Tumor Immunology for the Non-Immunologist

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Conflict of Interest

- Aduro: Under a licensing agreement between Aduro and the Johns Hopkins University, the University and Dr. Emens is entitled to milestone payments and royalty on sales of a vaccine product developed by Dr. Emens. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

- Genentech, Roche/EMD Serono/Amplimmune/Maxcyte: Research Funding

- Bristol Myers Squibb, Roche, Aveo, Celgene, Vaccinex: Advisory Board or Consultant

Learning Objectives

- Review the basic function and components of the immune system
- Appreciate the complexities of the interaction between cancer and the immune system
- Discuss basic strategies for cancer immunotherapy

Key Concept #1: Self/Non-Self Discrimination is the Functional Foundation of the Immune System

Self/NonSelf Discrimination

- Avoid self destruction
  - autoimmune disease
- Protect against threats
  - exogenous: infectious invaders
  - endogenous: cancers (dysregulated self)

Two Major Functional Arms Comprise the Immune System

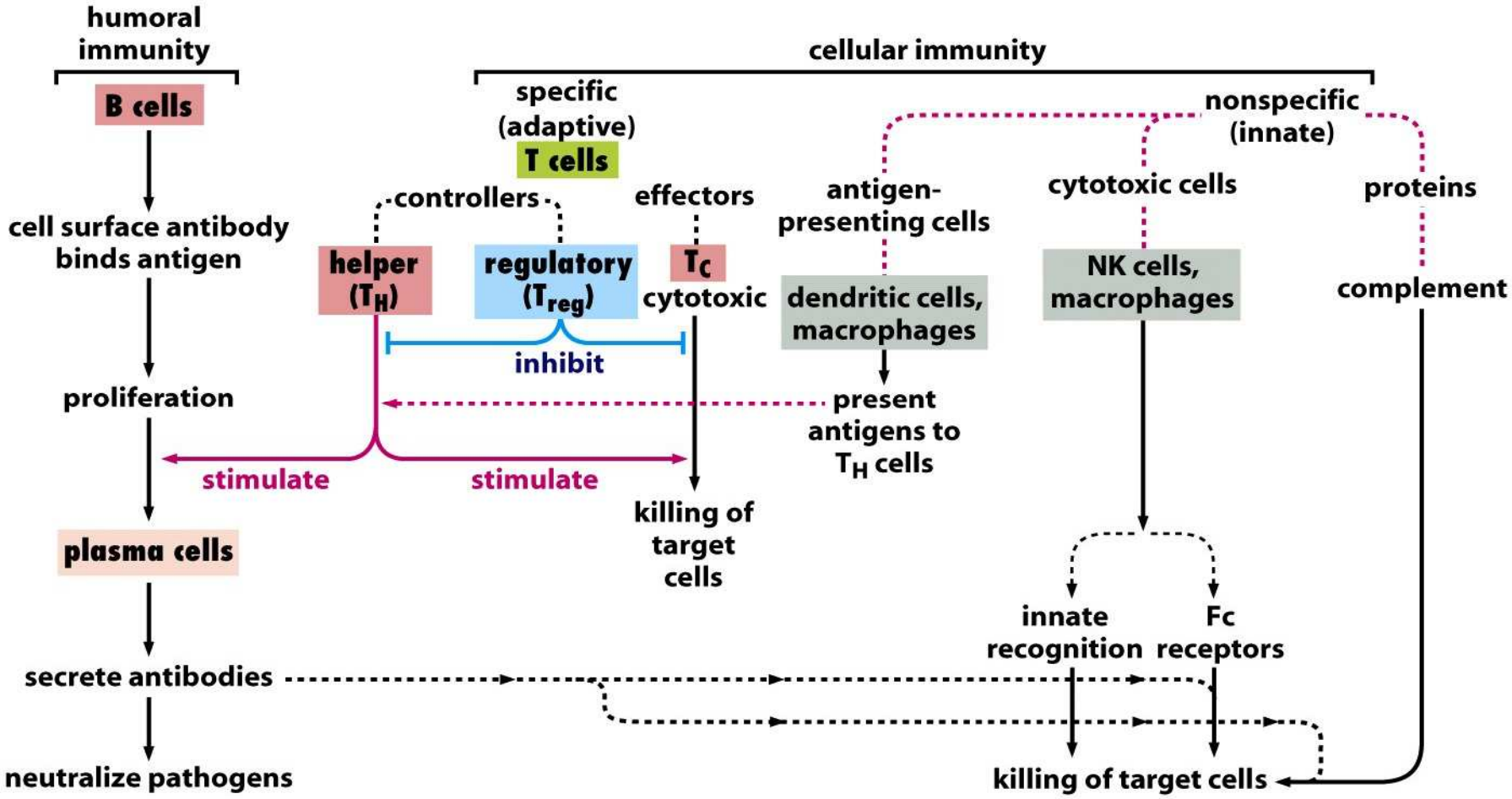
- **Innate**: first line of defense, serves a "sensing" function
  - Macrophages ,monocytes, neutrophils, dendritic cells (DC), natural killer (NK) cells
  - Complement, cytokines, chemokines, acute phase reactants

- **Adaptive**: antigen-specific immune effectors, serves a specific protection and threat elimination function
  - Helper $CD4^+$ and cytotoxic $CD8^+$ T cells, memory T cells, $CD4^+CD25^+FoxP3^+$ regulatory T cells (Treg), and B cells
  - Soluble antibodies

Innate vs. Adaptive Immune Responses

	Innate	Adaptive
Specificity	Non-specific	specific
Antigens	Unnecessary	Required
Immune memory	No	Yes
Kinetics of response	Immediate	Evolving over time
Duration of response	Transient	Durable

Key Concept #2: Innate and Adaptive Immune Cells Collaborate to Orchestrate an Immune Response



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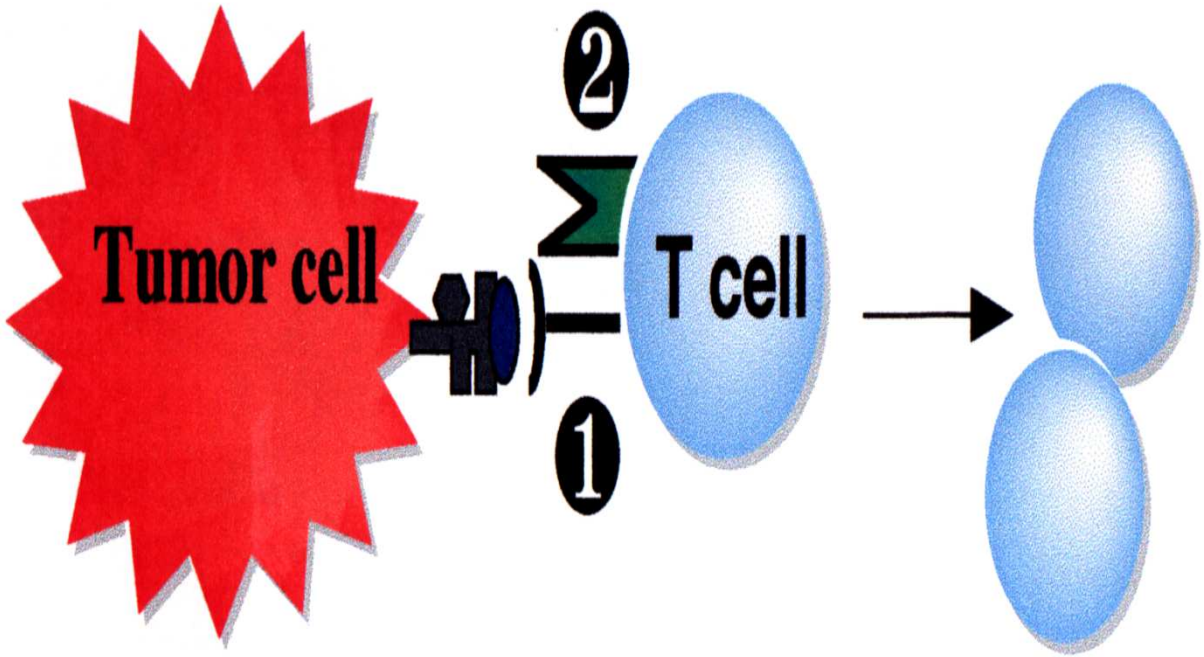
Key Concept #3: CD8$^+$ T Cells are the Major Effector of Tumor Immunity



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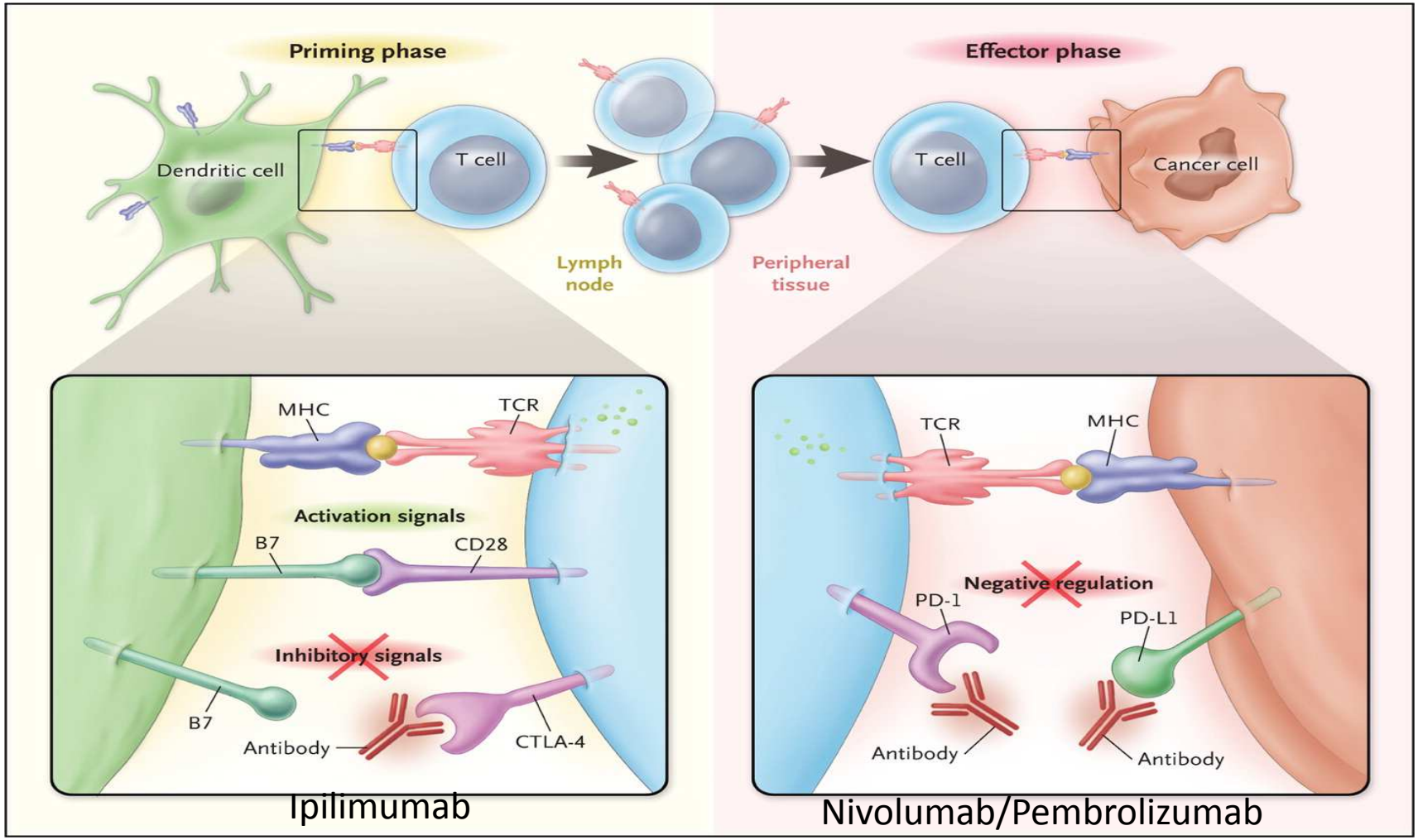

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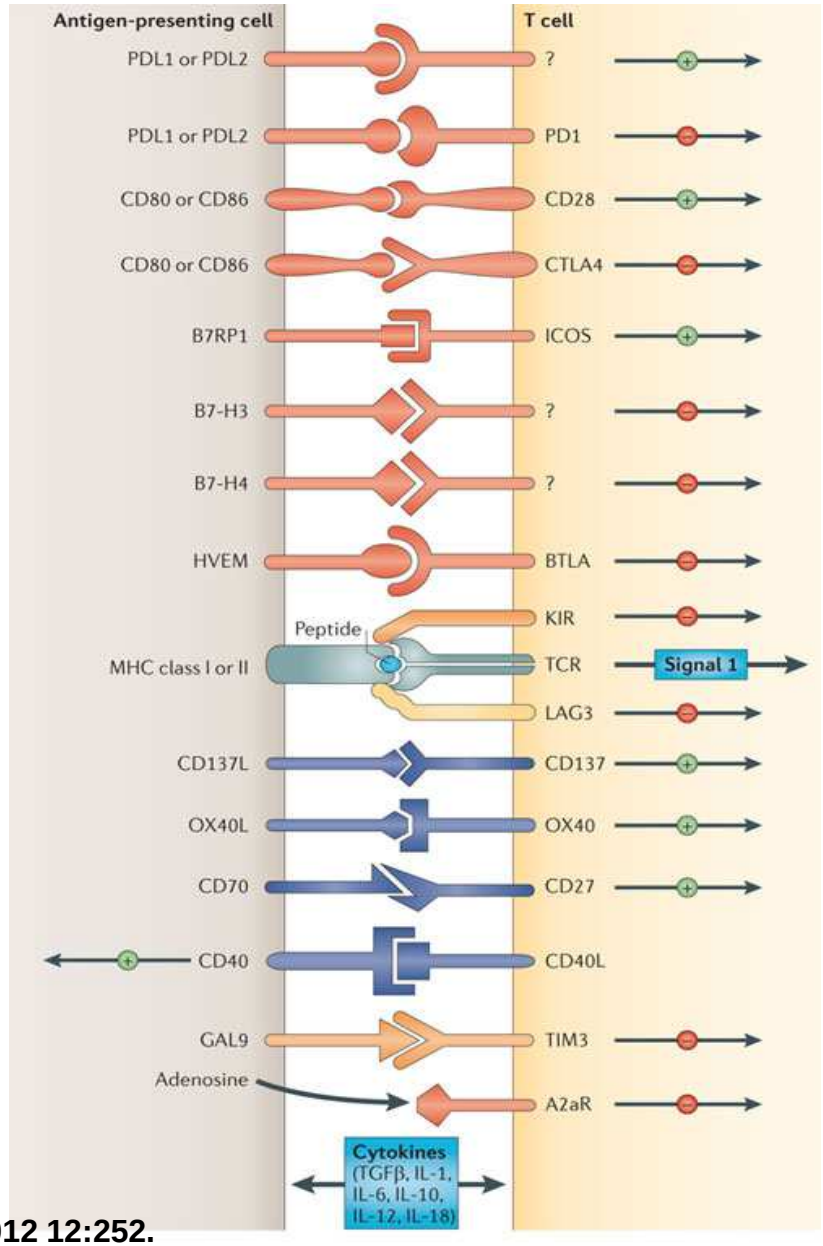
The Immunologic Synapse



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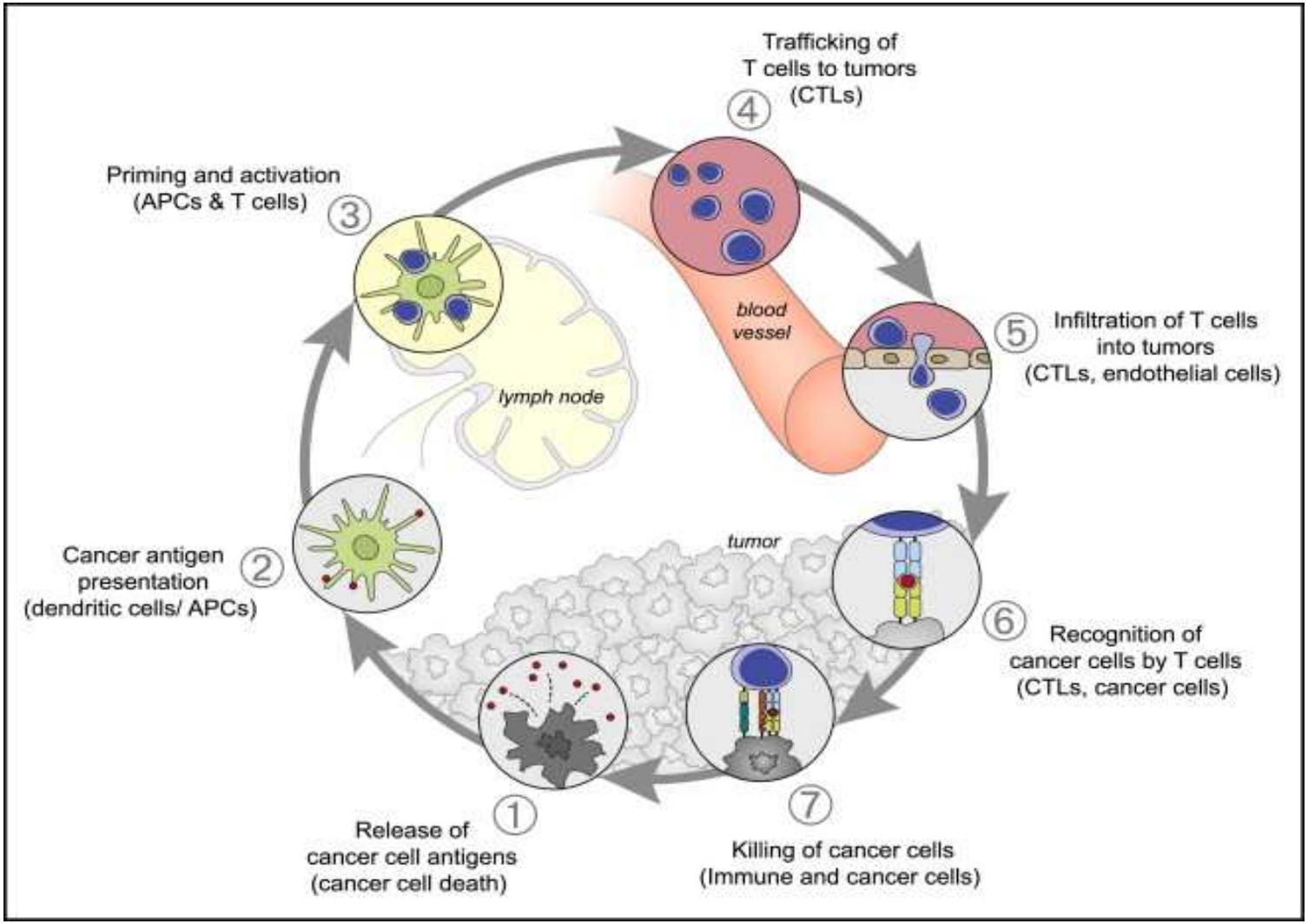
Immune Specificity for Tumors

Type of Antigen	Examples	Strength
Viral-associated antigens	EBV LMP2, HPV E6/7, HBV	Stronger response
Mutated tumor-associated antigens	k-ras (pancreas/lung), p53 (many cancers), chromosomal translocations--bcr/abl (CML)	Stronger response
Over-expressed, nonmutated antigens	HER-2 (breast/gastric), hTERT (many cancers), GD3 (melanomas)	Tolerizing response
Embryonic, oncofetal antigens	NY-ESO-1, MAGE, GAGE	Some response
Expression of antigen outside of immunologically privileged site	antigens specific to the eye and brain (testis)	Some response
Tissue-specific differentiation antigens	Mucin-1, CEA, MART-1, tyrosinase, gp100, WT1, PR1, PSMA, PSA	Tolerizing response

Key Concept #3: Interactions Between Cancer and the Immune System are Dynamic

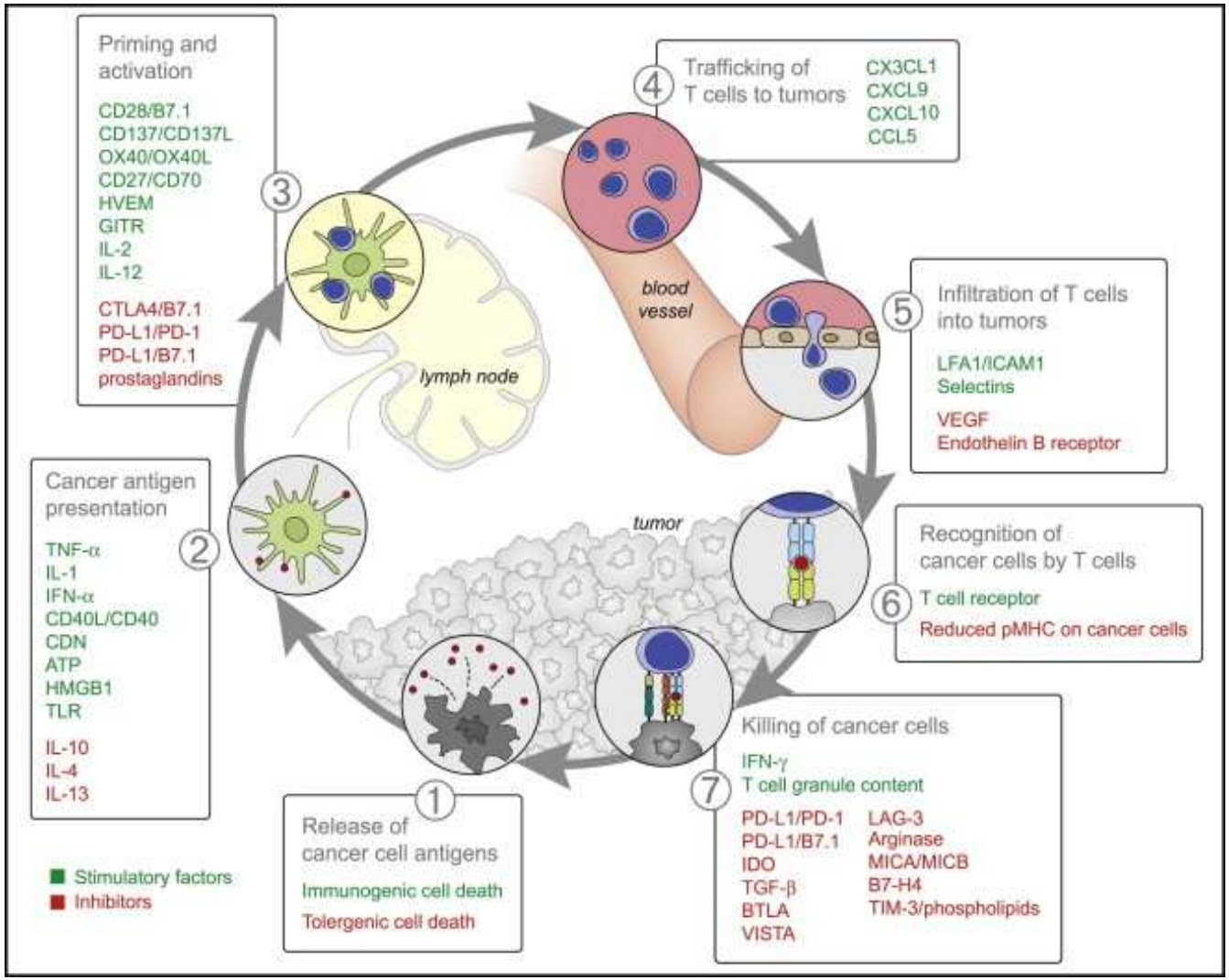


Chen DS, Mellman I. Immunity 2013;39:1.

How Tumors Evade the Immune System

- Tumors are self (suboptimal T cell repertoire due to thymic selection and low TCR avidity)
- Antigen loss variants due to selective pressure
- Inadequate co-stimulation
- Excessive counter-stimulation
- Ineffective T cell trafficking
- $CD4^{+}CD25^{+}FoxP3^{+}$ regulatory T cells (Treg)
- Myeloid-derived suppressor cells (MDSCs)
- Suppressive factors in the tumor microenvironment

Key Concept #4: Tumor Immunity is Controlled by a Balance of Positive and Negative Factors



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Types of Specific Immunotherapy

Passive Immunotherapy **Monoclonal antibody therapy** **Adoptive T cell therapy**	**Active Immunotherapy** **Vaccines** **Bacteria**
Passively transferred (given back)	Actively induced
Immediate therapeutic effect	Delayed therapeutic effect
Transient	Durable due to immune memory
Does not necessarily require functional immune system	Required functional immune system

Increase numbers of effector T cells

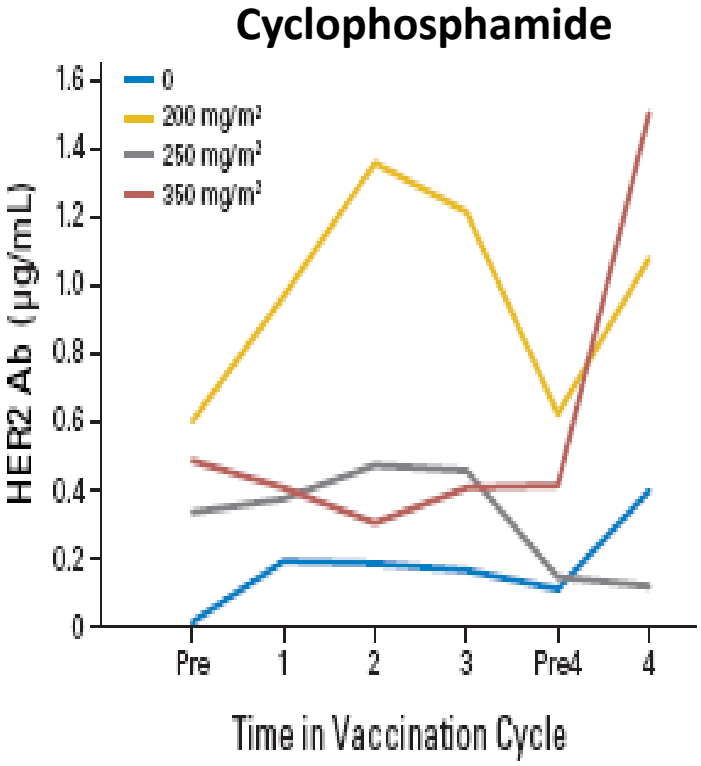
- Vaccines
- Adoptive T cell therapy

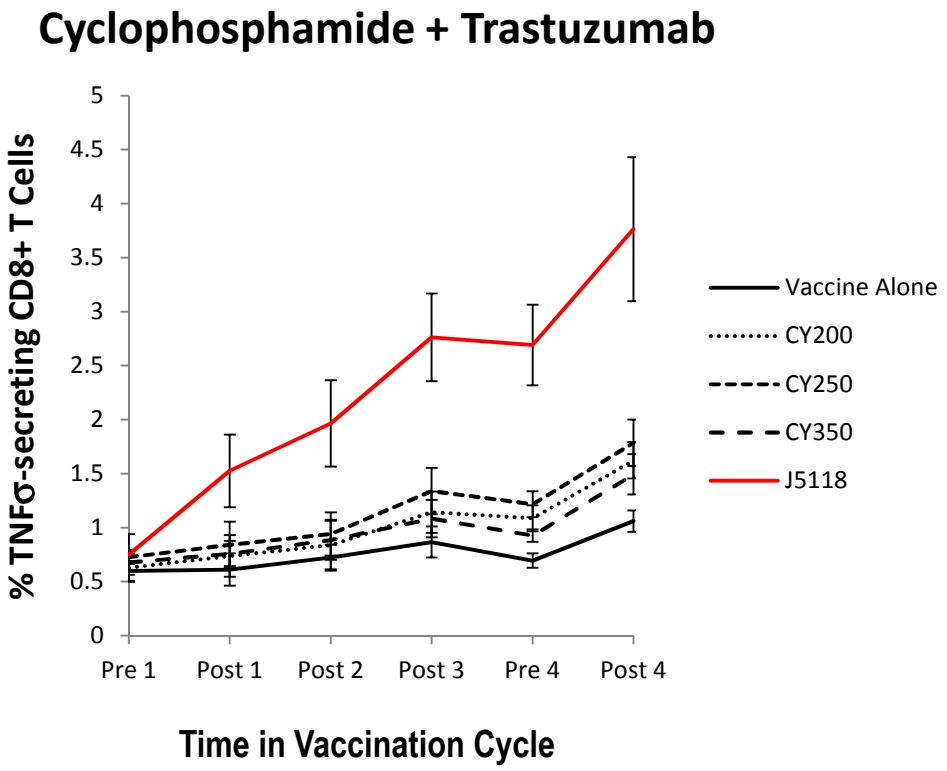
Augment existing or transferred immunity

- Checkpoint blockade
- Cytokine therapy (IL2, IL7, IL15),TLR agonists
- Depletion of Tregs or MDSCs
- Block suppressive cytokines (IL10, TGFβ)
- Chemotherapy, Monoclonal antibody, XRT

Vaccines

Chemotherapy and Trastuzumab-Modulated Vaccination Enhances Vaccine-Induced Immunity in Metastatic Breast Cancer Patients





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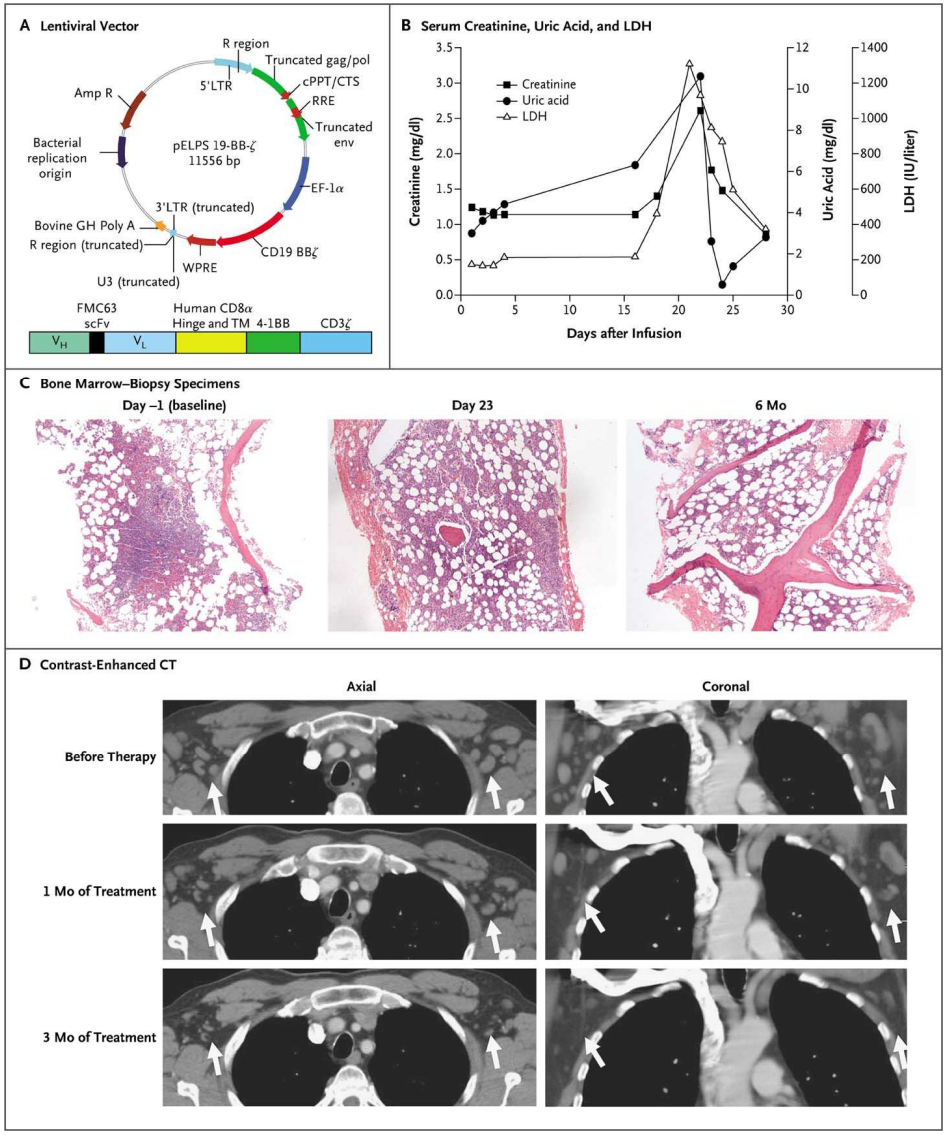
Adoptive T Cell Therapy

CAR Autologous T Cell Immunotherapy for CLL



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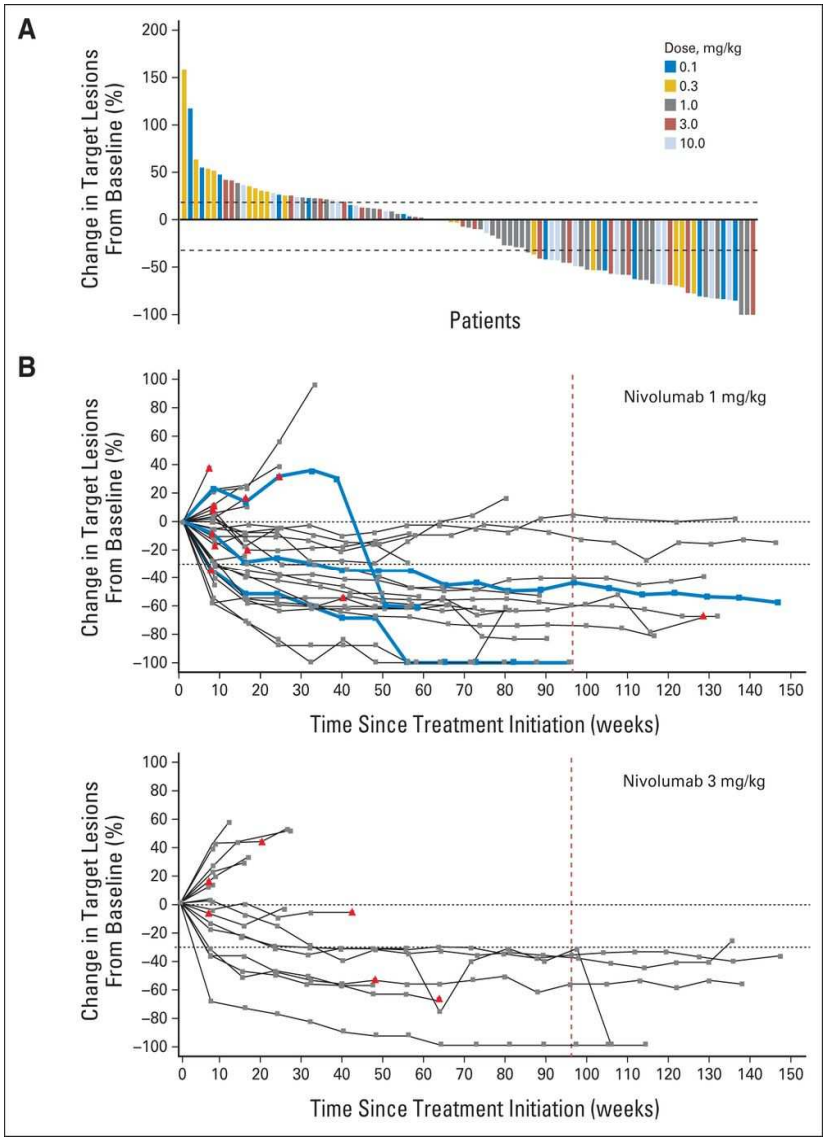
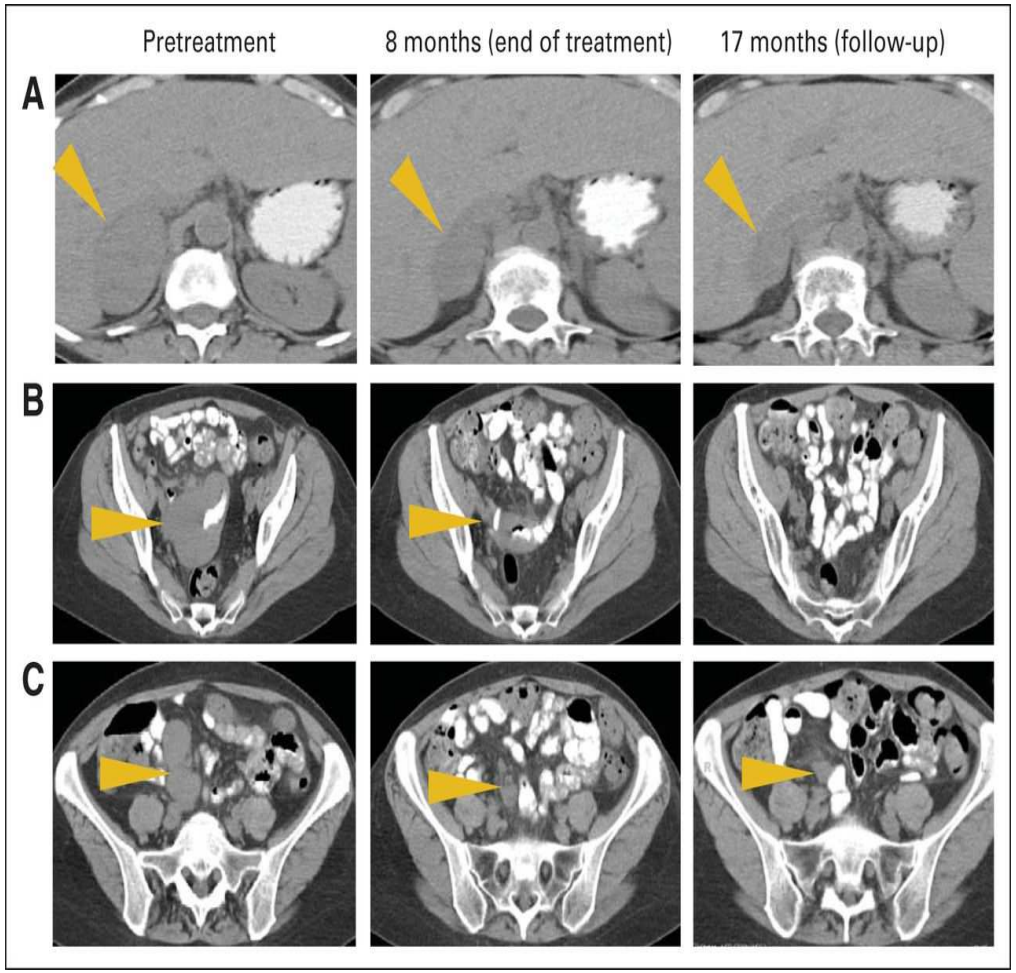
Immune Checkpoint Blockade

Single Agent Nivolumab Induces Durable Responses in Melanoma Patients





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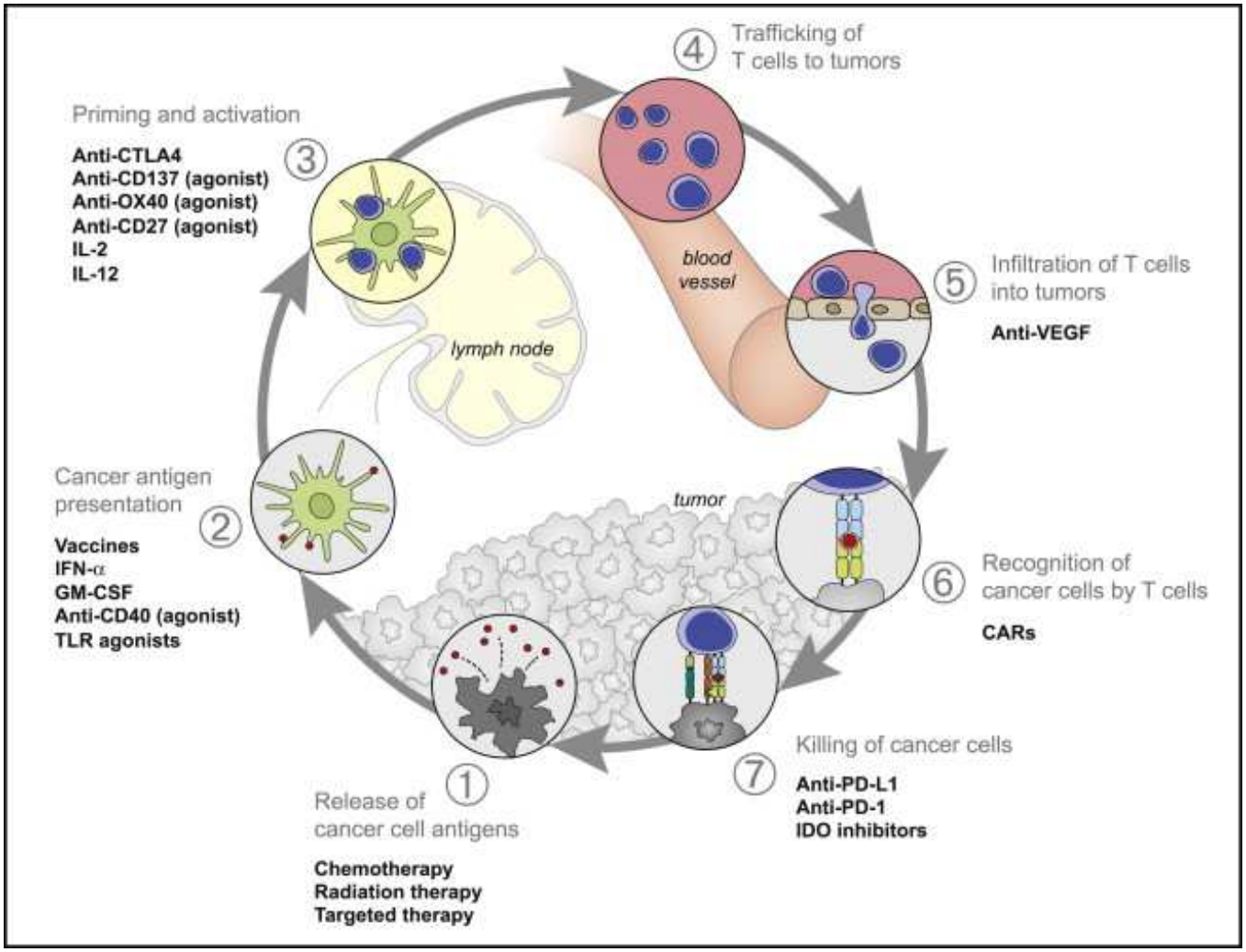
Immunotherapy: Targeting Distinct Nodal Points of the Tumor-Immune Interaction



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Conclusions

- Tumors and the immune system interact in a dynamic, reciprocal, evolutionary process to sculpt the cancer-specific immune response (and tumors themselves)
- Tumor-specific $CD8^+$ T cells are the end effectors of cancer immunity
- Standard cancer therapies can induce/support tumor immunity
- Tumor immunity is limited by normal systemic mechanisms of immune tolerance that prevent autoimmunity, and by local factors within the tumor microenvironment
- Immunotherapy strategies that target distinct interactions between the tumor microenvironment and the immune system hold tremendous potential for cancer therapy. Four agents, one vaccine (provenge) and three immune checkpoint antagonists (ipilimumab, pembrolizumab, and nivolumab), are already approved by the FDA. Many more immunomodulators are in development.

The Future for Cancer Patients is Bright!