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Mechanisms of Action of Immune Checkpoint Inhibitors

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Disclosures

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Personal financial interests, AstraZeneca, MSD International GmbH, BMS, Boehringer Ingelheim Italia S.p.A, Celgene, Eli Lilly, Ignyta, Incyte, Inivata, MedImmune, Novartis, Pfizer, Roche, Takeda, Seattle Genetics, Mirati, Daiichi Sankyo, Regerenon, Merck, Ose Immuno Therapeutics

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Historical roots of immunotherapy

William Coley (1862-1936)

1891: William Coley (Memorial Sloan Kettering Cancer Center-MSKCC, NY). Used the Coley toxin containing live or inactivated bacteria like Serratia Marcescens and Streptococcus pyogenes to treat over 1000 sarcoma patients by intratumor injections. Reproducibility was limited but some patients showed a benefit

Albert Calmette (1863-1933) and Camille Guèrin (1872-1961)

BCG is a vaccine used to prevent tuberculosis (TB). Is composed of mycobacterium Bovis that causes inflammation-dependen immunotherapy of superficial bladder cancer; it has been used for over 30 years. The most effective immunotherapy against a human tumor (ladder)

Paul Ehrlich (1854-1905) German Microbiologist 199 he suggests that some molecules in the body are able to fight cancers

Frank Macfarlane Burnet (1899-1989)

He suggests that some cancer cells are able to create an immune response able to destroy the tumor (1957Immune surveillance theory)

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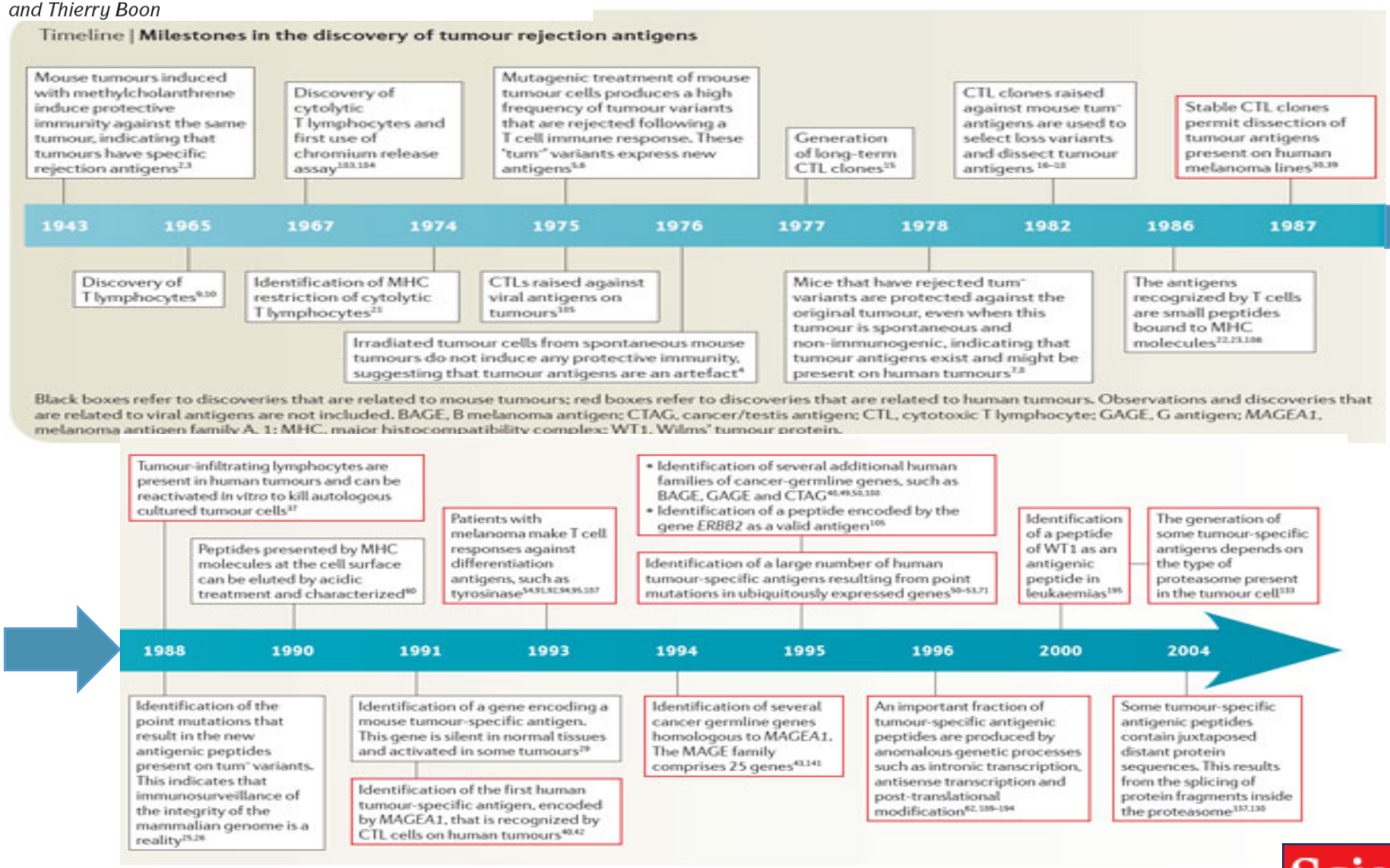
ADVANCES IN Cancer IMMUNOTHERAPY

Tumour antigens recognized by T lymphocytes: at the core of cancer immunotherapy

Pierre G. Coulie, Benoît J. Van den Eynde, Pierre van der Bruggen and Thierry Boon



NATURE REVIEWS | CANCER 14:135,2014

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The Rapid Pace of Cancer Immunotherapy Research

From the breakthrough of year 2013 for *Nature* and *Science* to the inspiration of the moonshot project for next generation immunotherapy

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
ACCC Association of Community Cancer Centers
HOPA Hematology/Oncology Pharmacy Association
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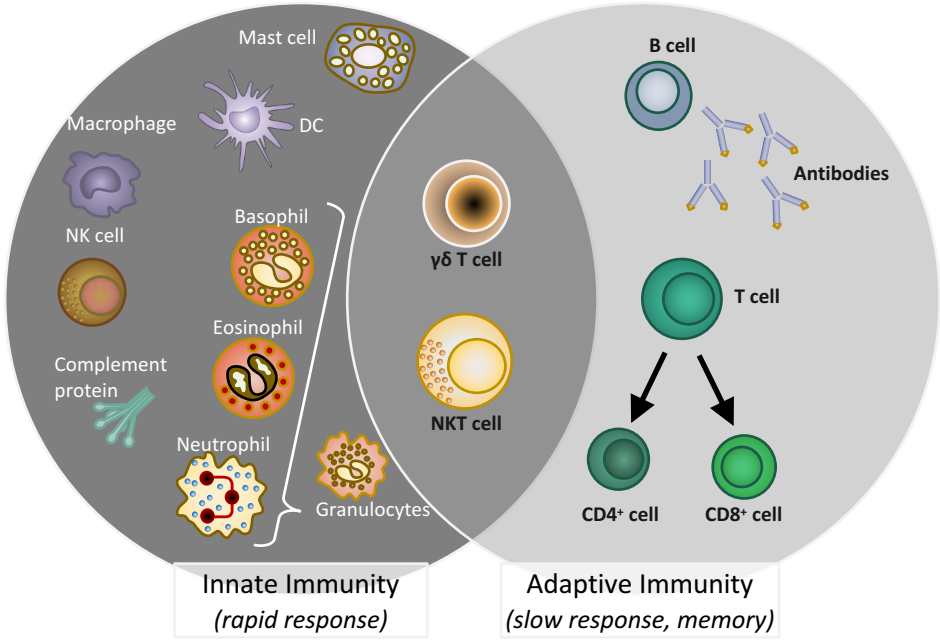
Cells of the Immune System

- **Innate immune system: involving proteins (chemokines and cytokines) and cells, is considered to be the first line of immune defense and does not generate an antigen-specific response1,2**



200 TIPI DI RECETTORI

10^9 TIPI DI RECETTORI

- **Adaptive immune system: mediated by B and T cells is highly specific and capable of generating an antigen-specific response[1,2]**
  - Induction requires presentation of antigens by cells of the innate immune system

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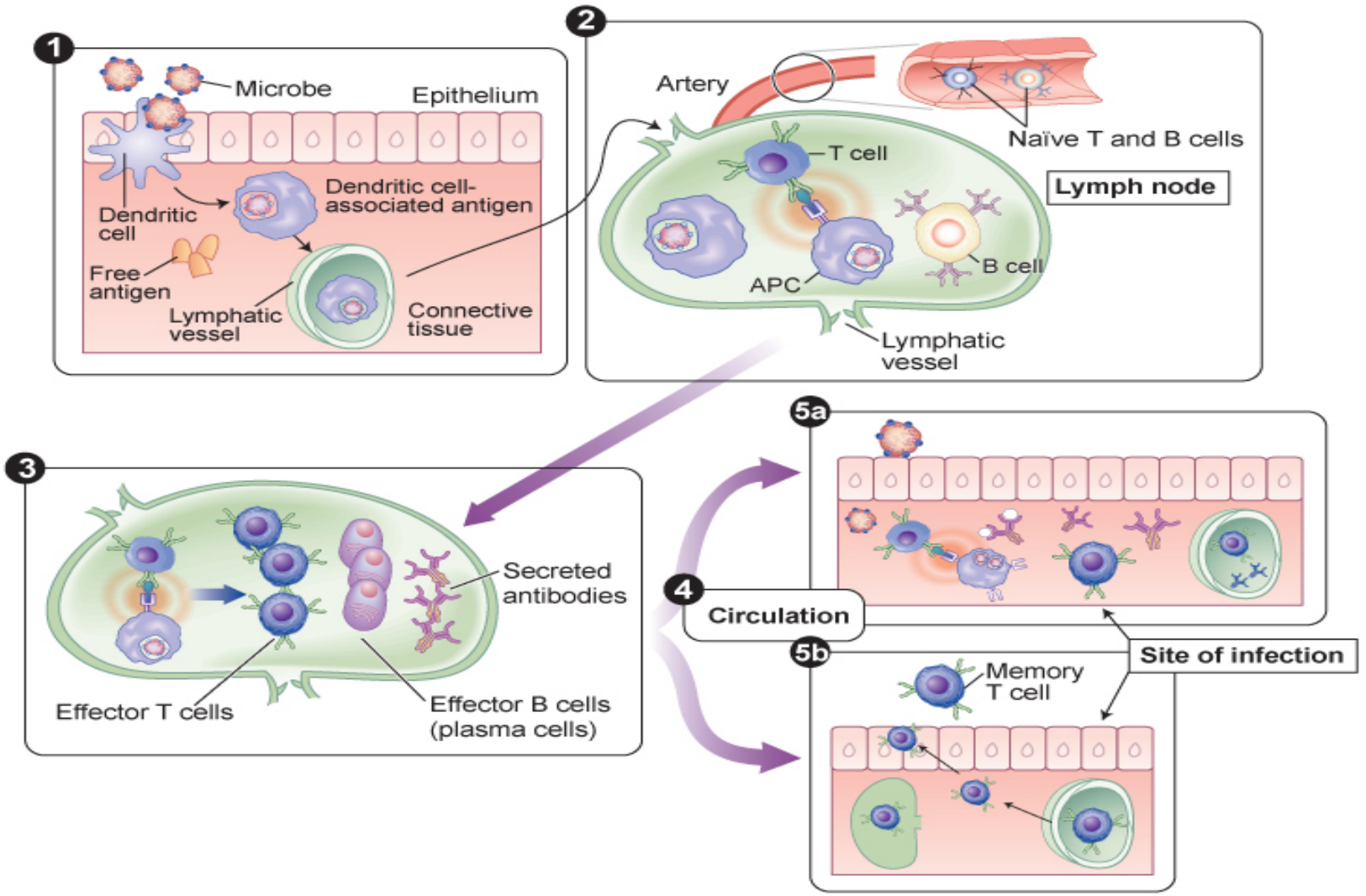
Adapted from Dranoff G.[1]

DC = dendritic cell; NK = natural killer.

1. Dranoff G. *Nat Rev Cancer*. 2004;4:11–22; 2. Janeway CA, et al. *Immunobiology: The Immune System in Health and Disease*. 6th ed. New York, NY: Garland Science; 2004.

Normal Immune Response



Abbas et al. Cellular and Molecular Immunology 5th ed. 2005, Elsevier Saunders
Adapted from Abbas and Lichtman, 2005

Escape from immune control is a hallmark of cancer

Elimination

Cancer immunosurveillance

- **Effective antigen processing/presentation**
- **Effective activation and function of effector cells**
  - e.g. T cell activation without co-inhibitory signals

Equilibrium

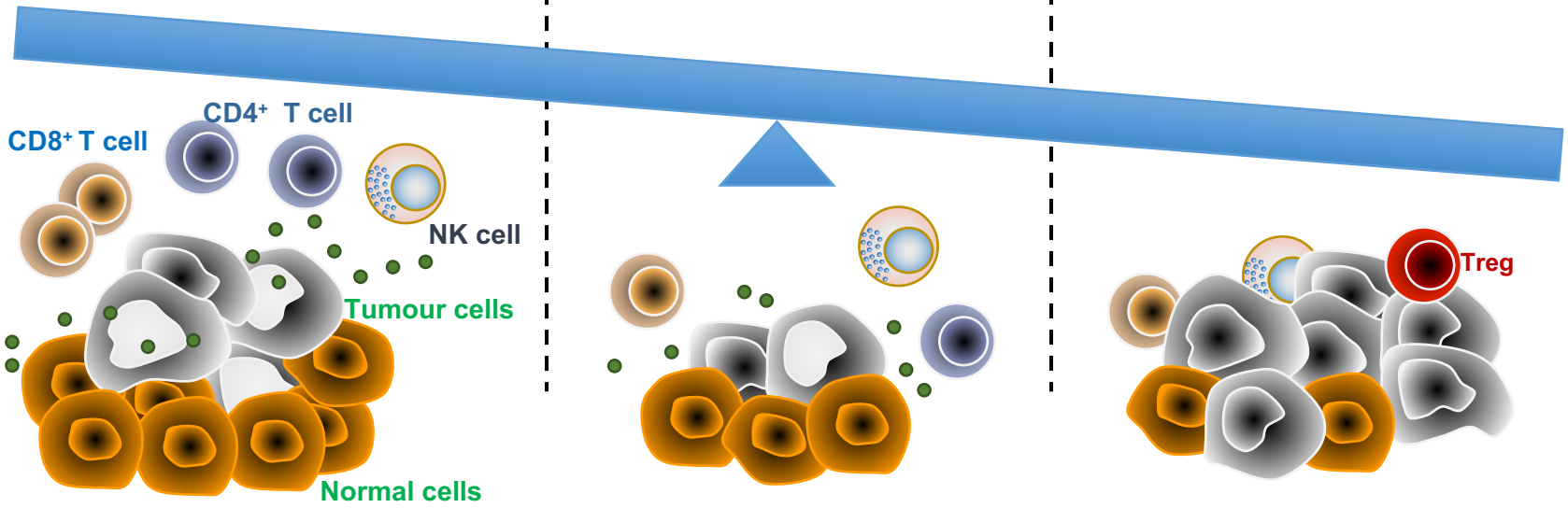
Cancer dormancy

- **Genetic instability**
- **Tumour heterogeneity**
- **Immune selection**

Escape

Cancer progression

- **Tumours avoid elimination through the outgrowth of tumour cells that can suppress, disrupt or 'escape' the immune system**
- **Reduced immunogenicity**



NK = natural killer; Treg = regulatory T cells.

Vesely M and Schreiber R. *Ann N Y Acad Sci.* 2013;1284:1–5.

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Tumours use various mechanisms to escape the immune system

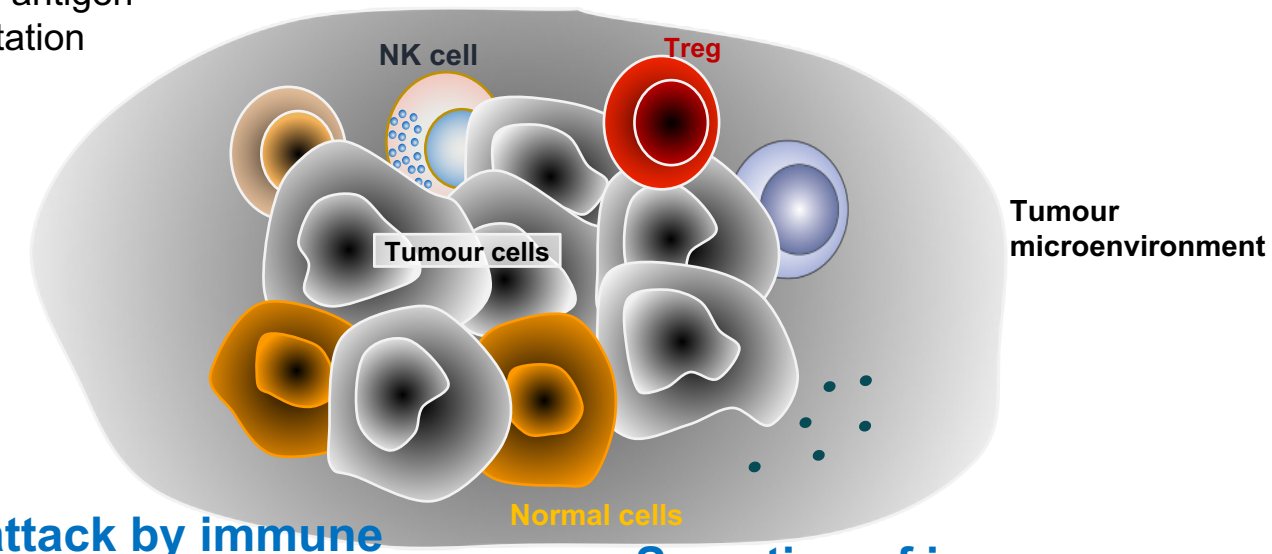
Immune escape mechanisms are complex and frequently overlapping

Ineffective presentation of tumour antigens[1]

e.g. down regulation of MHC I and DC/APC defects in antigen processing/presentation

Recruitment of immunosuppressive cell types[1,2]

e.g. Tregs, MDSC, others



Inhibition of attack by immune cells[1,2]

e.g. disruption of T cell-activating and checkpoint pathways (i.e. PD-1/PD-L1)

Secretion of immunosuppressive cytokines[1,2]

e.g. TGF-*B*, IDO, IL-10 inhibiting T cells directly

APC = antigen presenting cell; DC = dendritic cell; IDO = indoleamine 2,3-dioxygenase; IL-10 = Interleukin-10;
MDSC = myeloid-derived suppressor cells; MHC = major histocompatibility complex; TGF-β = transforming growth factor-β.

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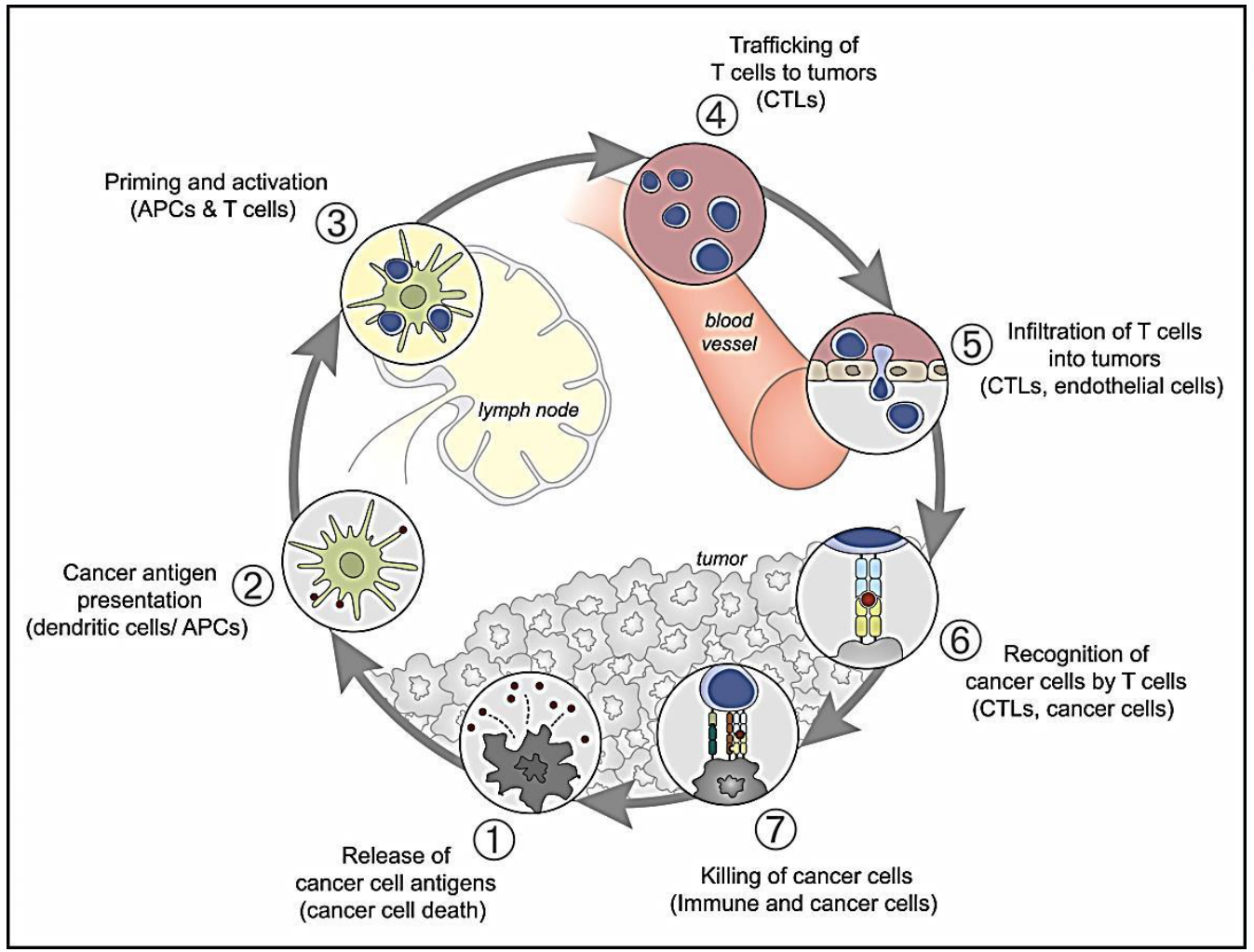
1. Jadus M, et al. *Clin Dev Immunol*. 2012:160724; 2. Quezada S, et al. *Immunol Rev.* 2011;241:104–118.

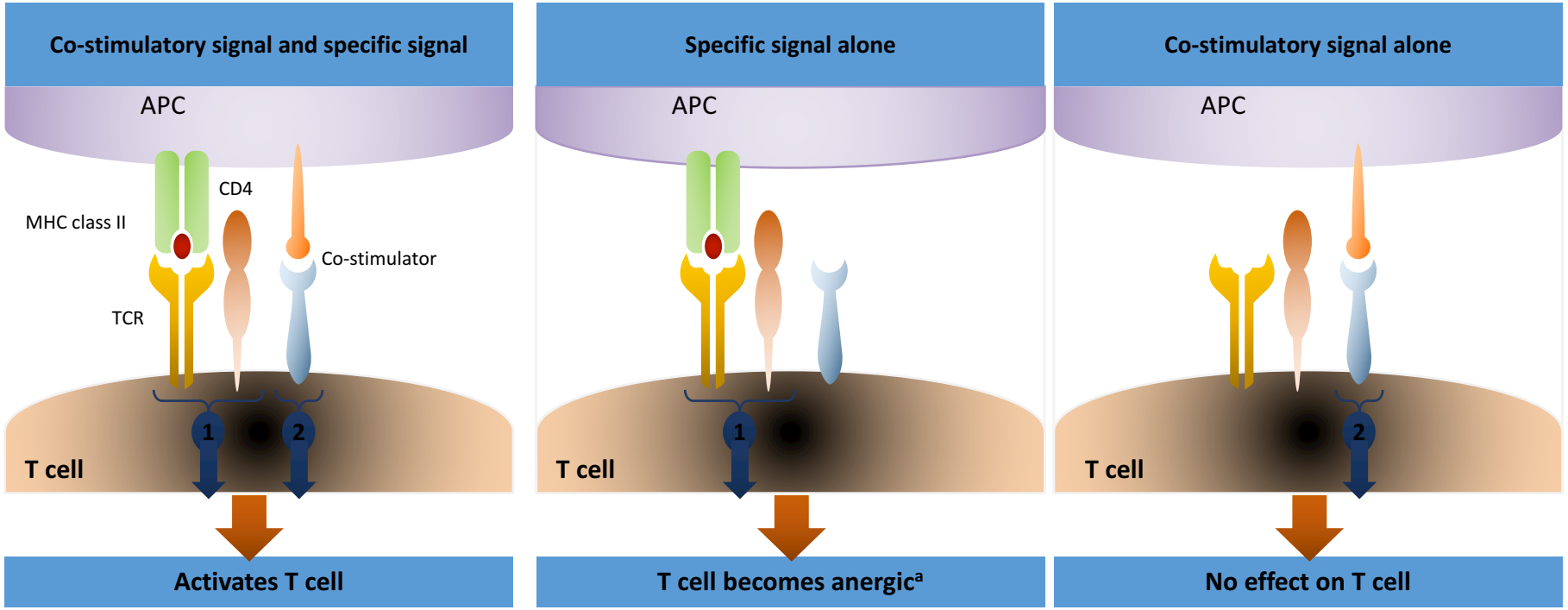
The cycle of cancer immunity



Chen D & Mellman I, Immunity 2013 39,1

Activation of Naïve T Cells

- T cells require multiple signals to become fully activated[1]
- In addition to antigen stimulation in the context of MHC molecules, positive co-stimulation is required[1]
- Co-stimulatory or activating receptors include CD28, CD137, CD40, and OX-40[2]



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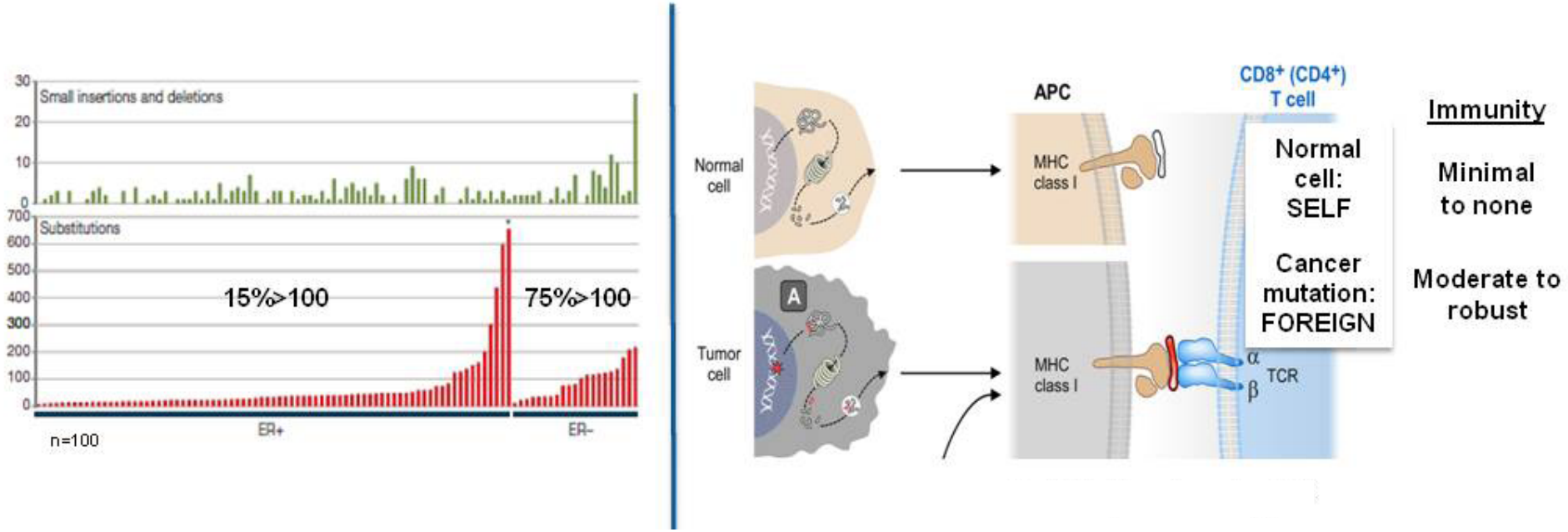
[a]Anergy describes a state of functional inactivation.

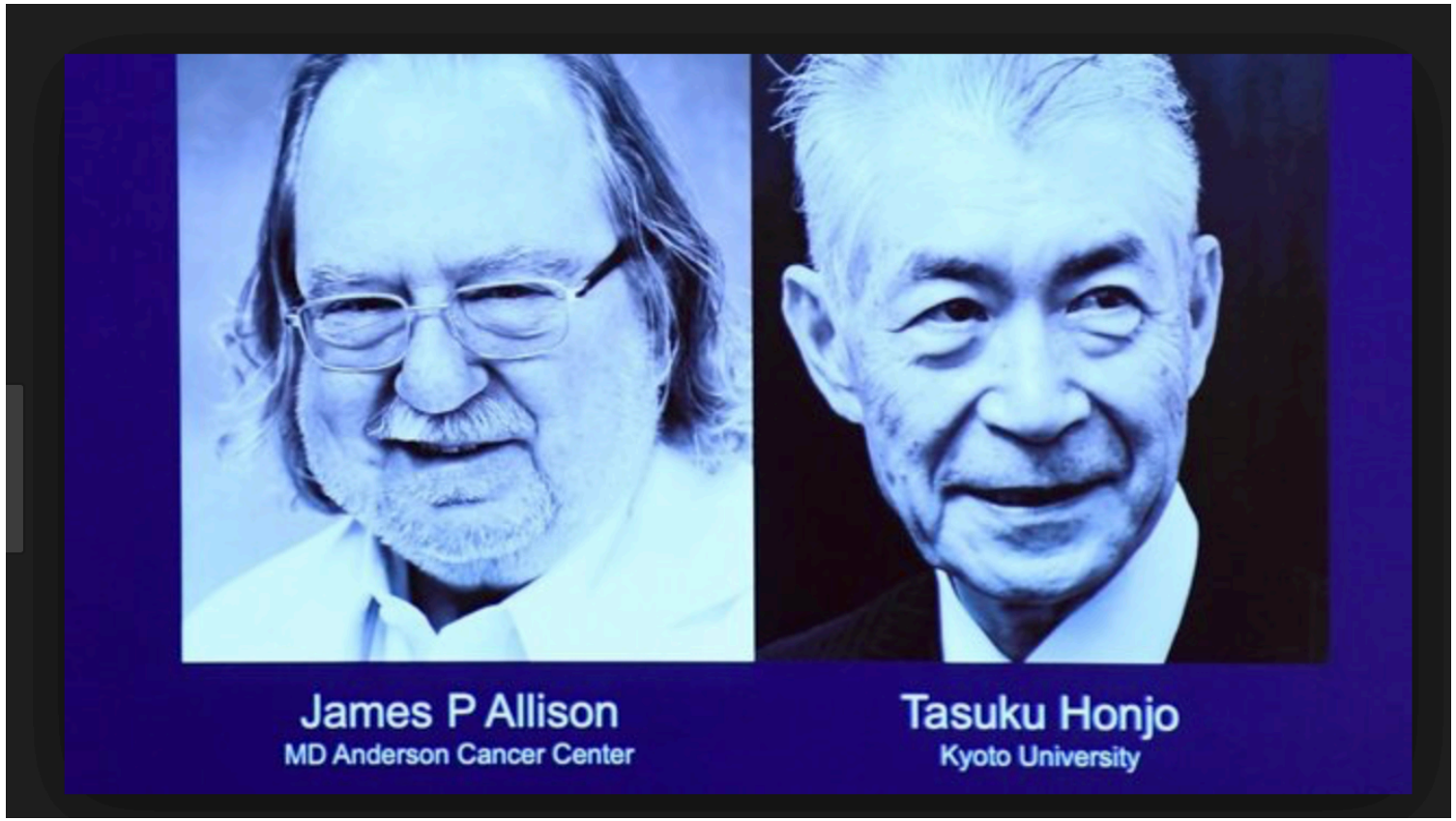
1. Janeway CA, et al. *Immunobiology*. 2008; 2. Pardoll DM. *Nat Rev Cancer.* 2012;12:252–264.

Mutational Load Creates Neoantigens

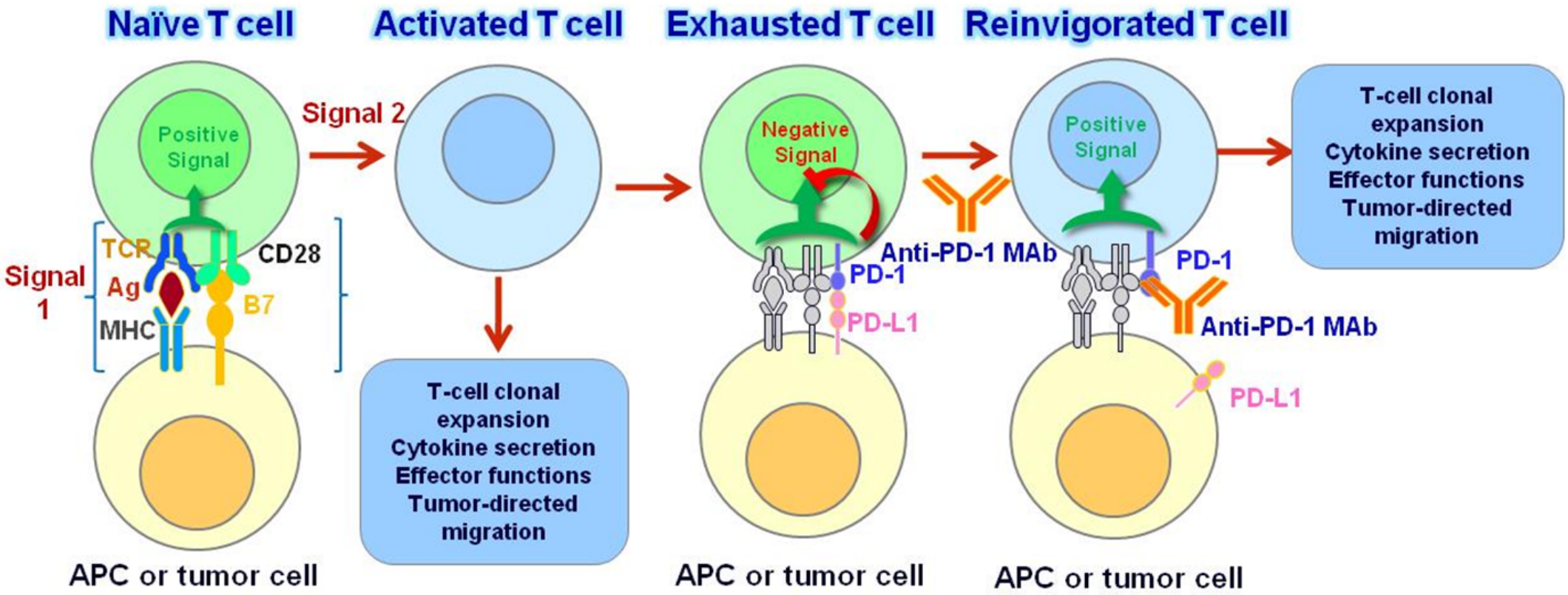


Stephens PJ, et al. *Nature*. 2012;486(7403):400-404. Fritsch EF, et al. *Oncoimmunology*. 2014;3:e29311

Nobel Prize 2018

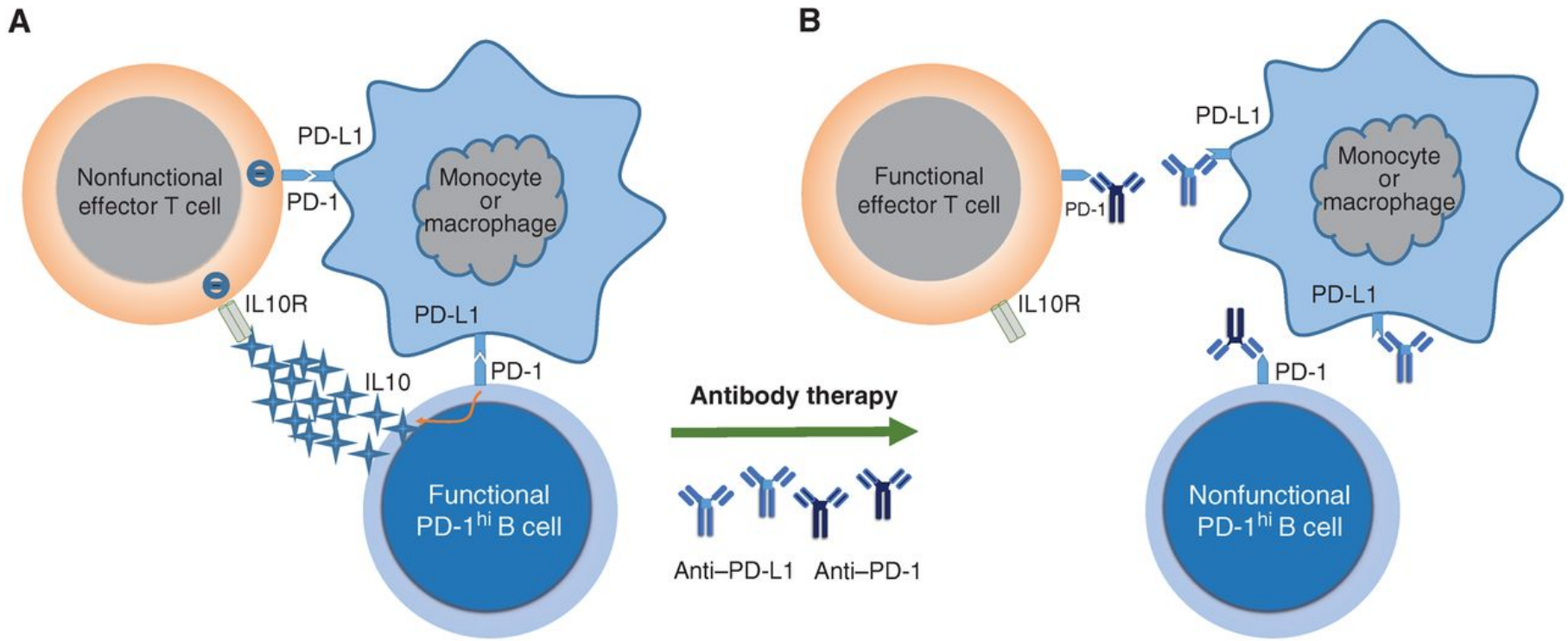


Activating and Inhibiting signals



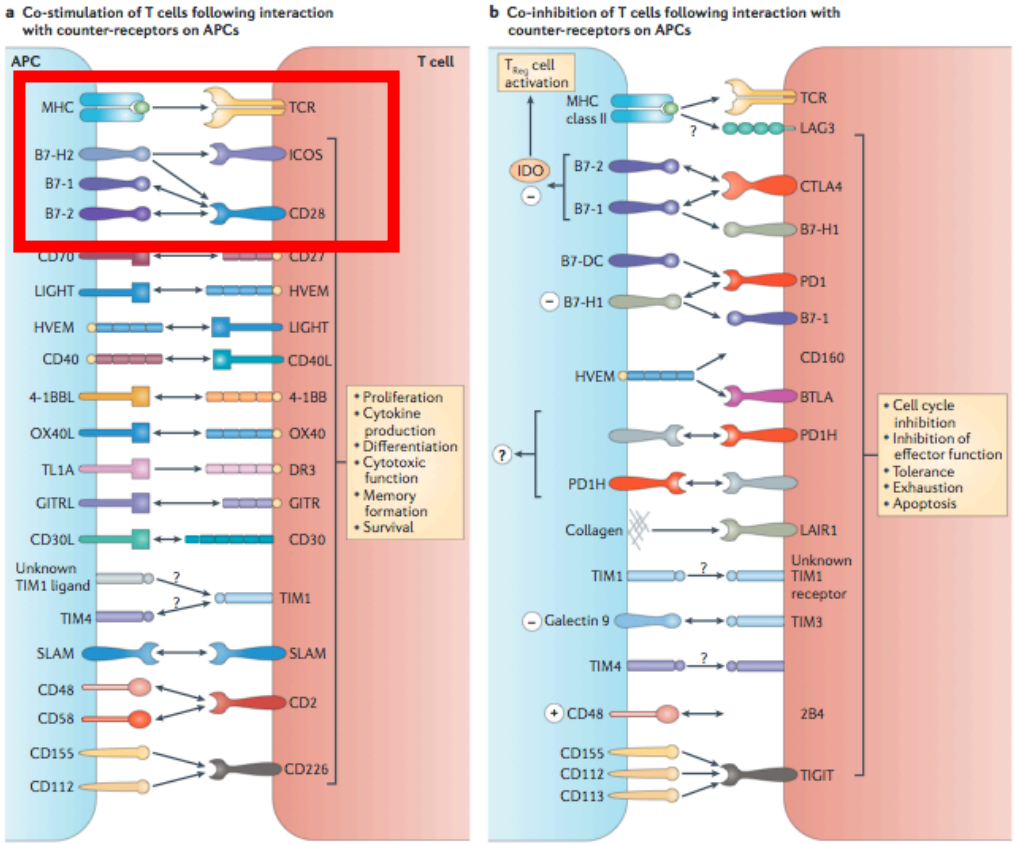
Topalian and Brahmer NEJM 2012

The Role of the PD-1–PD-L1 Interaction in Suppressing Tumor-Specific T-cells and the Potential Mechanism of How Anti–PD-1/Anti–PD-L1 Works in Tumor Treatment



Ren Z, et al. Cancer Discov; 2016, 6: 477–8.

IMMUNOLOGIC SYNAPSIS



L.Chen et al, Nature Reviews Immunology, 2013 Apr;13(4):227-42

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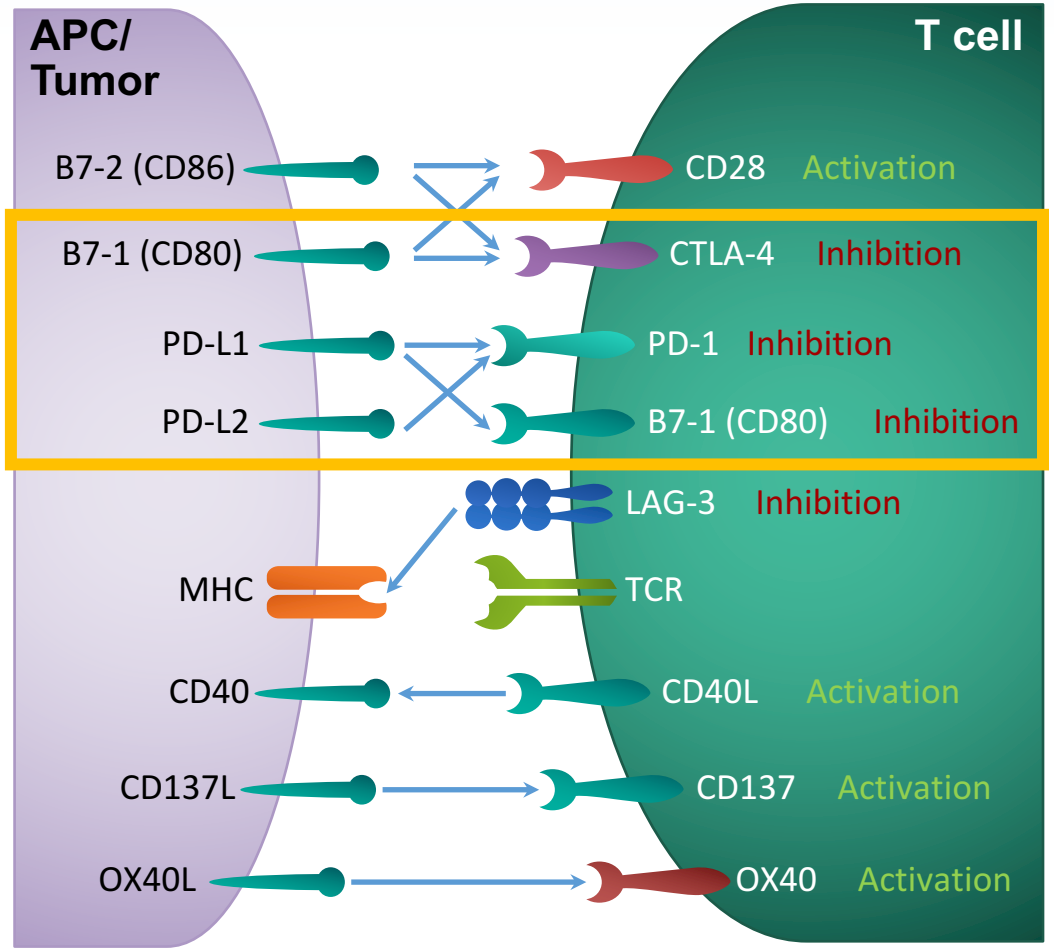
Regulation of T-Cell Activation: Balancing Activating and Inhibitory Signals

- Immune checkpoints limit, or "check," an ongoing immune response
- Prevents damage to the body's healthy tissues
  - Negative co-stimulation, also called "co-inhibition," helps shut down immune responses
  - PD-1, CTLA-4, and LAG-3 are examples of co-inhibitory "checkpoint" molecules
- Amplitude and quality of a T-cell response is regulated by a balance of activating and inhibitory signals



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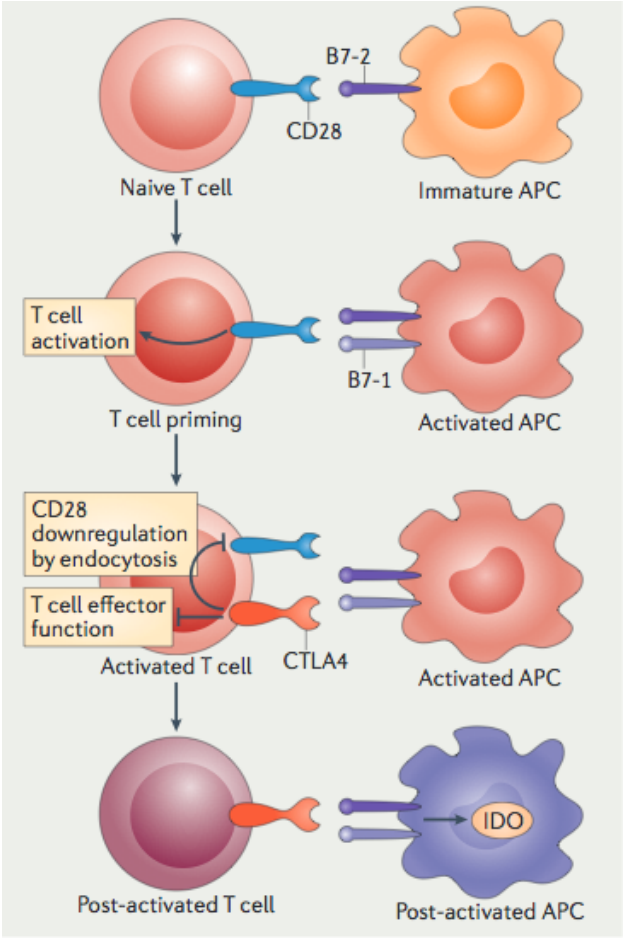
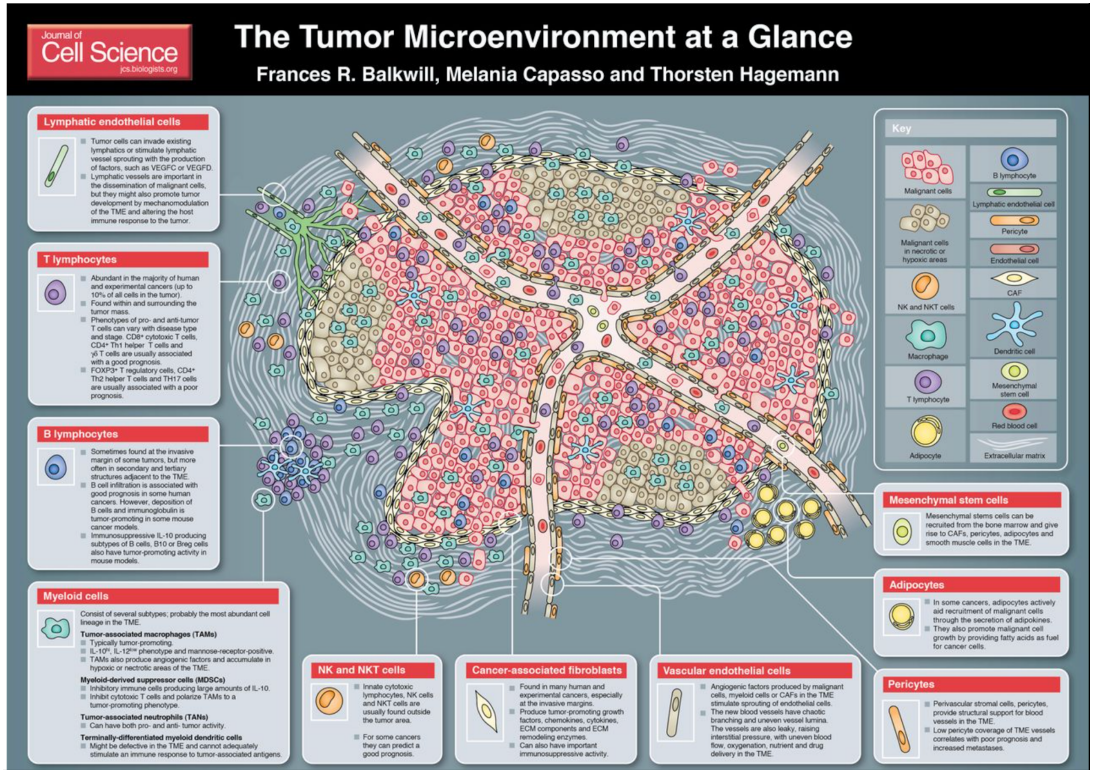
CTLA-4 = cytotoxic T-lymphocyte antigen-4; LAG-3 = lymphocyte activation gene-3; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1.

Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Explanation of the Molecular Mechanisms of Checkpoint Inhibitors and Other Key Emerging Immunologic Strategies

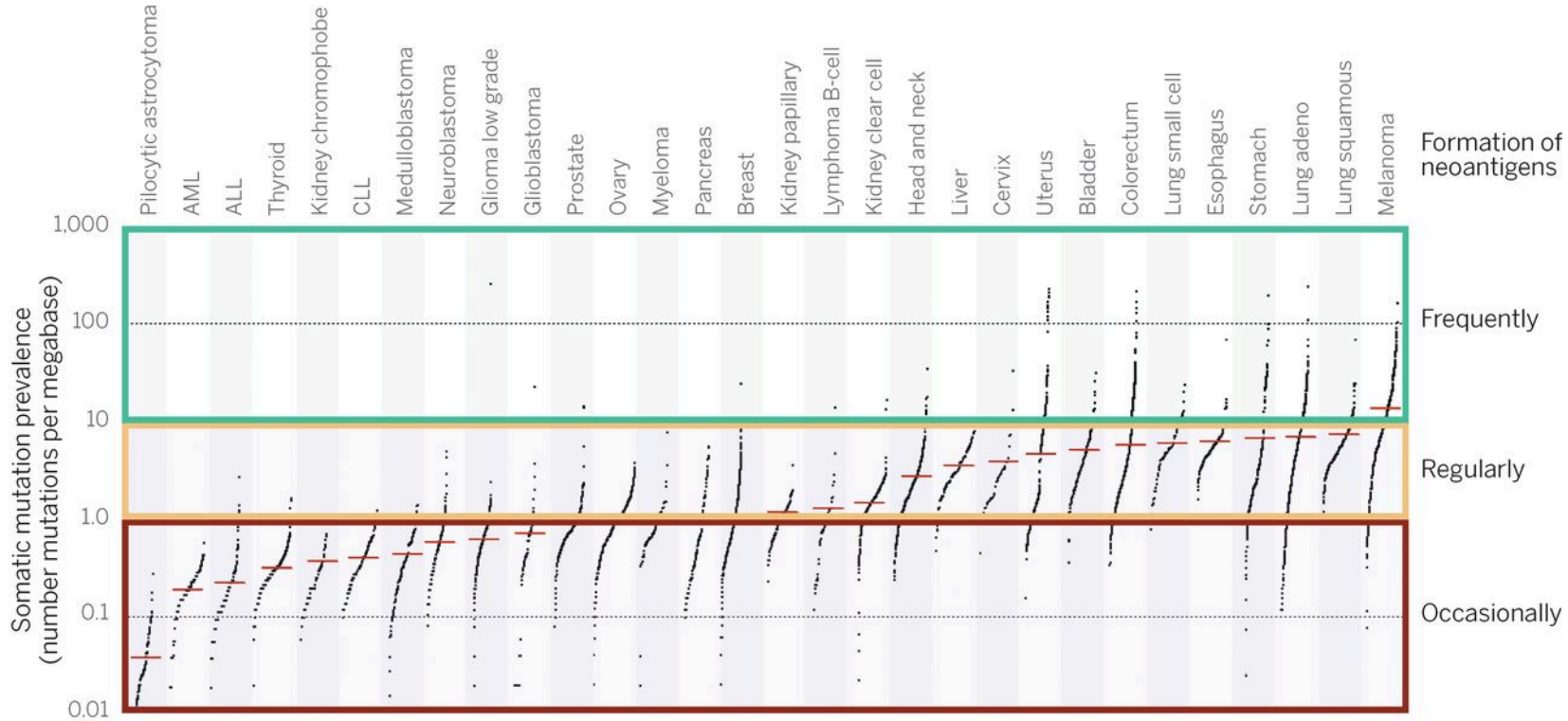




Chen L, et al. *Nat Rev Immunol.* 2013;13(4):227-242.

Mutational Heterogeneity in Cancer: Altered Proteins Contain Neo-Epitopes for Immune Recognition

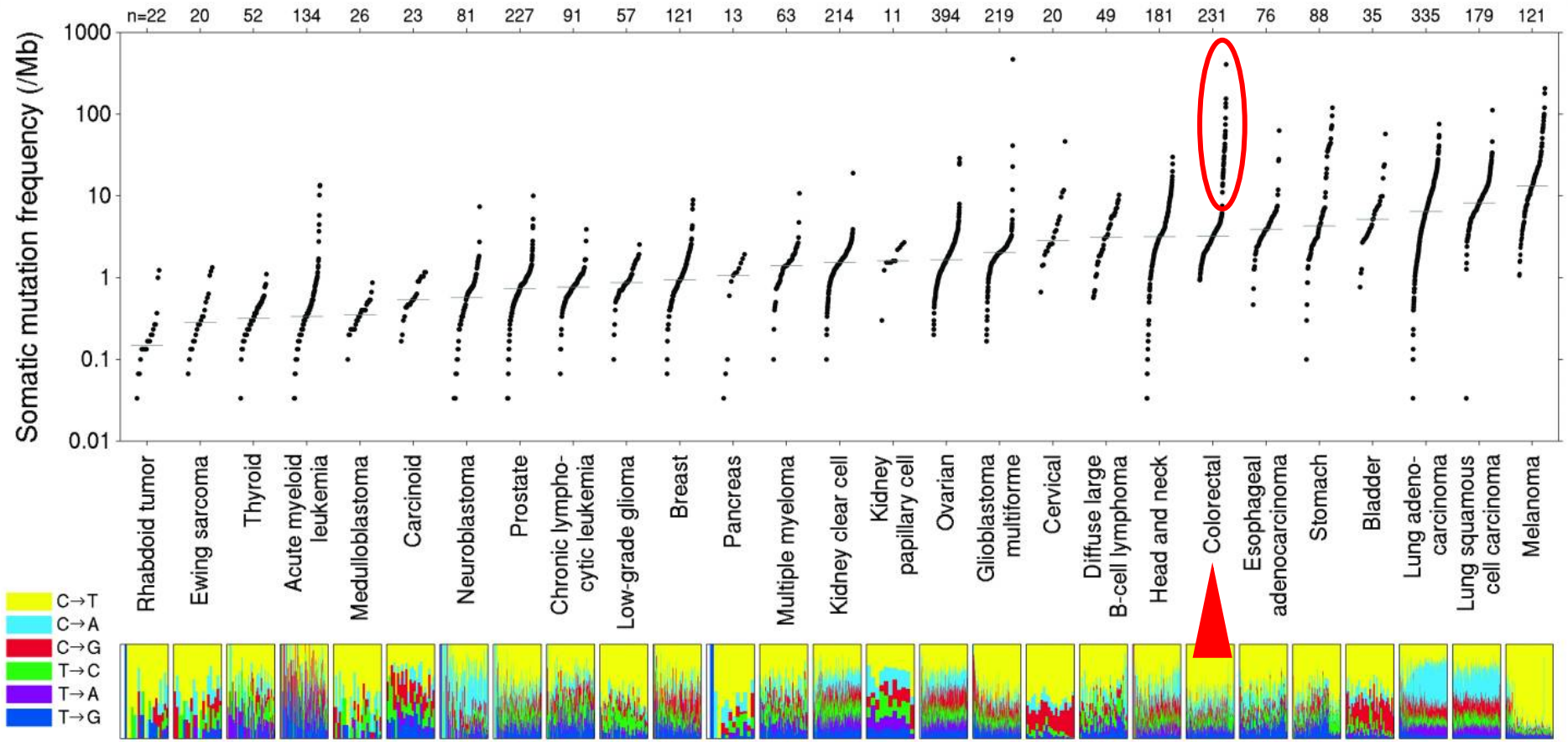
Fig. 2 Estimate of the neoantigen repertoire in human cancer.



Ton N. Schumacher, and Robert D. Schreiber Science 2015;348:69-74

Published by AAAS

Colorectal Cancers Are Generally Unresponsive to PD-1 Blockade, but the MSI-High Subset Has a High Mutational Load



Lawrence MS, et al. *Nature*. 2013;499(7457):214-218.

Microsatellite instability (MSI): Genetic hypermutability resulting from deficient mismatch repair (dMMR), present in ~15% colon cancers and in some other tumor types

Topalian SL, et al. *J Clin Oncol.* 2013;31(suppl): Abstract 3002.

Tumors Use Complex, Overlapping Mechanisms to Evade and Suppress the Immune System

3

Priming and Activation

CD28/B7.1, CD137/CD137L
OX40/OX40L, CD27/CD70
HVEM, GITR, IL-2, IL-12

CTLA4/B7.1
PD-L1/PD-1
PD-L1/B7.1 Prostaglandins

2

Cancer antigen presentation

TNF-α, IL-1
IFN-α, CD40L/CD40
CDN, ATP
HMGB1, TLR

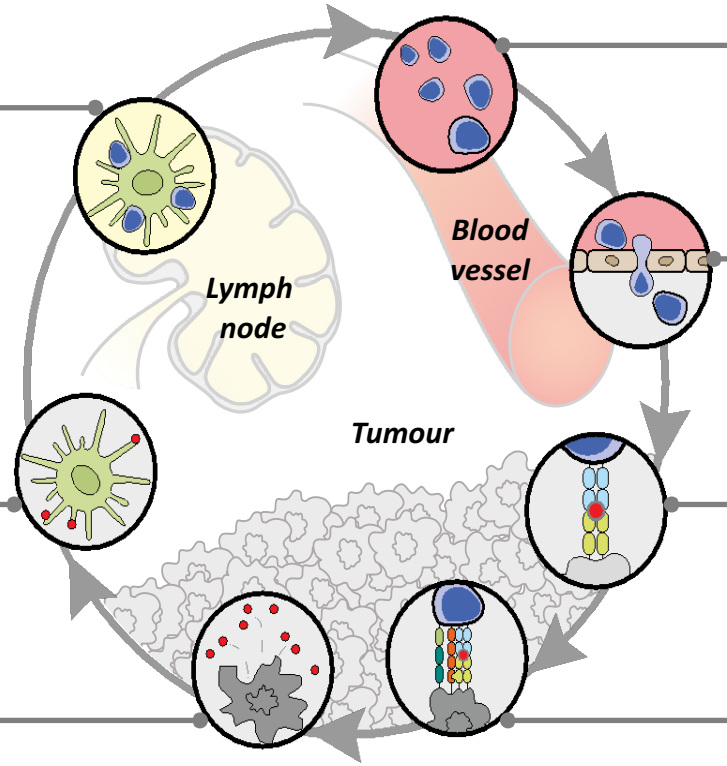
IL-10, IL-4, IL-13

1

Release of cancer cell antigens

Immunogenic cell death

Tolergenic cell death



4

Trafficking of T cells to tumours

CX3CL1, CXCL9, CXCL1
CCL5

5

Infiltration of T cells into tumours

LFA1/ICAM1
Selectins

VEGF
Endothelin-B receptor

6

Recognition of cancer cells by T cells

T cell receptor

Reduced pMHC on cancer cells

7

Killing of cancer cells

IFN-γ , T-cell granule content

TIM-3/phosphatidylserine

PD-L1/PD-1	VISTA
PD-L1/B7.1	LAG-3
IDO	Arginase
TGF-β	MICA/MICB
BTLA	B7-H4

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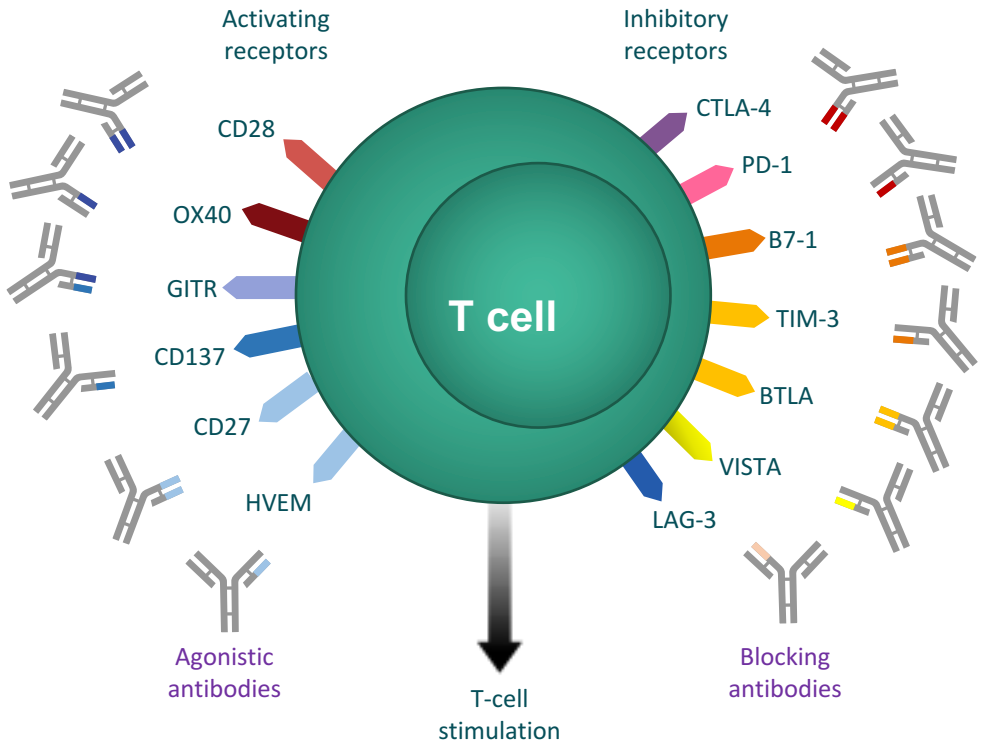
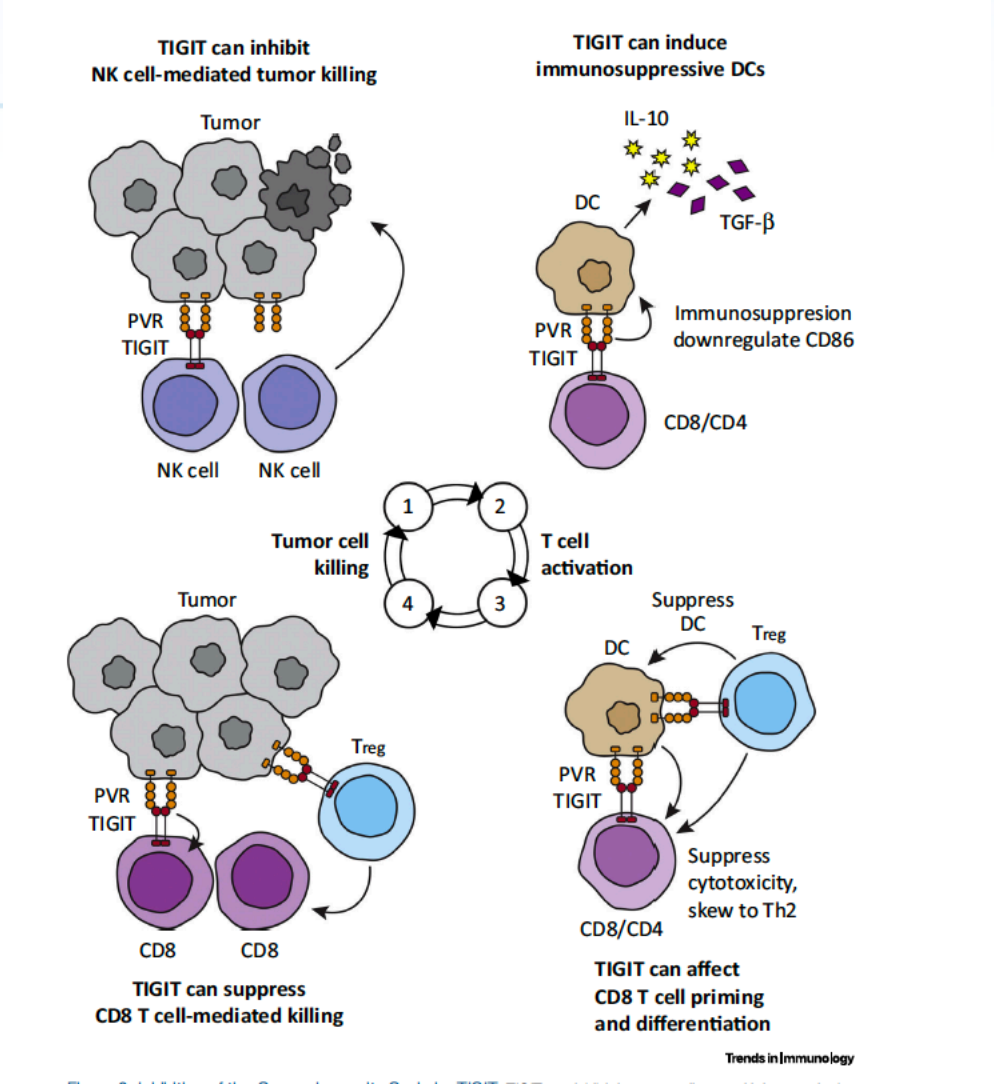
Selected T-Cell Checkpoints: Targets for Active Immunotherapy



- T-cell responses are regulated though a complex balance of inhibitory ("checkpoint") and activating signals
- Tumors can dysregulate checkpoint and activating pathways, and consequently, the immune response
- Targeting checkpoint and activating pathways is an evolving approach to active immunotherapy, designed to promote an immune response

[a]The image shows only a selection of the receptors/pathways involved.

1. Adapted from Mellman I, et al. *Nature*. 2011:480;481–489; 2. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.



Trends in Immunology

CellPress

Review

TIGIT: A Key Inhibitor of the Cancer Immunity Cycle

Nicholas A. Manieri,[1] Eugene Y. Chiang,[1] and Jane L. Grogan[1,*]

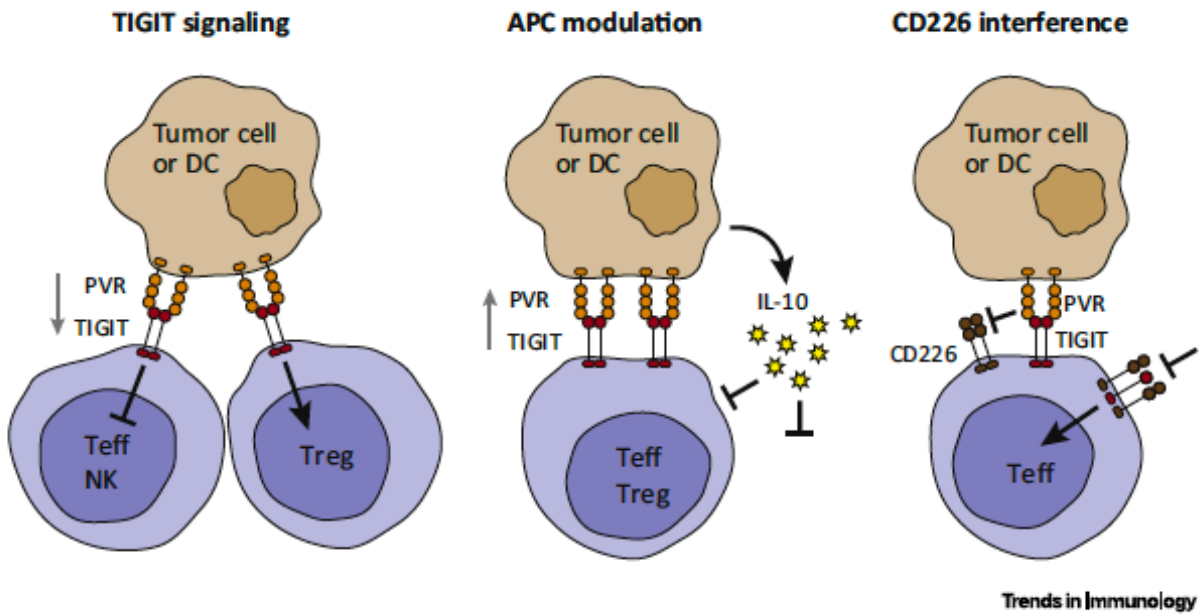


Figure 3. Modes of Action of TIGIT. TIGIT can inhibit lymphocytes through three distinct mechanisms of action. TIGIT can signal through the ITIM and/or ITT motifs on its intracellular tail after binding to PVR (left). TIGIT can induce PVR signaling in adjacent dendritic cells or tumor cells by binding to PVR (middle). TIGIT can inhibit CD226 signaling by binding to PVR at a higher affinity or disrupting CD226 homodimerization (right). Abbreviations: APC, antigen-presenting cell; PVR, poliovirus receptor; TIGIT, T cell immunoglobulin and ITIM domain; Teff, effector T cell; Treg, regulatory T cell.

Trends in Immunology
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TIGIT: A Key Inhibitor of the Cancer Immunity Cycle

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therapeutic targets for chronic infection and cancer.

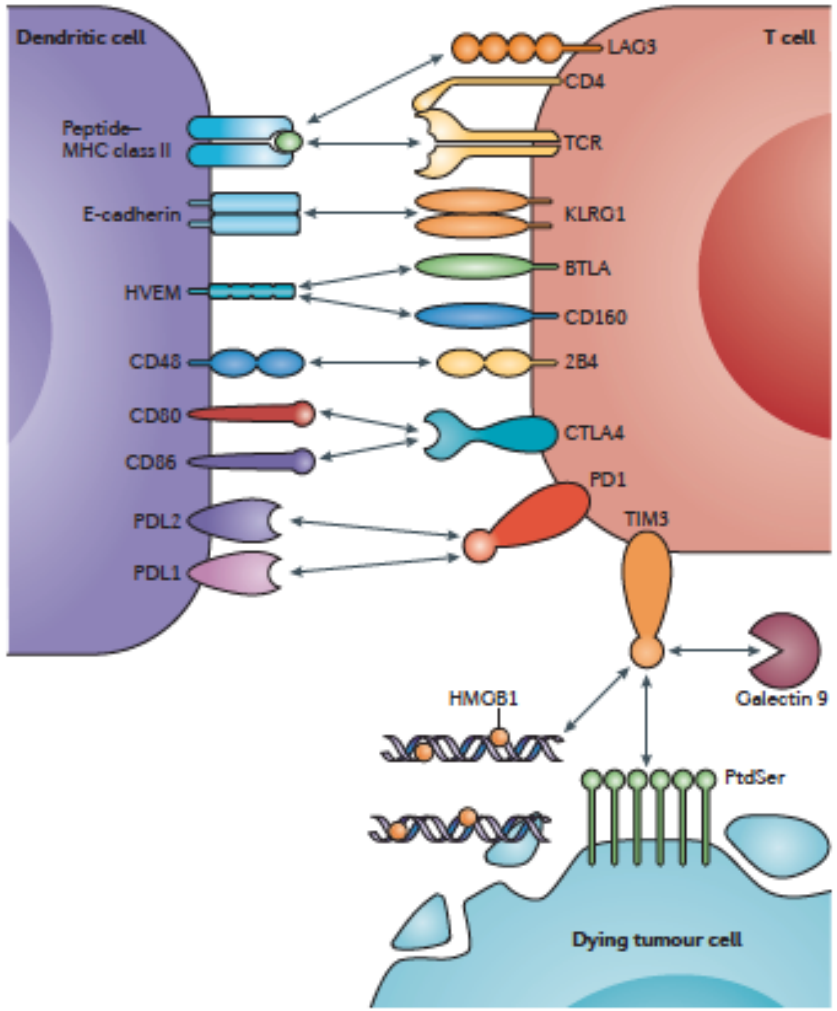

Figure 1 | **Receptors that negatively regulate T cell function.** Inhibitory receptors

Clinical blockade of PD1 and LAG3 — potential mechanisms of action

Linh T. Nguyen and Pamela S. Ohashi

Abstract | Dysfunctional T cells can render the immune system unable to eliminate infections and cancer. Therapeutic targeting of the surface receptors that inhibit T cell function has begun to show remarkable success in clinical trials. In this Review, we discuss the potential mechanisms of action of the clinical agents that target two of these receptors, programmed cell death protein 1 (PD1) and lymphocyte activation gene 3 protein (LAG3). We also suggest correlative studies that may define the predominant mechanisms of action and identify predictive biomarkers.

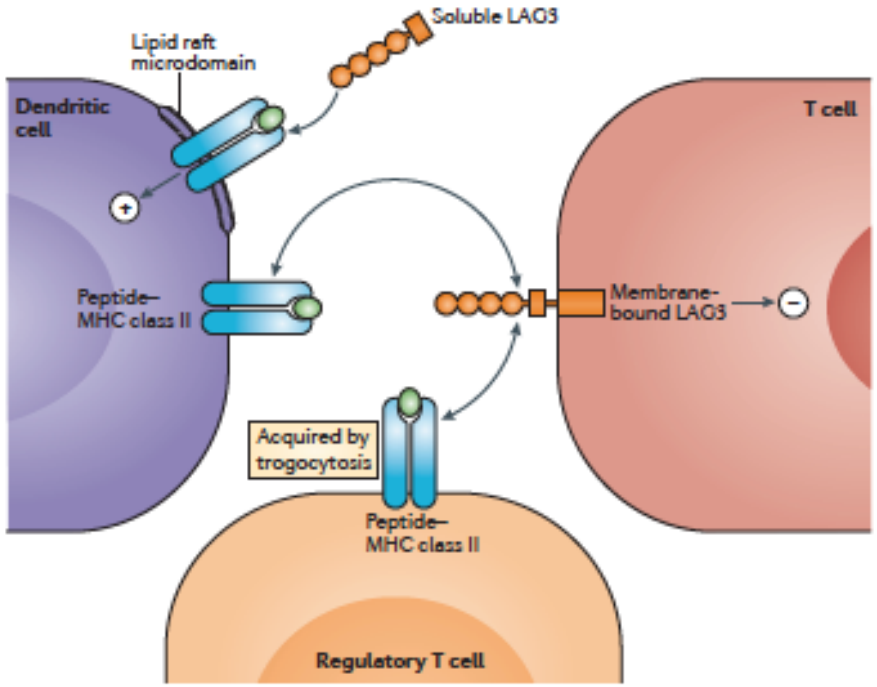

Figure 4 | **Membrane-bound versus soluble LAG3.** The different outcomes of the interaction of lymphocyte activation gene 3 protein (LAG3) alternative spice variants with their MHC class II ligands are depicted. Signalling through membrane-bound LAG3 on T cells after it binds to MHC class II molecules negatively regulates T cell function. By contrast, signalling through MHC class II in lipid raft microdomains on a subset of dendritic cells after it is bound by soluble LAG3 (sLAG3) results in dendritic cell activation. In addition to interacting with MHC class II molecules on DCs, LAG3 is also reported to bind to MHC class II molecules that have been acquired by regulatory T cells in the process of trogocytosis. The addition sign denotes an interaction that positively stimulates cell function; the minus sign denotes an interaction that negatively regulates cell function.

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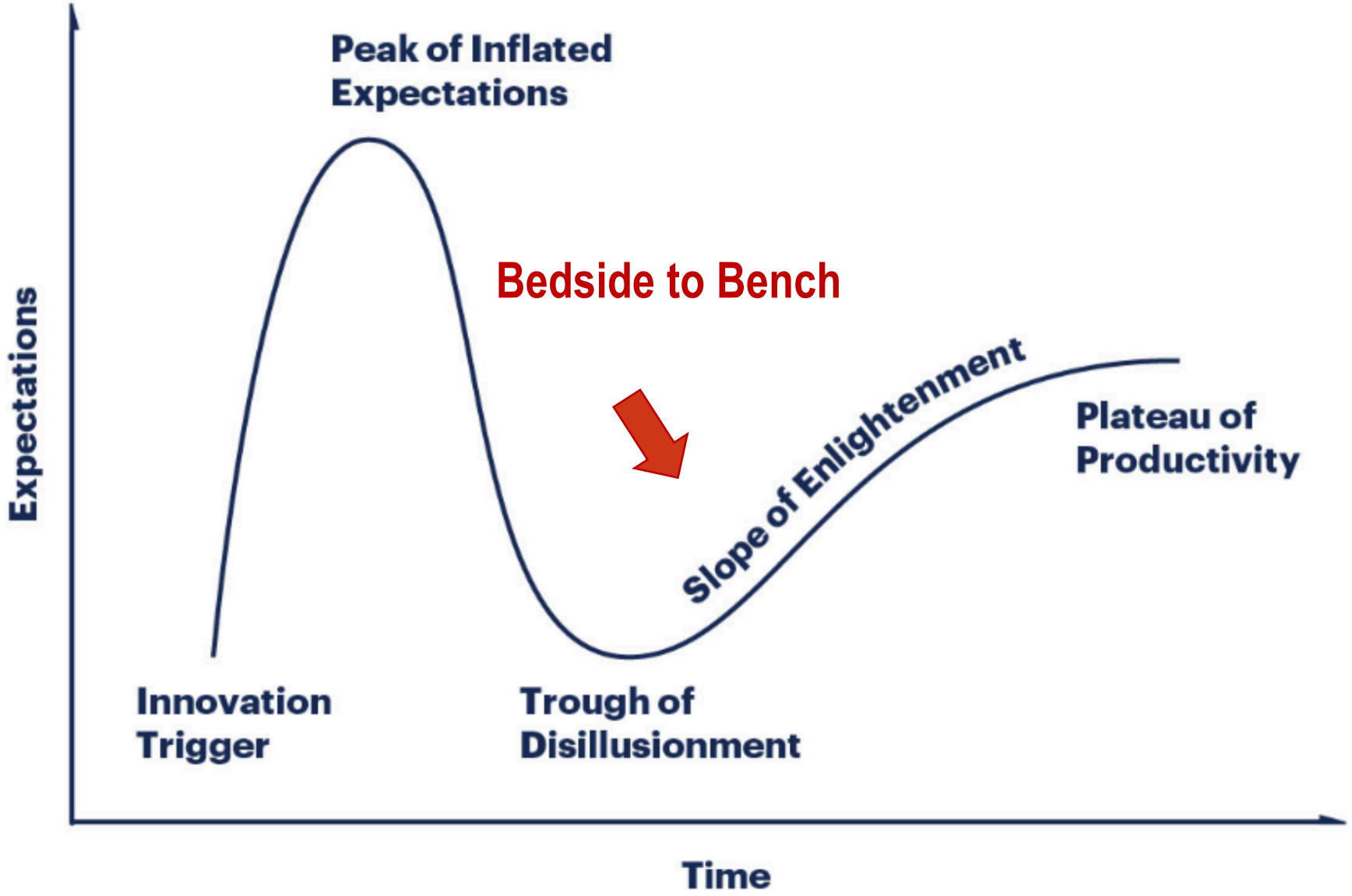
#immunoconfusion



Conclusions

- Immune-checkpoint inhibitors have revolutionized the treatment of many cancers
- There is a continuous balance of co-stimulatory and co-inhibiting signals
- There is a continuous cross talk between innate immunity and adaptive immunity
- immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins. This prevents the “off” signal from being sent, allowing the T cells to kill cancer cells.
- Targeting PD1/PD-L1 and CTLA4 are the most effective strategies
- Other promising targets are on drug development