Tumor Immunity and Immunotherapy

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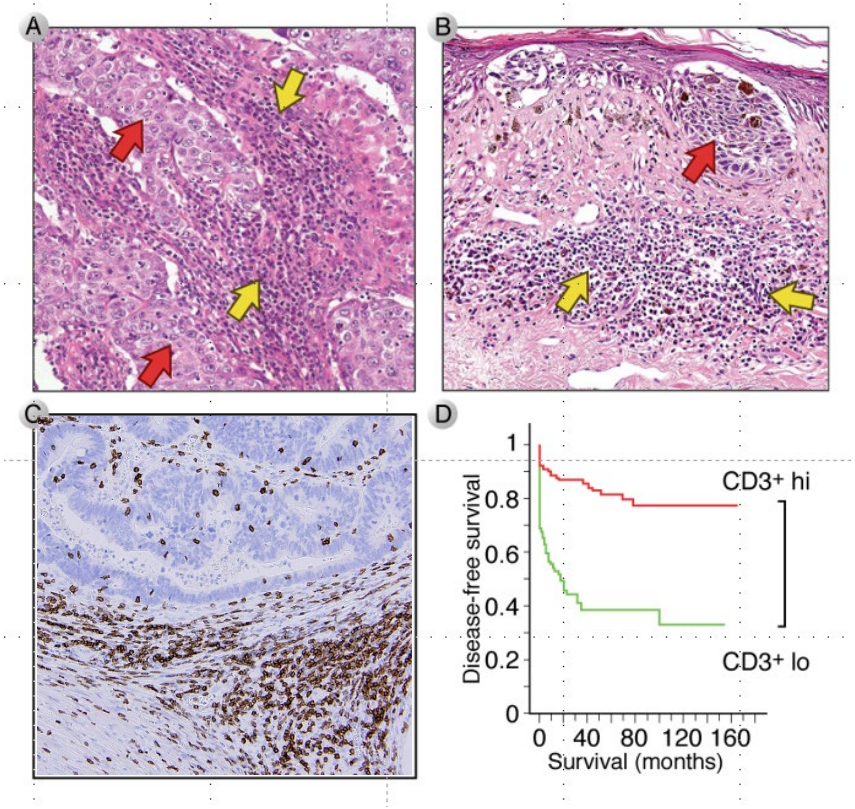
Outline

- 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

Tummor Immunity: General principles

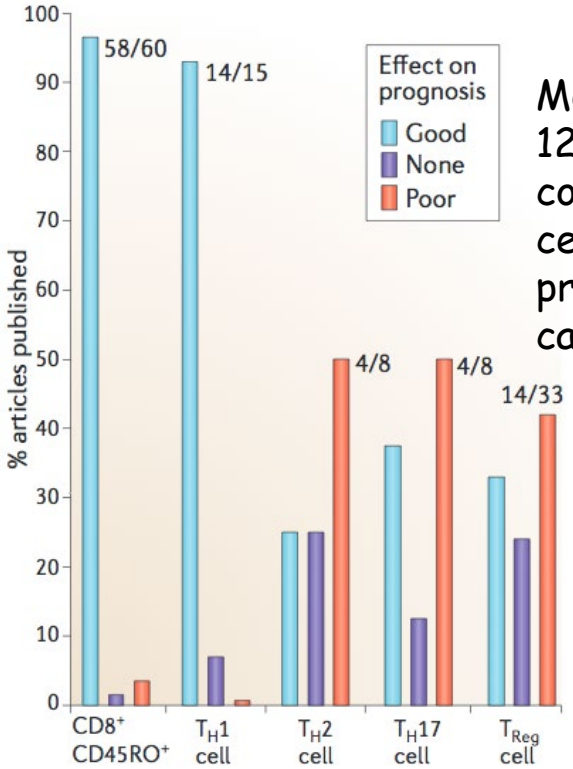
- The immune system recognizes and reacts against cancers
- The immune response against tumors is often dominated by regulation or tolerance
  - Evasion of host immunity is one of the hallmarks of cancer cancer (Hanahan and Weinberg Cell 144:646, 2011)
- Some immune responses promote cancer growth
- Defining the immune response against cancers will help in developing new immunotherapies

T lymphocytes infiltration of tumors improves prognosis



CD3 Stain

Galon J et al.. J. Pathology. 2014 232:199-209.

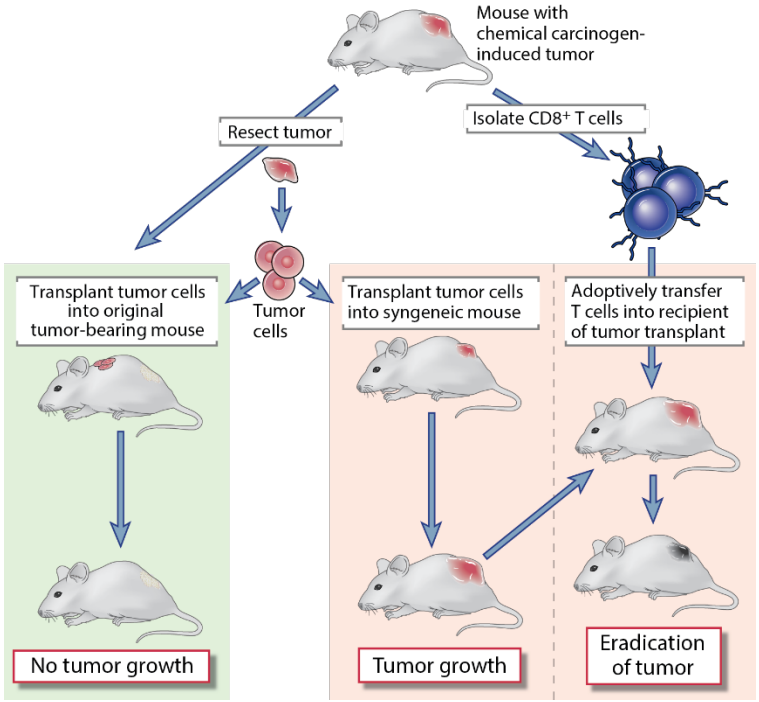


Meta analysis of 124 studies of correlation of T cell subsets and prognosis of 20 cancer types

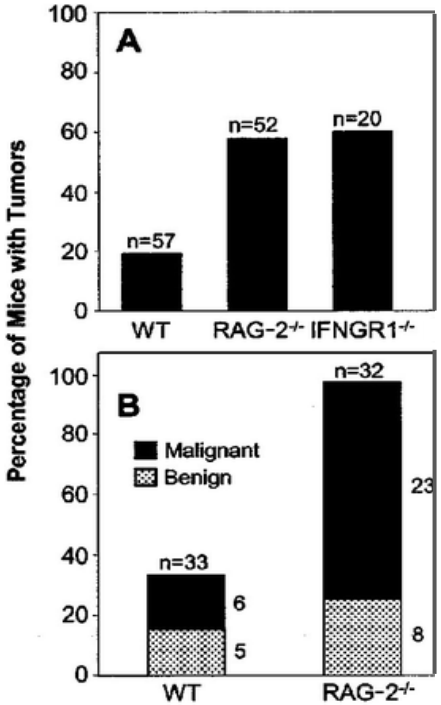
Fridman et al. Nat Rev Cancer 12:298, 2012

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

Rodent Work in Tumor Immunology Established Importance of T Cells



Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2015

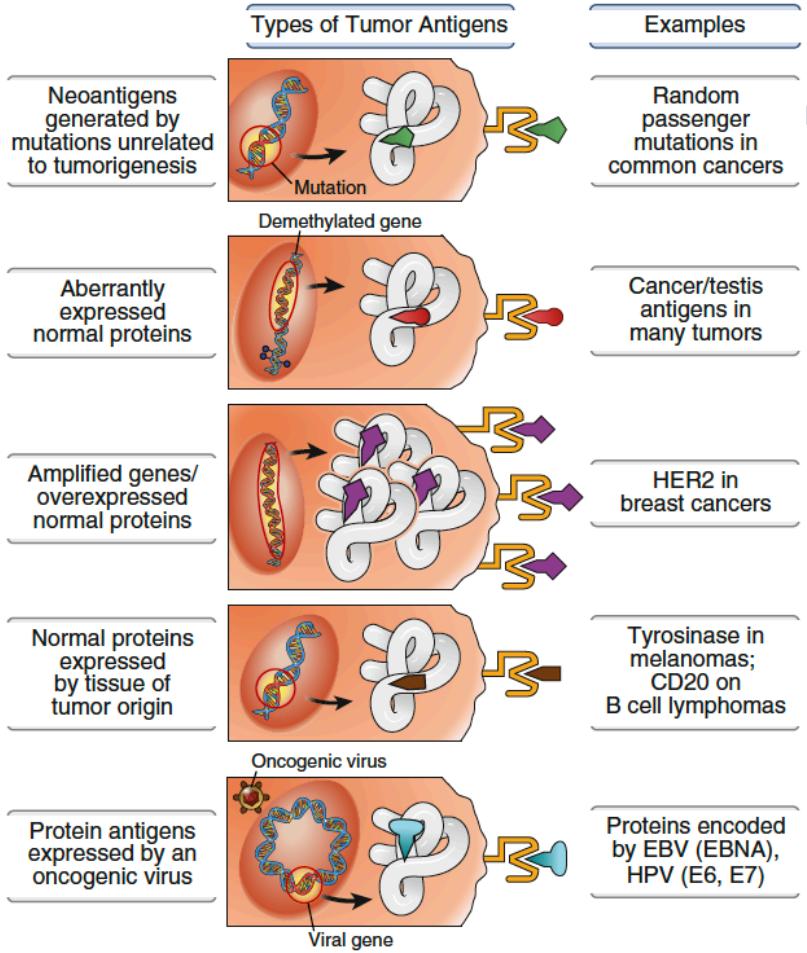


Chemical carcinogen induced tumors

Spontaneous tumors in aged mice

Dunn, Old and Schreiber· Ann Rev Imm 22:329. 2004

Patients' T cells Respond to Unmutated Proteins Expressed by Tumor

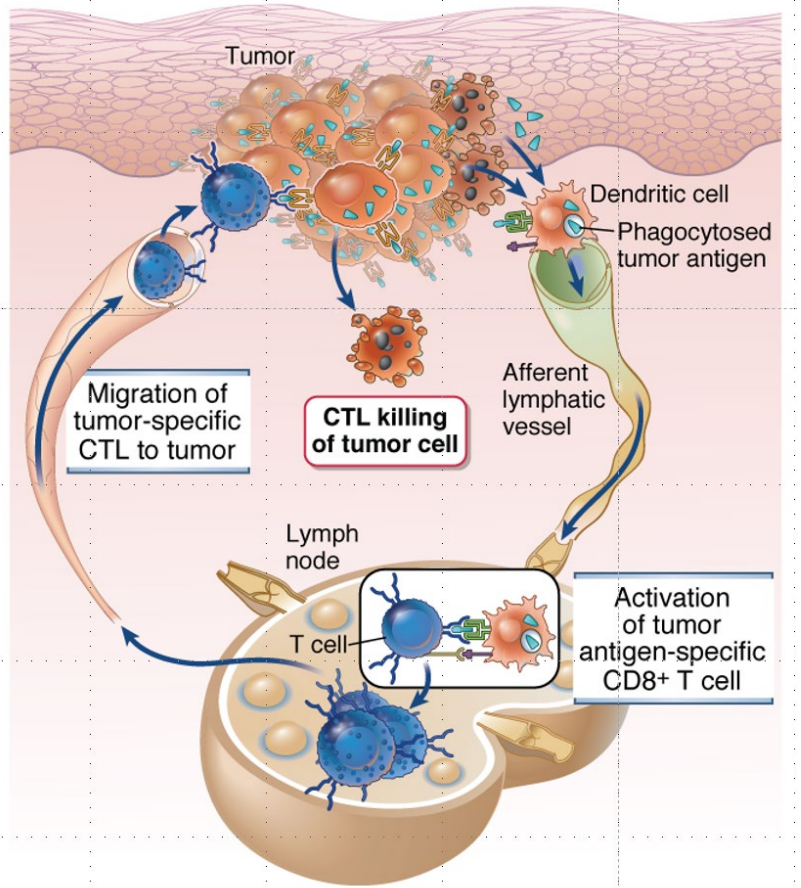


Most tumor antigens that elicit immune responses are neoantigens generated by random passenger mutations (not related to oncogenesis, but are result of genomic instability due to mutations of other genes in cancer cells)

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

Steps in the Generation of an Anti-Tumor CD8+ T Cell Response

Inefficient migration of effector T cells into tumors may impair anti-tumor responses to common cancers

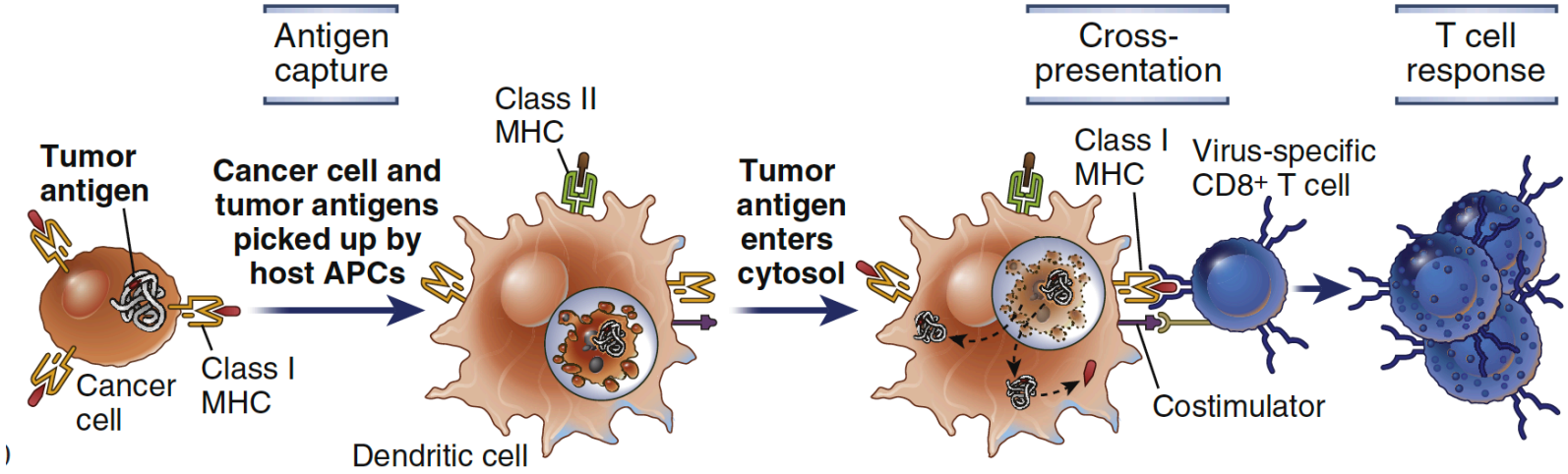


Cell injury/death at tumor site will generate DAMPs that activate DCs

CD4+ T cell responses will also occur; most evidence indicates CTLs are the most important effectors

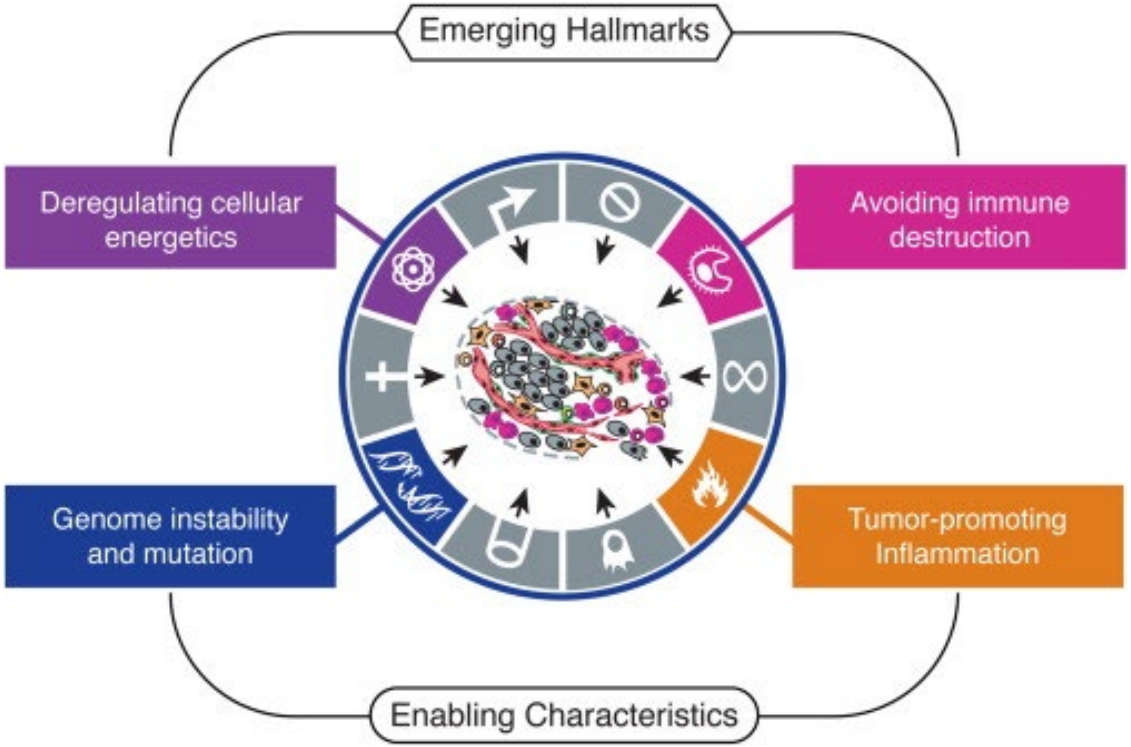
Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017

Cross-Presentation of Tumor Antigens



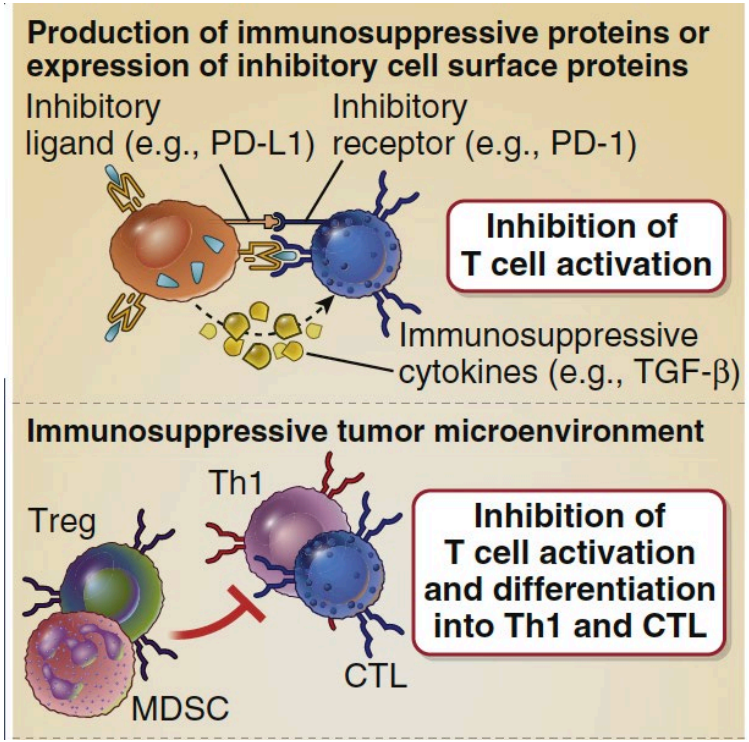
Allows DCs to initiate CD8+ T cell responses to tumor antigens

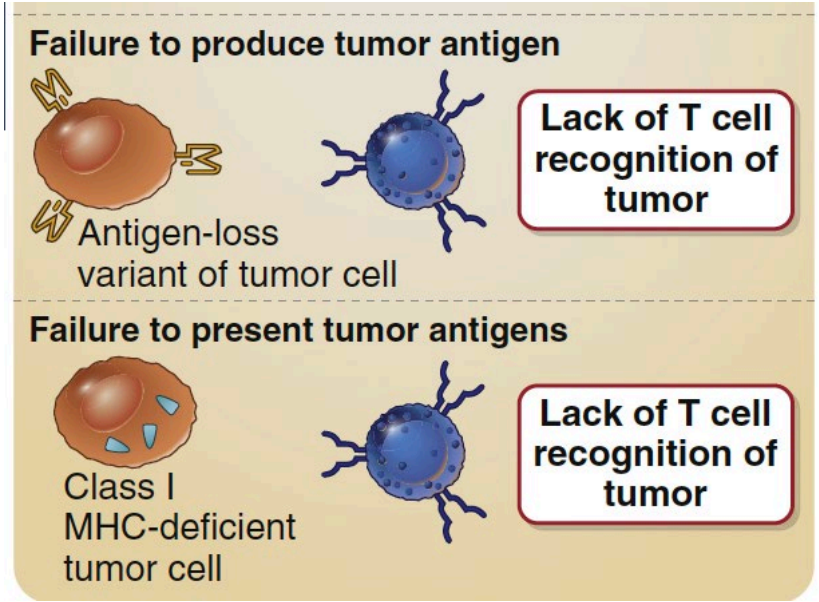
Evasion of the Immune System is a Hallmark of Cancer



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

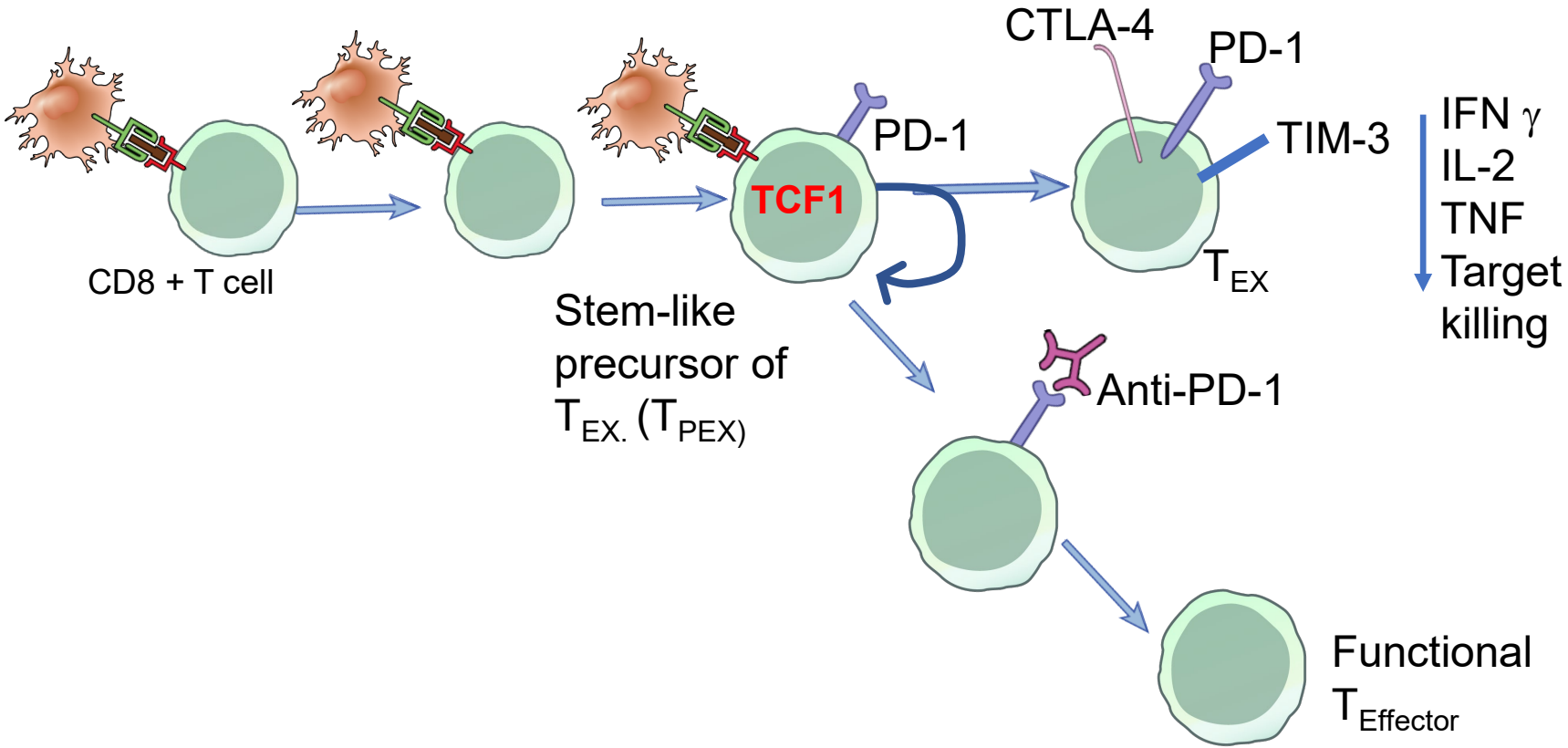
Tumors Have Many Ways of Evading the Immune System



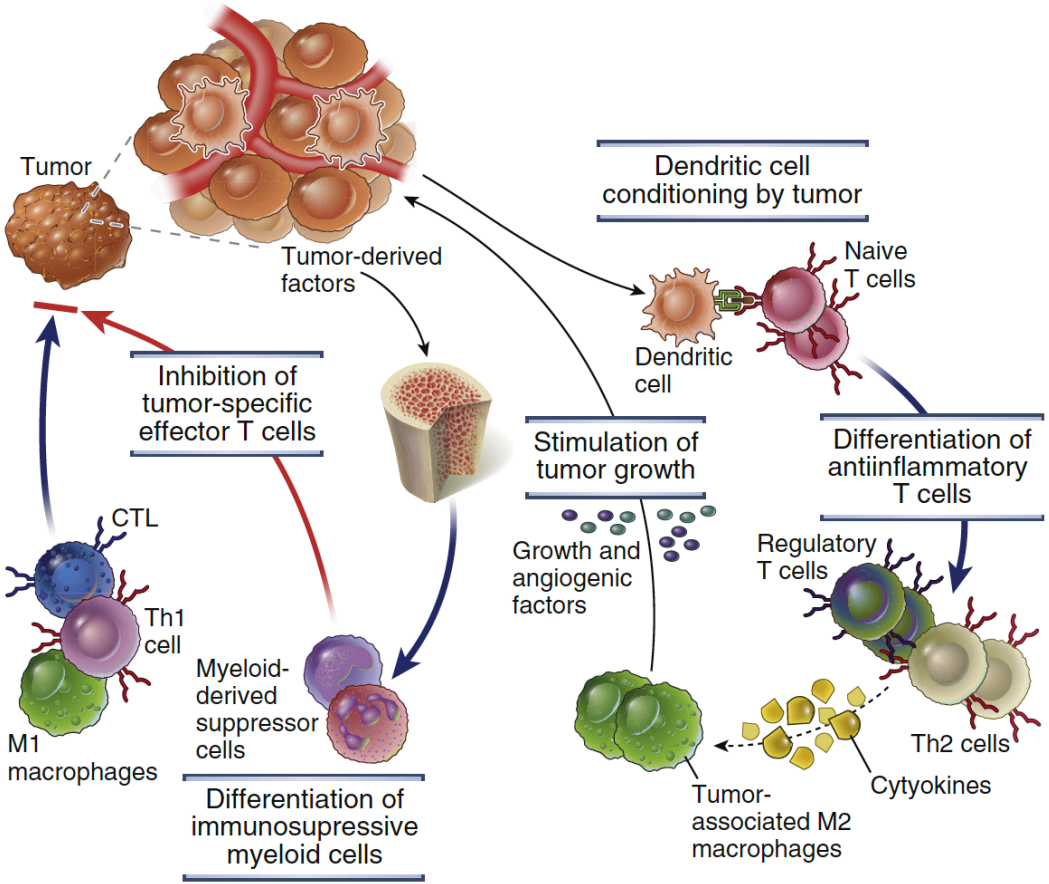


Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2021

Generation of Exhausted T cells and Prevention



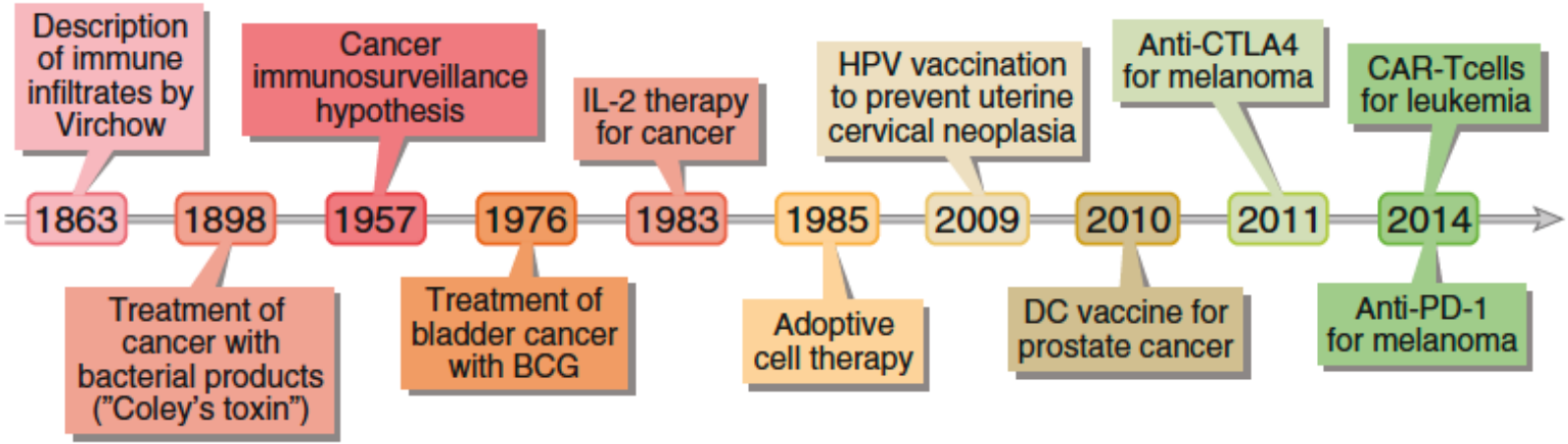
The Immunosuppressive Tumor Microenvironment



Cancers evolve many ways to suppress immune responses, including MDSCs, altered DCs, Treg, M2-like macrophages, others

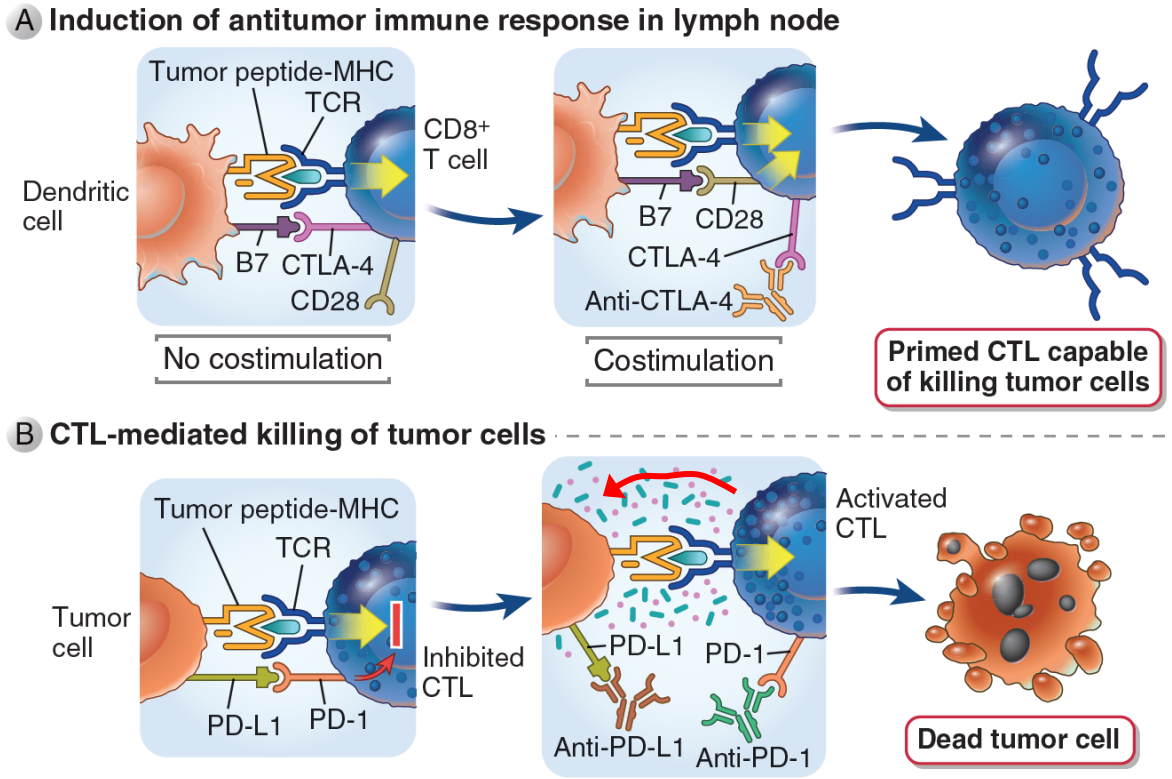
Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2021

History of Cancer Immunotherapy



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

"Immune Checkpoint blockade": Inhibit the inhibitors and increase anti-tumor immunity



CTLA-4 and PD-1 inhibit T cells by distinct mechanisms, thus anti-CLTA-4 and anti-PD-1 work to enhance T cells responses by different mechanisms

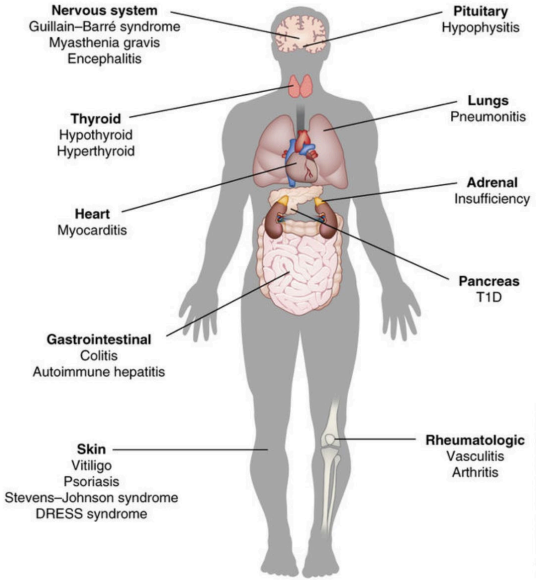
Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2021

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, which is 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, and PD-L1; 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 were invariably fatal within months under older therapies have now survived for years on ICB therapy, with no evidence of tumor progression.

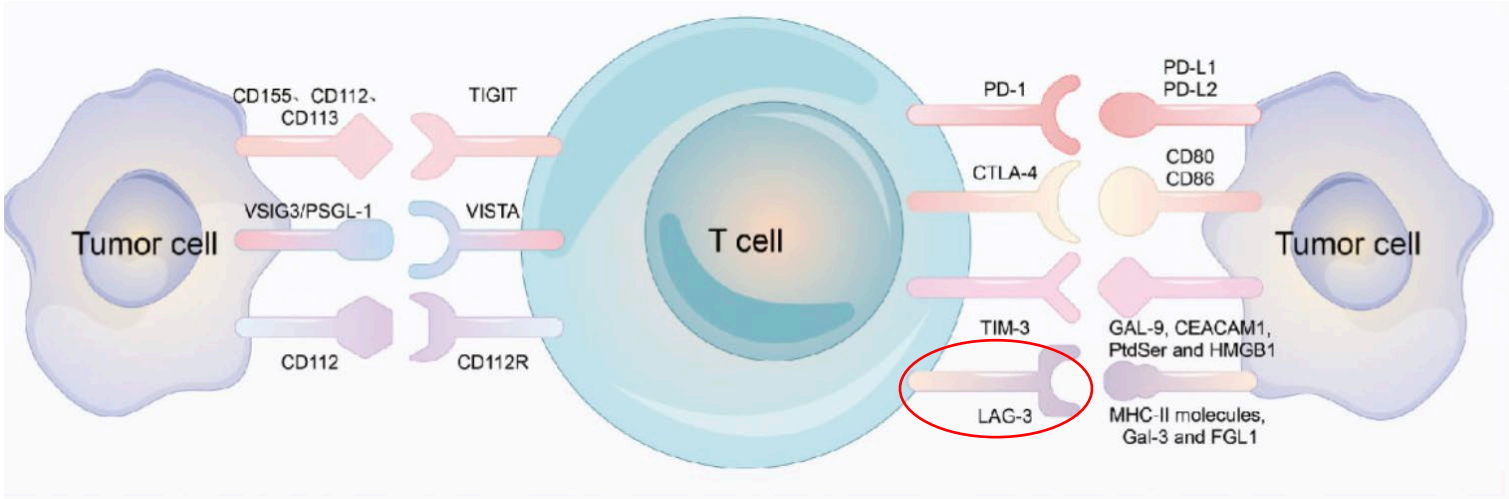
Challenges to Overcome in ICB Therapy

- 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

Other T cell Checkpoint Molecules



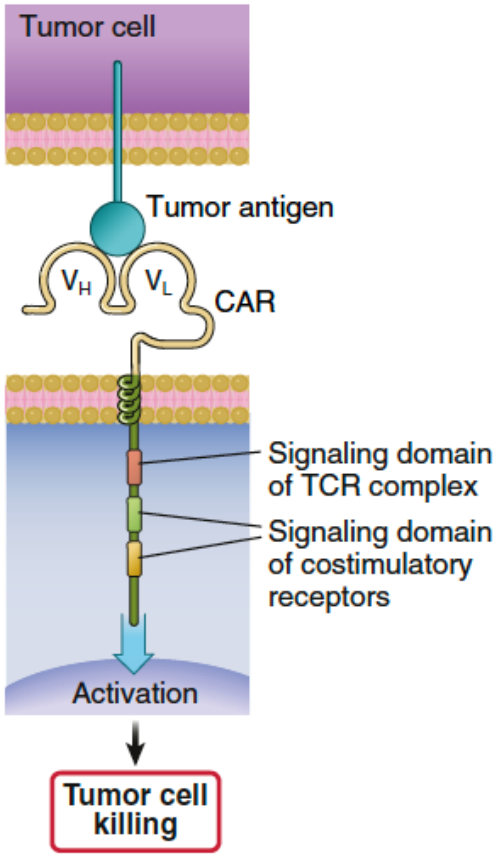
Guo et al. Fronteirs Cancer Immunity and Immunotherapy . Volume 14 - 2023 | https://doi.org/10.3389/fimmu.2023.1121285

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

Chimeric Antigen Receptor Design

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

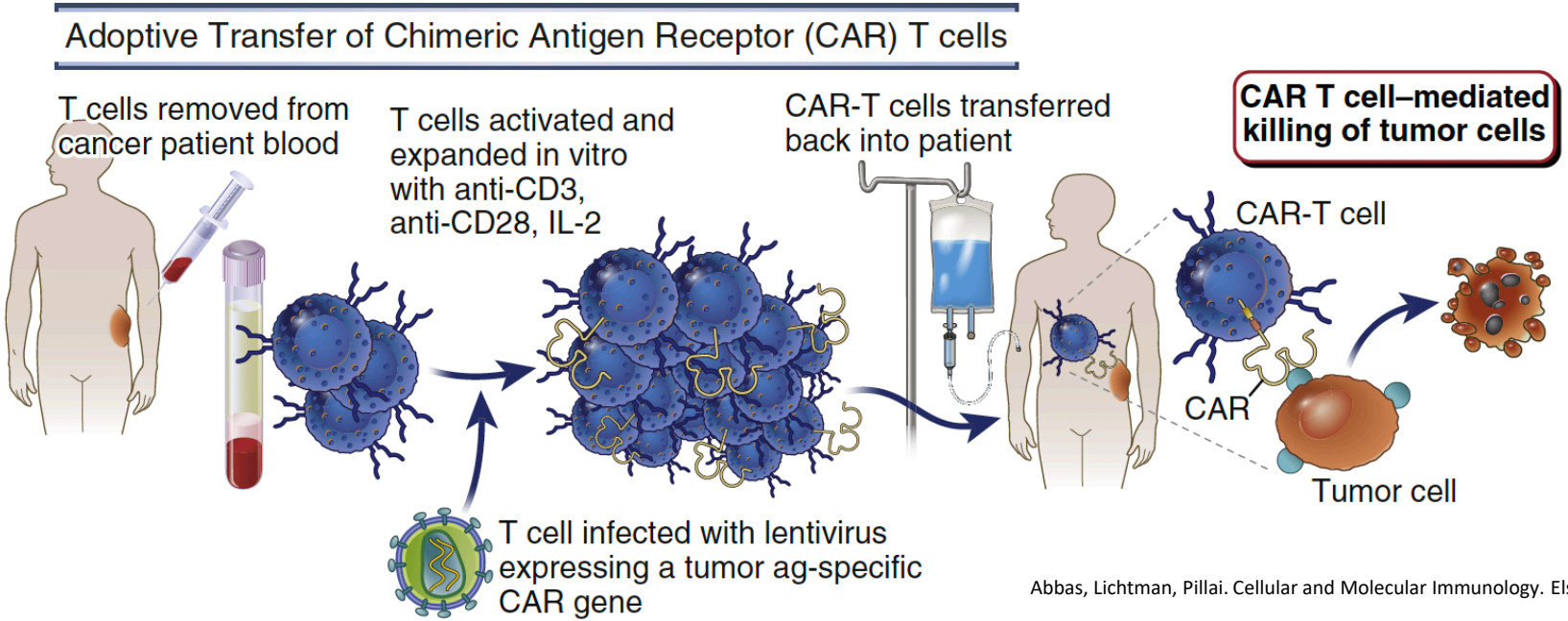
CARs use signaling motifs from TCR complex and costimulatory receptors to activate the T cells



Chimeric antigen receptors (CARs) can make any T cell specific for a tumor antigen

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

Adoptive T Cell Therapy: CAR T cells



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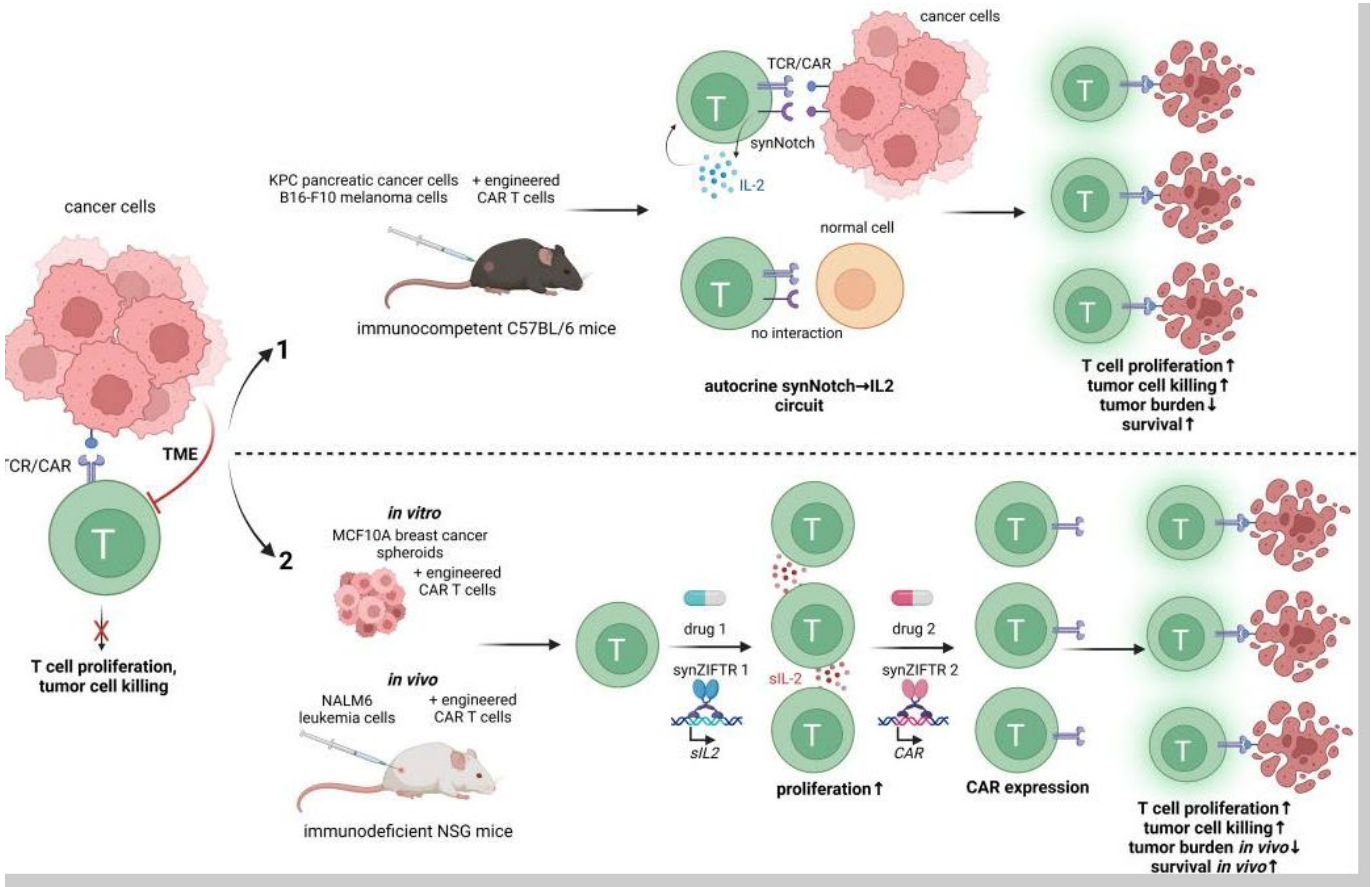
FDA approved CAR-Ts or treatment of B cell-derived tumors: acute lymphocytic leukemias, B cell lymphomas (CD19); and multiple myeloma (targeting BCMA)

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)
- Effectiveness against solid tumors has been limited
  - Problem of T cells entering tumor site
- 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

Future CAR-T Cell Therapies

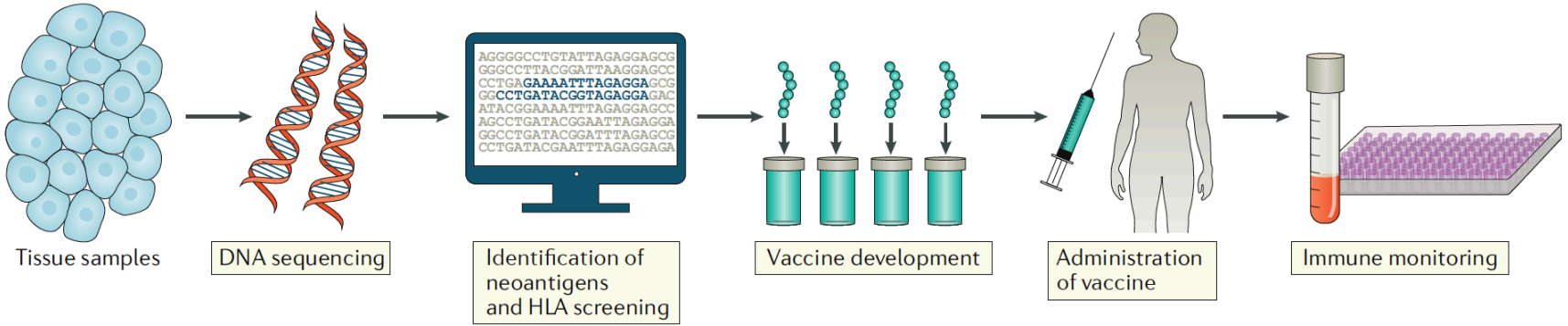


Jessica Hoppstädter and Alexandra K. Kieme. Signal Transduct Target Ther. 2023

Allen, G. M. et al. Synthetic cytokine circuits that drive T cells into immune-excluded tumors. *Science* 2022

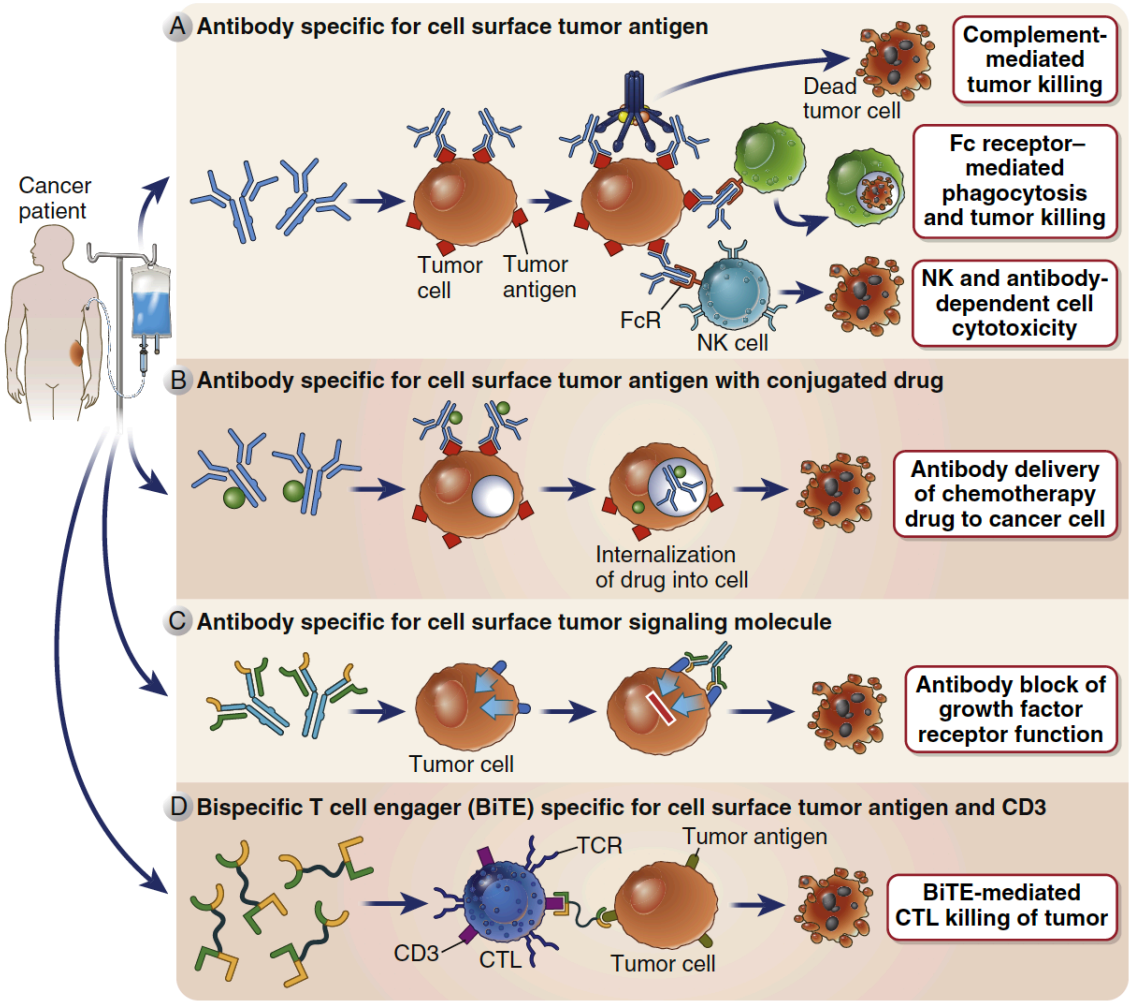
Li H-S, et al. Multidimensional control of therapeutic human cell function with synthetic gene circuits. *Science*

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

Antibody-based Cancer Therapies



Anti-CD20
for B cell lymphoma (rituximab)

Anti-CD33:calicheamicin
for AML (gemtuzumab)

Anti-EGFR for
Colon CA (Cetuximab)

Anti-CD3/Anti-CD19
for B cell leukemia (Blinatumomab)

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