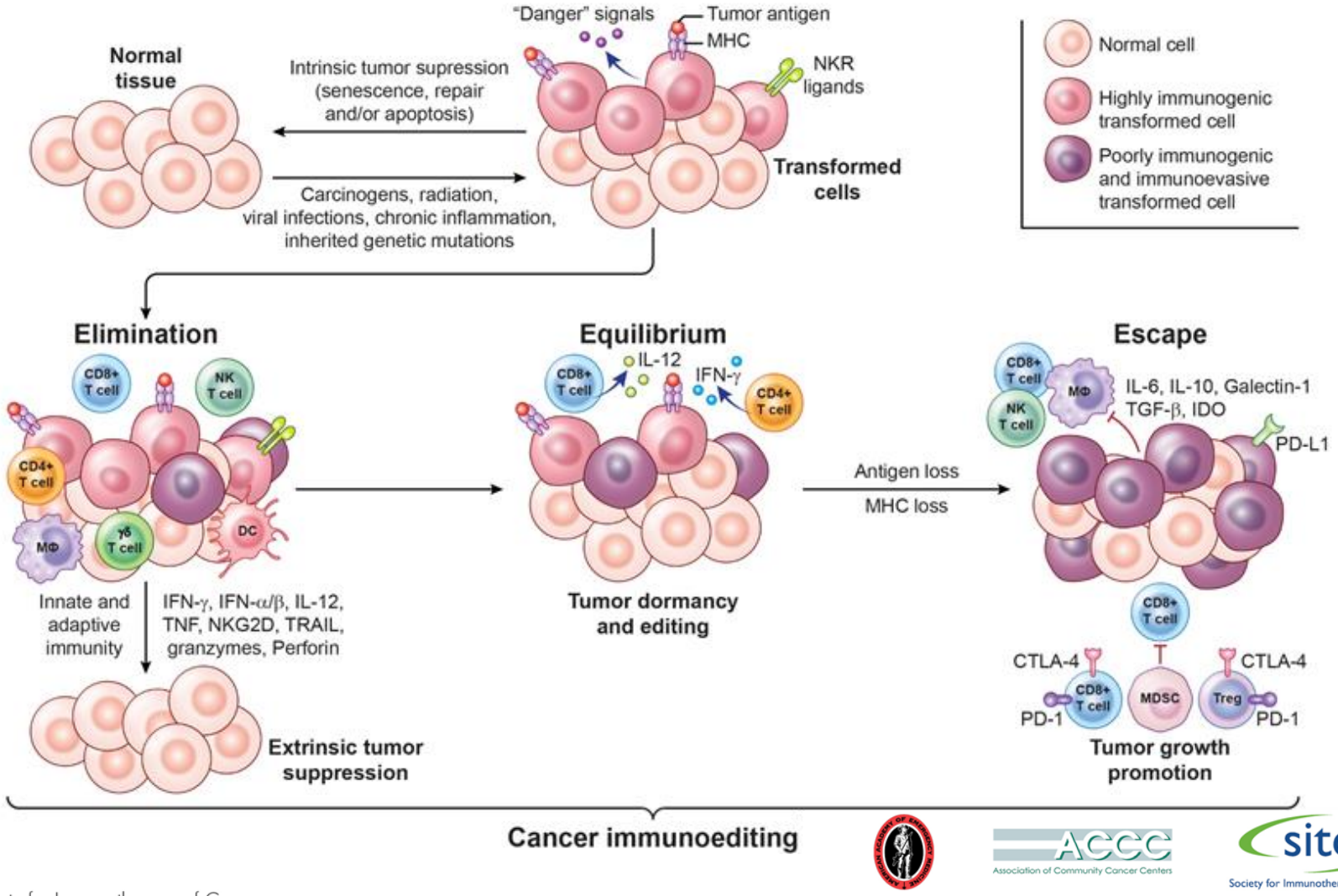

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To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

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

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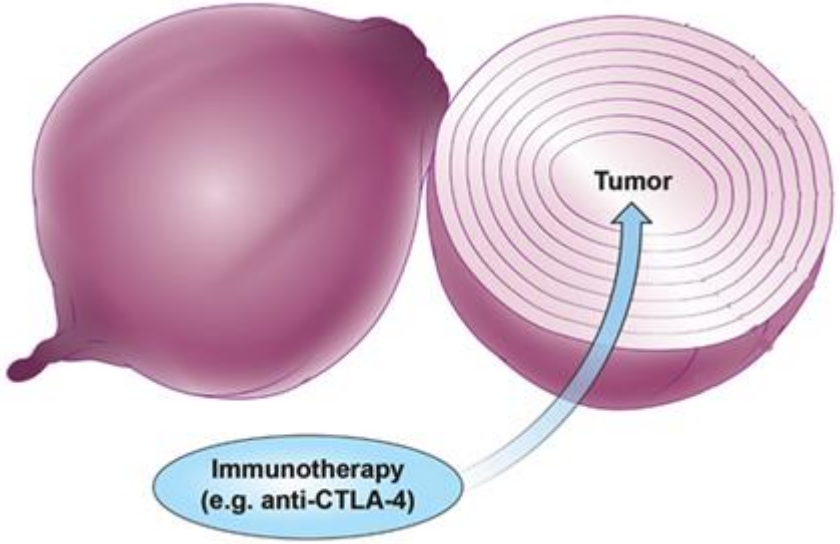
Multi-layered immunosuppression

- 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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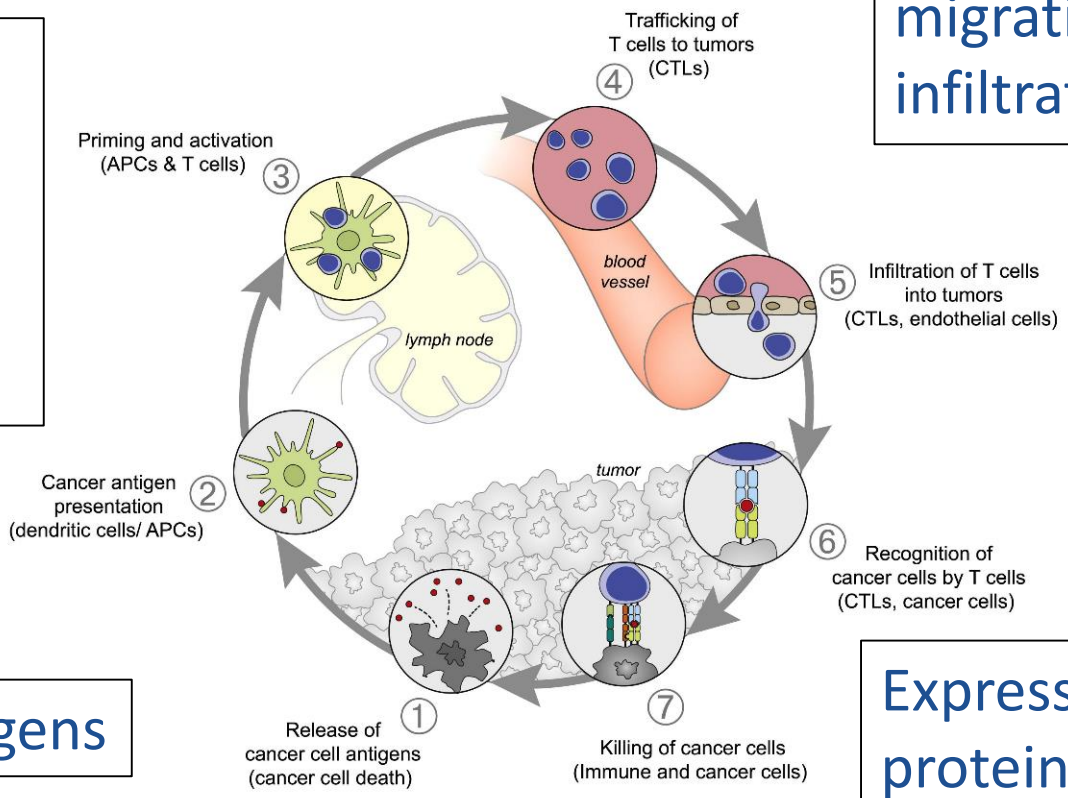
Anti-tumor immunity

Produce suppressive cytokines that prevent migration and infiltration

Promote immature, suppressive DCs and macrophages



Loss of neoantigens

Express checkpoint proteins

Chen & Mellman, Immunity, 2013

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Strategies for Immunotherapy

	Target	Therapeutic Strategies
	Tumor-specific antigens that can be recognized by the immune system	Vaccines, Chemotherapy/Radiation, Oncolytic Viruses, Epigenetic Agents
	Effective antigen presentation/recognition	Macrophage/DC Polarizing Agents, Oncolytic Viruses
	Antigen-specific T cell production	Adoptive T Cell Therapy
	Improve T cell migration into the tumors	Microenvironment (TKI & Cytokine Inhibitors/Inducers, Chemotherapy, Radiation, Oncolytic Viruses)
	T cells are activated rather than suppressed	Drugs that boost stimulatory receptors
	Counteract immunosuppression	Checkpoint inhibitors, anti-Tregulatory cells

Adapted from Jedd Wolchok and others
Wilky & Goldberg, Discov Med, 2017

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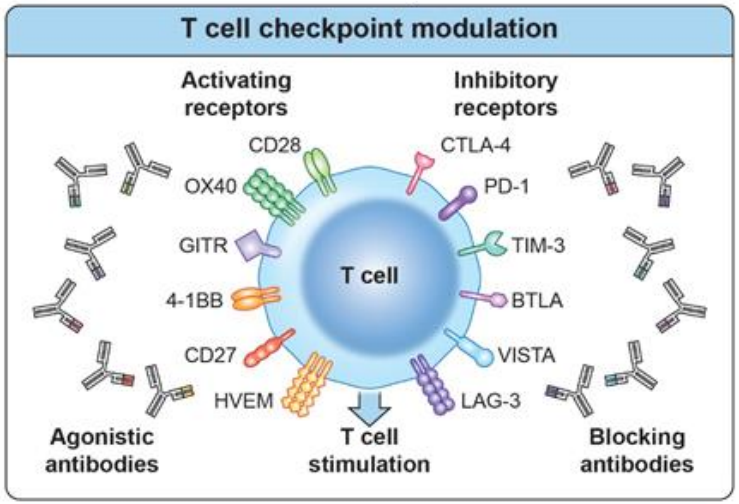
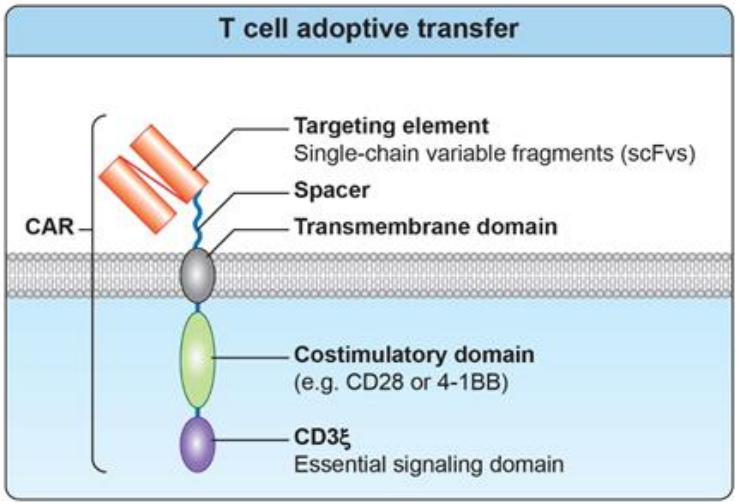
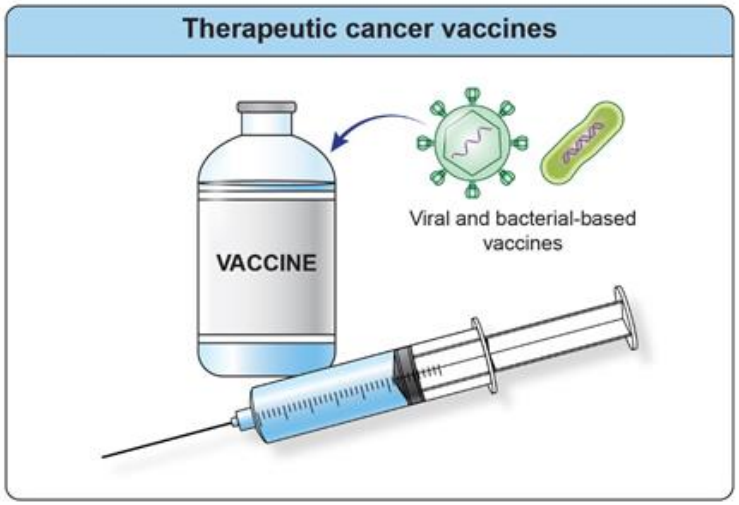
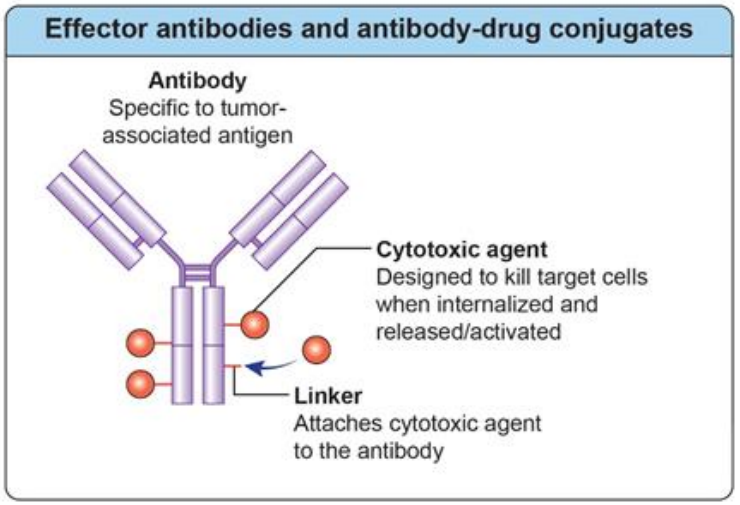
Types of immunotherapy









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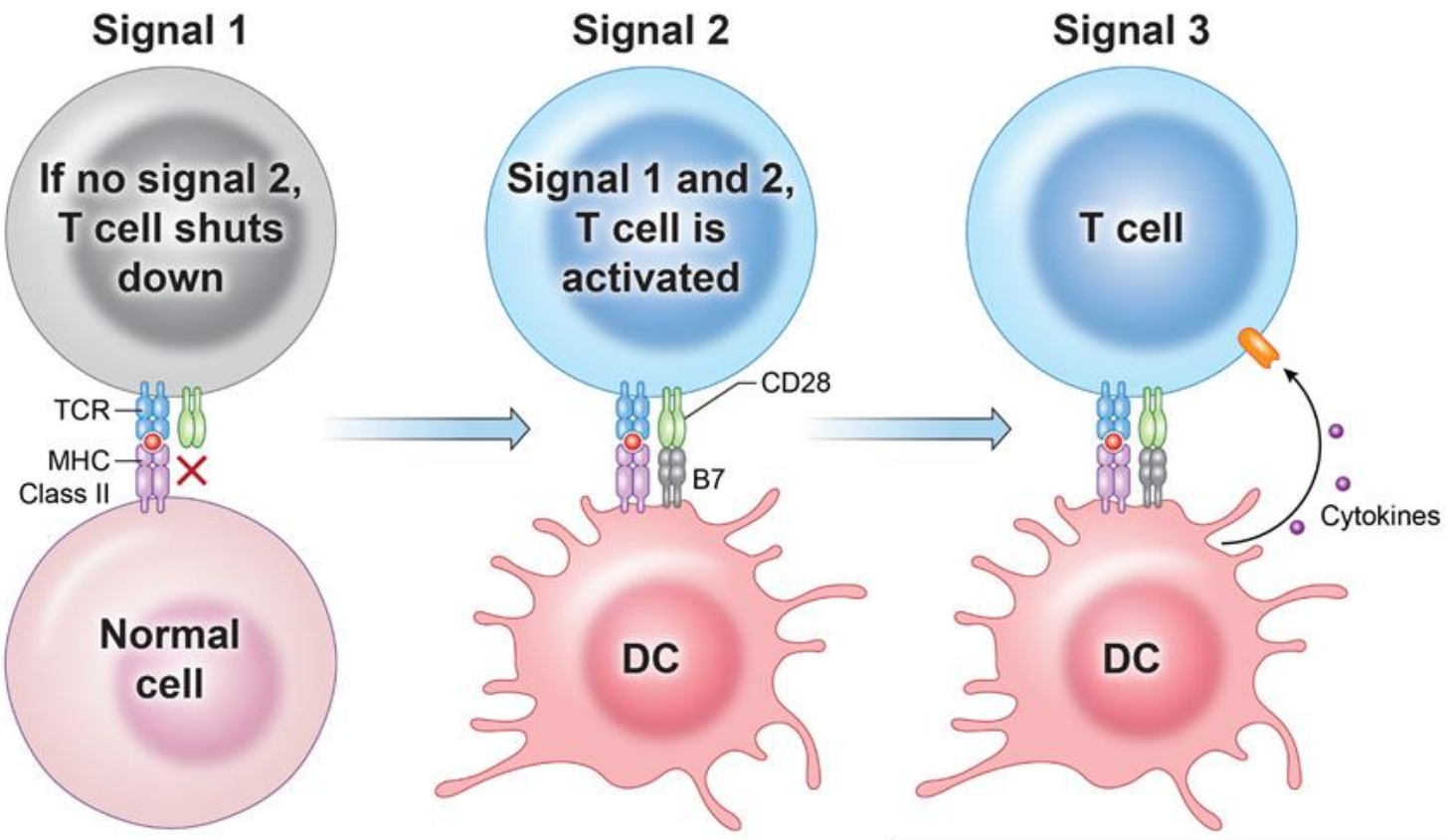
Three signals for antigen-specific T cell activation



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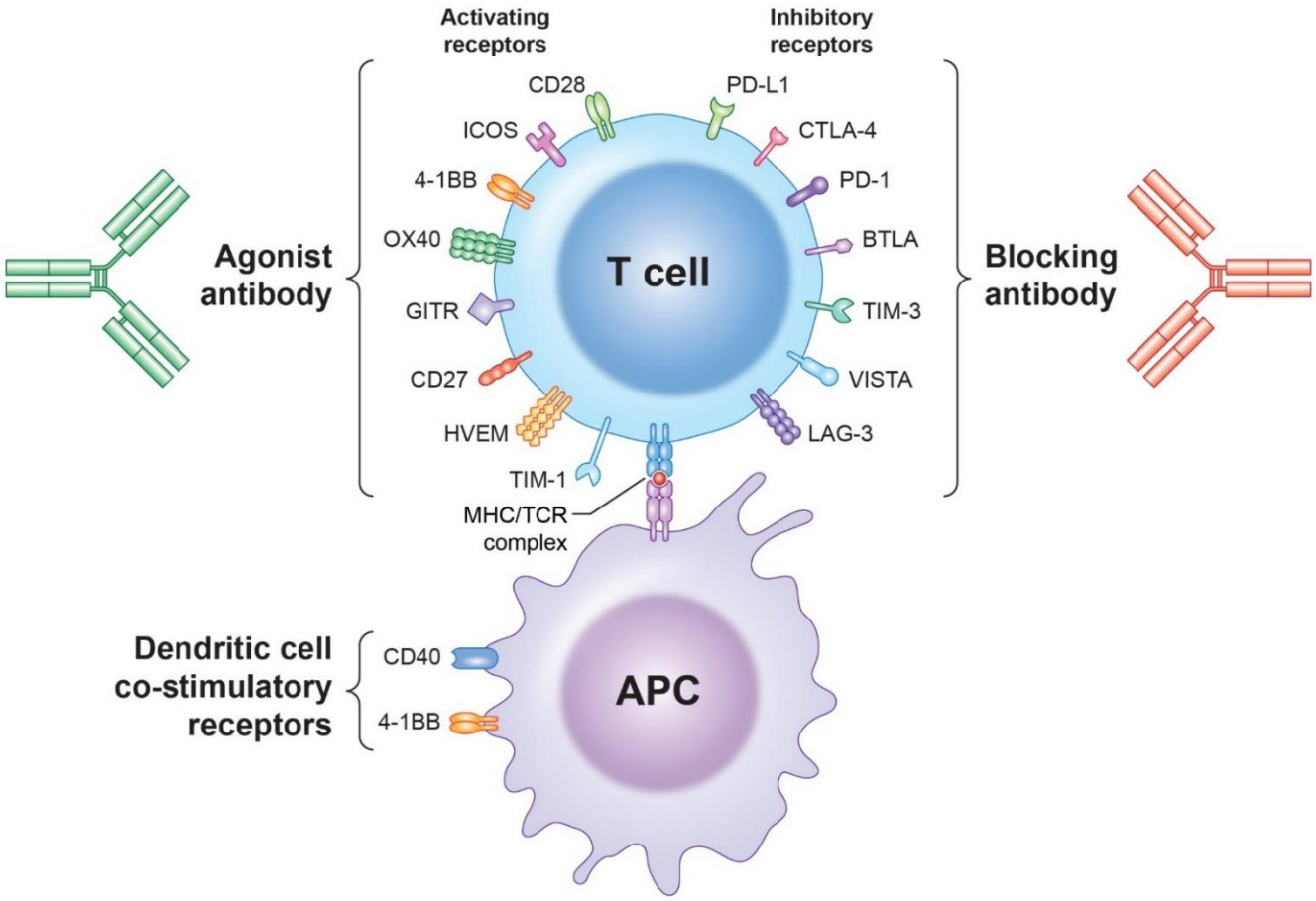
T cell checkpoint modulation



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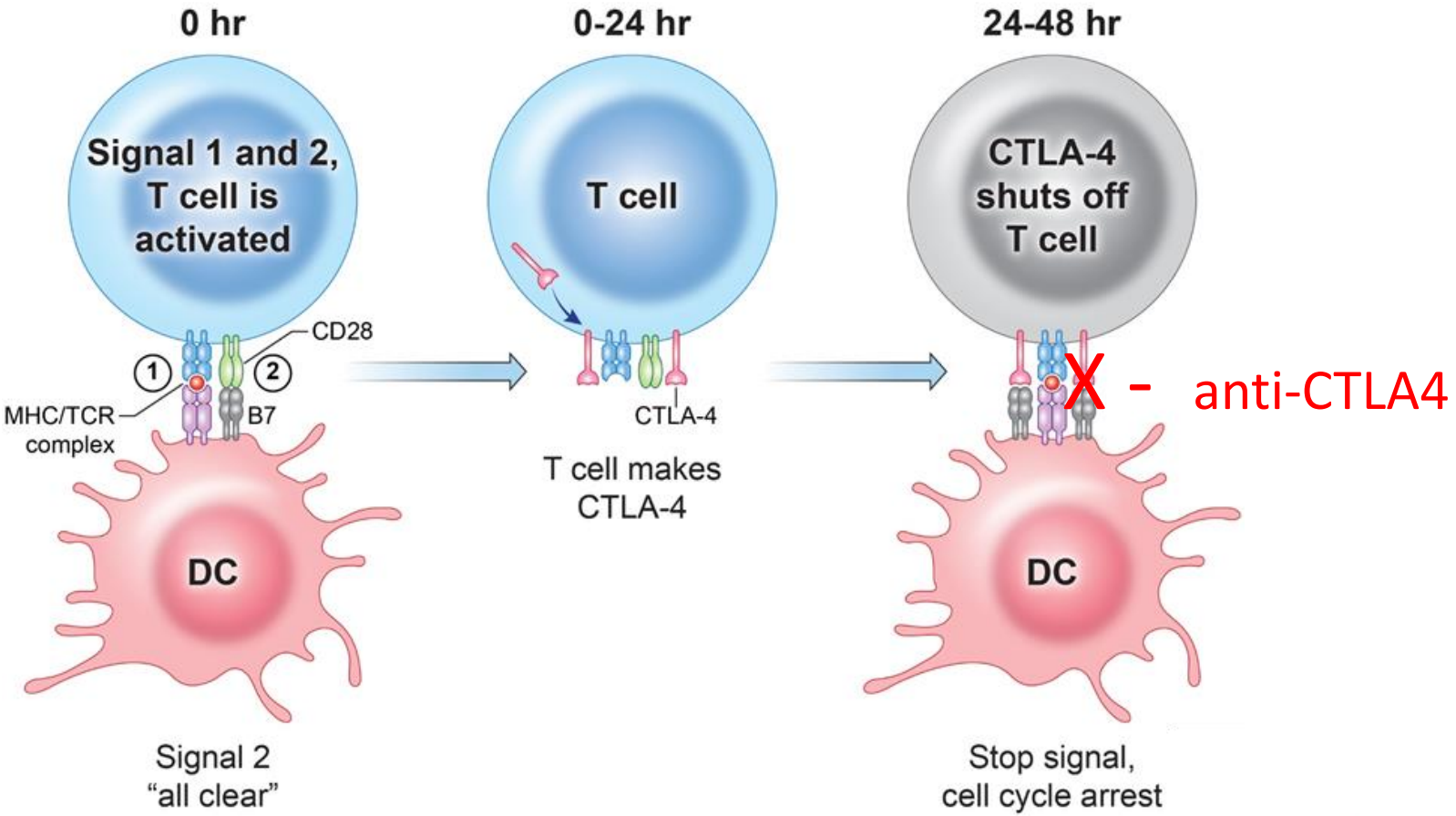
CTLA-4, a negative regulator of T cell activity limits the responsiveness of activated T cells



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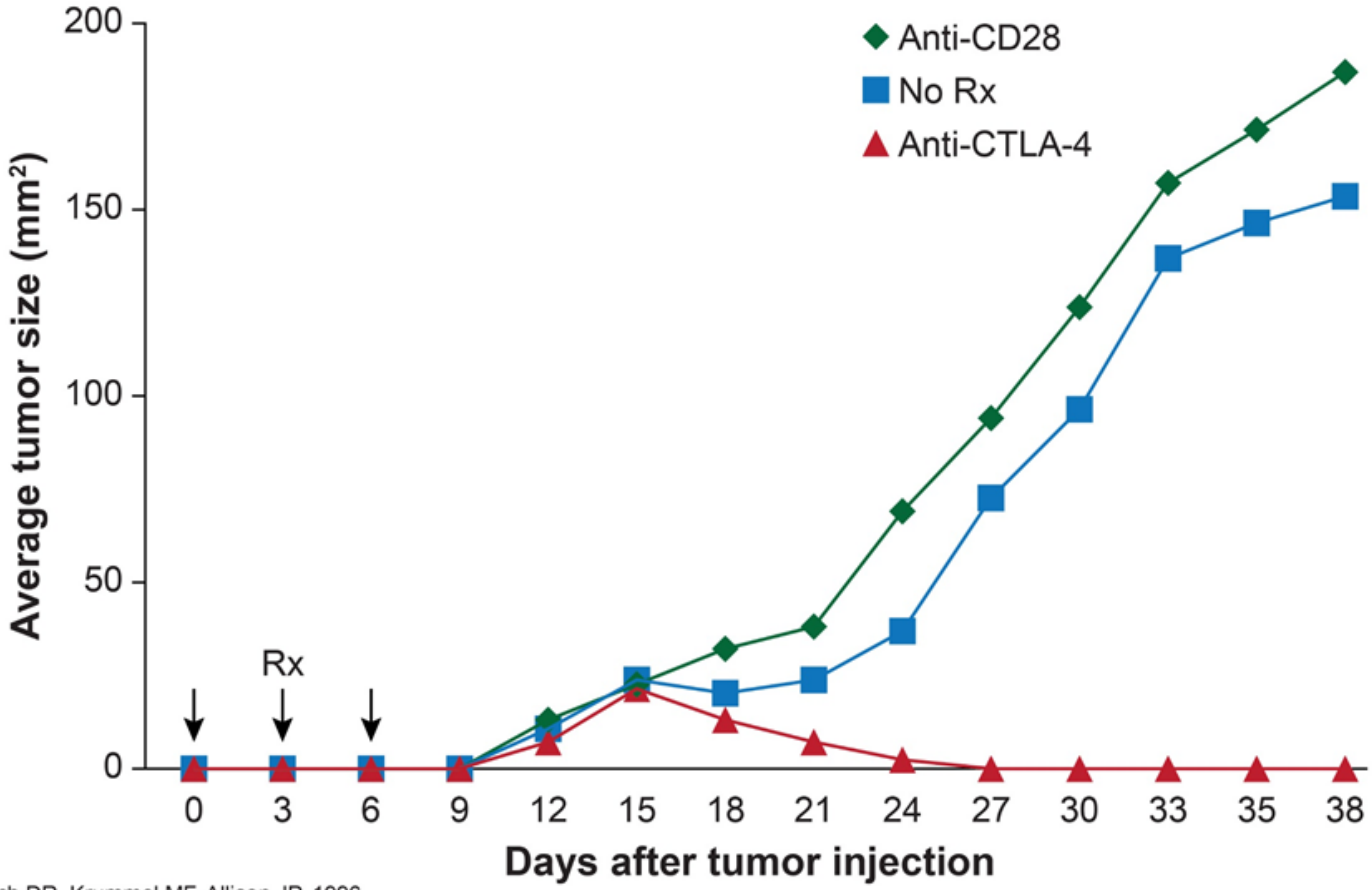
Anti-CTLA-4 induces regression of transplantable colon carcinoma



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

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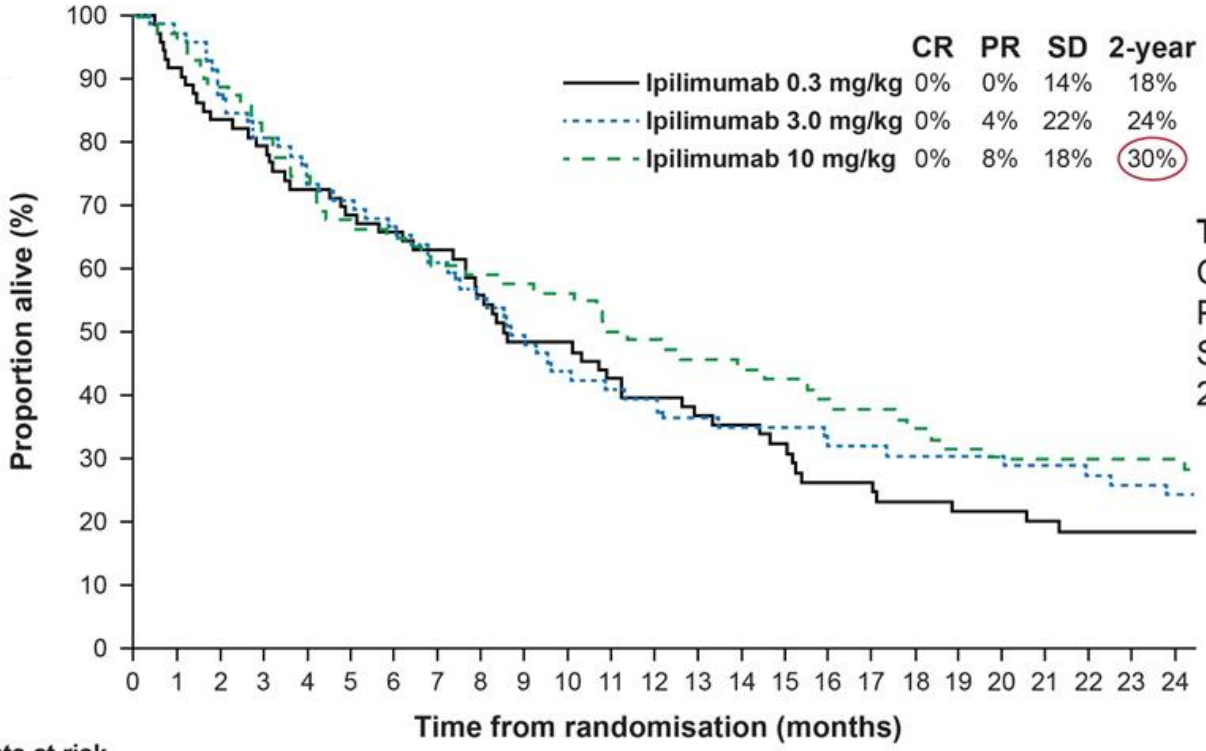
Ipilimumab (human anti-CTLA-4) was approved for the treatment of metastatic melanoma by FDA in 2010



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.

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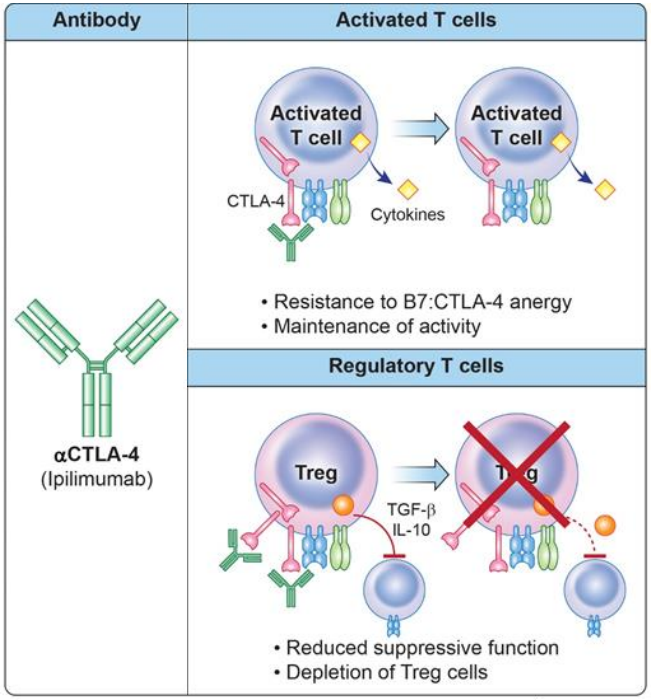
Which T cells are affected by ipilimumab (αCTLA-4)?



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

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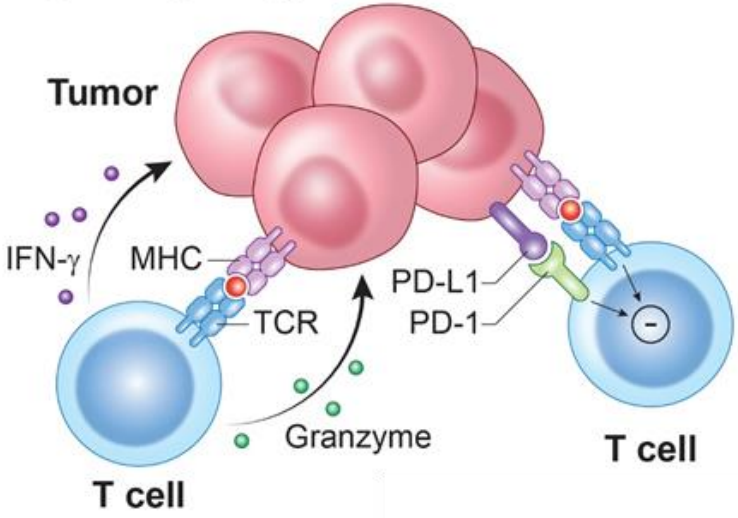
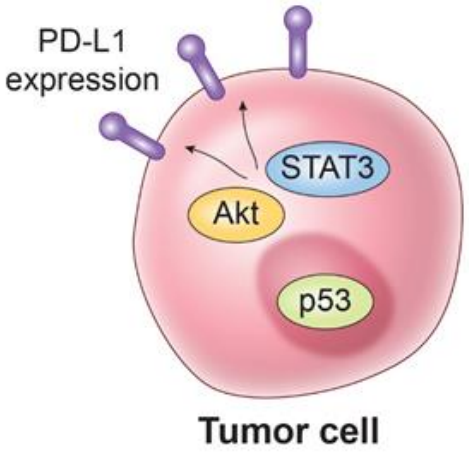
PD-1: PD-L1 inhibitory pathway

- 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-γ
  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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Current approvals for PD-1/PD-L1 inhibitors

Pembrolizumab	PD-1	• Advanced/unresectable melanoma • Metastatic NSCLC (PDL1) • Recurrent squamous cell carcinoma of head and neck • MSI high, all solid tumors • First line NSCLC • Urothelial carcinoma • Hodgkin lymphoma • Gastric cancer (accelerated approval)
Nivolumab	PD-1	• Advanced/unresectable melanoma after ipilimumab or BRAF inhibitor • NSCLC with progression after platinum • Metastatic renal cell carcinoma • MSI high colorectal cancer • Squamous cell carcinoma head and neck • Hodgkin lymphoma
Atezolizumab	PD-L1	• NSCLC with progression after platinum • Urothelial carcinoma
Avelumab, durvalumab	PD-L1	• Urothelial carcinoma • Merkel cell carcinoma (avelumab)

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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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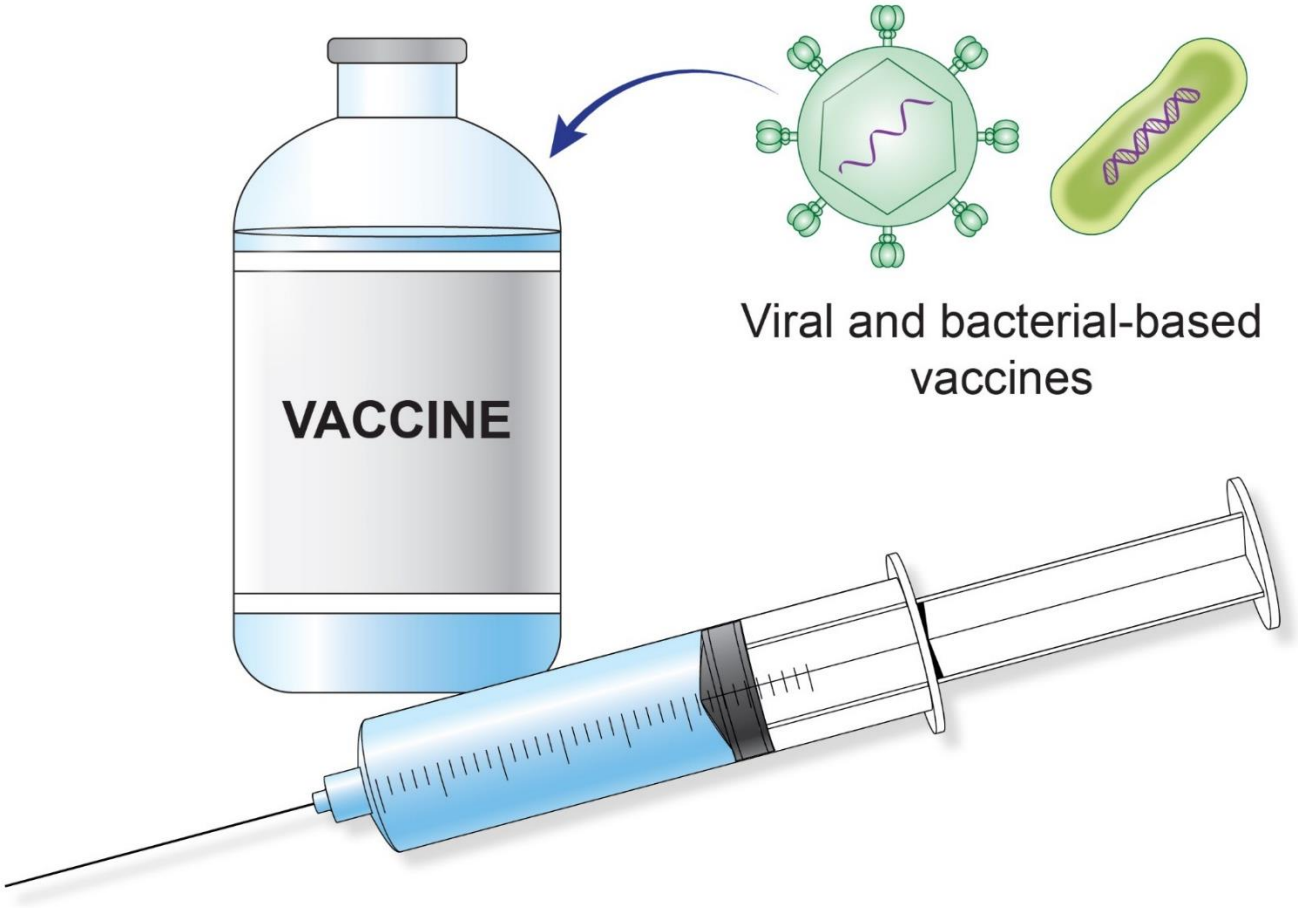
Therapeutic cancer vaccines



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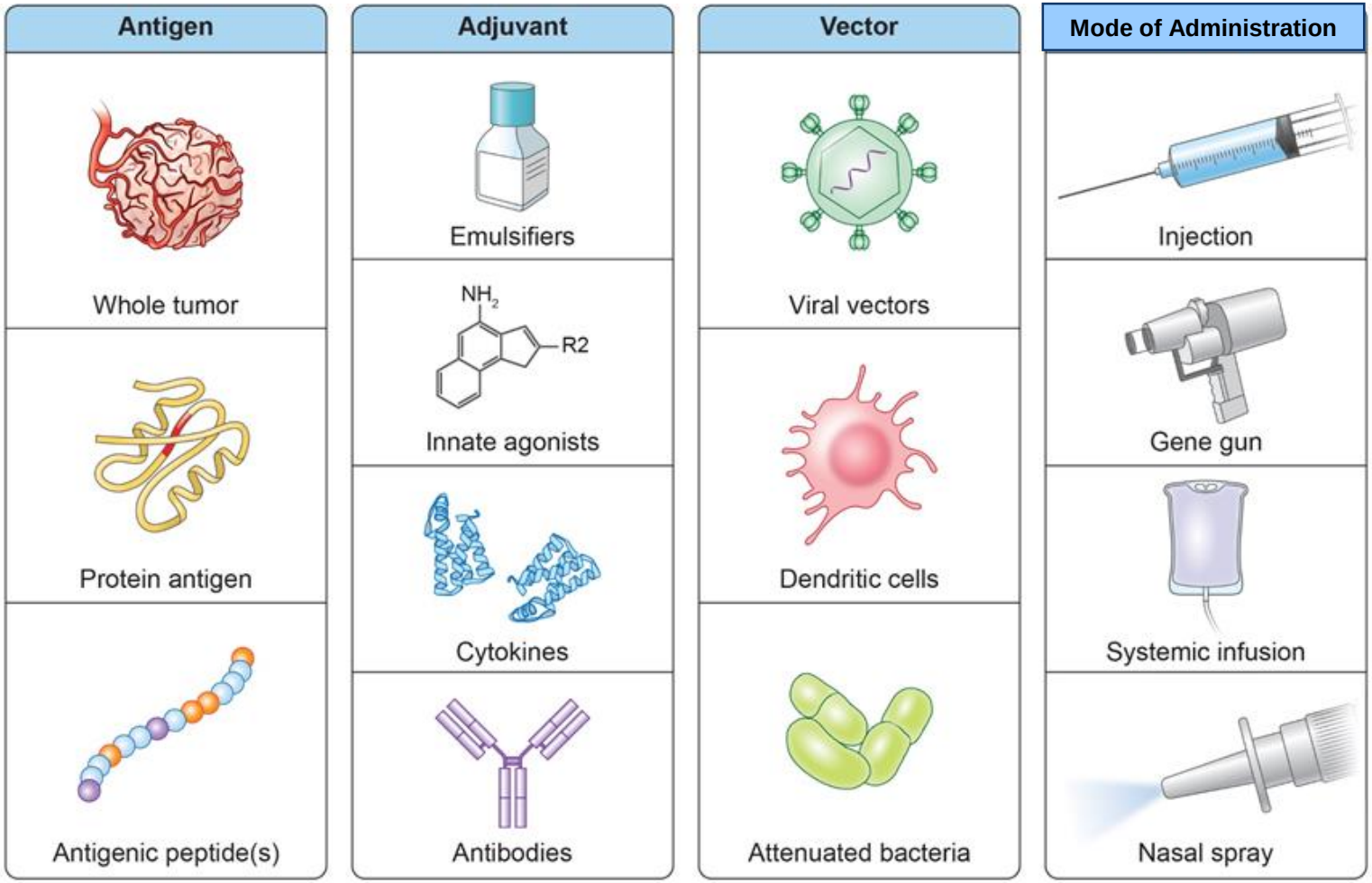
Components of a cancer vaccine



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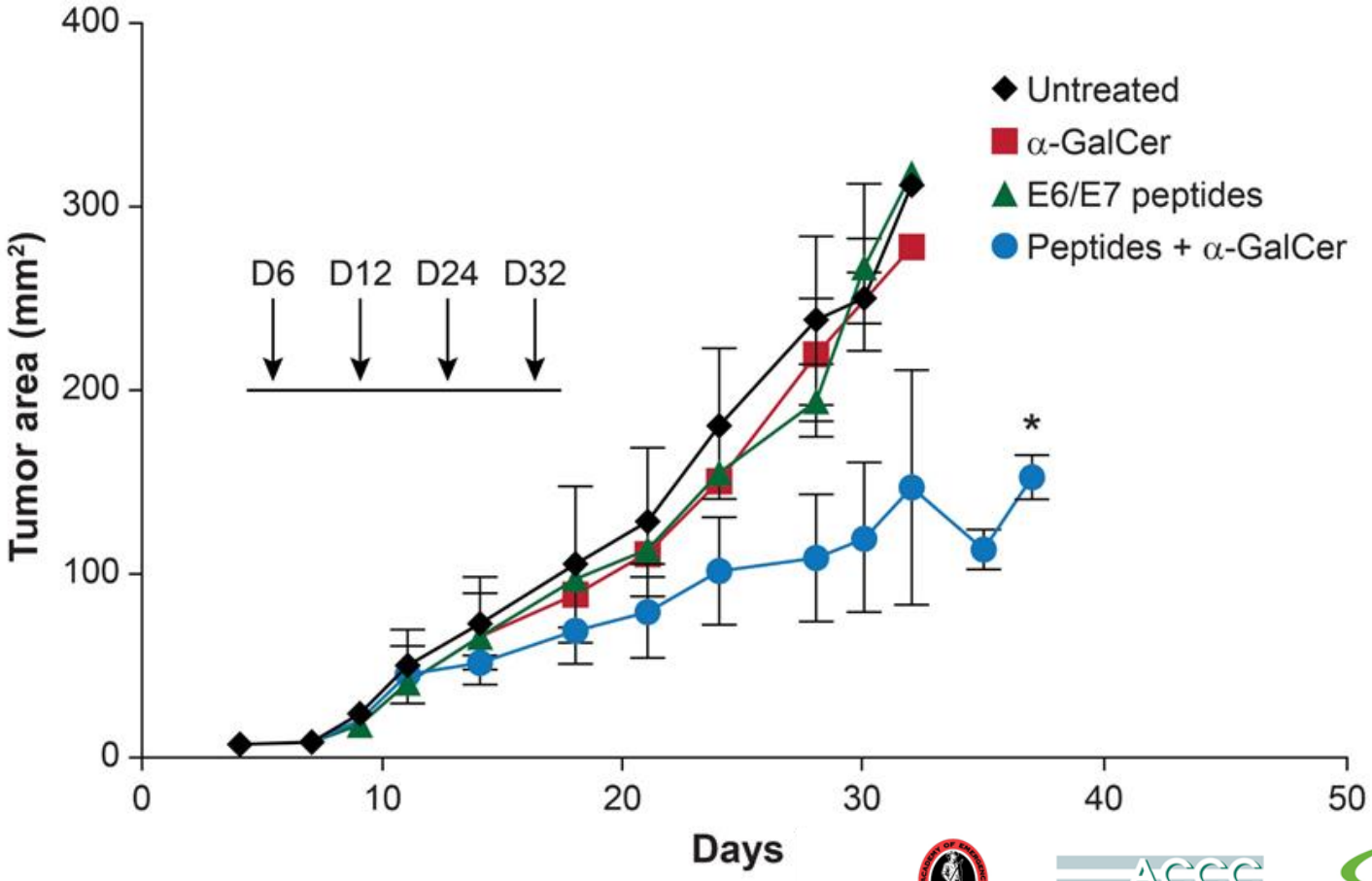
An intra-nasal HPV E6/E7: α-GalCer vaccine slows growth of TC-1 tumors



Shailbala Singh

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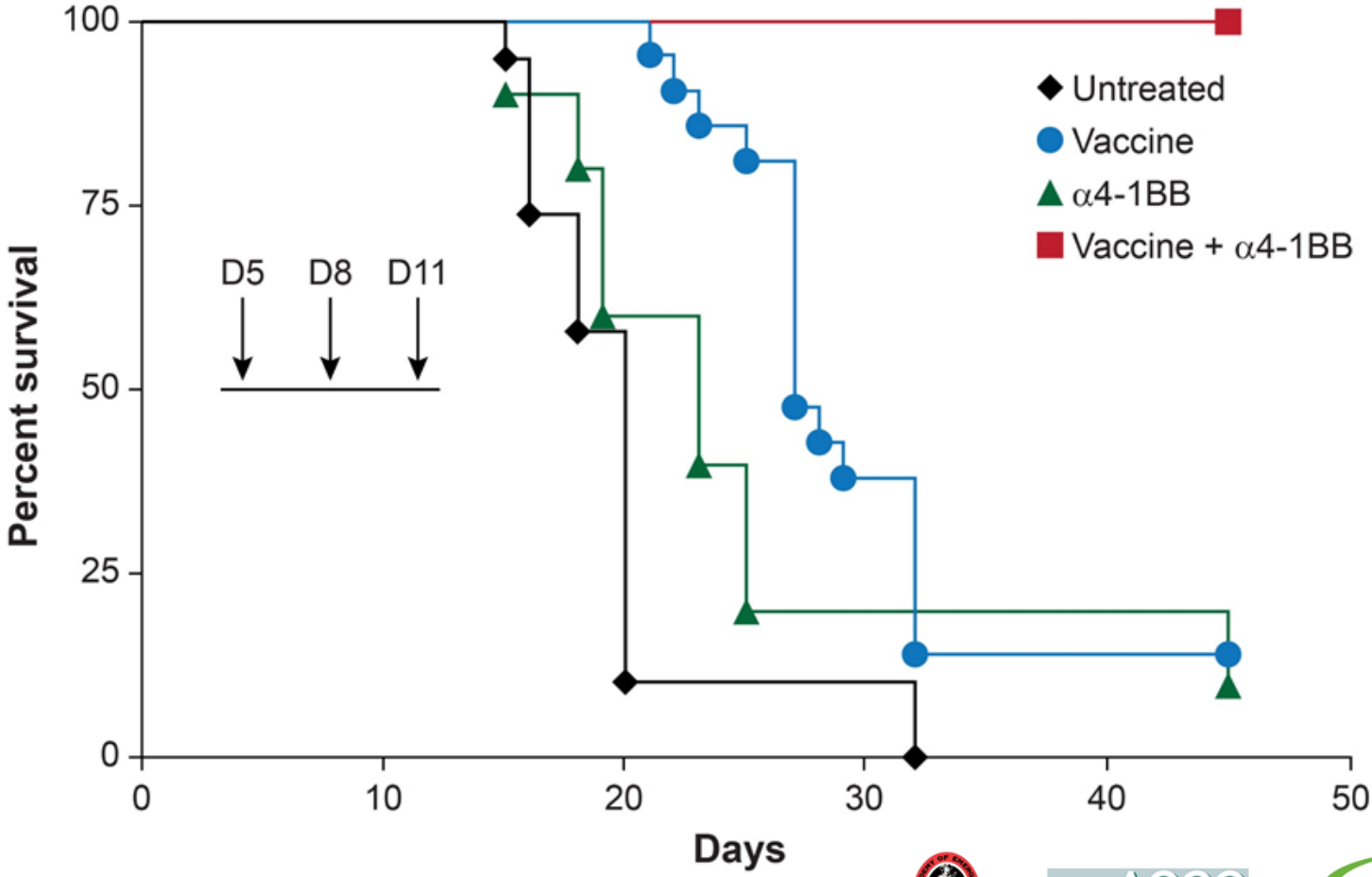
4-1BB agonist antibody and HPV E6/E7 vaccine synergize in curing TC-1 tumors



Todd Bartkowiak, M.S.

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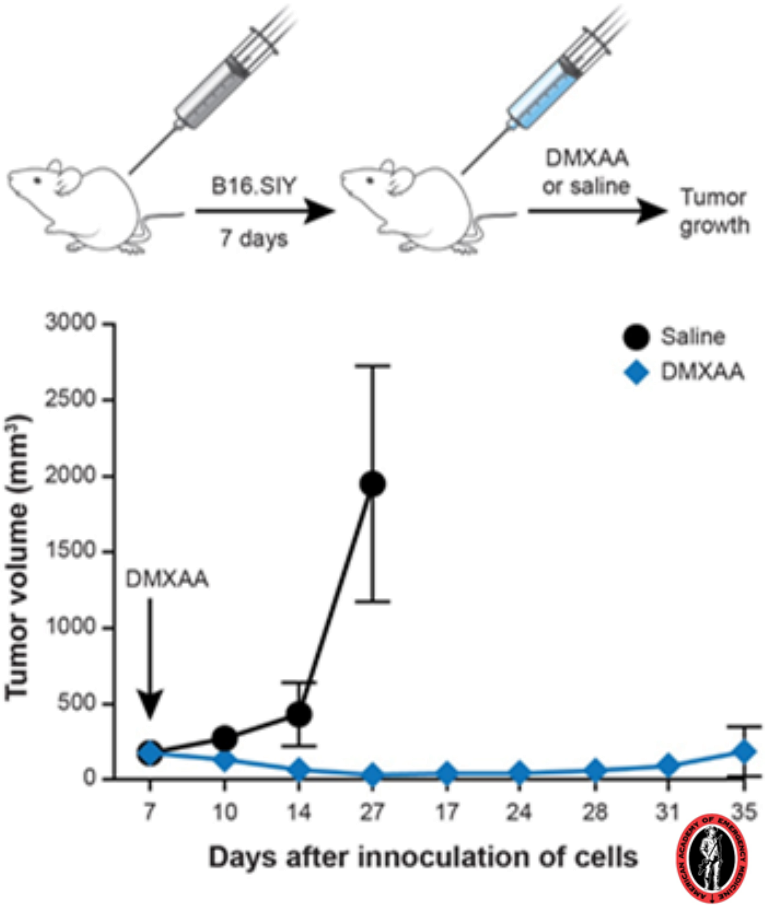
Intratumoral injection of innate immune agonists: The direct vaccination approach

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



Corrales L and Gajewski TF

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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.

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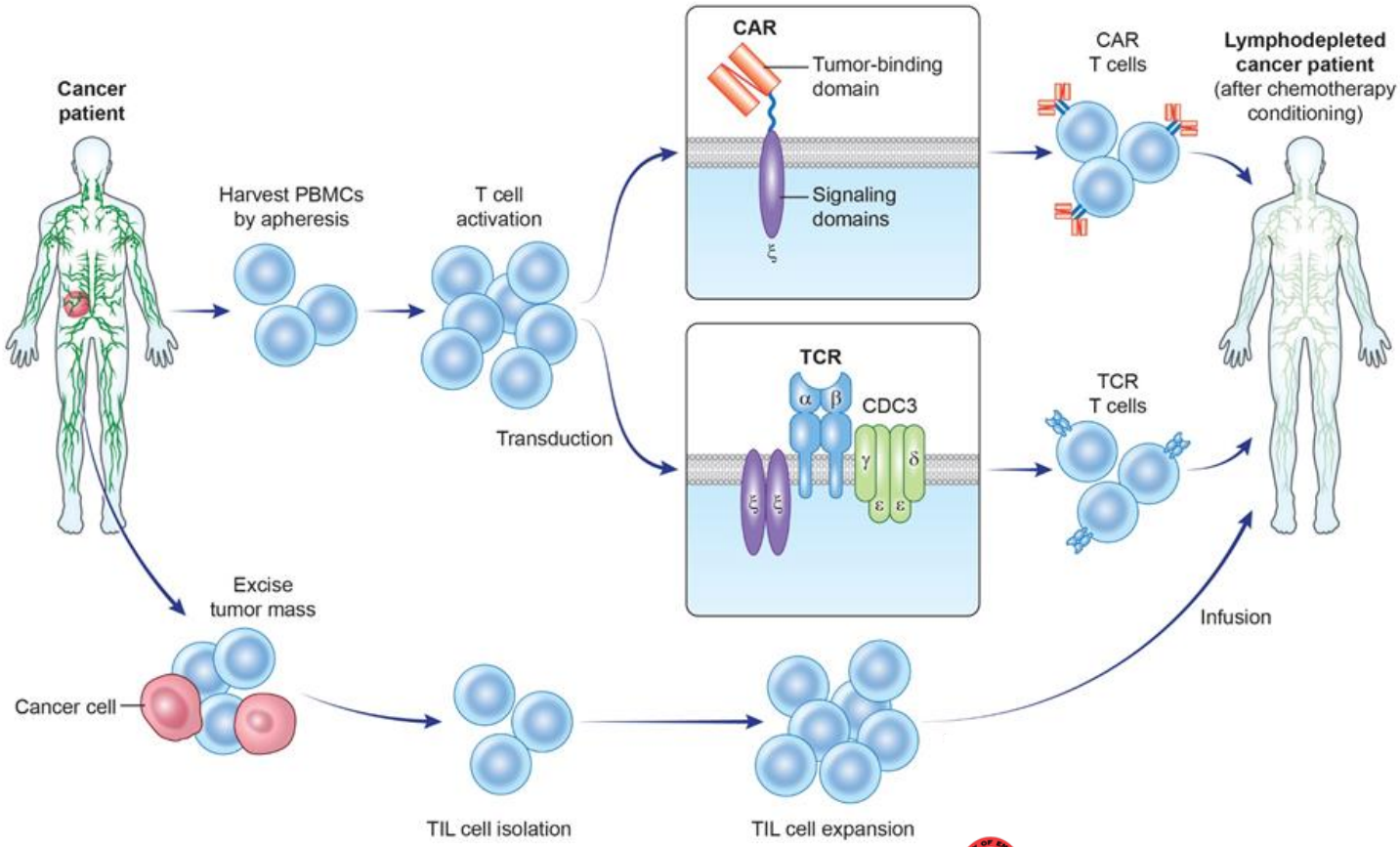
Adoptive T cell therapy can involve engineered (CAR, TCAR) or patient-derived (TIL, PBMC) T cells



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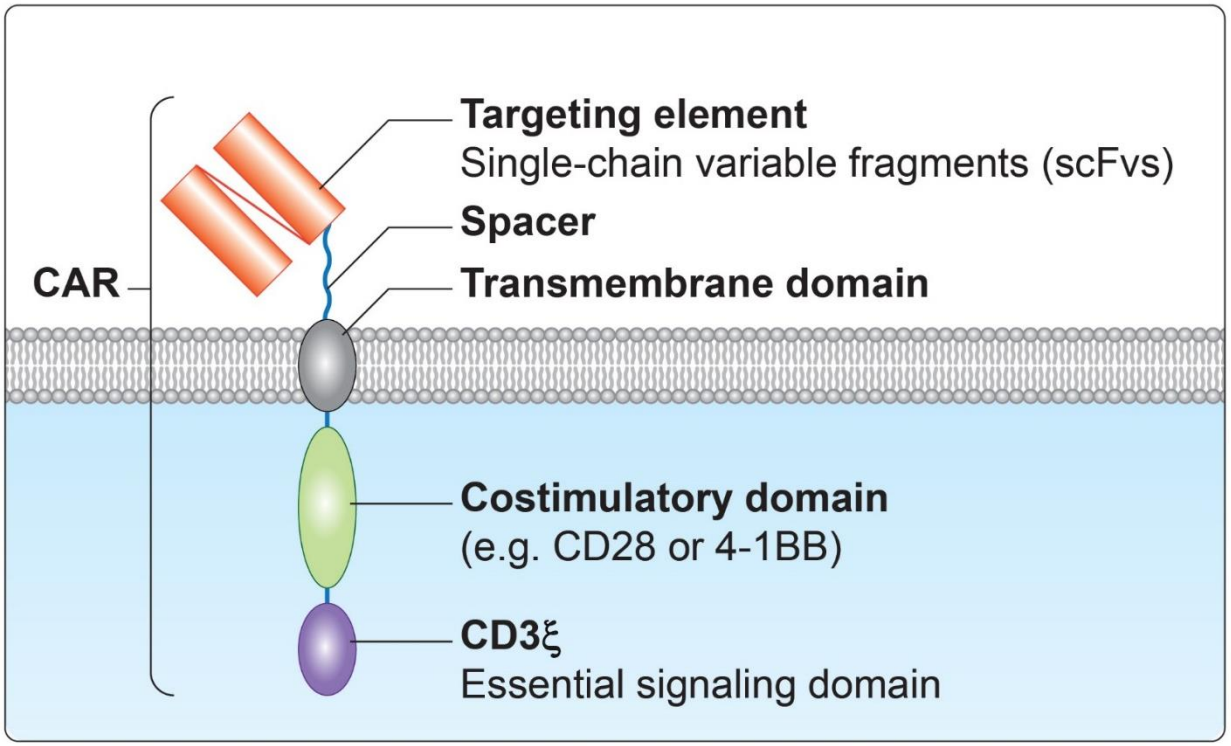
T cell adoptive transfer



CARs, TIL, TCR, PBMCs

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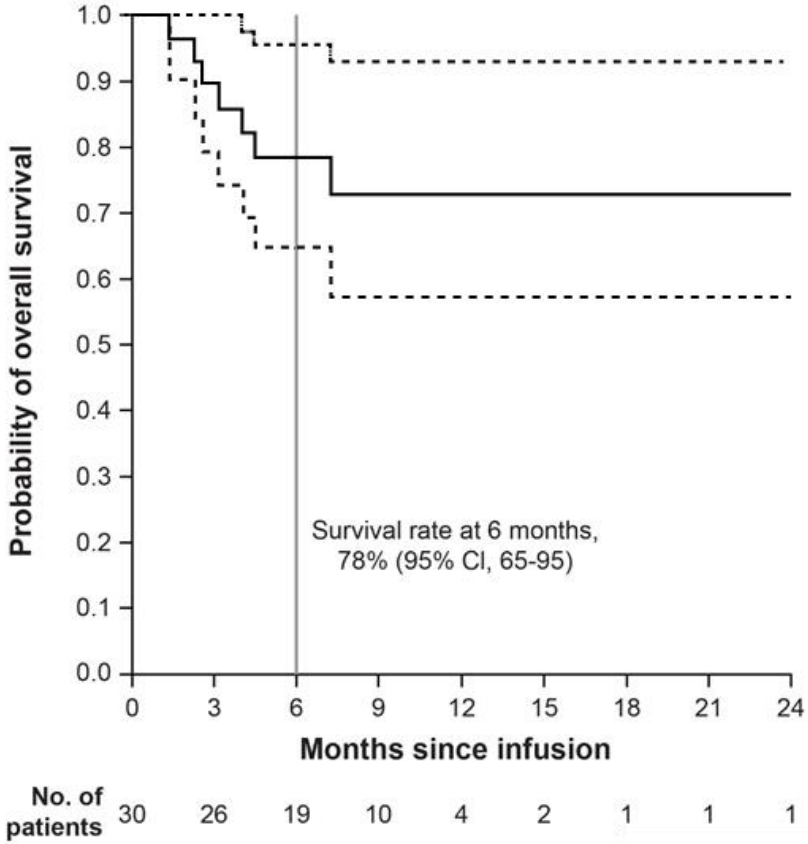
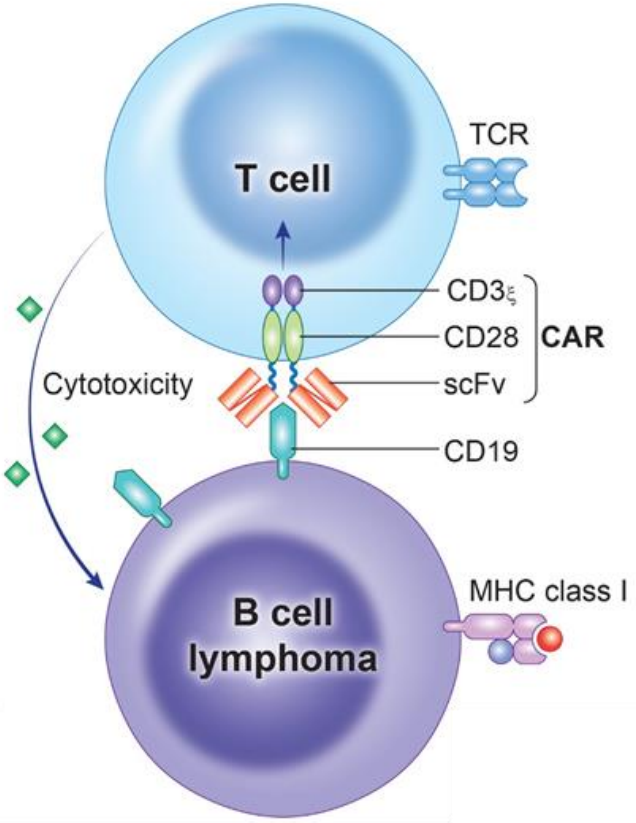
Effective treatment of relapsed B cell ALL with CD19 CAR T cell therapy





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.

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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.

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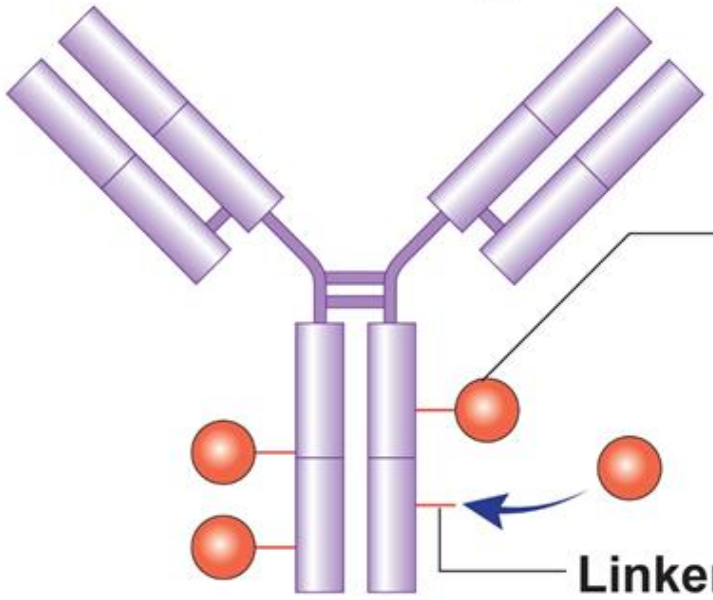
Effector antibodies and antibody-drug conjugates (ADCs)



Antibody
Specific to tumor-associated antigen

Radiolabeled or Cytotoxic agent
Designed to kill target cells when internalized and released or activated

Linker
Attaches cytotoxic agent to the antibody

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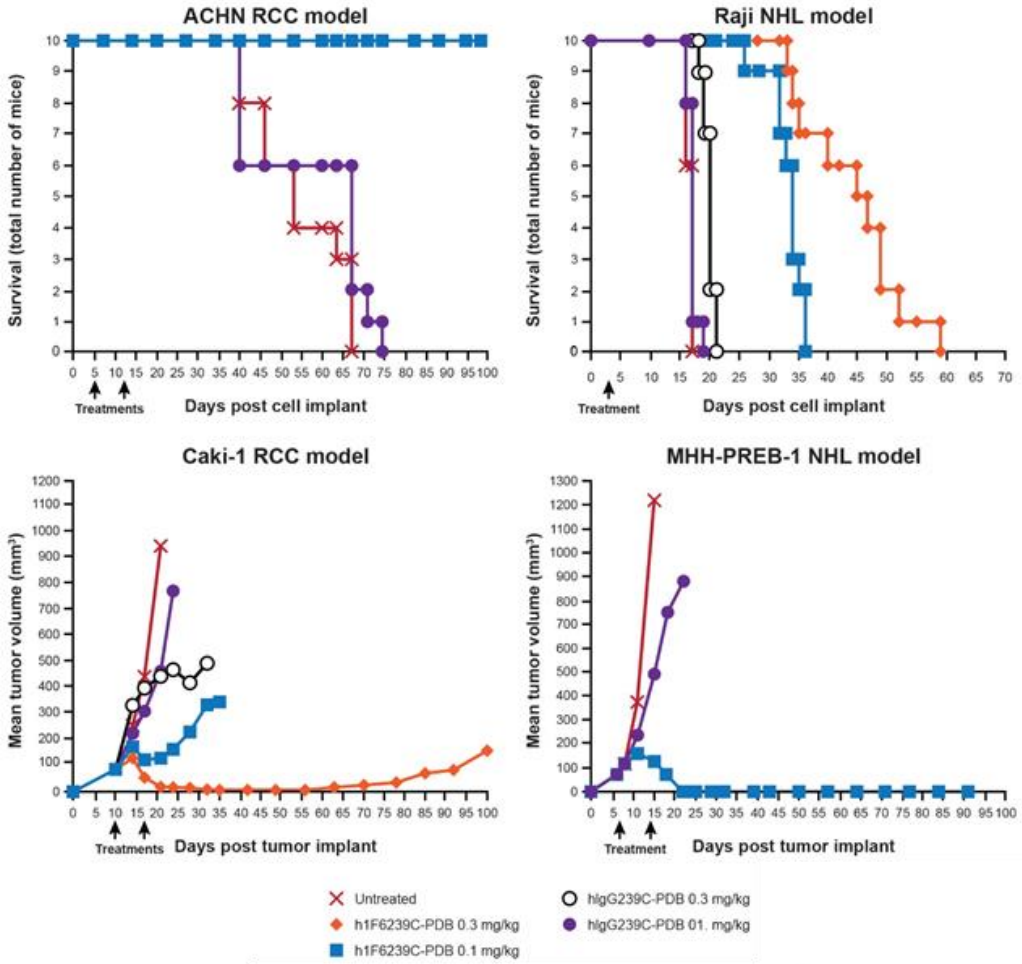
Key ADC / antibody principles

- **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.

SGN-70A in the clinic for NHL and RCC



Jeffrey SC et al. 2013. Bioconjug Chem. 24(7): 1256-63

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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.

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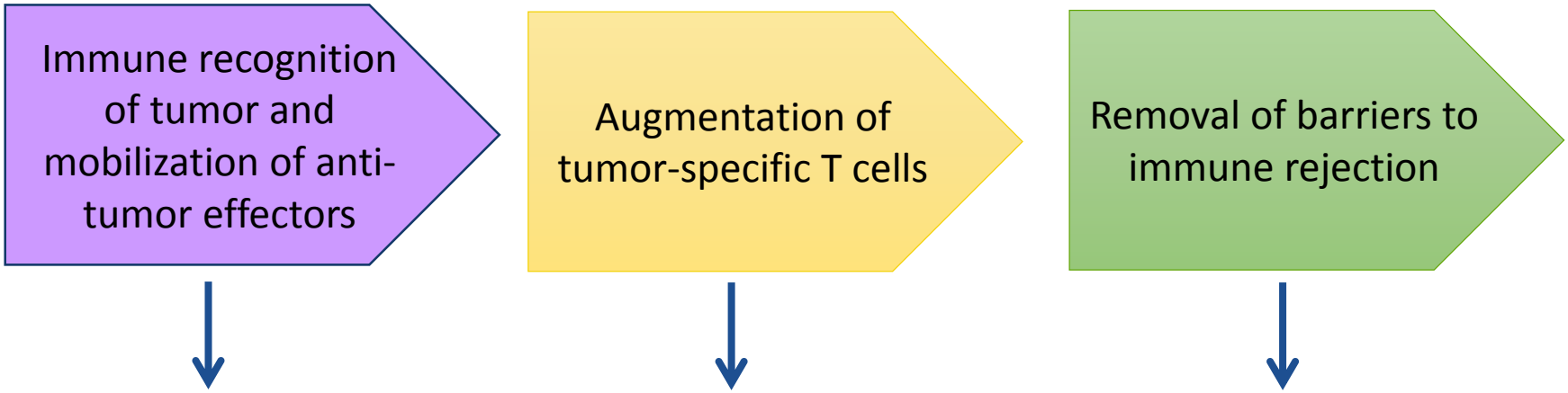

- Vaccines
- Chemotherapy
- Radiation
- ACT (CARs, TCR transfer)

- Co-inhibitory blockade
- Co-stimulatory activation
- Activation of APCs
- Innate immune recognition

- Tumor vascular resistance
- Desmoplastic stroma
- Hypoxic microenvironments

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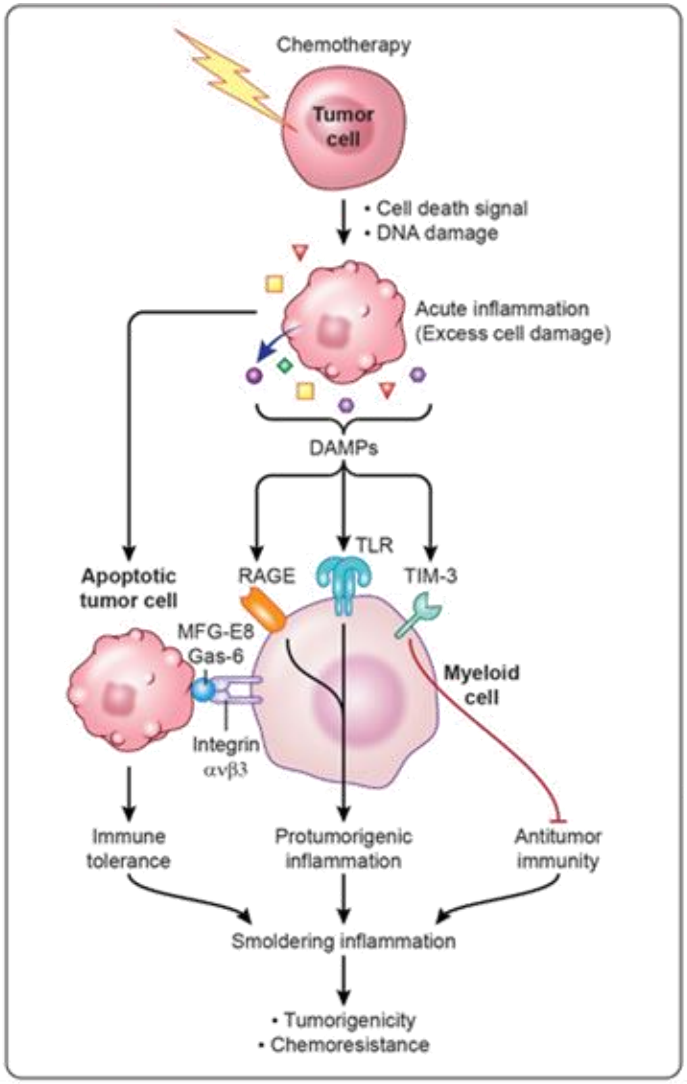
A different perspective on chemotherapy

Immunogenic versus non-immunogenic cell death



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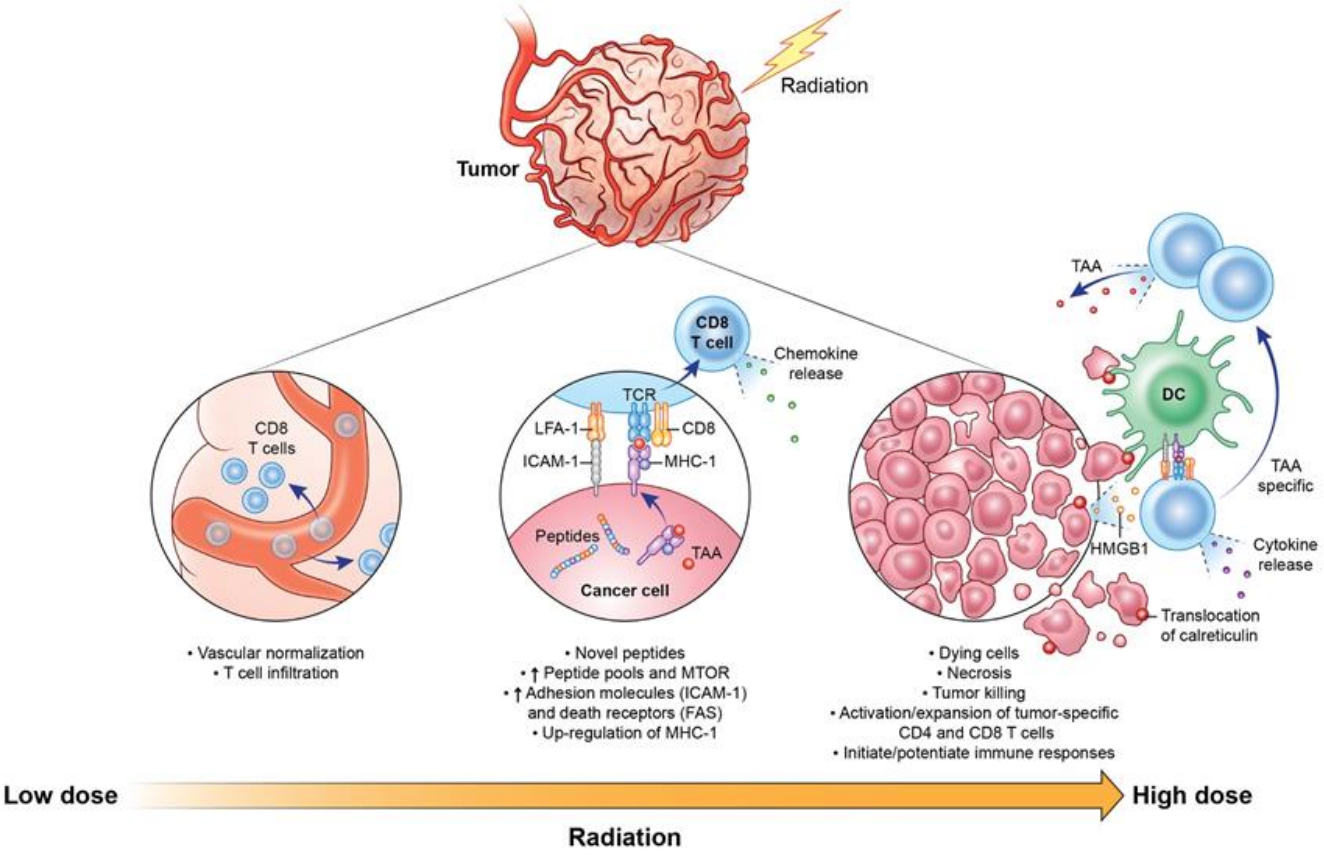
Radiation Therapy:

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

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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.

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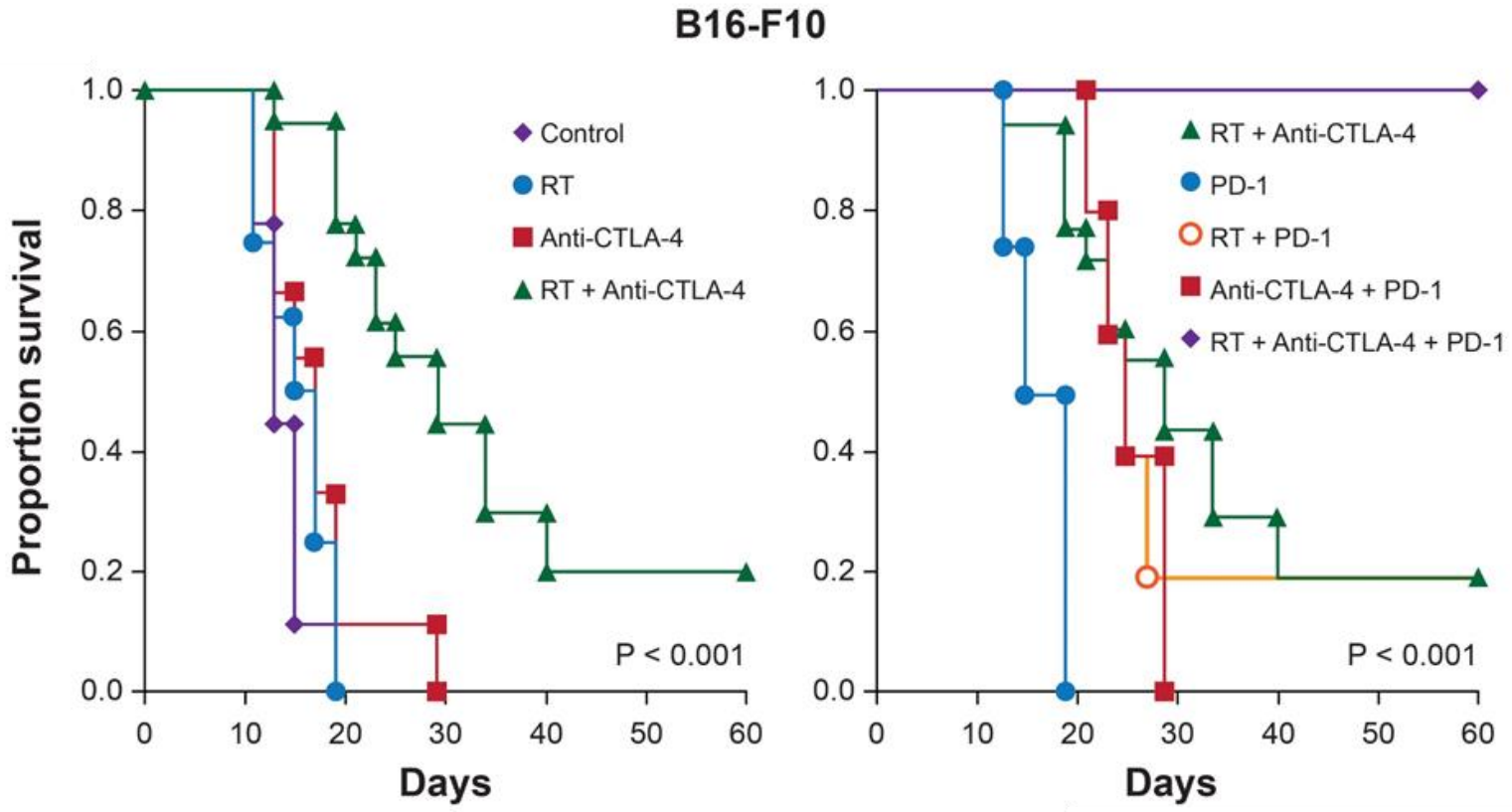
Radiotherapy synergizes with blockade of CTLA-4 and PD-1 to cure melanoma lung metastases



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.

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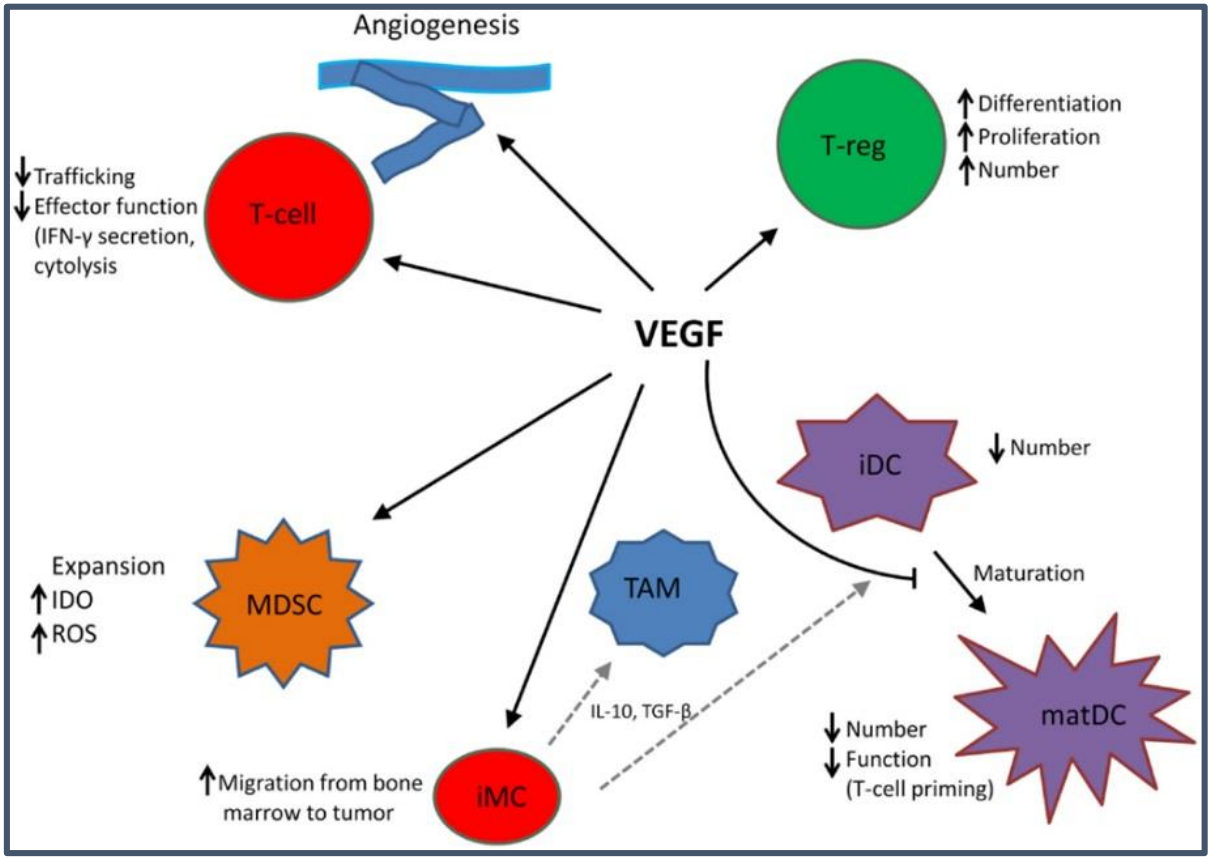
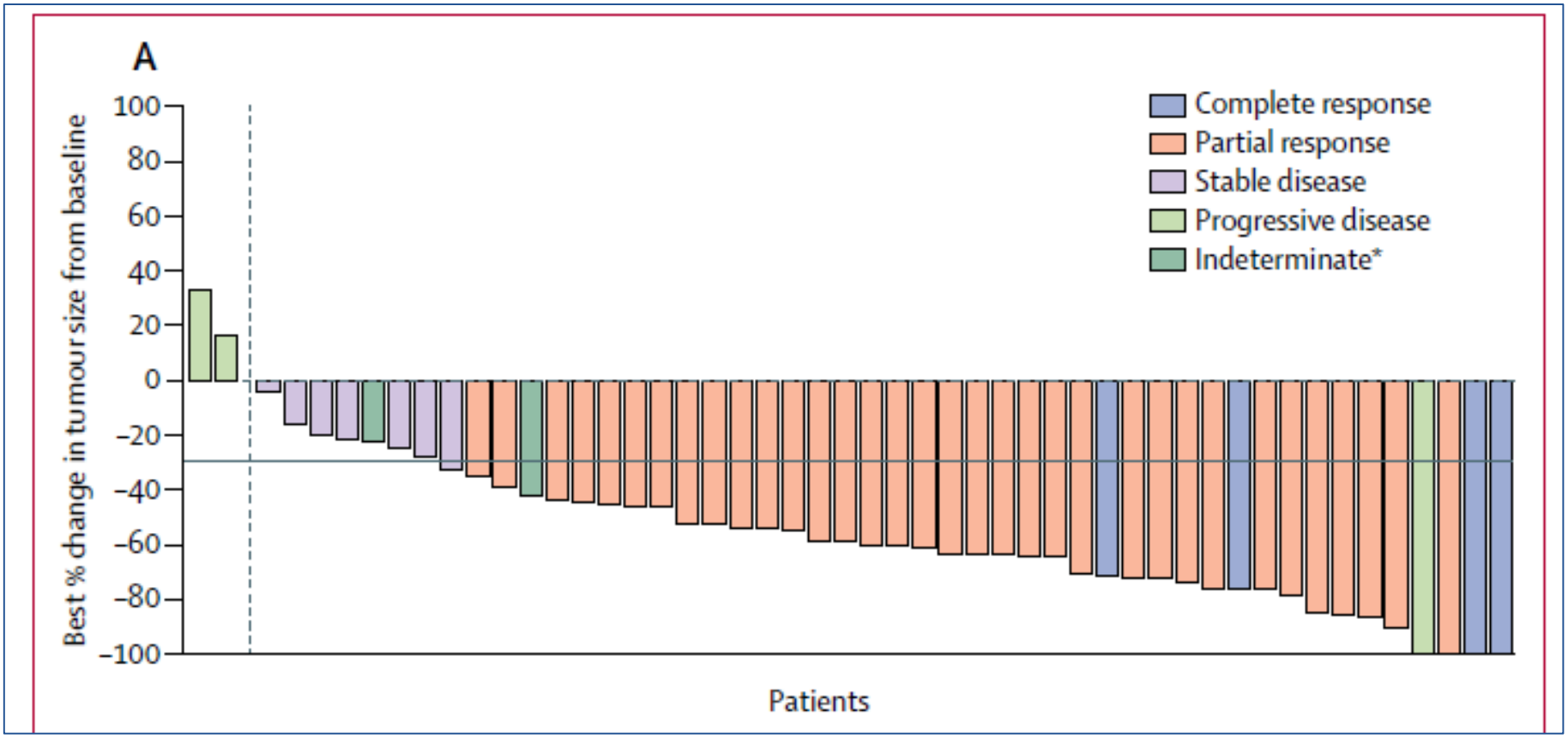
Targeted therapy combinations

- Inhibits dendritic cell maturation and antigen presentation
- Impedes migration of lymphocytes across endothelium into tumor deposits
- Promotes accumulation of MDSC, TAM, Treg



Kumar & Gabrilovich, Immunology 1996

Axitinib plus pembrolizumab for untreated RCC



Atkins et al, Lancet Oncol 2018.

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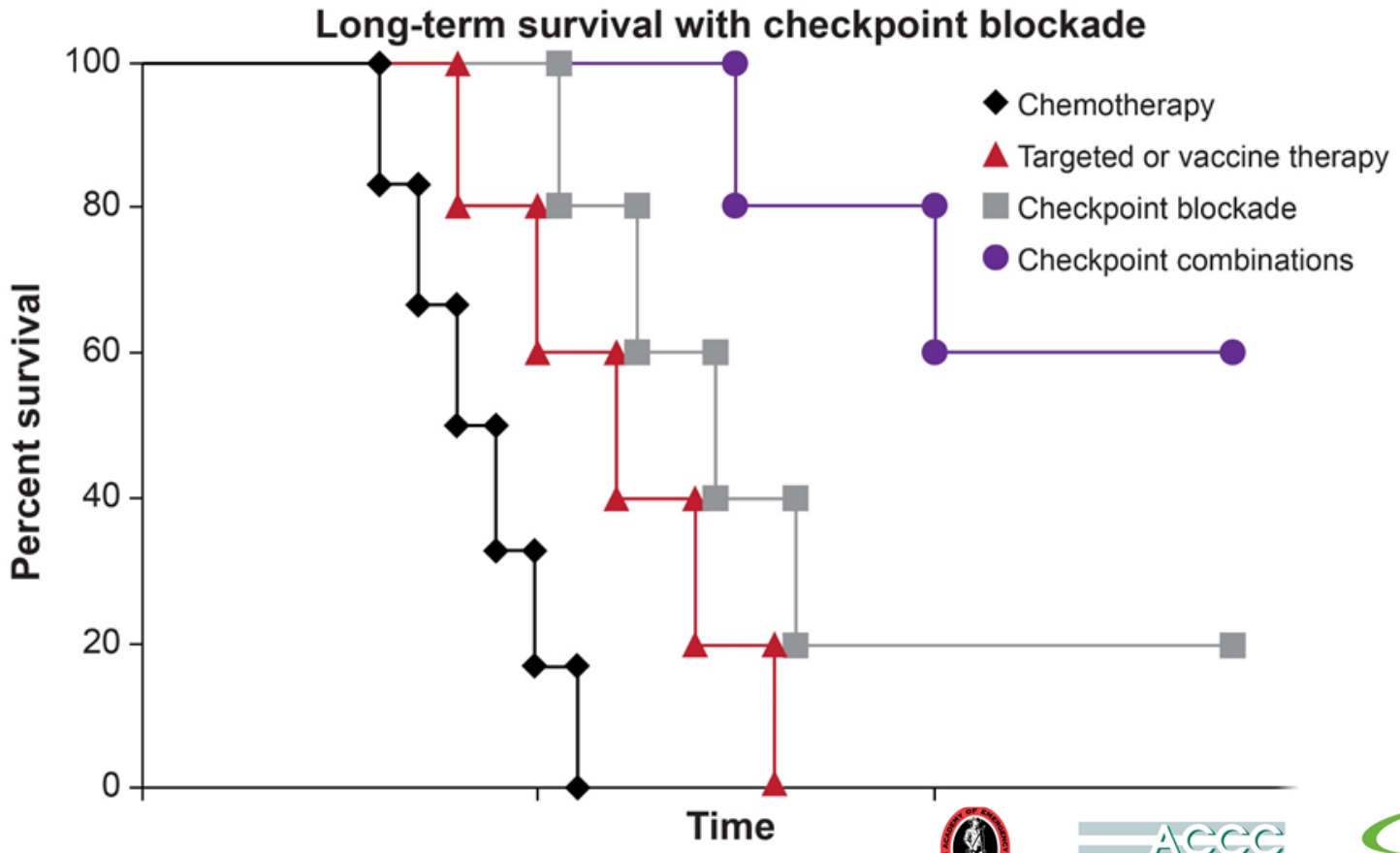
Why combination immunotherapy is the future?

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



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A future precision medicine approach?

Immunobiomarkers?

- Genetic mutational burden
- IHC for MSI
- PD-L1 expression
- Immunosignature
- Hot vs. Cold tumors

Chemotherapy

+

Checkpoint Inhibitor(s)

+

Radiation

→

Checkpoint Inhibitor maintenance

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A future precision medicine approach?

Immunobiomarkers?

- Genetic mutational burden
- IHC for MSI
- PD-L1 expression
- Immunosignature
- Hot vs. Cold tumors

Targeted therapy + Checkpoint Inhibitor(s)

→

Surgery

→

Checkpoint Inhibitor maintenance

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A future precision medicine approach?

Immunobiomarkers?

- Genetic mutational burden
- IHC for MSI
- PD-L1 expression
- Immunosignature
- Hot vs. Cold tumors

Chemotherapy

→

Checkpoint Inhibitor(s) + Customized Vaccine

OR

TCR/CAR T cells

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Conclusions and Take-Homes

- Anti-tumor immunity is complex and challenges remain due to tumor and patient heterogeneity, and the multiple layers of immunosuppression
- We need to improve our understanding of hot and cold tumors, and use this to evolve immunotherapy recommendations for individual cancers and individual patients
- The majority of cancers are likely to require combination approaches for best outcomes

Thank you!

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