



Basic Principles of Tumor Immunotherapy

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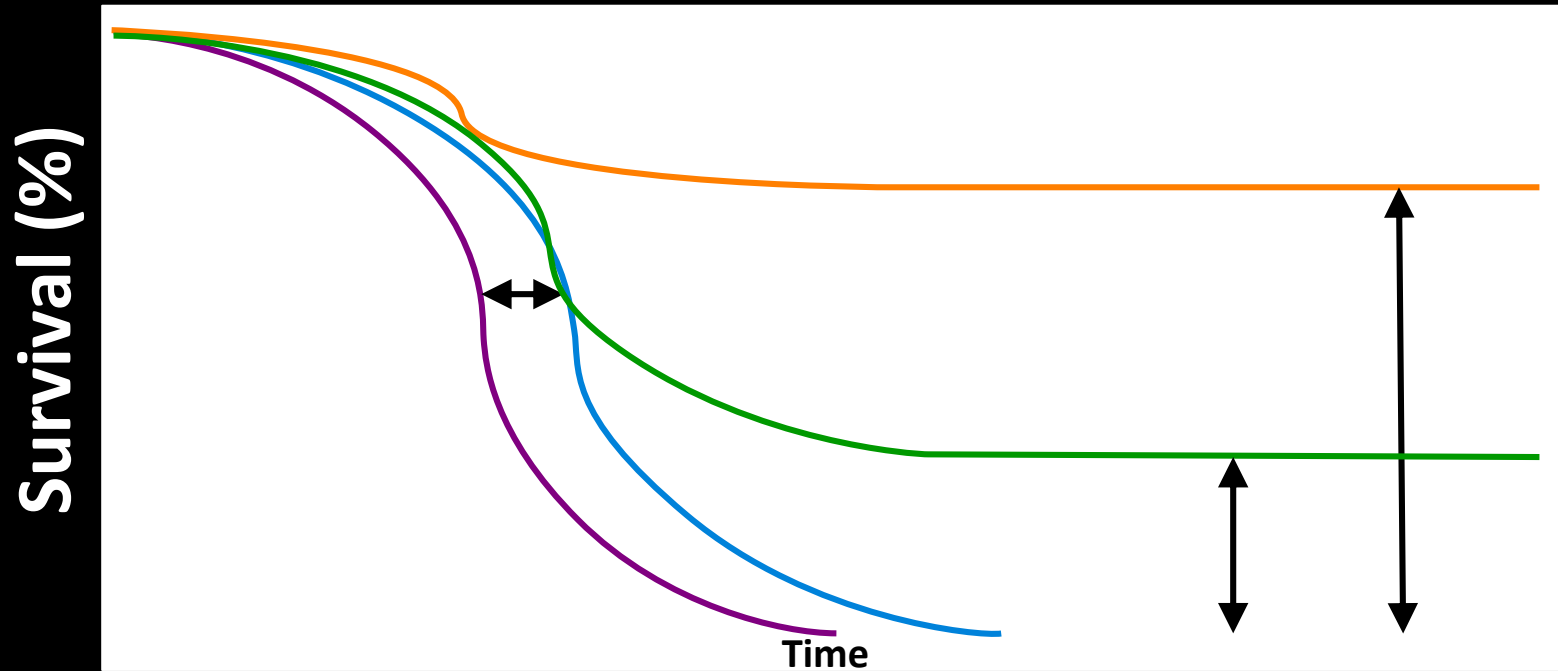
Disclosures

- Consulting
 - Pfizer, Merck, BMS, Amgen, AstraZeneca, Human Longevity Inc.
- DMC
 - GenMab
- I will not be discussing non-FDA approved treatments

Overview

- How cancer and the immune system learn to co-exist
- Potential immune related interventions in cancer
- Interventions currently being pursued
 - Checkpoint blockade
 - Adoptive cell transfer
 - Vaccines
- Toxicity of immunotherapy

The promise of immunotherapy: The Kaplan-Meier curve tail



- Chemotherapy
- Genomically targeted therapy
- Immune checkpoint therapy
- Combination with genomically targeted agent and immune checkpoint therapy

Ipilimumab ± Nivolumab in Previously Untreated Metastatic Melanoma

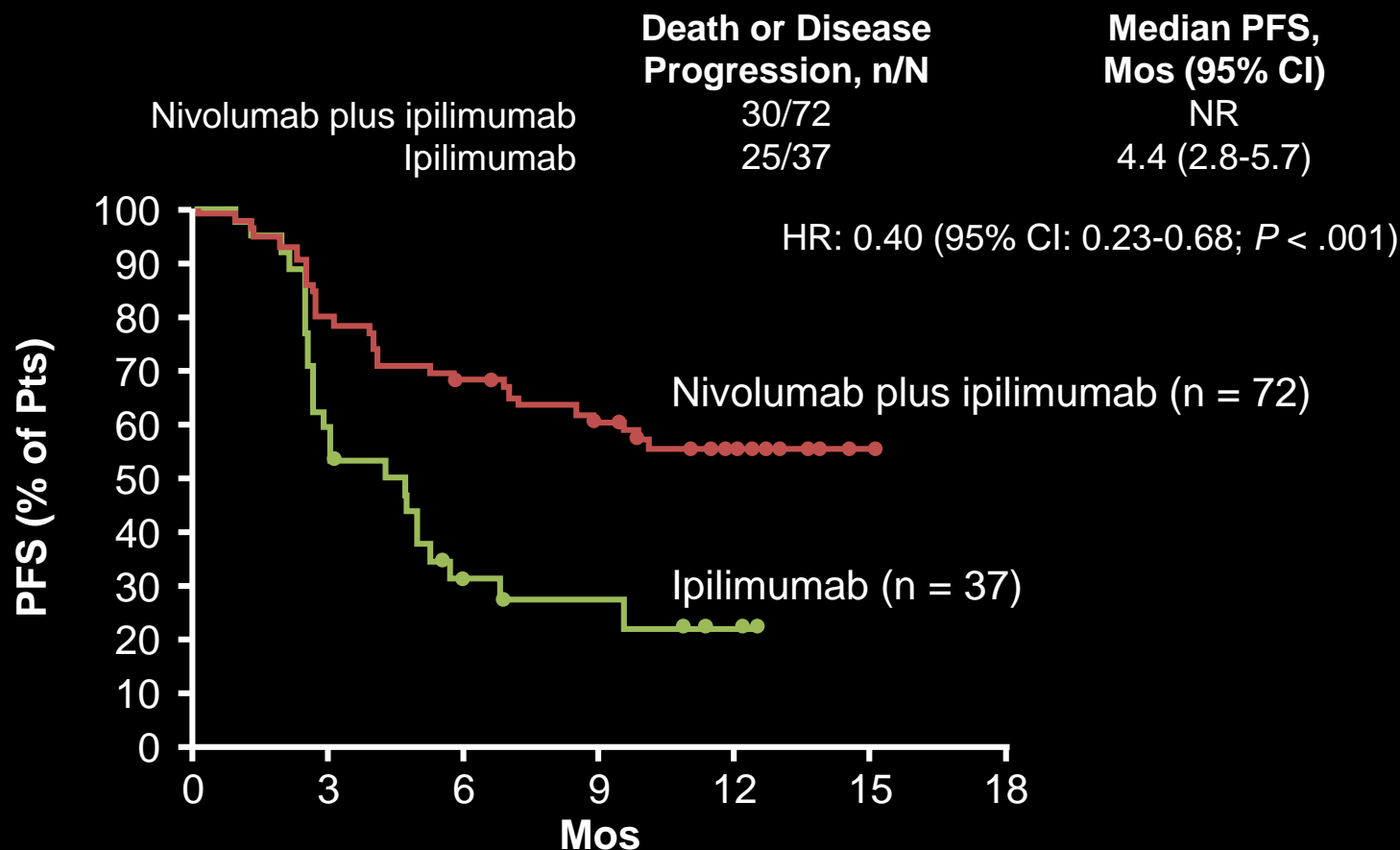
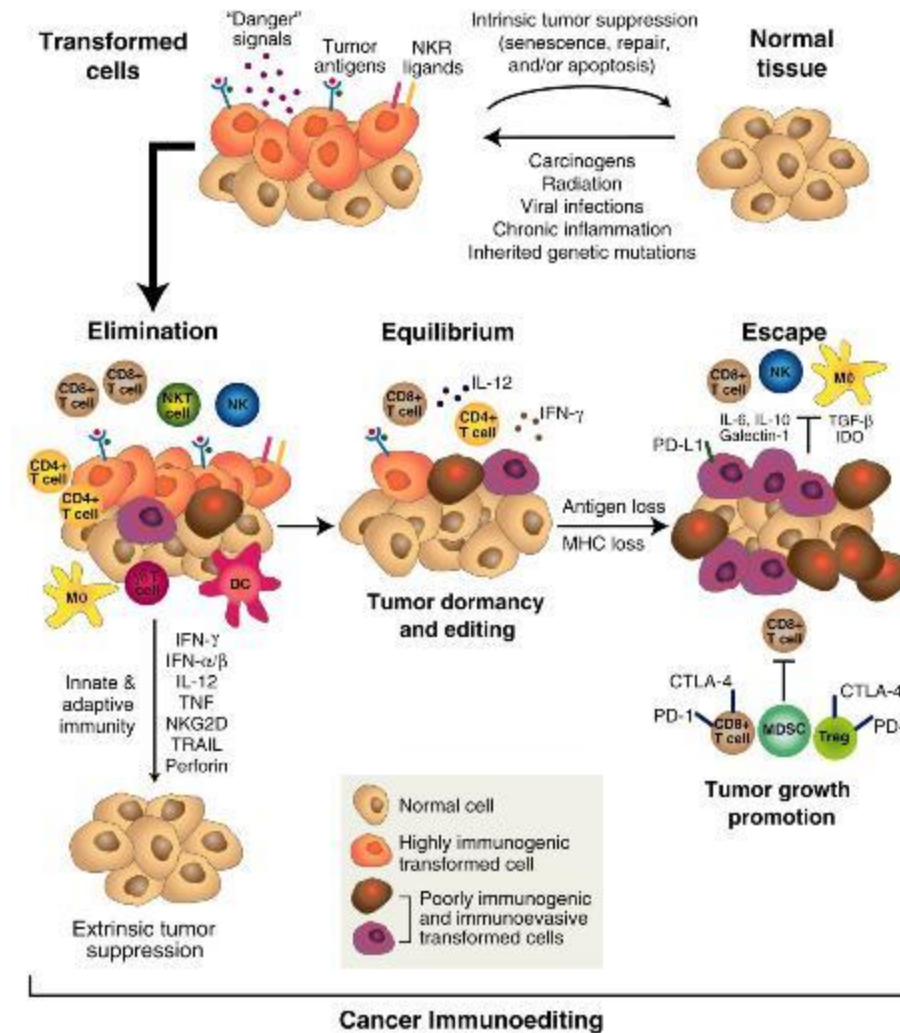
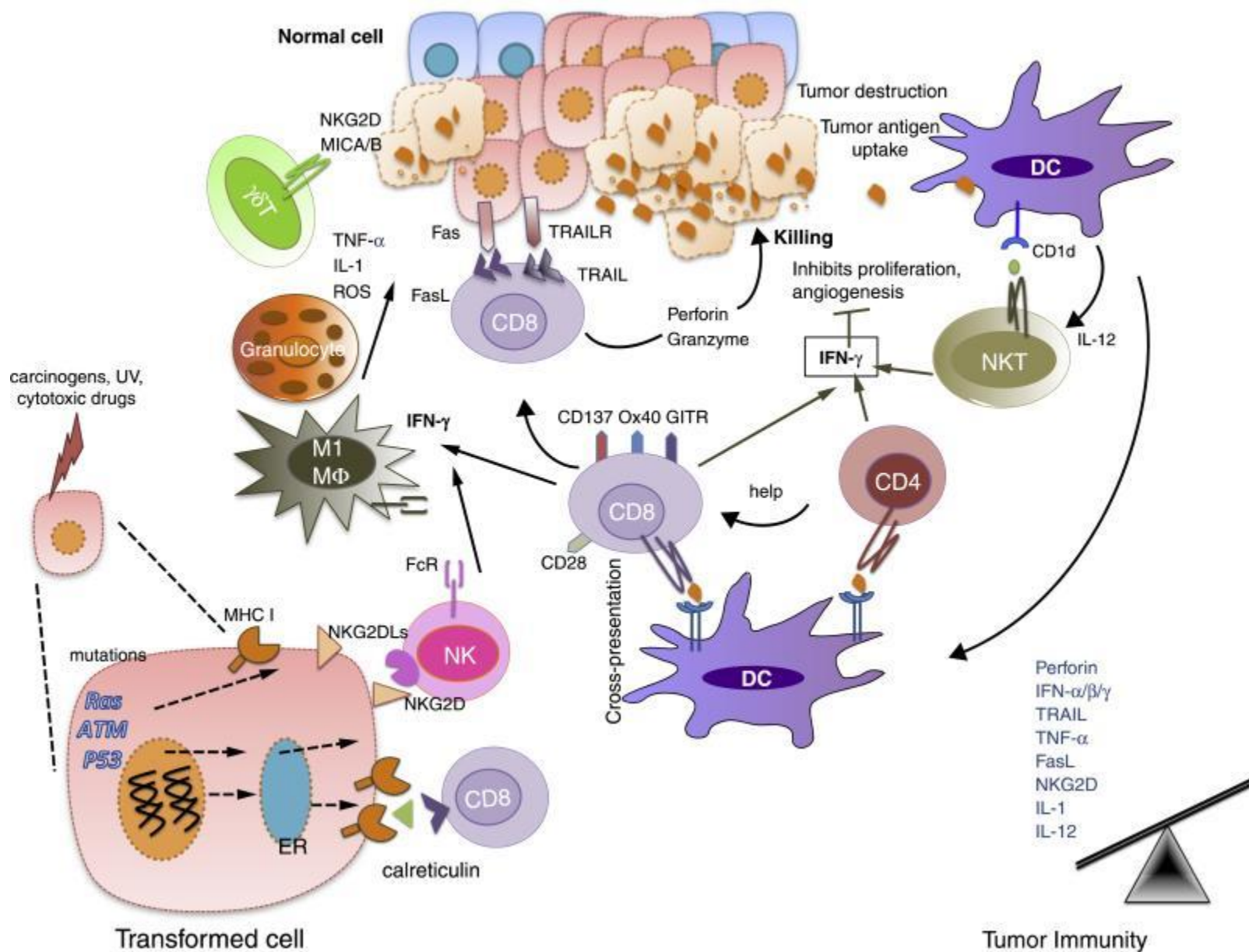
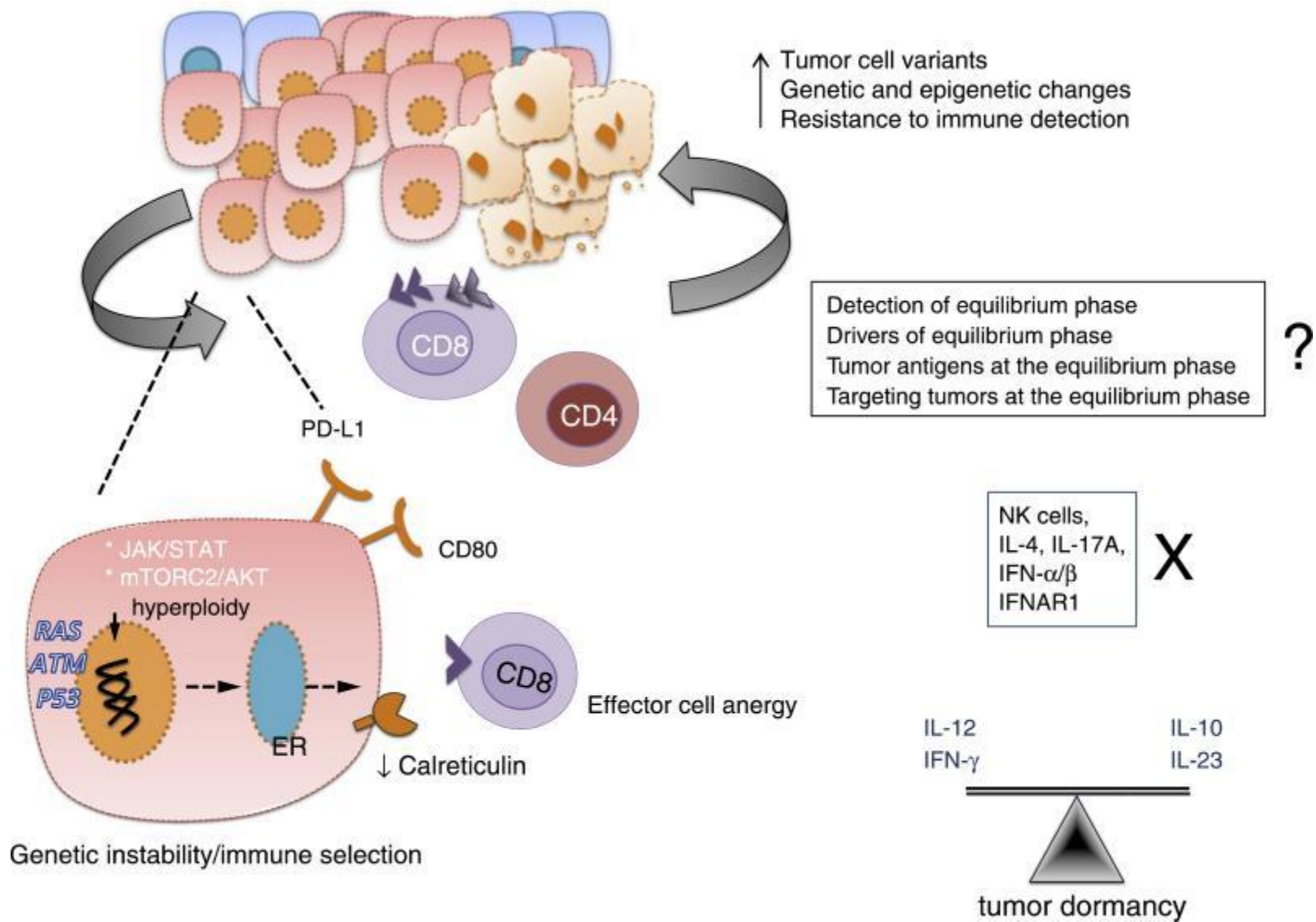


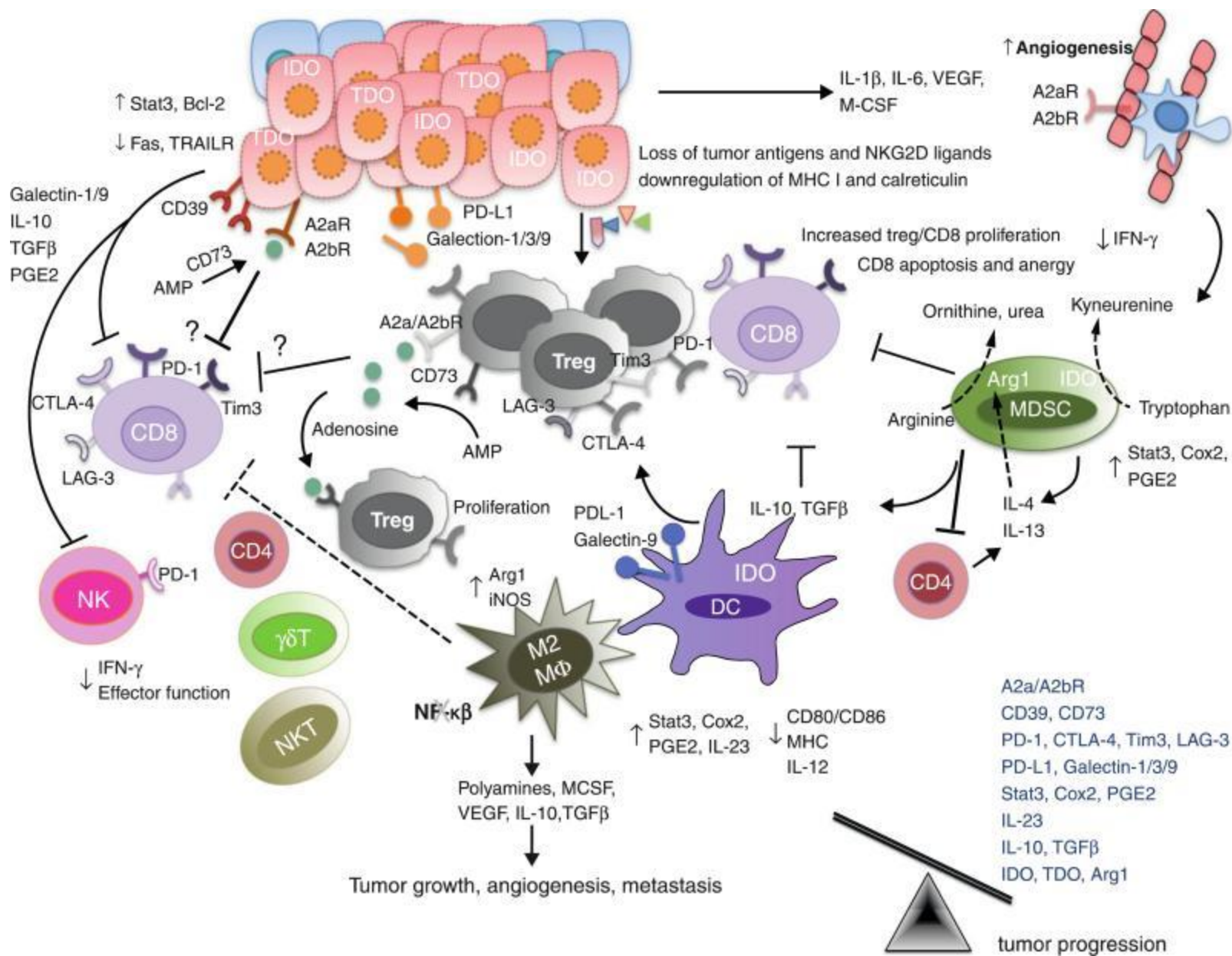
Fig. 3 The cancer immunoediting concept.



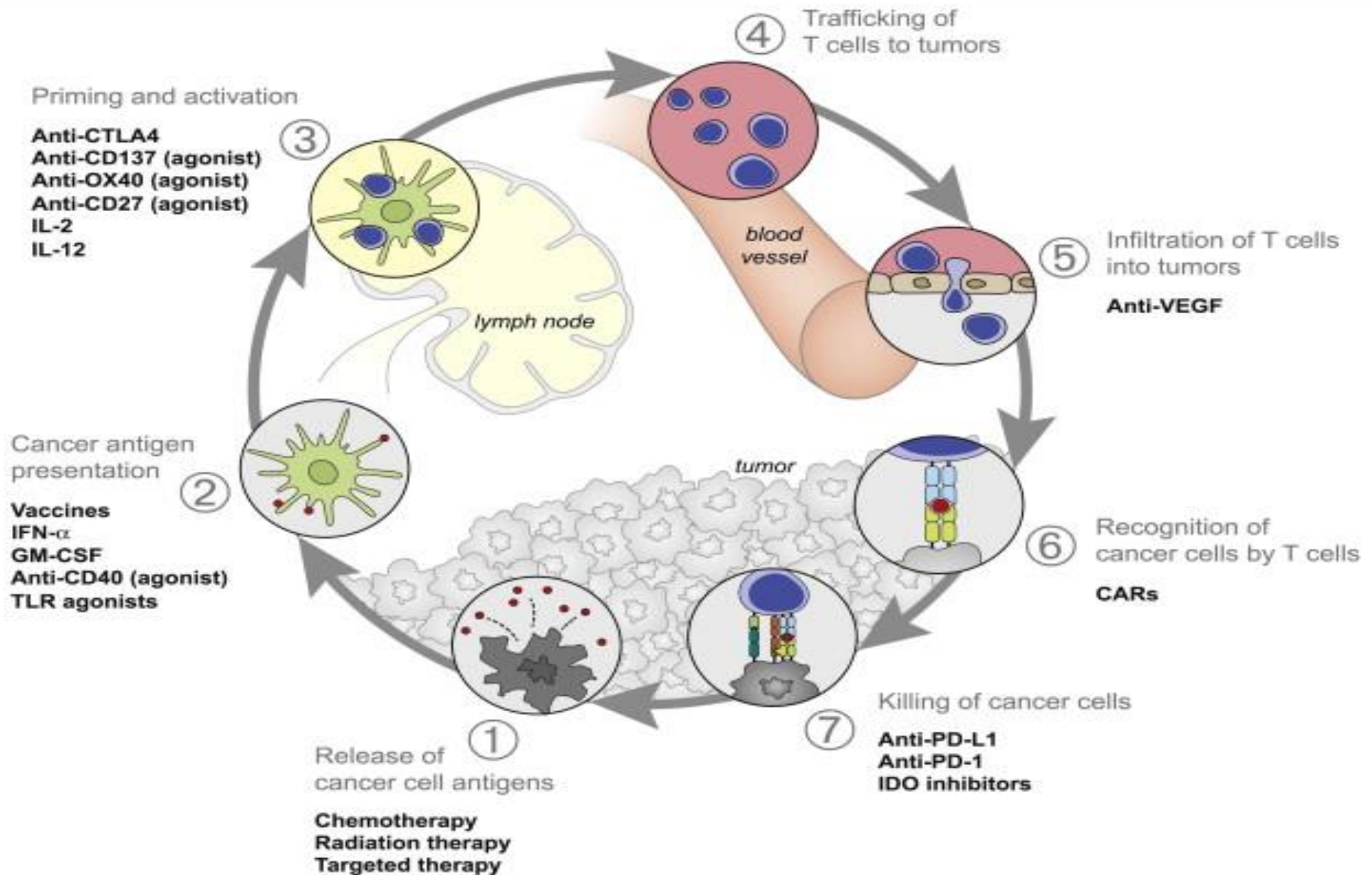
Robert D. Schreiber et al. Science 2011;331:1565-1570



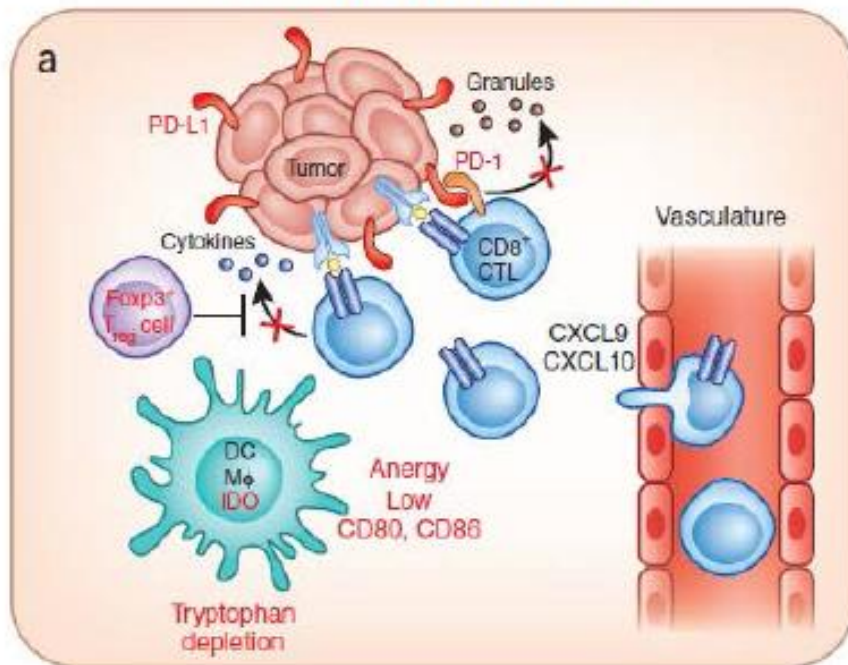




Cancer Immune Cycle

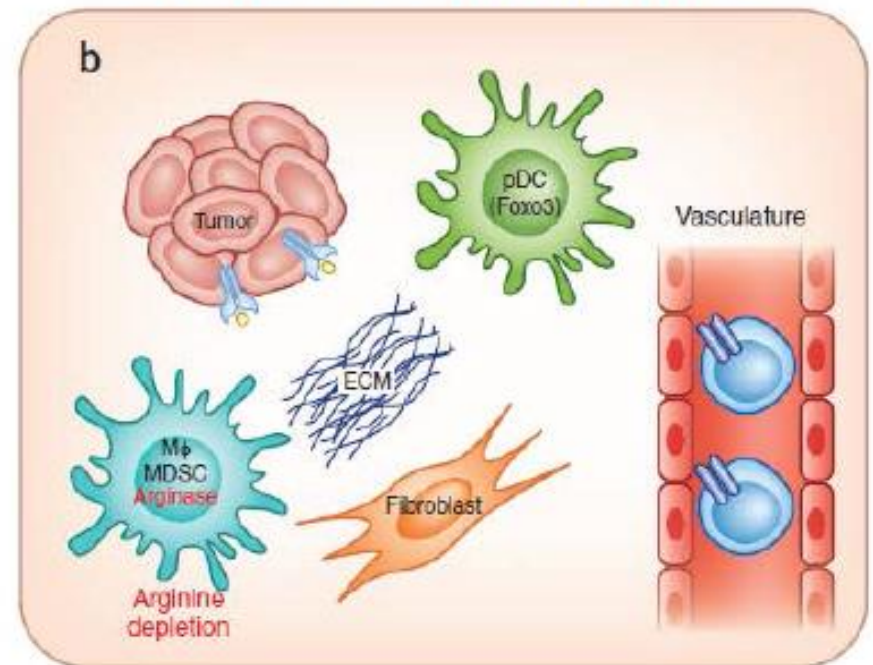


T cell-inflamed



- Chemokines
- CD8⁺ T cells
- Type I IFN signature
- Immune escape: Inhibitory pathways
- *Most immunotherapy responders have this phenotype*

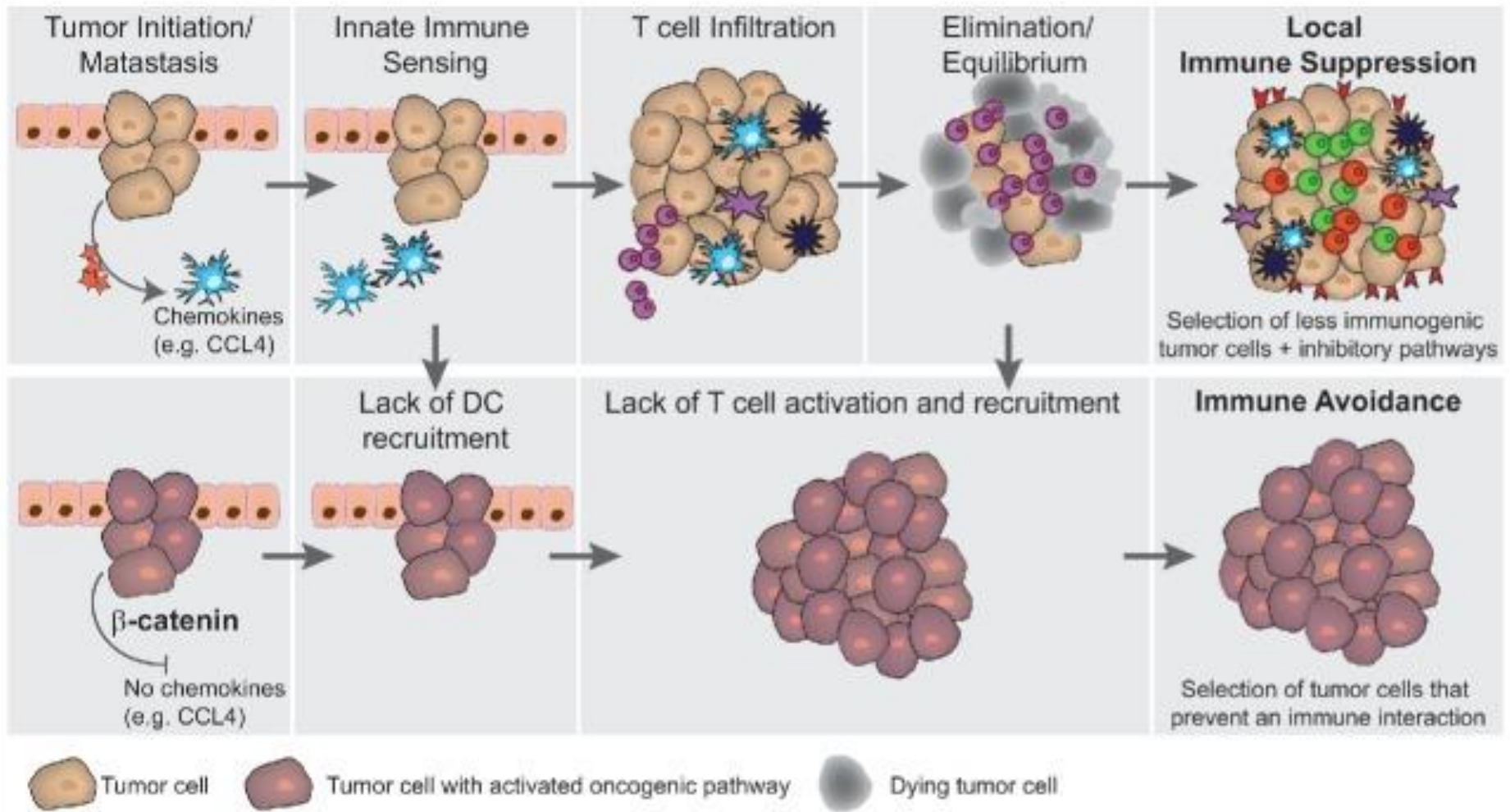
Non- T cell-inflamed



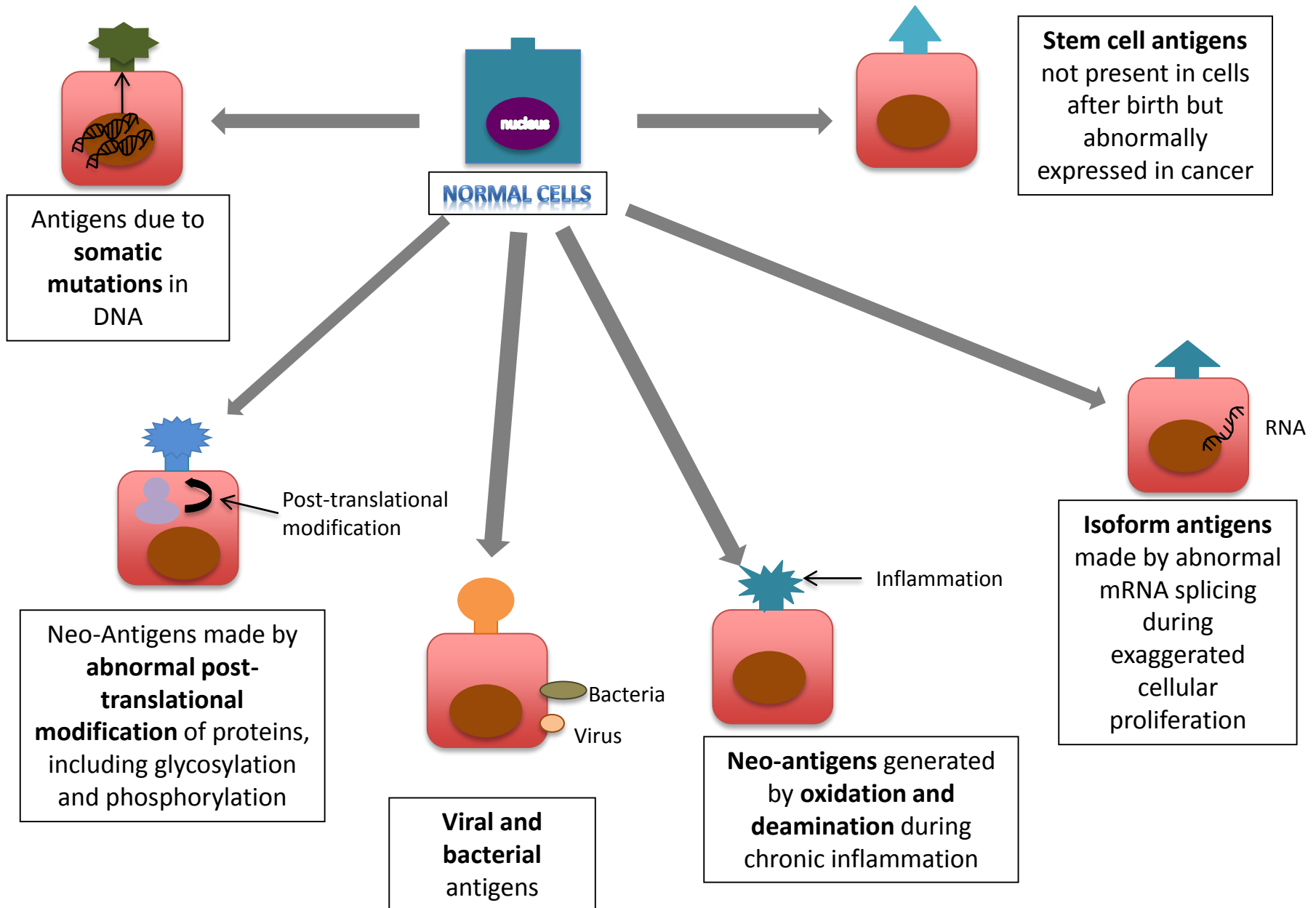
- Low inflammatory signature
- Absent intratumoral CD8⁺ T cells
- Immune escape: T cell exclusion

Nature Immunol. 2013

Immune Avoidance vs. Immunogenic Escape

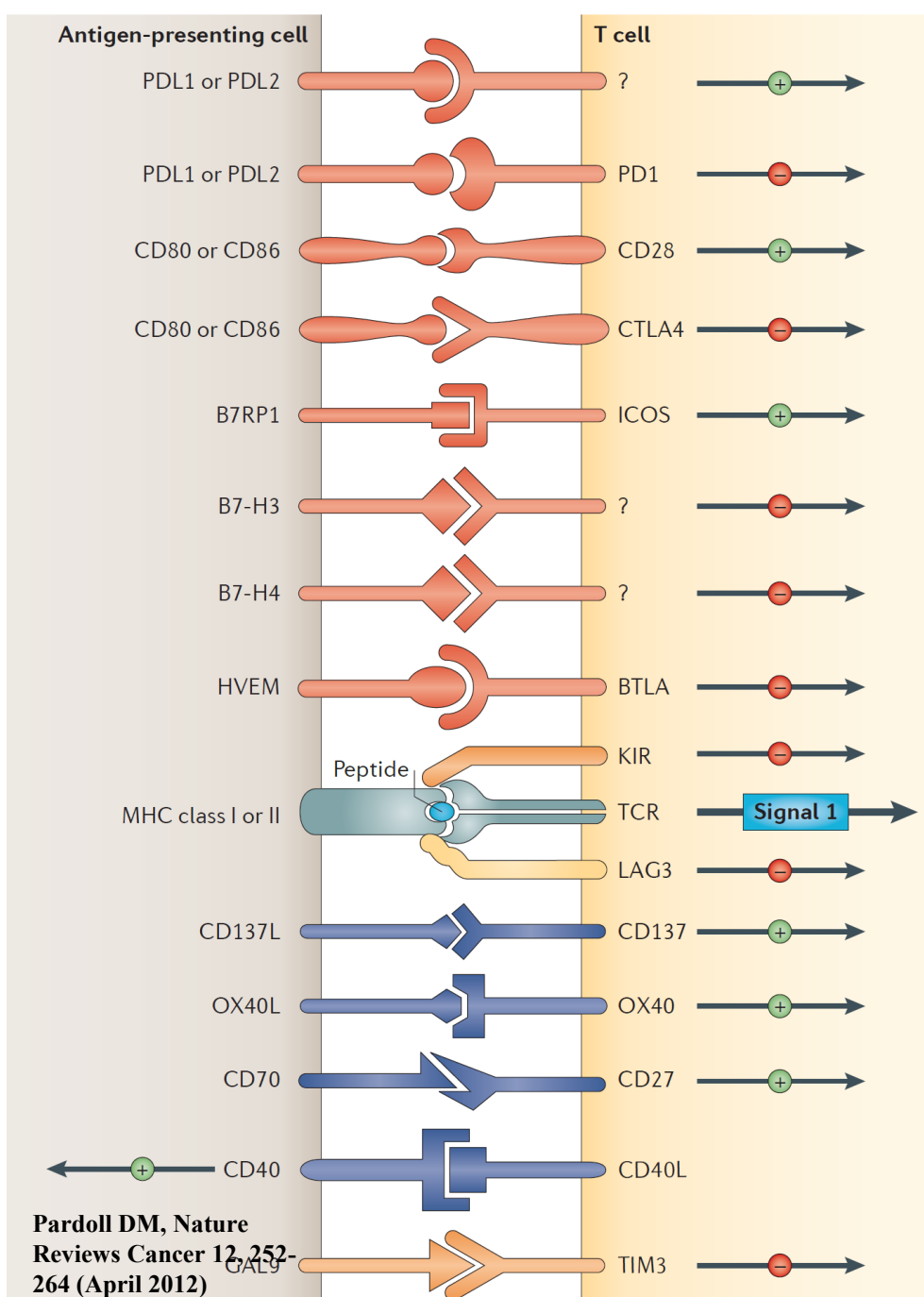
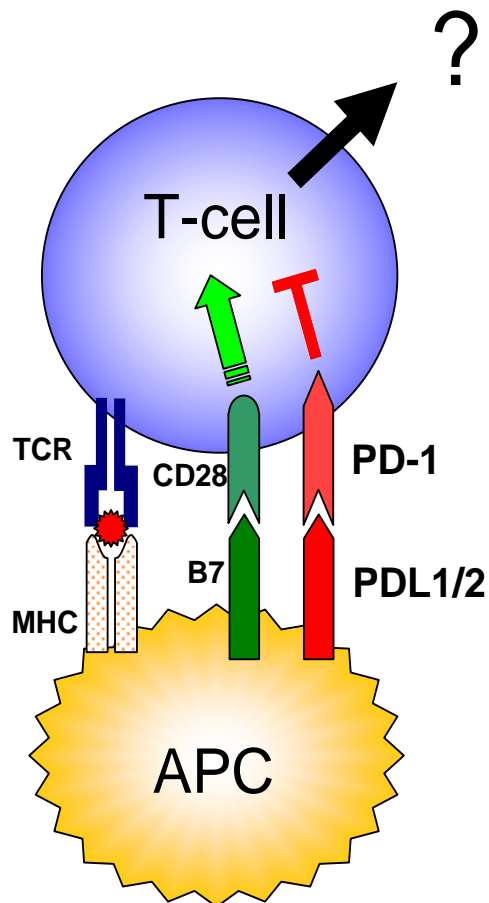


Types of Cancer Antigens



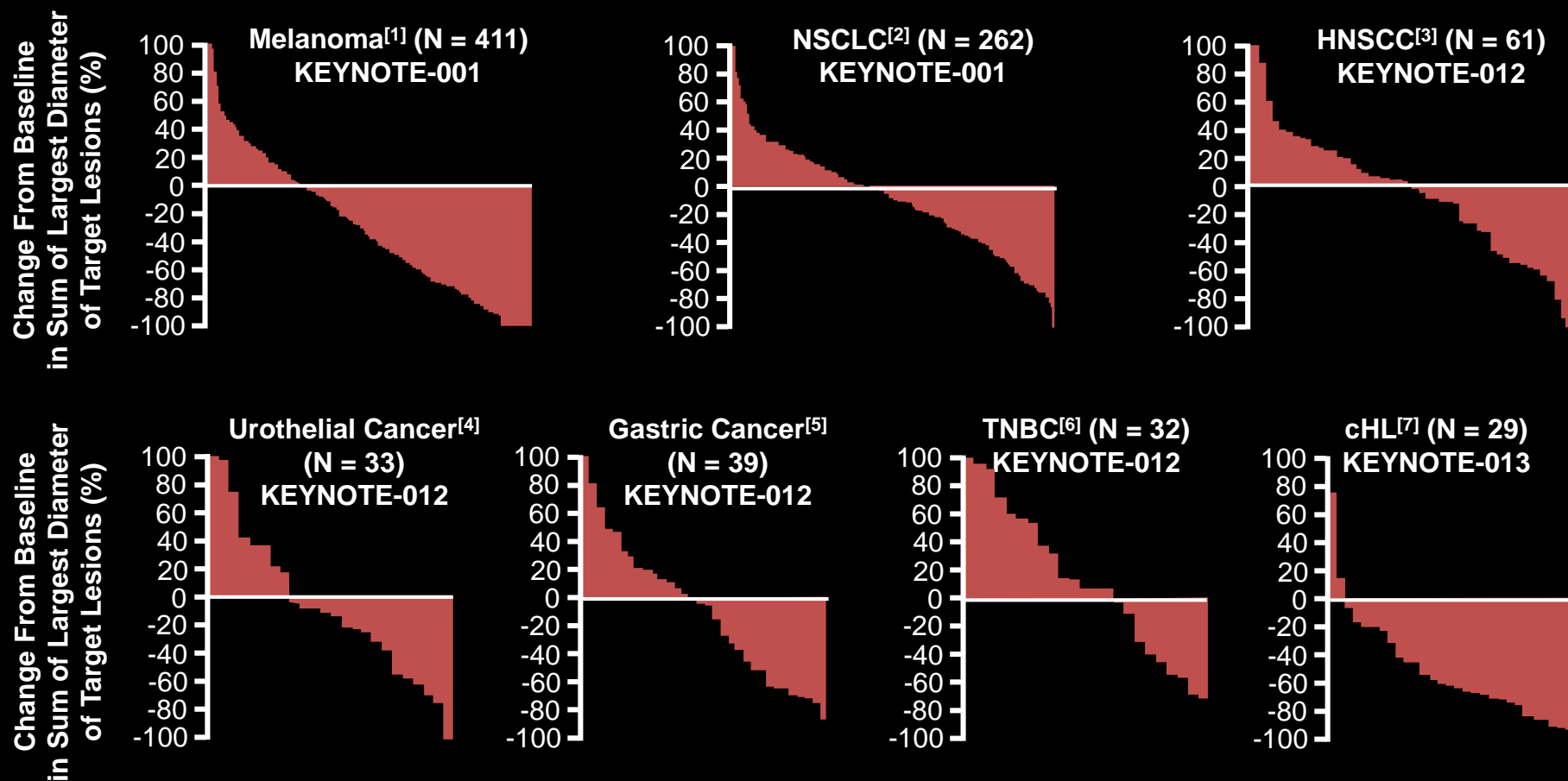
Checkpoint Blockade

Checkpoint Blockade



Pardoll DM, Nature Reviews Cancer 12, 252-264 (April 2012)

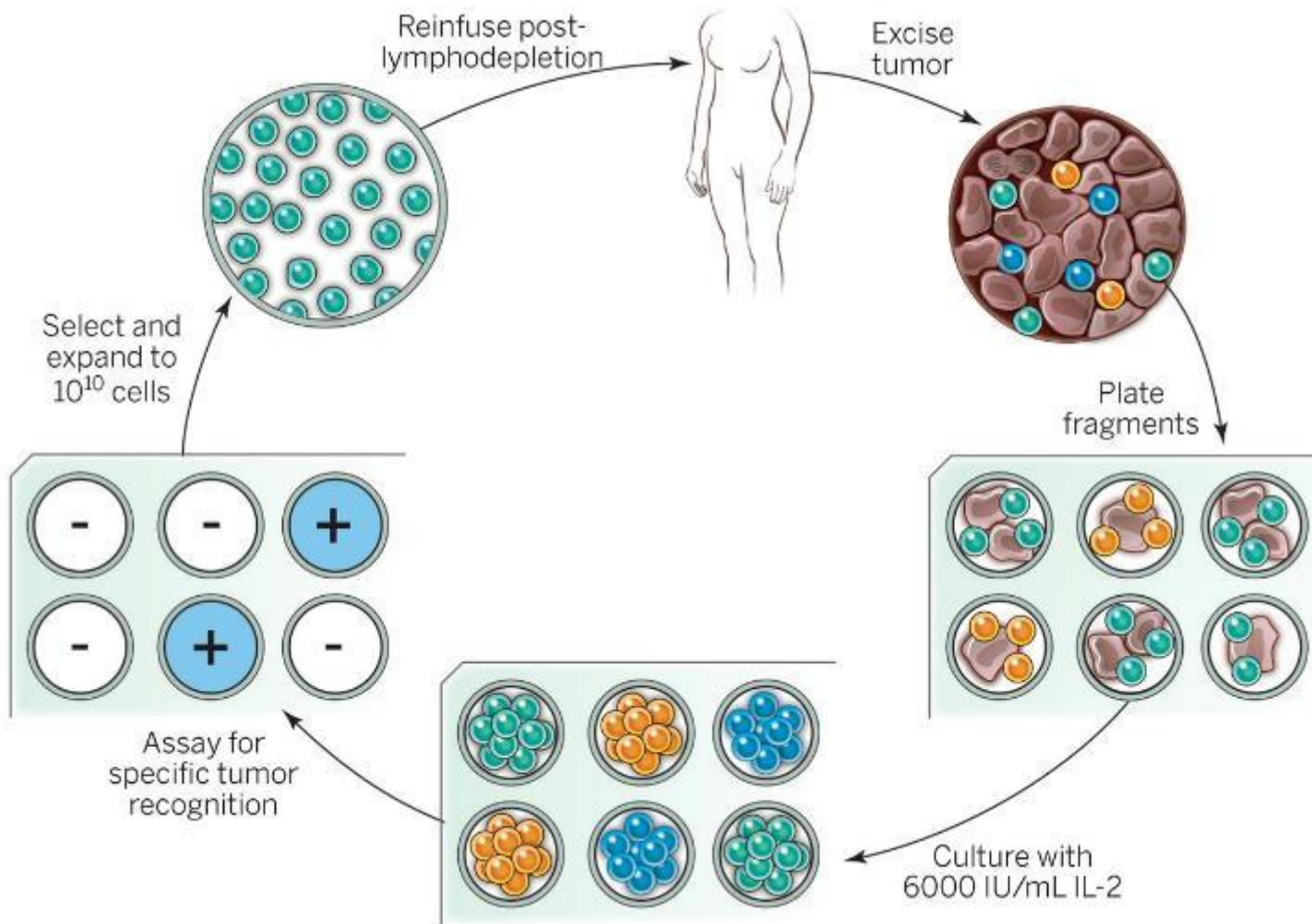
Pembrolizumab Antitumor Activity



1. Robert C, et al. Lancet. 2014;384:1109-1117. 2. Garon EB, et al. ESMO 2014. LBA43. 3. Chow LQ, et al. ESMO 2014. LBA31. 4. O'Donnell P, et al. ASCO GU 2015. Abstract 296. 5. Muro K, et al. ASCO GI 2015. Abstract 03. 6. Nanda R, et al. SABCs 2014. Abstract S1-09. 7. Moskowitz C, et al. ASH 2014. Abstract 290.

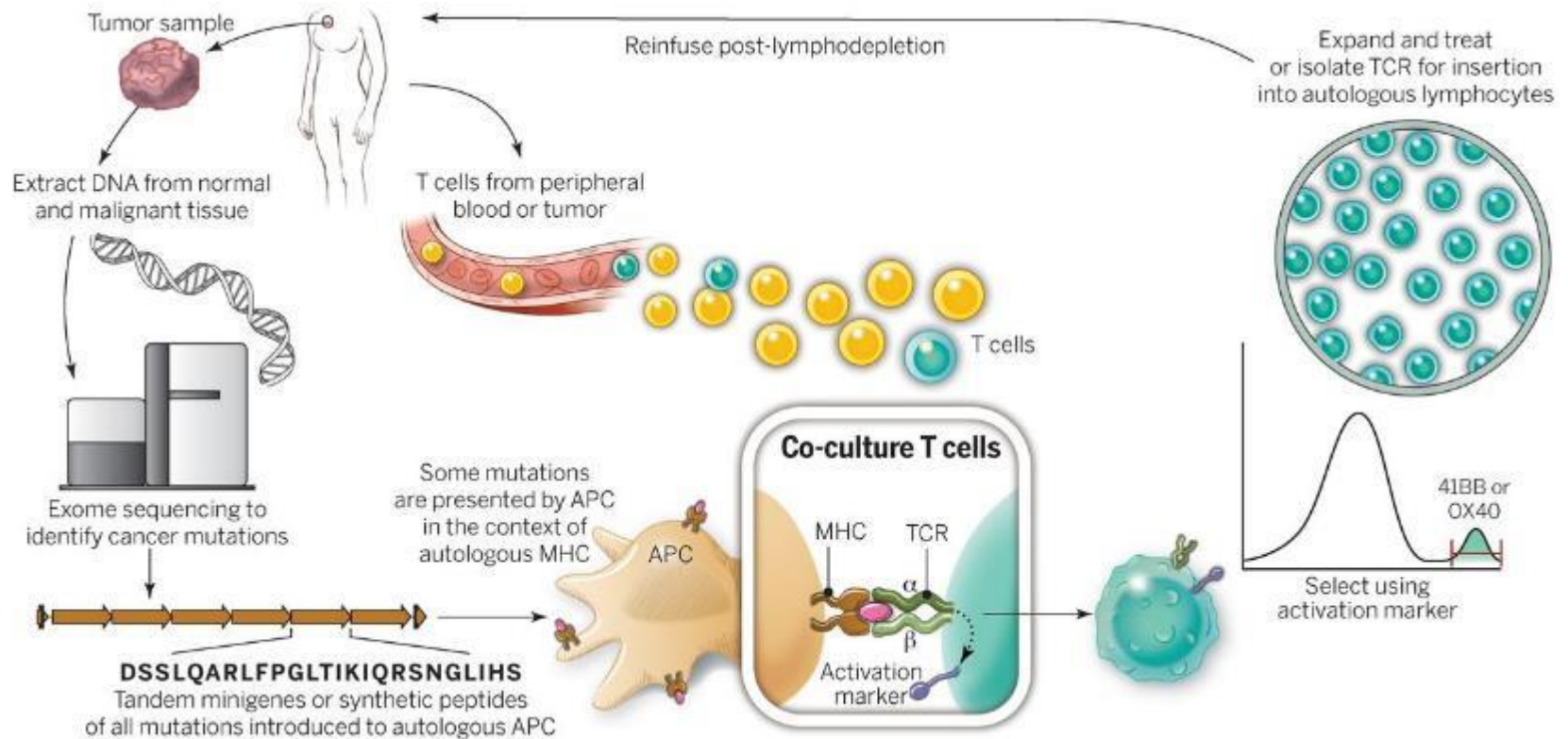
Adoptive Cell Transfer

Fig. 1 General schema for using the adoptive cell transfer of naturally occurring autologous TILs.



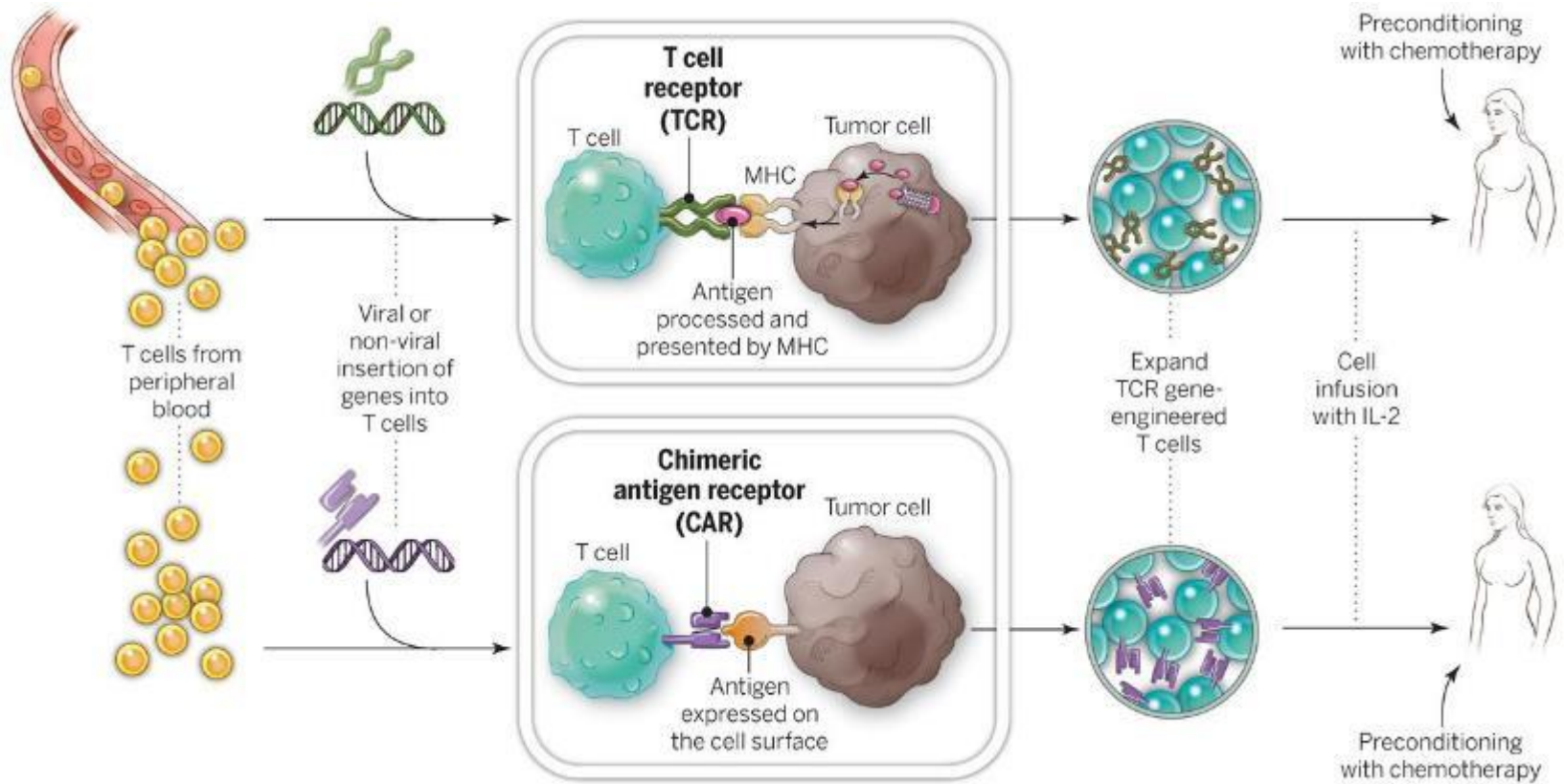
Steven A. Rosenberg, and Nicholas P. Restifo *Science*
2015;348:62-68

Fig. 3 A “blueprint” for the treatment of patients with T cells recognizing tumor-specific mutations.



Steven A. Rosenberg, and Nicholas P. Restifo *Science* 2015;348:62-68

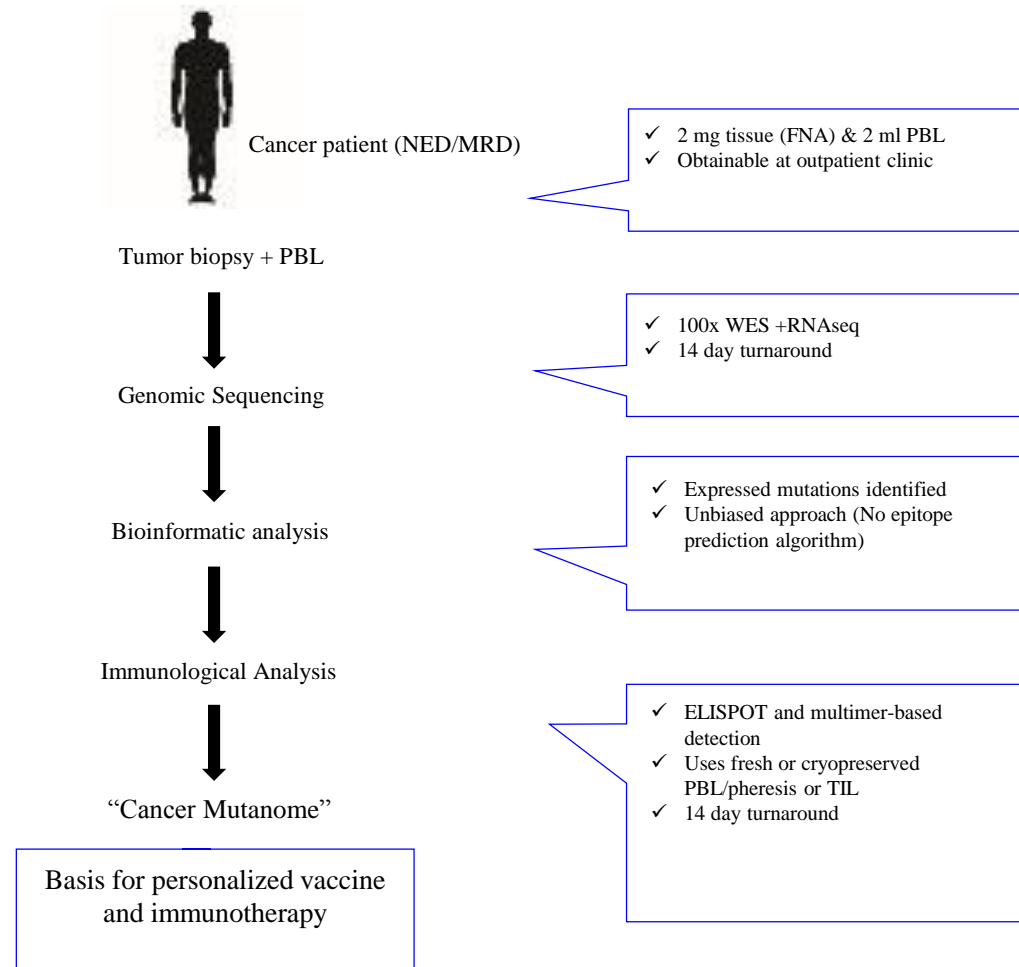
Fig. 4 Gene-modification of peripheral blood lymphocytes.



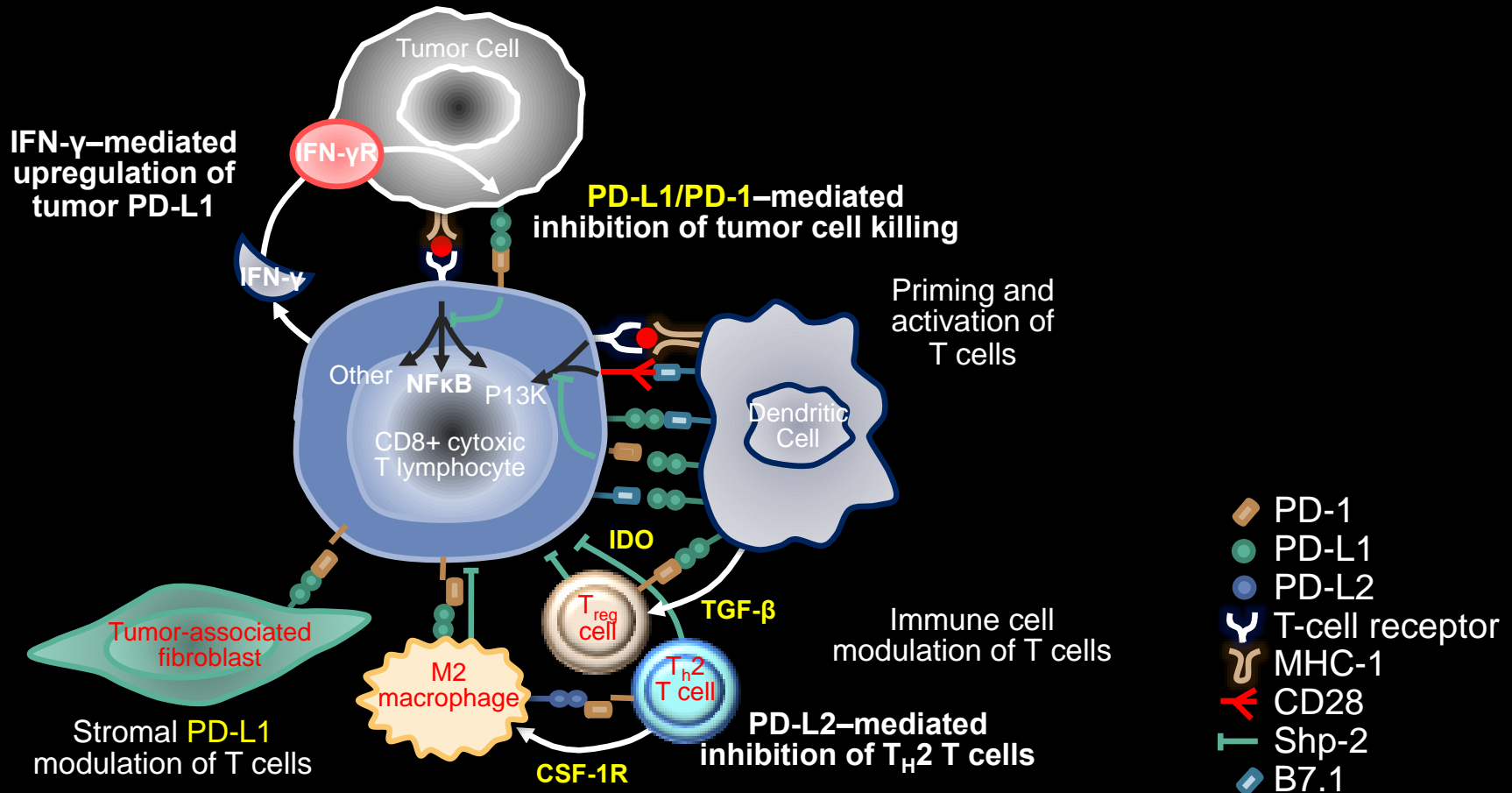
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Neoantigen Based Vaccines

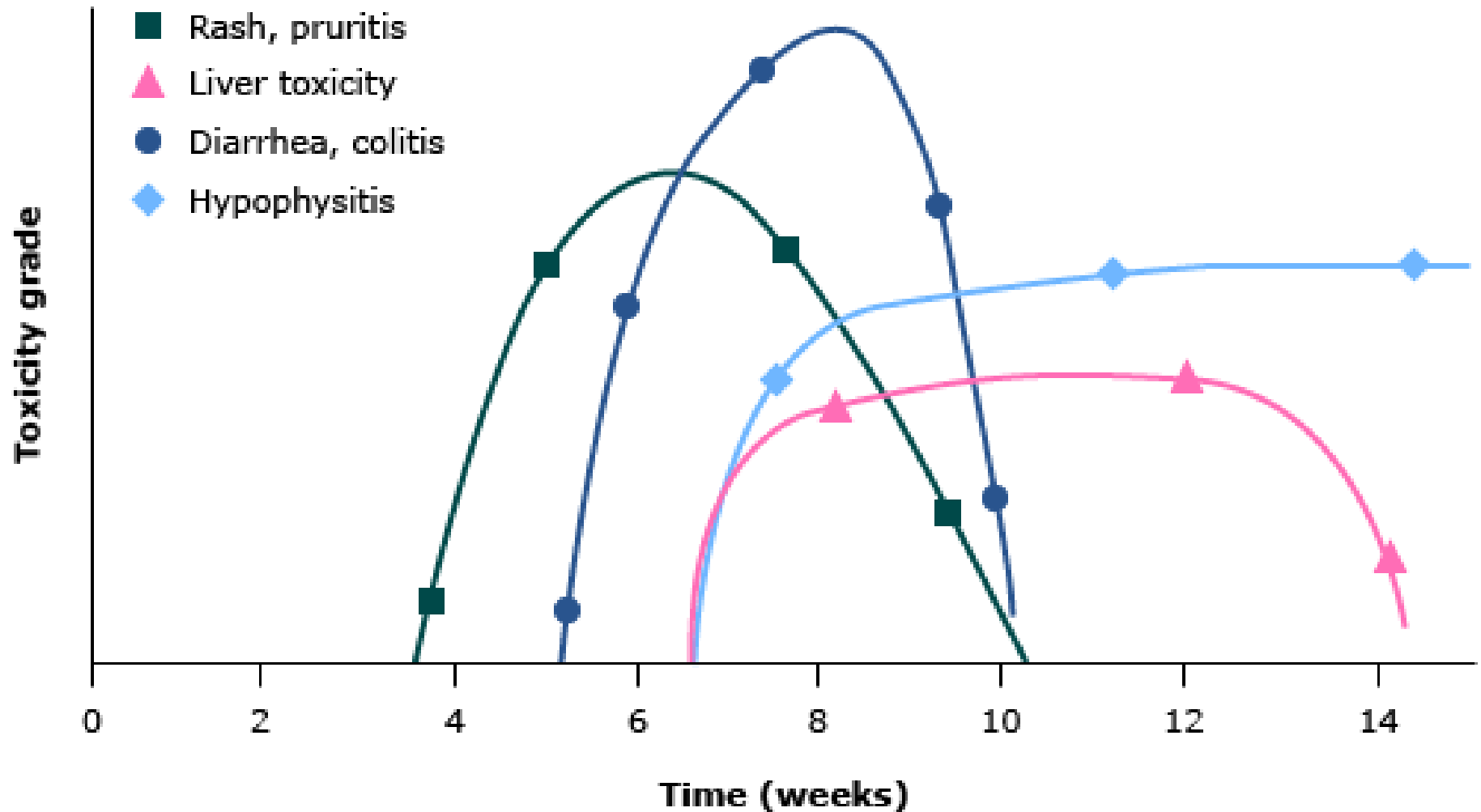
Neoantigen-based Immunotherapy



Combination Therapy



Checkpoint Blockade Toxicity



CONCLUSIONS

- Tremendous excitement about immunotherapy in cancer
- Predicated on a better understanding of the interactions between the immune system and tumor
- Immunotherapy now represents standard of care for several cancers
- Specific considerations need to be remembered
 - Efficacy
 - Toxicity

Oncology Redux

Before Immunotherapy



After Immunotherapy

