Tumor Immunity and Immunotherapy

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FOCiS® Federation of Clinical Immunology Societies

Outline

- Immune surveillance
- Tumor antigens
- Immune responses to tumors and anti-tumor effector mechanisms
- Tumor evasion of immune system
- Cancer immunotherapy
    - Checkpoint blockade
    - Adoptive cellular therapy
    - Personalized vaccines
    - Antibody-based therapies

Tumor Immune surveillance: hypotheses

Paul Ehrlich
1909

"[during development] aberrant cells become unusually common. Fortunately, in the majority of people, they remain completely latent thanks to the organism's positive mechanisms"

Frank MacFarlane Burnet
1957

"Small accumulation of tumor cells may develop and because of their possession of new antigenic potentialities provoke an effective immunological reaction with regression of the tumor and no clinical hint of its existence."

Lewis Thomas
1959

"The immune system recognizes newly arising tumors through the expression of tumor specific neo-antigens on tumor cells and eliminate them"

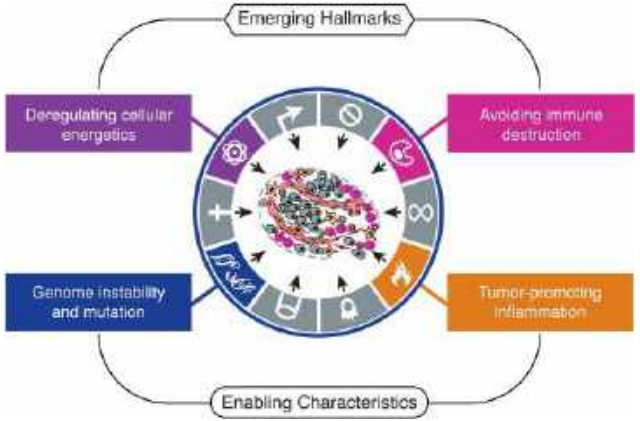
Tumor Immune surveillance modified by data

- Some types of malignant tumors arise more frequently in immunocompromised exp. animals and in humans.
- In humans, many of these tumors are caused by viruses.
- Nonetheless, cancers are very common and arise in overtly immunocompetent people.
- Human cancers stimulate innate and adaptive immune responses (antibodies, T cells).

Tumor Immune surveillance modified by data

- Most often, the immune responses fail to control the cancers, in large part because of selective outgrowth of tumors that have can evade immune responses.

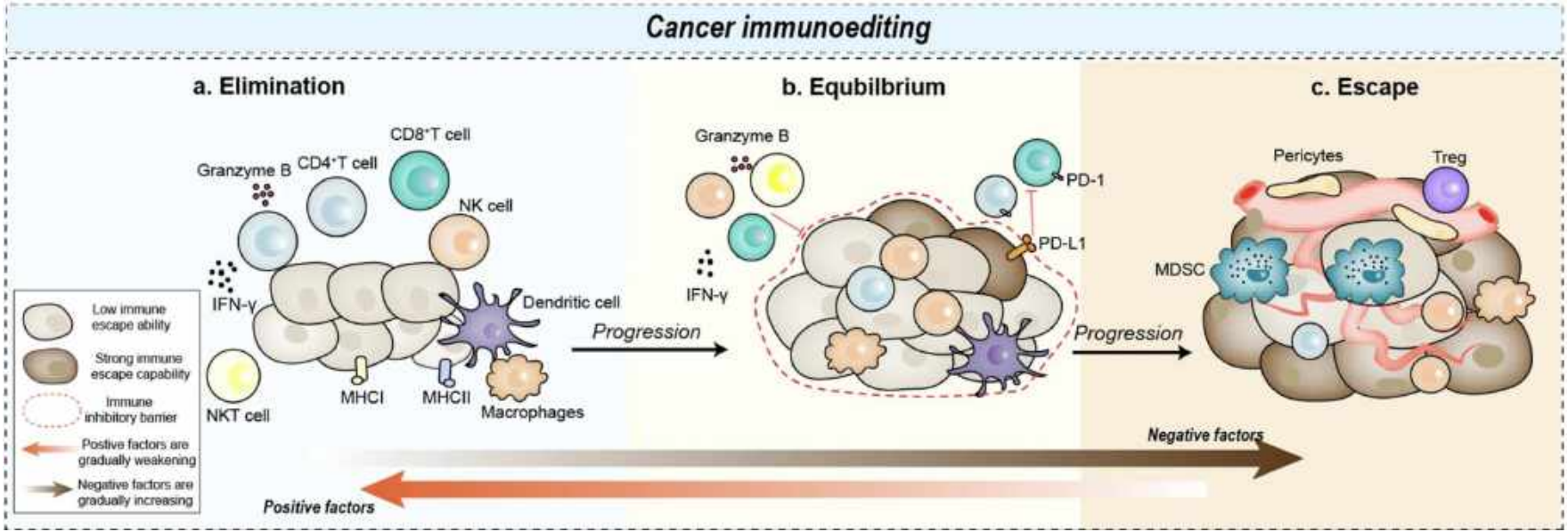
- Evasion of host immunity is one of the hallmarks of cancer cancer



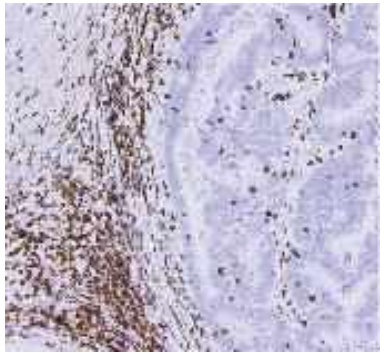
Hanahan D . Robert A. Weinberg RA. Hallmarks of Cancer: The Next Generation Cell. 2011;144:646-74.

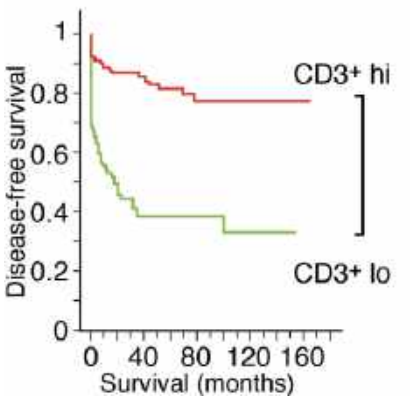
How Do Tumor Evade Host immunity

- *Cancer cells are like many microbes…they have high growth and mutation rates*
- *The immune response selects for variant cells that are resistant to or not seen by the host immune system (described by* Schreiber in 2002 as “Immunoediting”)



In combination with therapeutic intervention, the hosts immune response can control and eliminate cancers….e.g. Colon Cancer after Colectomy

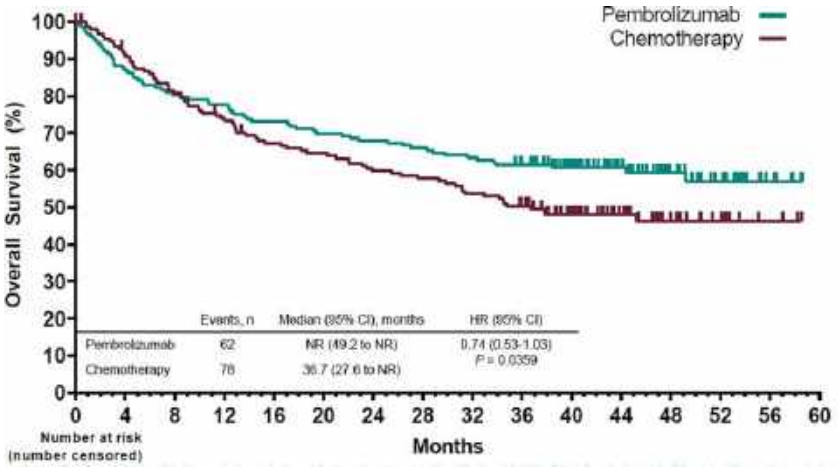




More T cells in tumor, longer disease-free survival

Th1 responses, high density of $CD3^+$, $CD8^+$, and $CD54RO^+$ T cells predicted good clinical outcome

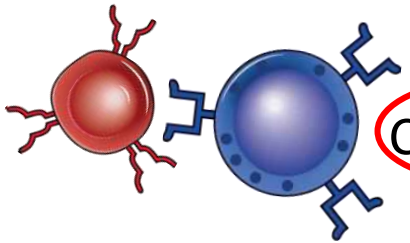
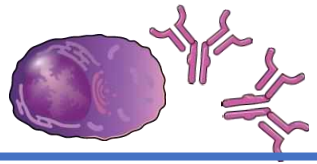
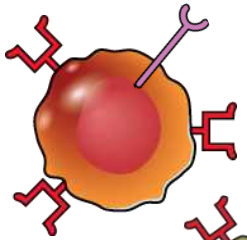
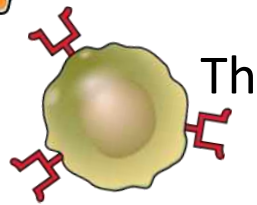
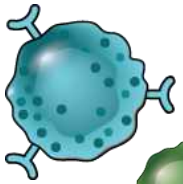
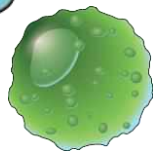
(Galon et al. (2006) .*Science*)



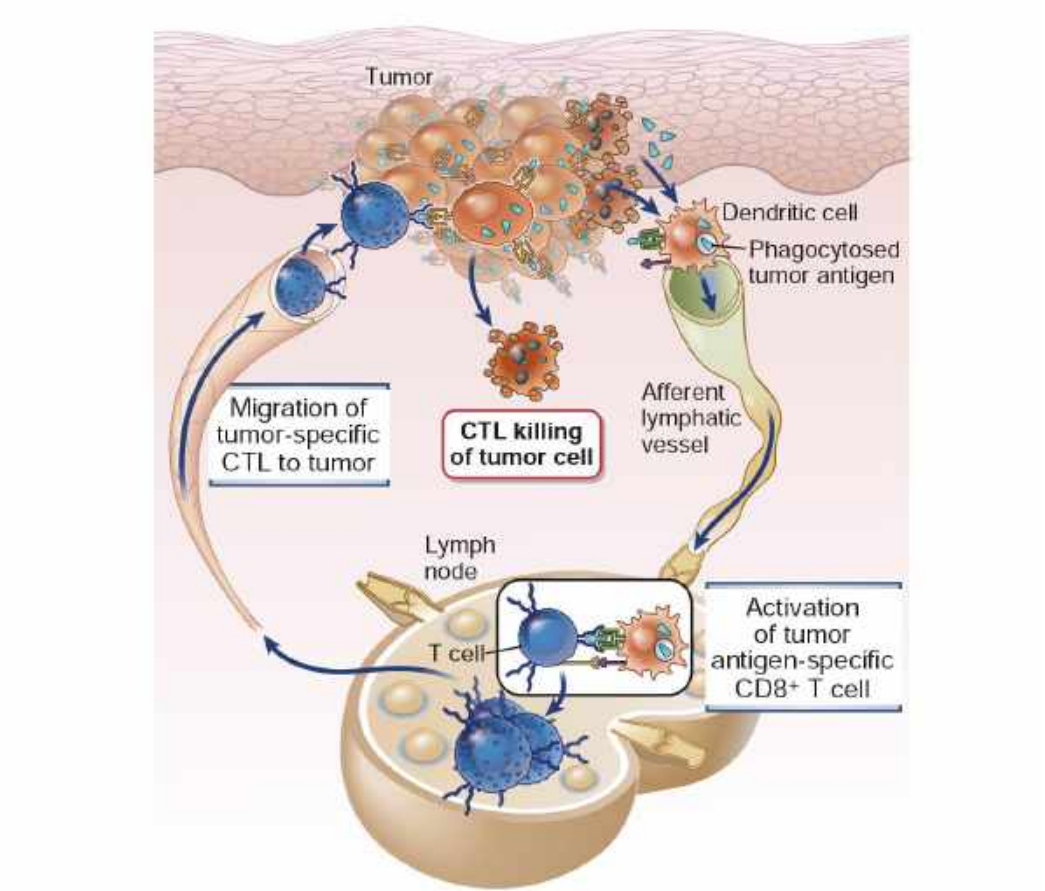
T cell-targeted immunotherapy better than chemotherapy for overall survival

Lancet Oncol. 2022 May; 23(5): 659–670.

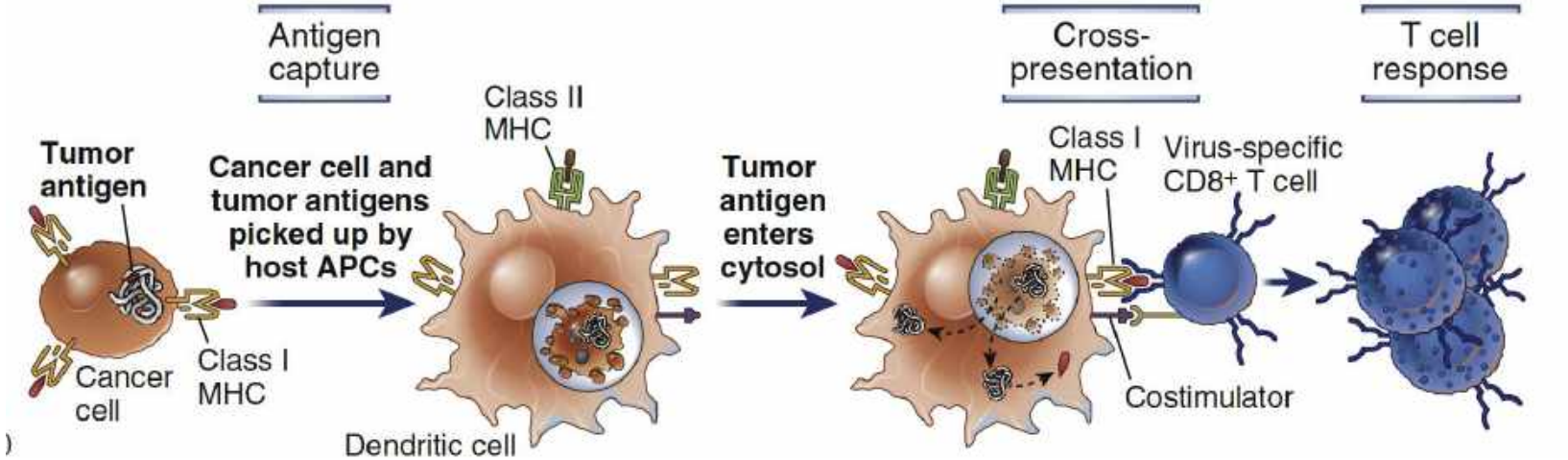
What kind of host immune responses to cancers matter most?

	Anti-tumor	Pro-tumor
Adaptive	 T cells: CD8 CTL > CD4 Th1  Ig /B cells ???	 Regulatory T cells  Th2 cells
Innate	 NK cells ??  M1 Macrophages	 M2 Macrophages/ TAM  PMN/MDSC

Steps in a CD8 T cell Response to a Tumor

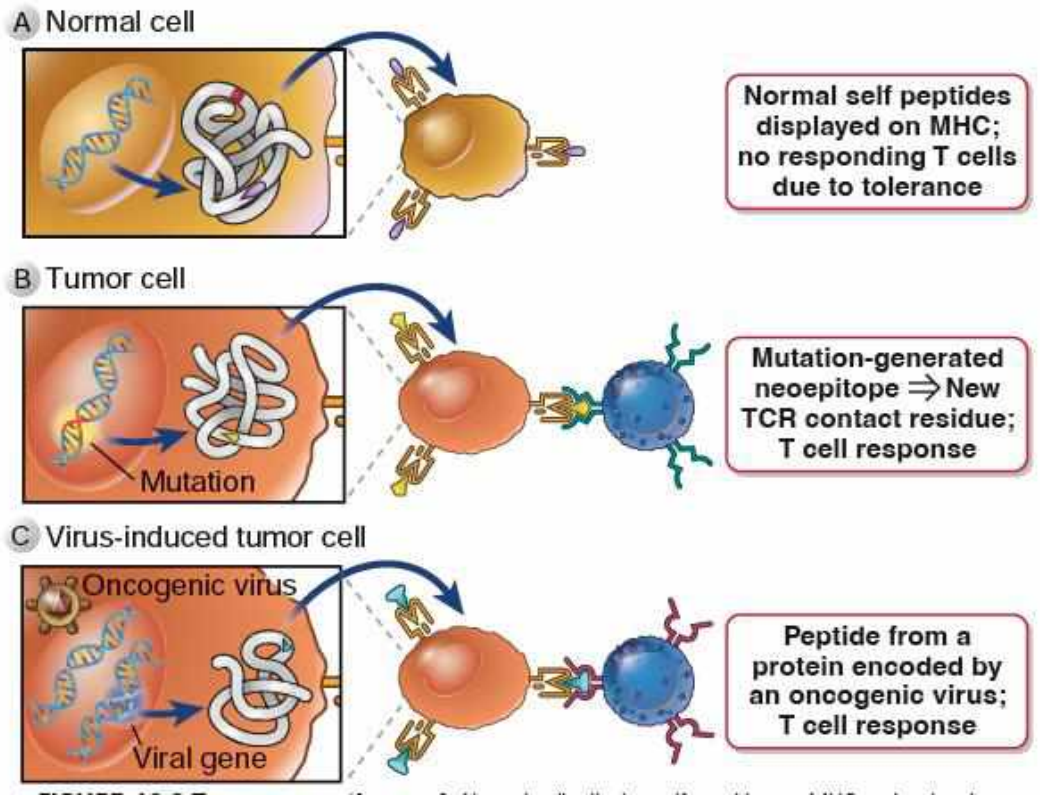


Cross-Presentation of Tumor Antigens



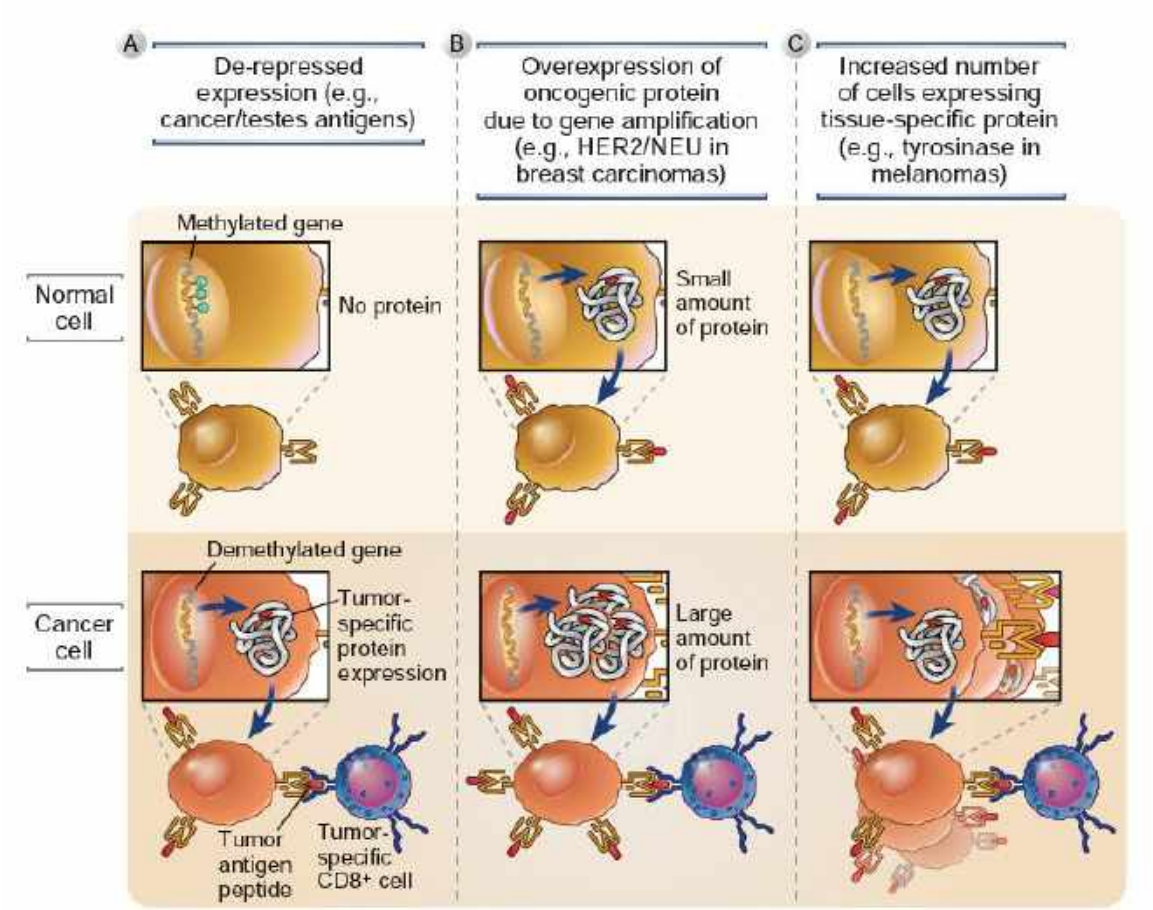
Allows DCs to initiate CD8+ T cell responses to tumor antigens

Types of Tumor Antigens Recognized by T cells: Mutant pertides



- *Cancers are genetically unstable*
- *Some mutations drive malignant phenotype*
- *Many more mutations are random, "passenger"*
- *MHC-binding peptides containing mutations will be seen as foreign, and induce T cell responses*

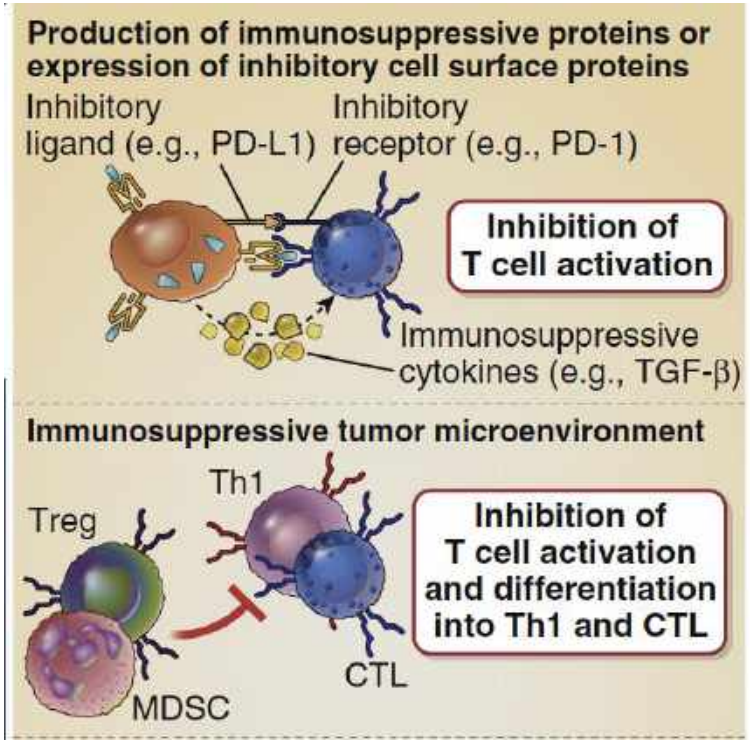
Non-mutated Tumor Antigens Recognized by T cells

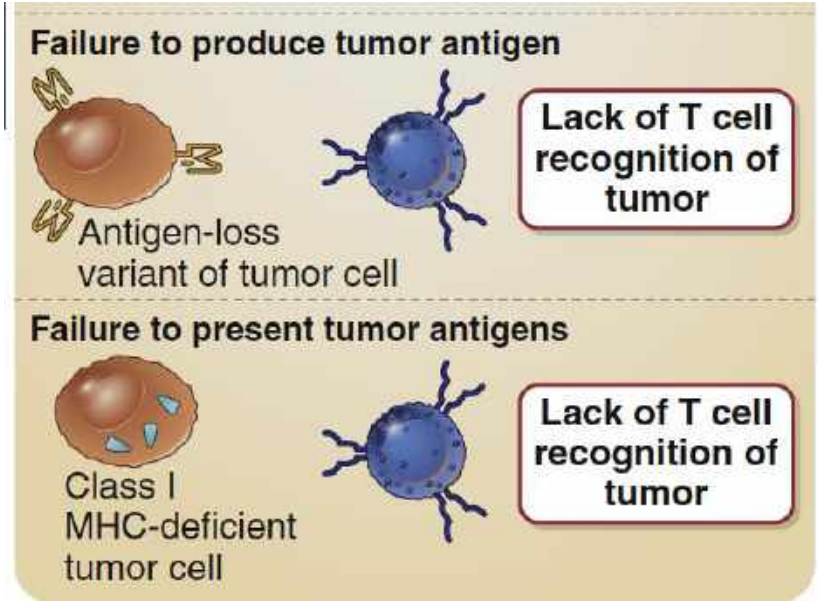


- *Ig and T cell responses to all three can be detected in cancer patients*
- *All three types are targets for immunotherapy*

  NY-ESO-1, MAGE-A,HER2/neu; tyrosinase

Tumors Have Many Ways of Evading the Immune System

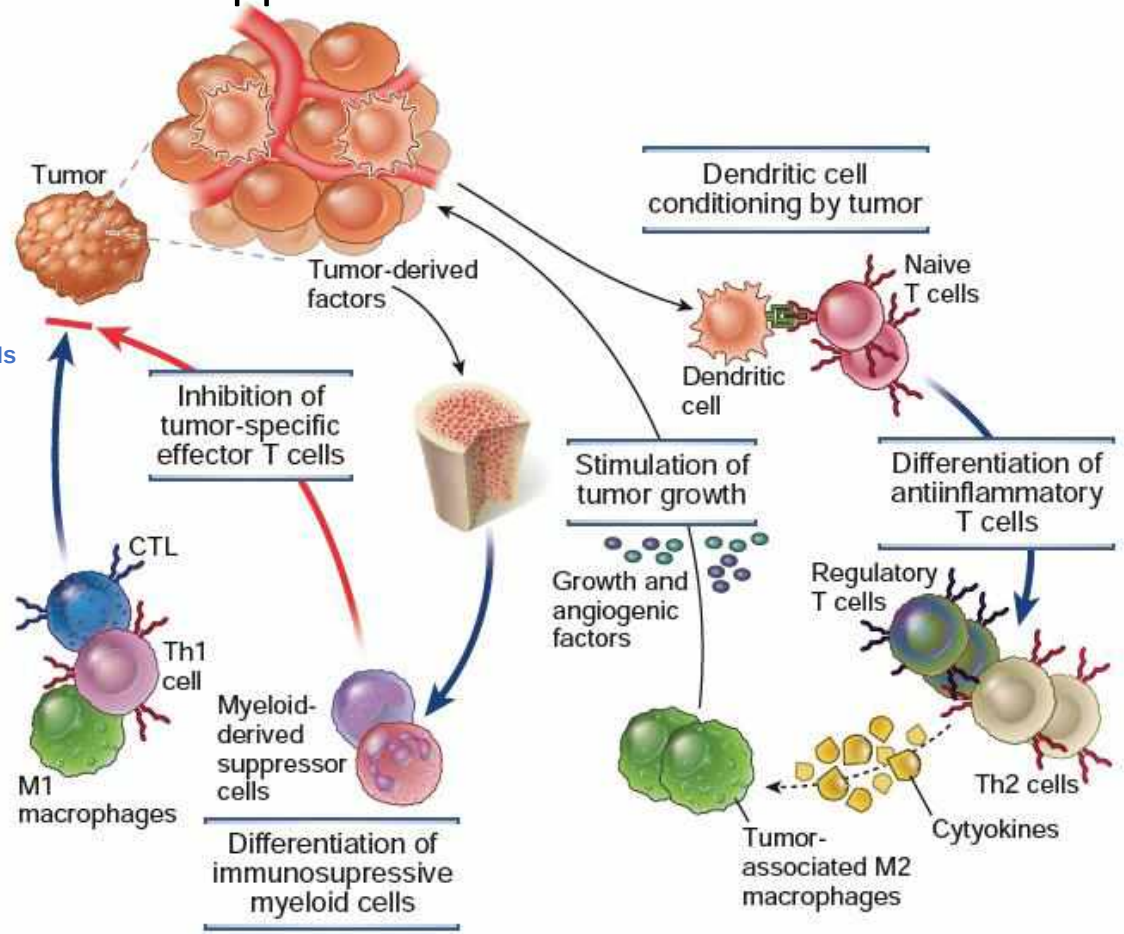




Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2021

Immunosuppressive Tumor Microenvironment

Amino Acid Depletion
Reactive Oxygen Species (ROS)
IL-10 and TGF-beta 1
Inhibition of T Cell Homing to LNs



T Cell Exhaustion

Cancers evade host anti-tumor T cell responses by inducing a dysfunctional T cell state called **exhaustion**.

Exhaustion is ***the progressive decline of T cell function due to chronic TCR stimulation in the setting of persistent antigen exposure.***

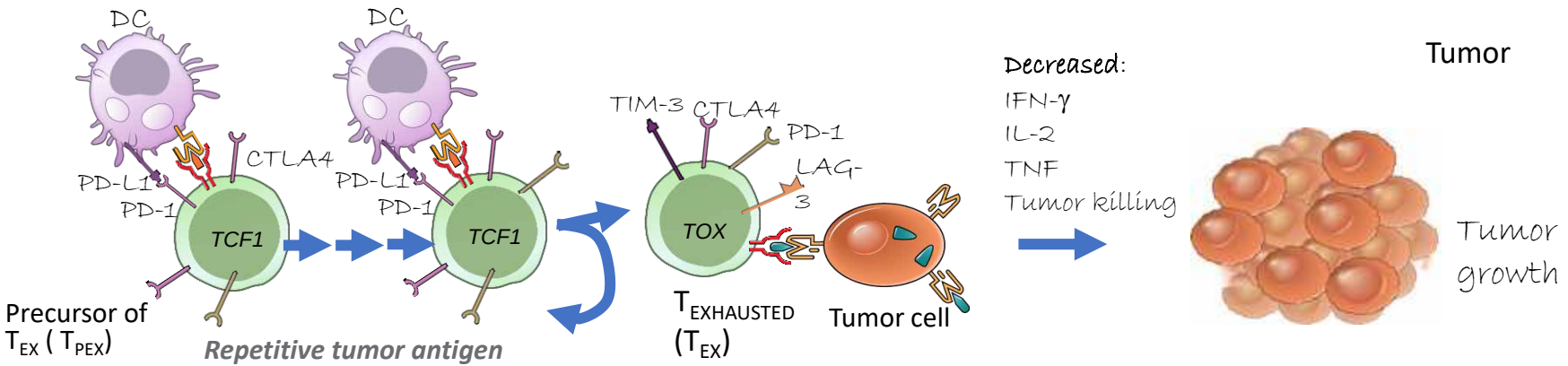
T_{EX} cells show reduced cytokine production and they express inhibitory receptors such as PD-1, CTLA-4 and LAG3.

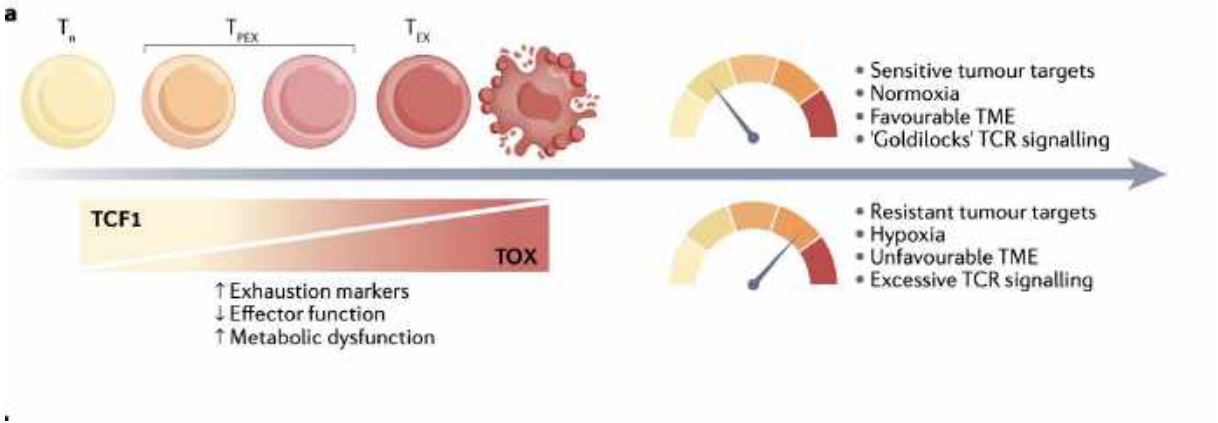
PD-1 contributes to the induction and maintenance of exhaustion.

Exhausted T cells are derived from a stem cell-like precursor which express some of these inhibitory molecules such as PD-1 and CTLA

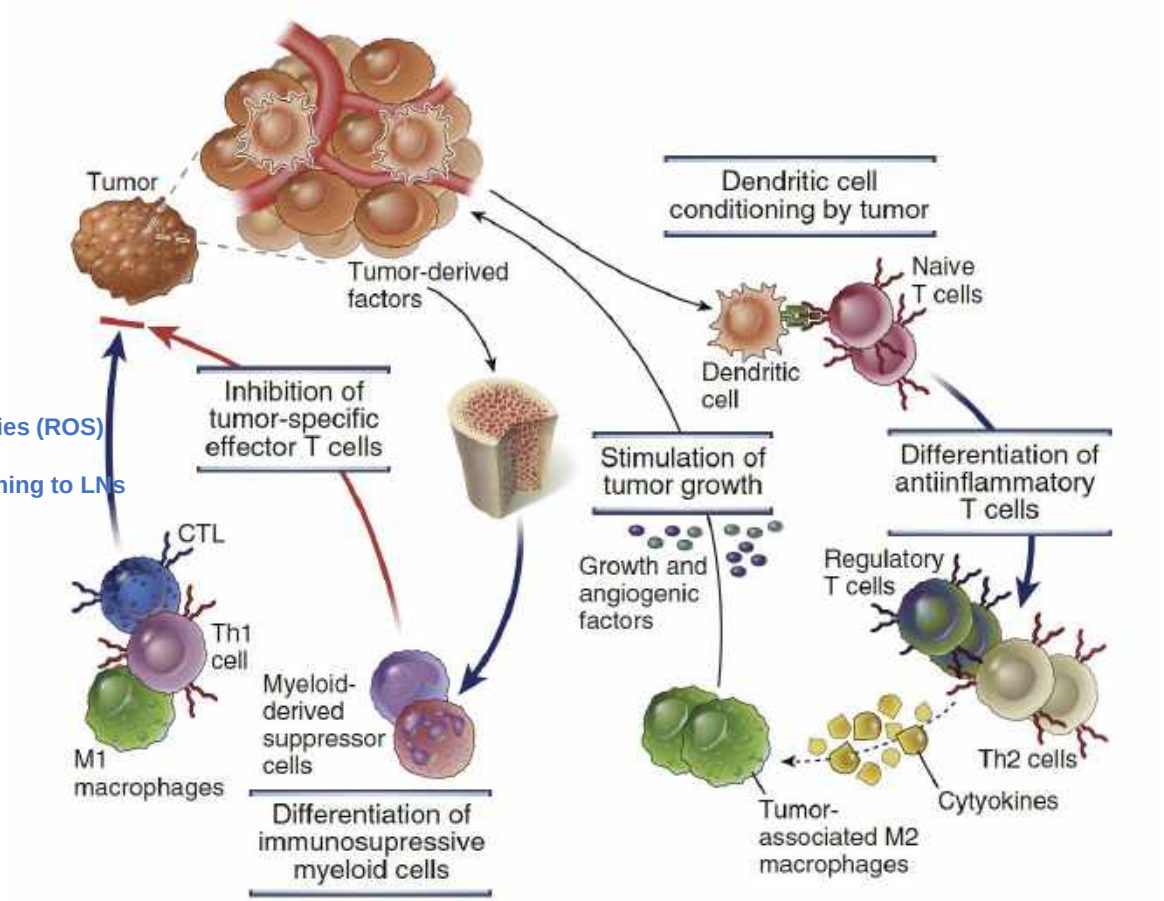
T Cell Exhaustion

Lymph node or TLO





The Immunosuppressive Tumor Microenvironment

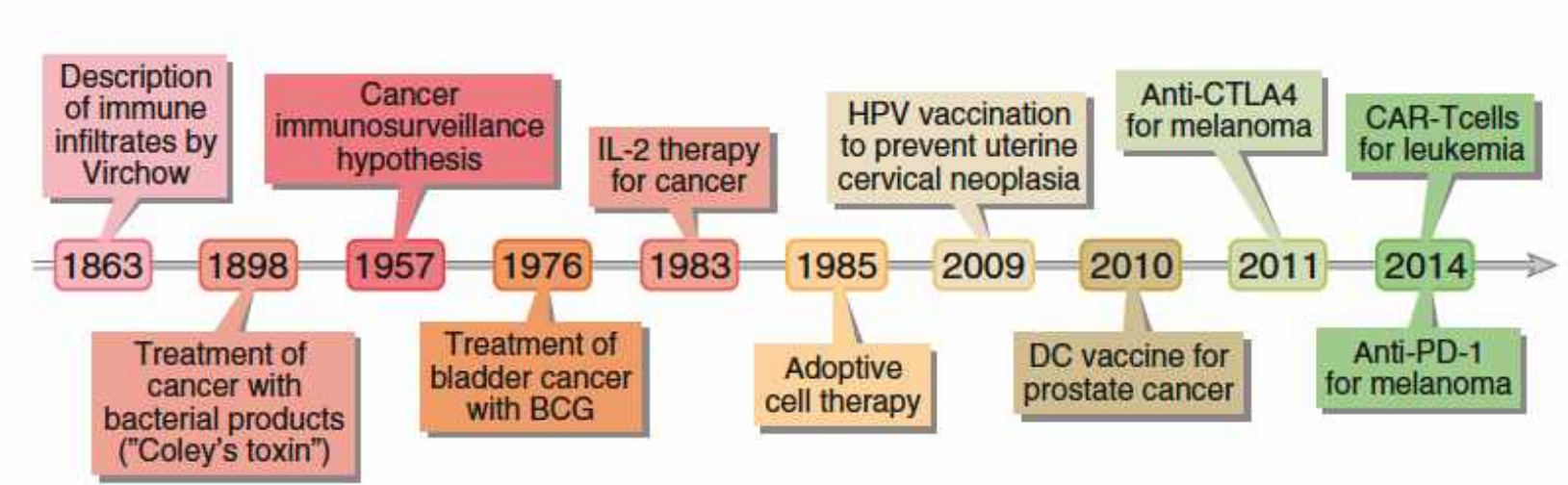


Amino Acid Depletion
Reactive Oxygen Species (ROS)
IL-10 and TGF-beta 1
Inhibition of T Cell Homing to LNs

*Cancers evolve many ways to suppress immune responses, including MDSCs, altered DCs, Treg, M2-like macrophages, others….contributing to a permissive tumor microenvironment (**TME**)*

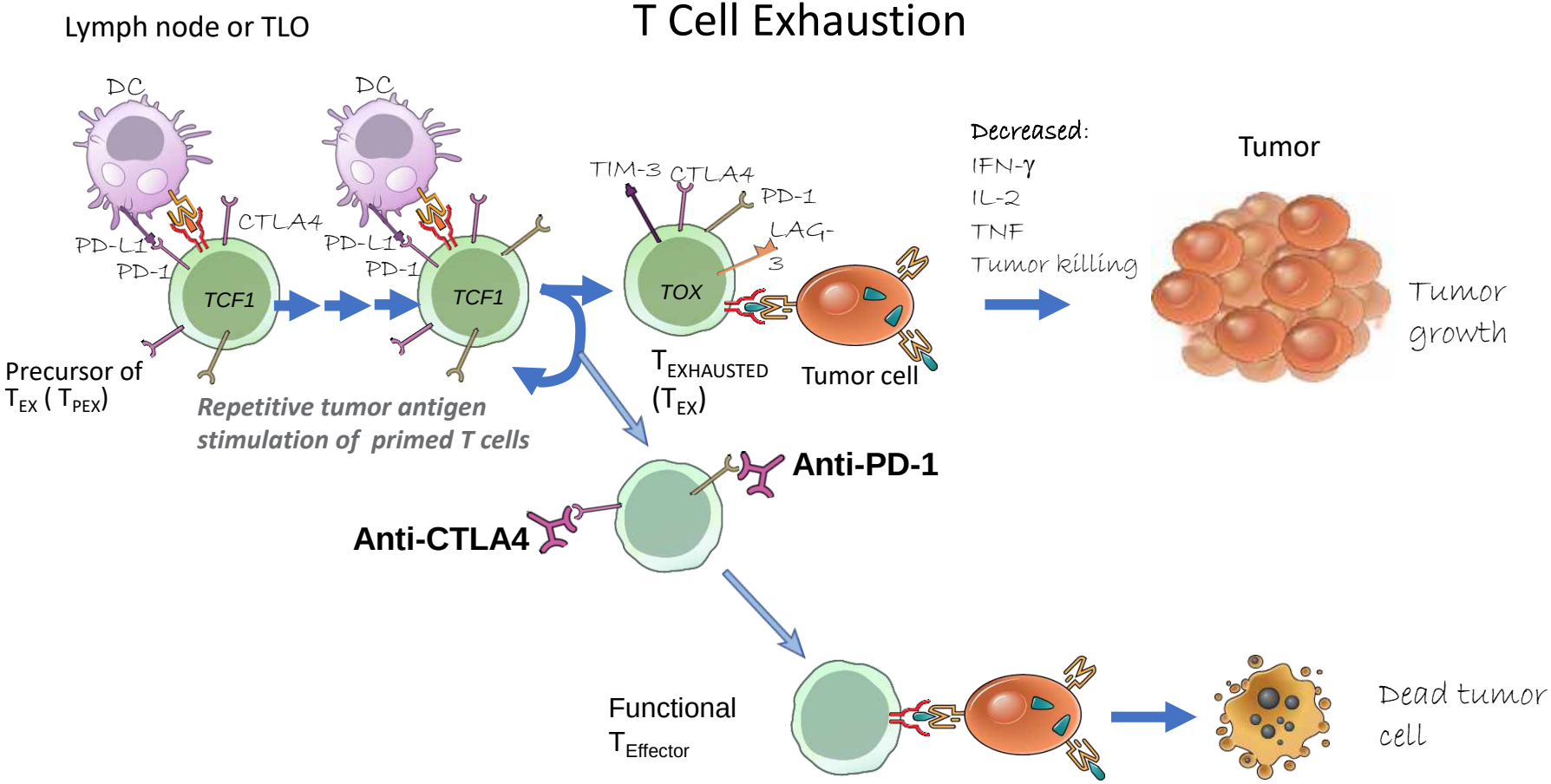
Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2021

History of Cancer Immunotherapy



Abbas, Lichtman, Pillai. Basic Immunology 7 ed. Elsevier. 2023

T Cell Exhaustion

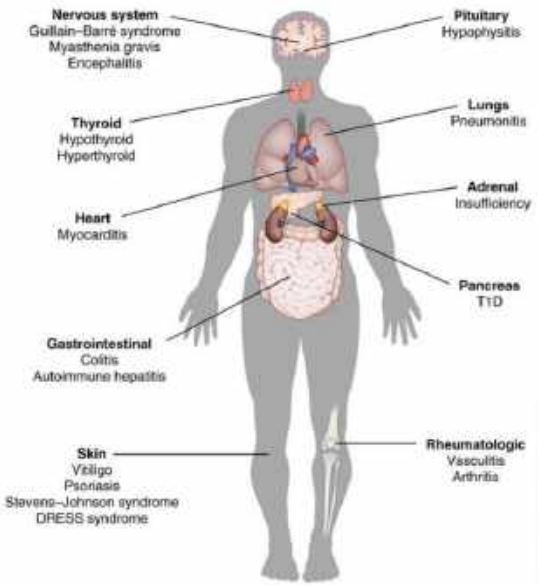


Immune Checkpoint Blockade (ICB) Counteracts a Common Tumor Evasion Mechanism

- Many tumors express checkpoint ligands (e.g. PD-L1) and/or induce expression of checkpoint receptors on T cells (e.g. PD-1).
- Tumor-specific T cells often acquire an exhausted phenotype, in part characterized by upregulated expression of immune checkpoint molecules.
- ICBs are inhibitors of these inhibitors of anti-tumor T cell immunity and can reverse the exhausted phenotype.
- Approved ICB drugs are function blocking monoclonal antibodies specific for CTLA-4, PD-1, PD-L1, LAG-3; clinical trials for others are in progress.
- Melanomas were the first tumors treated by ICBs, but now ICBs (mostly anti-PD-1 or anti-PD-L1) are used for many different tumor types.
- Many patients with metastatic tumors that would have been invariably fatal within months under older therapies have now survived for years on ICB therapy, with no evidence of tumor progression.

Challenges to Overcome in ICB Therapy

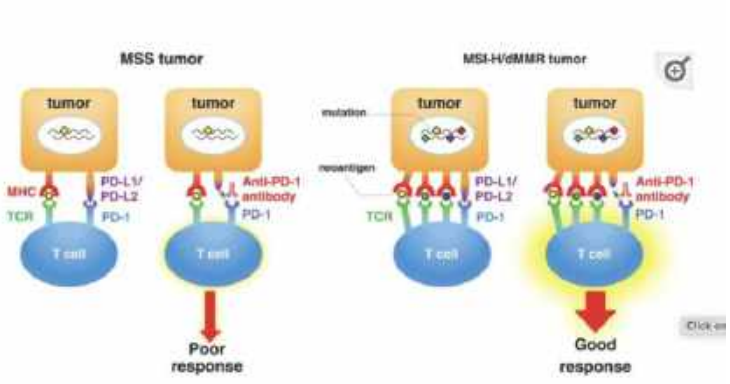
- Overall, only ~15% of ICB-treated patients respond to ICB therapy; why is not clear.
  - How to predict who will respond? (e.g. neoantigen burden)
  - How to convert non-responders to responders? (e.g. make tumors ”hot”)
  - Use of combinations of ICBs or ICB plus other types of therapies ? (ICB angiogenesis inhibitors)
- ~ 50% of ICB treated patients develop immune related adverse events IRAEs. (Autoimmunity is a predictable complication given that the checkpoint molecules’ normal functions are to prevent autoimmunity)
  - How do we predict who will develop IRAEs?
  - How can IRAEs be treated or avoided
  - What do IRAEs teach us about autoimmunity?
- Many responders will eventually suffer recurrences of tumor.
  - What are the mechanisms of developed resistance to ICB therapy?
  - How can this resistance be overcome?



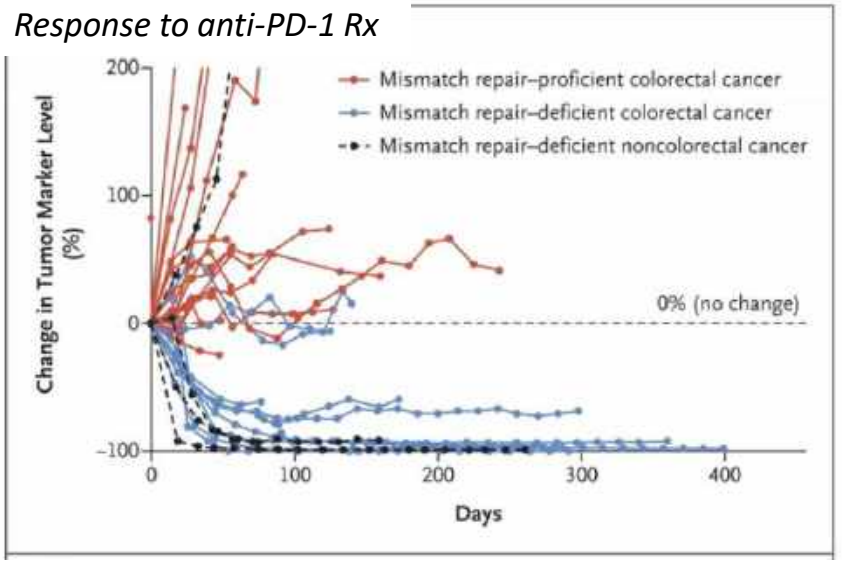
From: June, Warshauser and Bluestone Nat Med 2017

High Mutational Burden Predicts Responsiveness to ICB Therapy

- Mismatch repair deficiency/ microsatellite instability in tumors is associated with high mutational burden.
- High mutational burden leads to more frequent T cell responses, and more likely tumor evasion through checkpoint inhibitor pathways.
- ***FDA has approved anti-PD-1 therapy for any MMR-deficient tumor, regardless of histological type.***
- Suggests that making immunologically cold tumors more antigenic, via radiation or chemotherapy will improve responsiveness to ICB

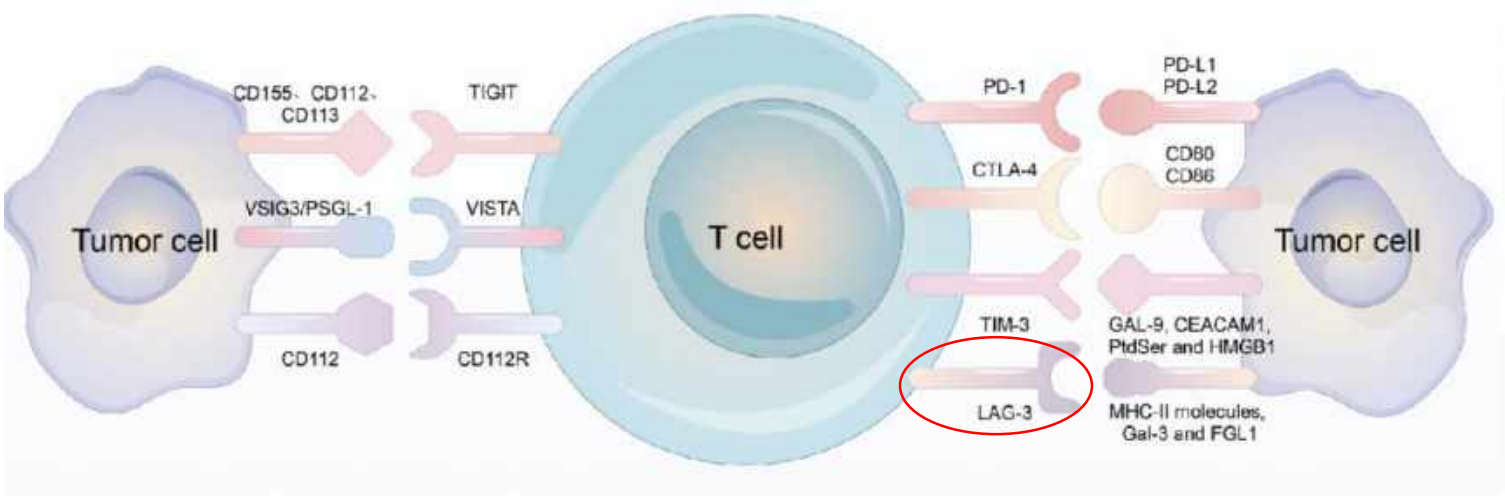


Response to anti-PD-1 Rx



Li et al. N Engl J Med 2015 DOI: 10.1056/NEJMoa1500596

Other T cell Checkpoint Molecules



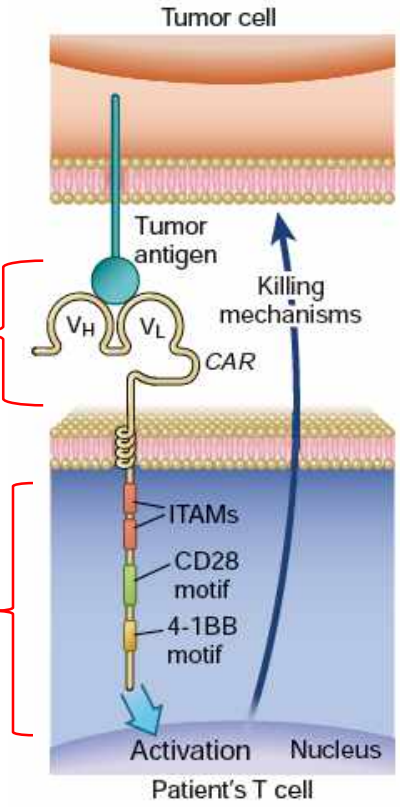
Guo et al. Fronteirs Cancer Immunity and Immunotherapy . Volume 14 - 2023 | https://doi.org/10.3389/fimmu.2023.1121285

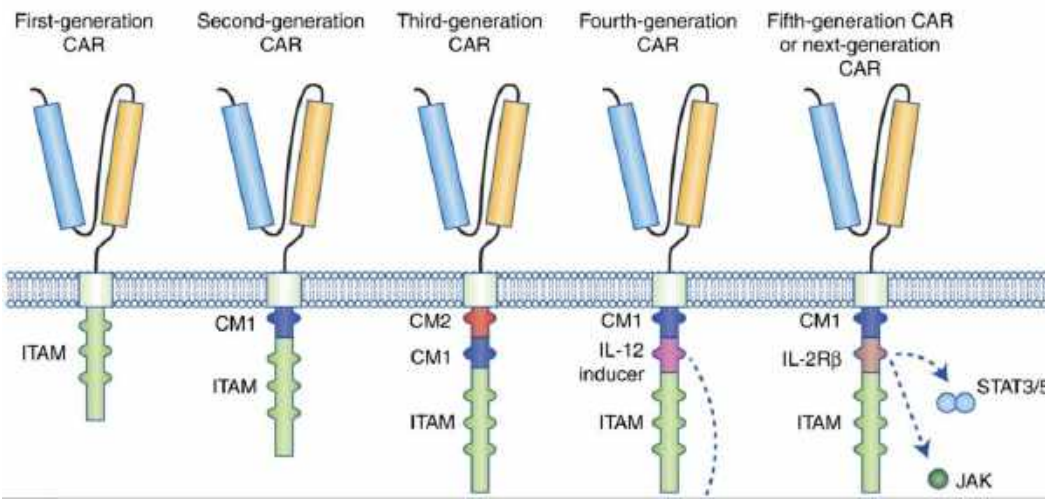
Nivolumab and Relatlimab (anti-PD-1 + anti-LAG3 mAbs) –*FDA approved to treat melanoma in 2022*

Chimeric Antigen Receptor T Cells

Antigen Recognition: Antibody-like single chain variable fragment (no MHC restriction)

CARs use signaling motifs from TCR complex and costimulatory receptors to activate the T cells

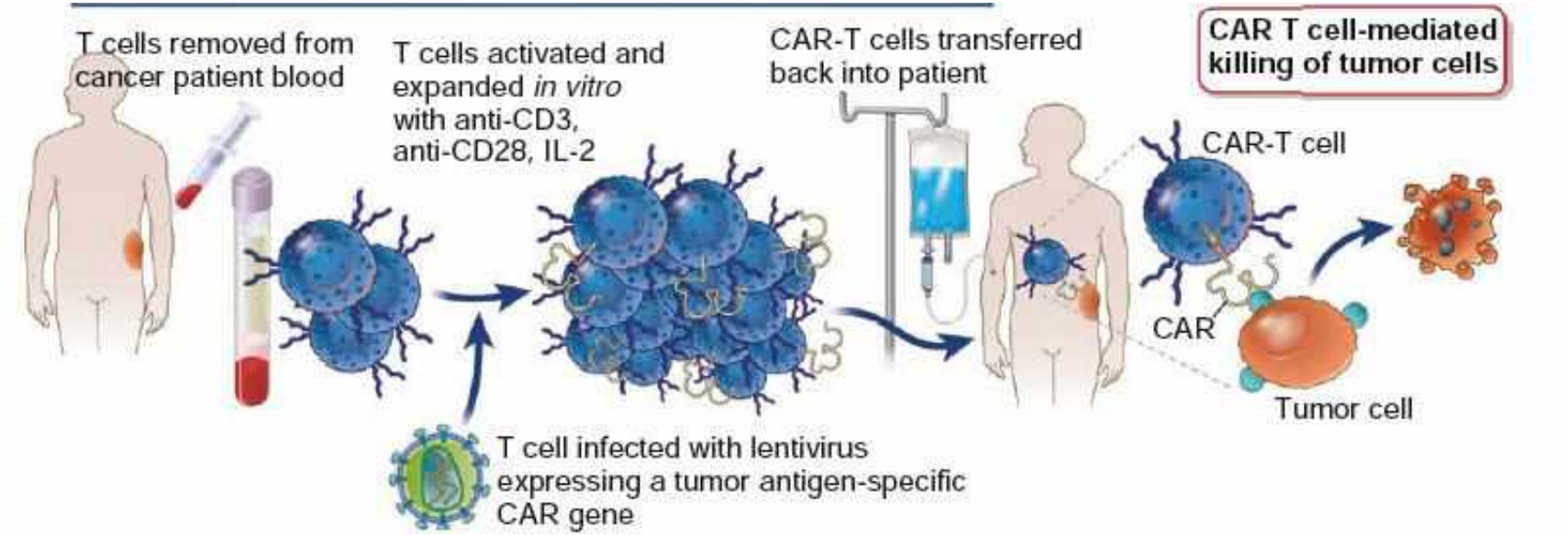




Tokarew *et al. Br J Cancer* **120**, 26–37 (2019)

- Does not require MHC restricted recognition to activate the T cells
- Target could be any cell surface protein on tumor cells
- Modifications of signaling domain can improve function: ”armored CAR” and TRUCK (T cells redirected for universal cytokine-mediated killing) CARs

CAR T Cell Therapy

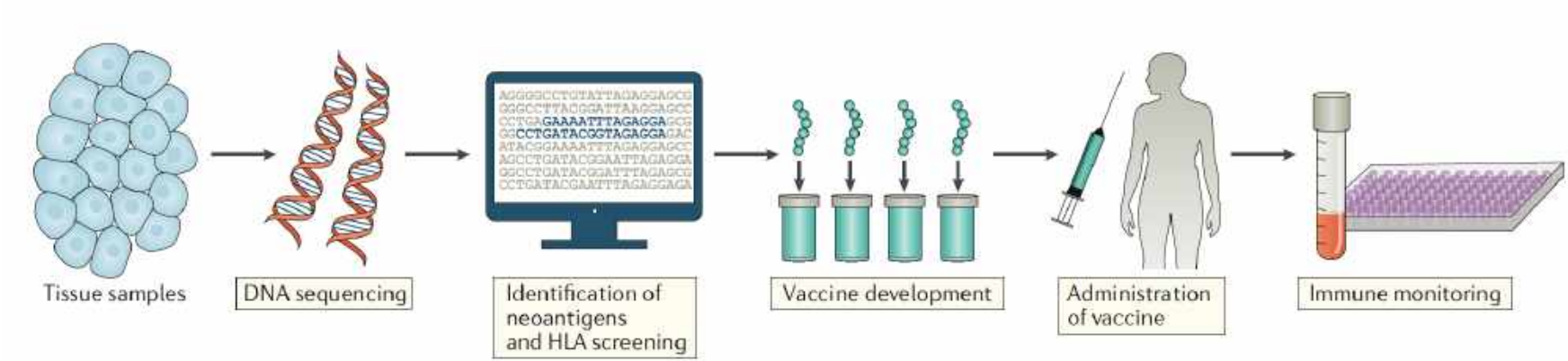


- "Living Drug"- long lived memory/effector T cells present years after treatment
- Unprecedented cures of refractory/relapsed childhood B cell leukemias
- Long term remissions of refractory/relapsed B cell lymphoma, multiple myeloma

Limitations and Challenges of CAR-T Cell Therapy

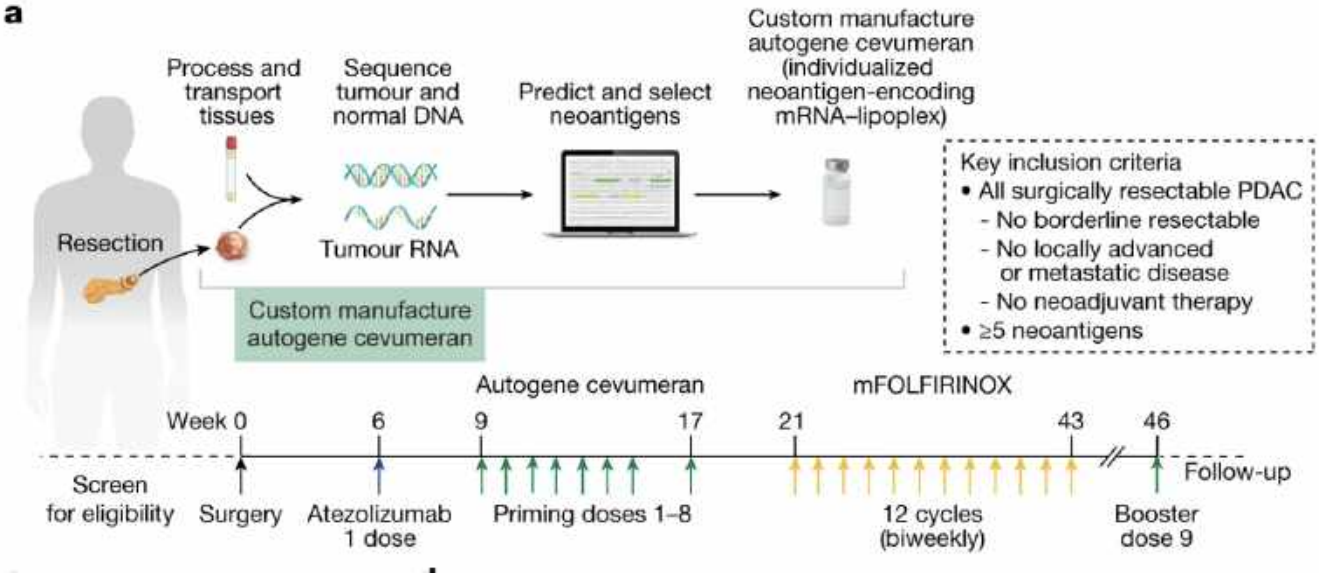
- Cytokine release syndrome – many T cells respond to target antigen, activate macrophages
  - Requires anti-inflammatory therapy (e.g. anti-IL-6R)
  - Risk of long-term damage (especially brain)
- Will tumors lose target antigen and develop resistance?
- Finding target antigens specific for tumors, not normal cells
  - Target pairs of antigens dual specificity CARs?
- Technical and regulatory challenges of producing genetically modified CAR-T cells for each patient
  - Prospect of gene-edited “universal” CAR-T cells?
- Exhaustion of transferred T cells
  - Use CRISPR gene editing to delete PD-1 or genes regulating exhaustion from T cells
- Only proven effective in B cell derived tumors (CD19 specific CARs for leukemias and ymphoma, BCMA specific CARs for MM)
- Impaired migration into and effector function against sold tumors

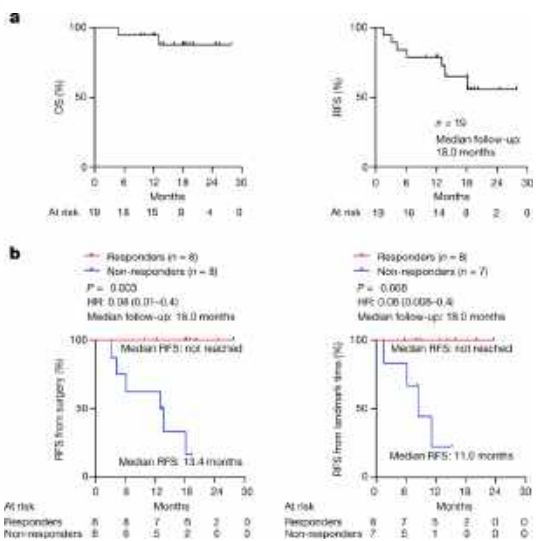
Tumor Neoantigens Personalized Vaccines



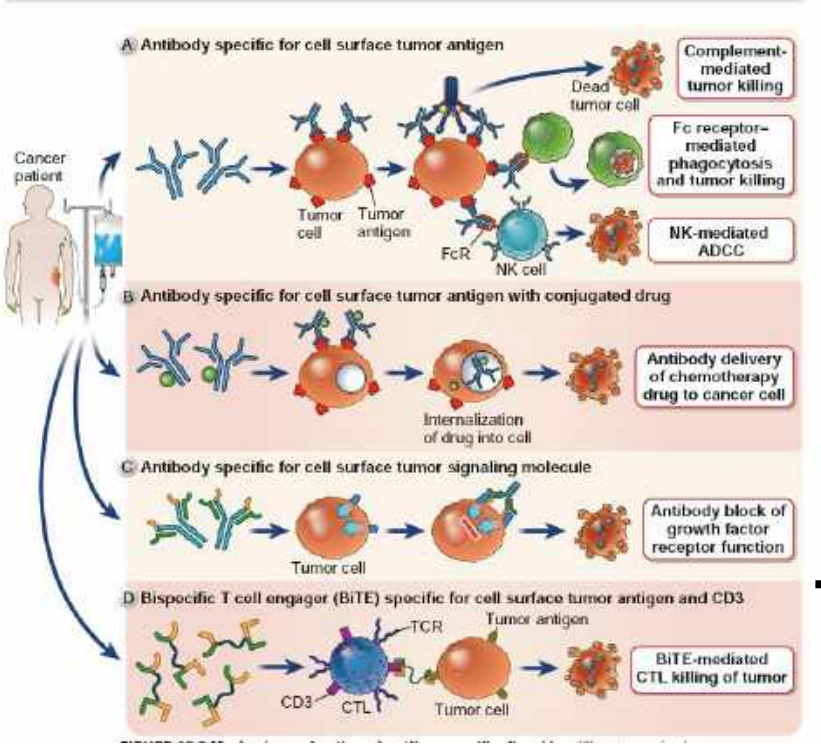
Waldman, A.D., Fritz, J.M. & Lenardo, M.J. A guide to cancer immunotherapy: from T cell basic science to clinical practice. *Nat Rev Immunol* (2020). https://doi.org/10.1038/s41577-020-0306-5

Individualized mRNA neoantigen vaccines for Prostate Carcinoma

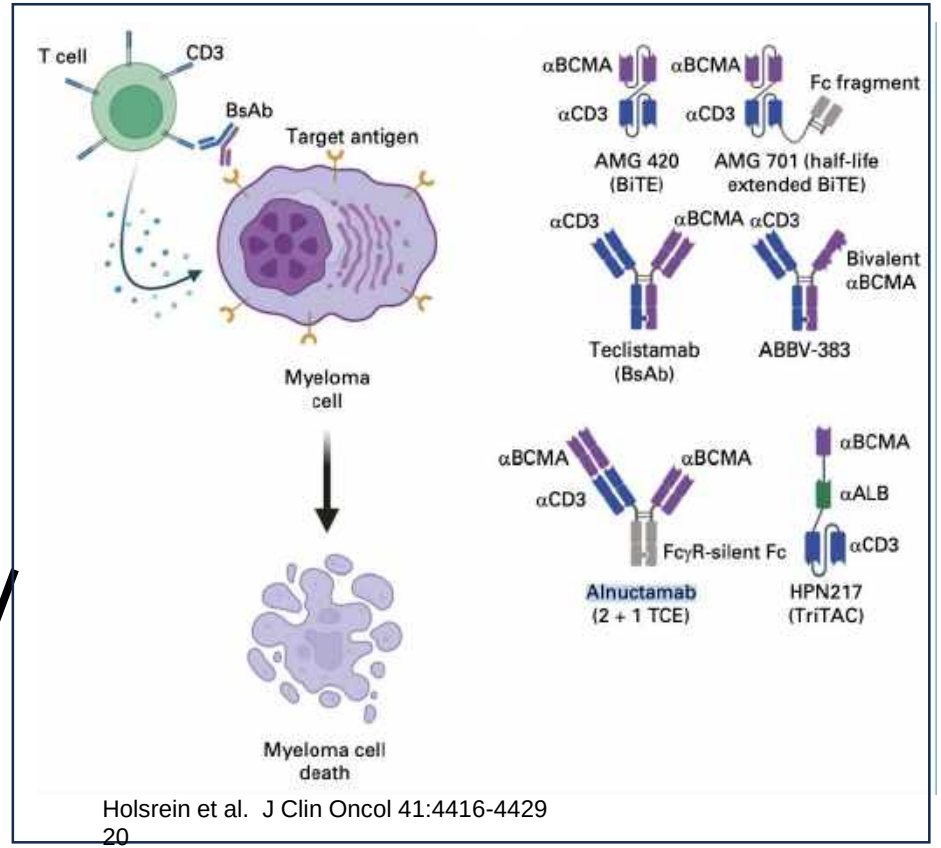




Antibody-based Cancer Therapies



Bispecific Antibodies



Holsrein et al. J Clin Oncol 41:4416-4429