Immunology and Immunotherapy 101 for the Non-Immunologist

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&
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Disclosures

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- Asterias Inc: *Consultant fees*
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Learning Objectives

- *To review the function and organization of the immune system*
- *To highlight the fundamentals of immune response to cancer*
- *To discuss the basic principles of cancer immunotherapy*

What is the immune system?

- A network of organs, tissues, cells, and effector molecules that cooperate to protect the organism from *pathogenic infection*
- Able to *evolve* to match the ever-changing threats of the microbial world
- Immune-related diseases include autoimmunity, allergy, organ graft rejection, & metabolic disorders, among others.

Why is the immune system?

Key concepts:

The immune system exists to respond to that which is both ***foreign*** (i.e. non-self) & ***dangerous*** (i.e. capable of causing damage).

The immune system 'senses' the dangerous potential and 'learns' the distinct molecular features of a given invader.

Why is the immune system?

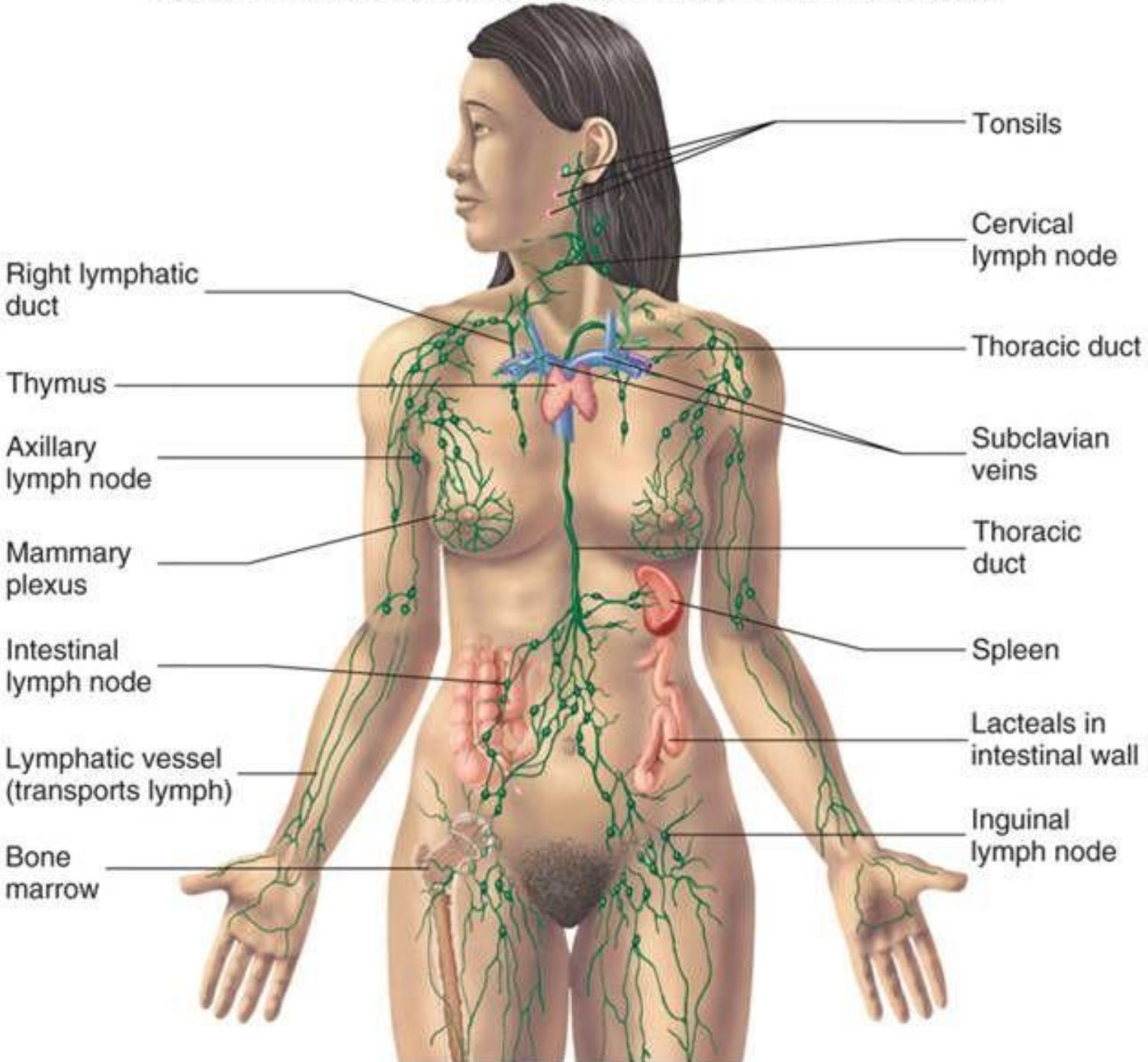
Key concepts:

The immune system can then ‘remember’ these features in the form of antigen-specific memory cells that can mount faster & stronger recall responses

Optimal immune responses require coordination of both *sensing* and *learning* components

Where is the immune system?

- Cellular and molecular components are located throughout the entire body
- Most immune cells are produced in bone marrow from hematopoetic stem cells
- Specialized organizing centers include spleen, lymph nodes, & thymus

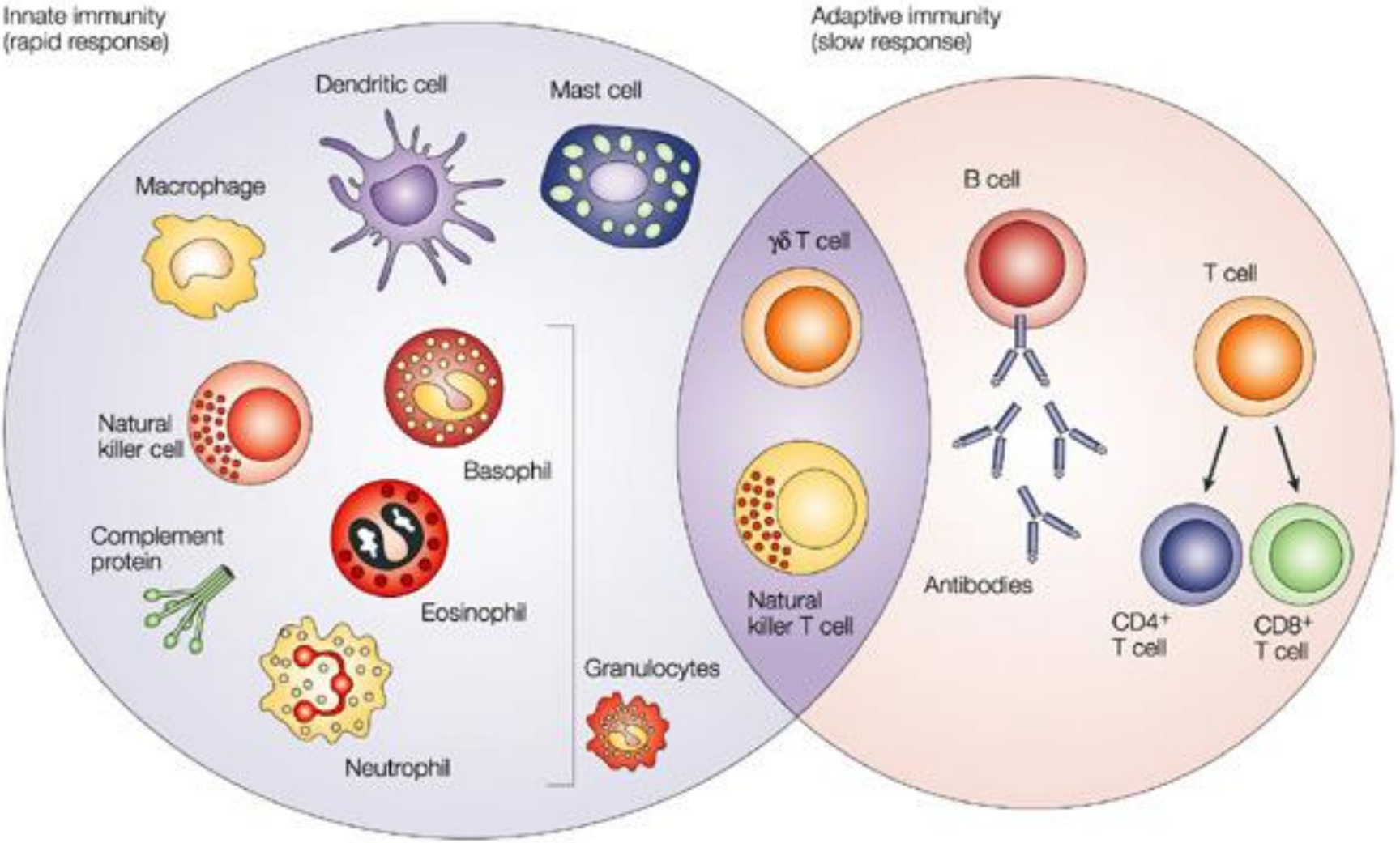


How is the immune system organized?

Two main arms: Innate and Adaptive:

- The innate system is always “on” and ready to mount an immediate early response by sensing molecules common to entire classes of microbes
- The adaptive system takes days to respond, but can resolve infections and confer immune memory by sensing molecules specific to a particular invader

Innate & Adaptive Immune systems



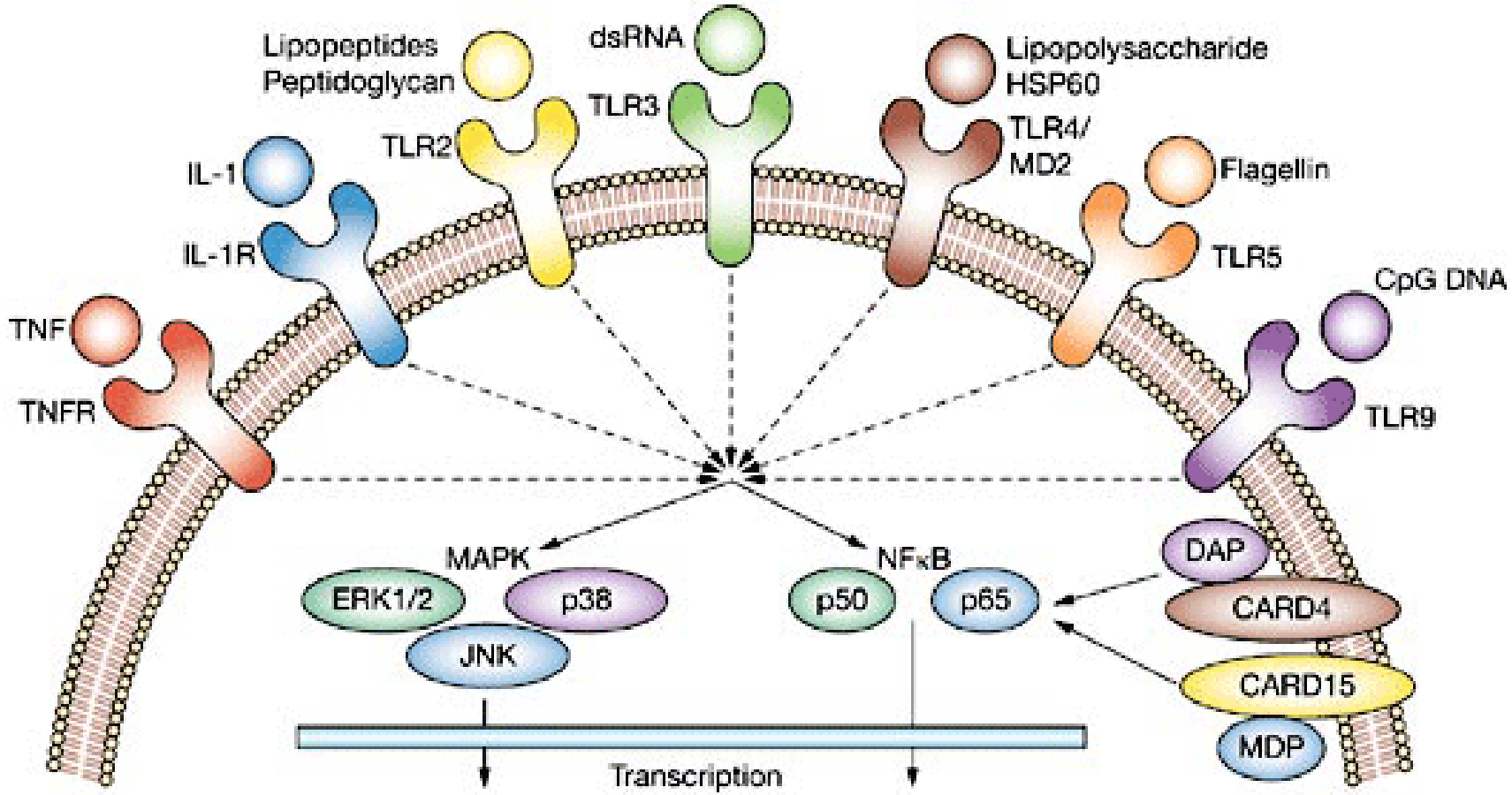
G. Dranoff, Cytokines in cancer pathogenesis and cancer therapy , Nature Reviews Cancer 4:11-122

Innate immune system

Notable features

- Response time minutes to hours
- Cells include macrophages, monocytes, neutrophils, dendritic cells, NK cells
- Effector molecules include complement, cytokines, chemokines, among others
- Recognize molecular features common to classes of microbes (flagellin, LPS, dsRNA, etc) or ‘alarm’ cytokines

Innate immune cells recognize microbes through specialized surface receptors called TLRs



Adaptive immune system

Notable features

- Response time days to weeks
- Cells express clonally distinct Ag receptors:

  $CD4^+$ *'helper'*

  $CD8^+$ *'killer'* T cells

  $CD25^+$ $FoxP3^+$ *'regulatory' T cells*

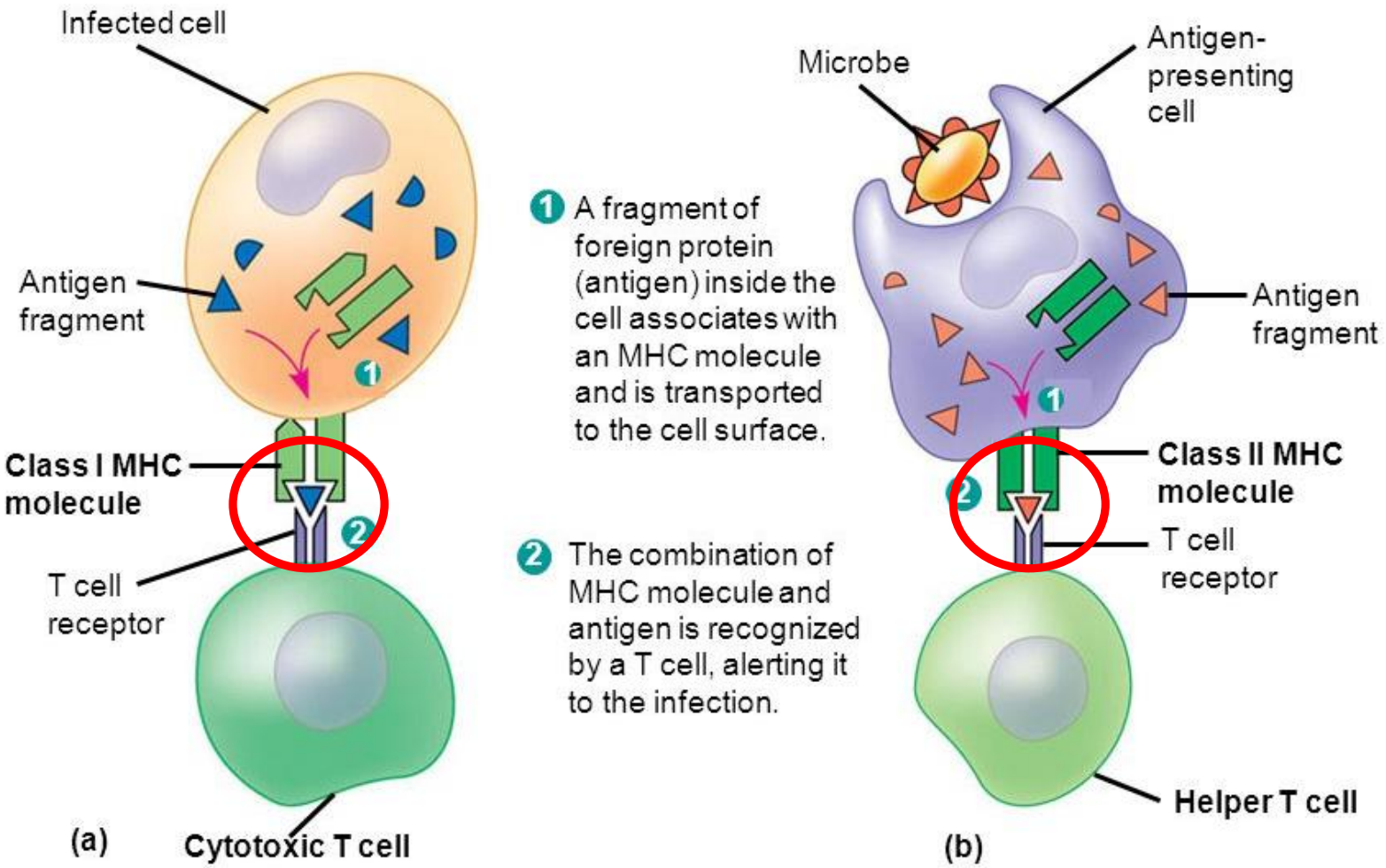
  B cells

Adaptive immune system

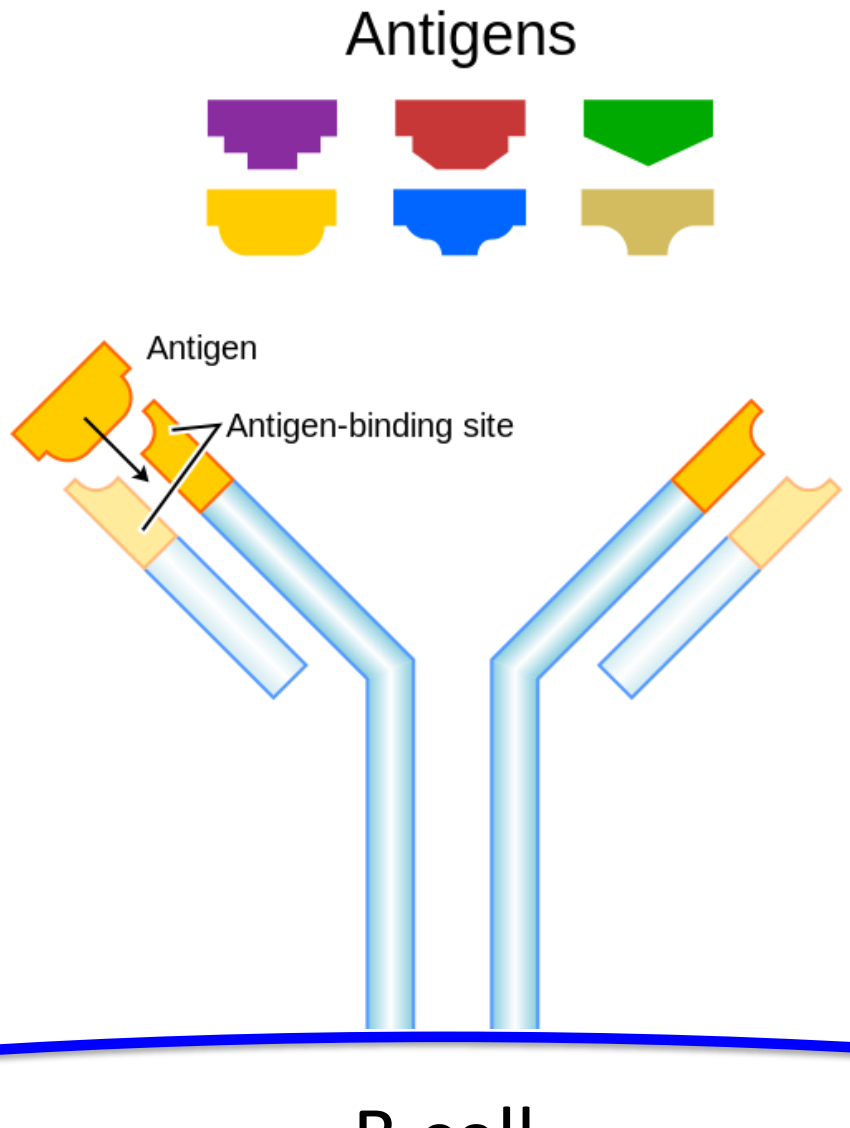
Notable features

- Effector molecules include inflammatory cytokines, chemokines, growth factors, *cytotoxic molecules and antibodies*
- Response of a single clone involves short-lived effector cells and long-lived memory cells
- Memory cells can undergo rapid expansion upon re-exposure to same Ag

T cells recognize protein fragments bound to surface MHC molecules

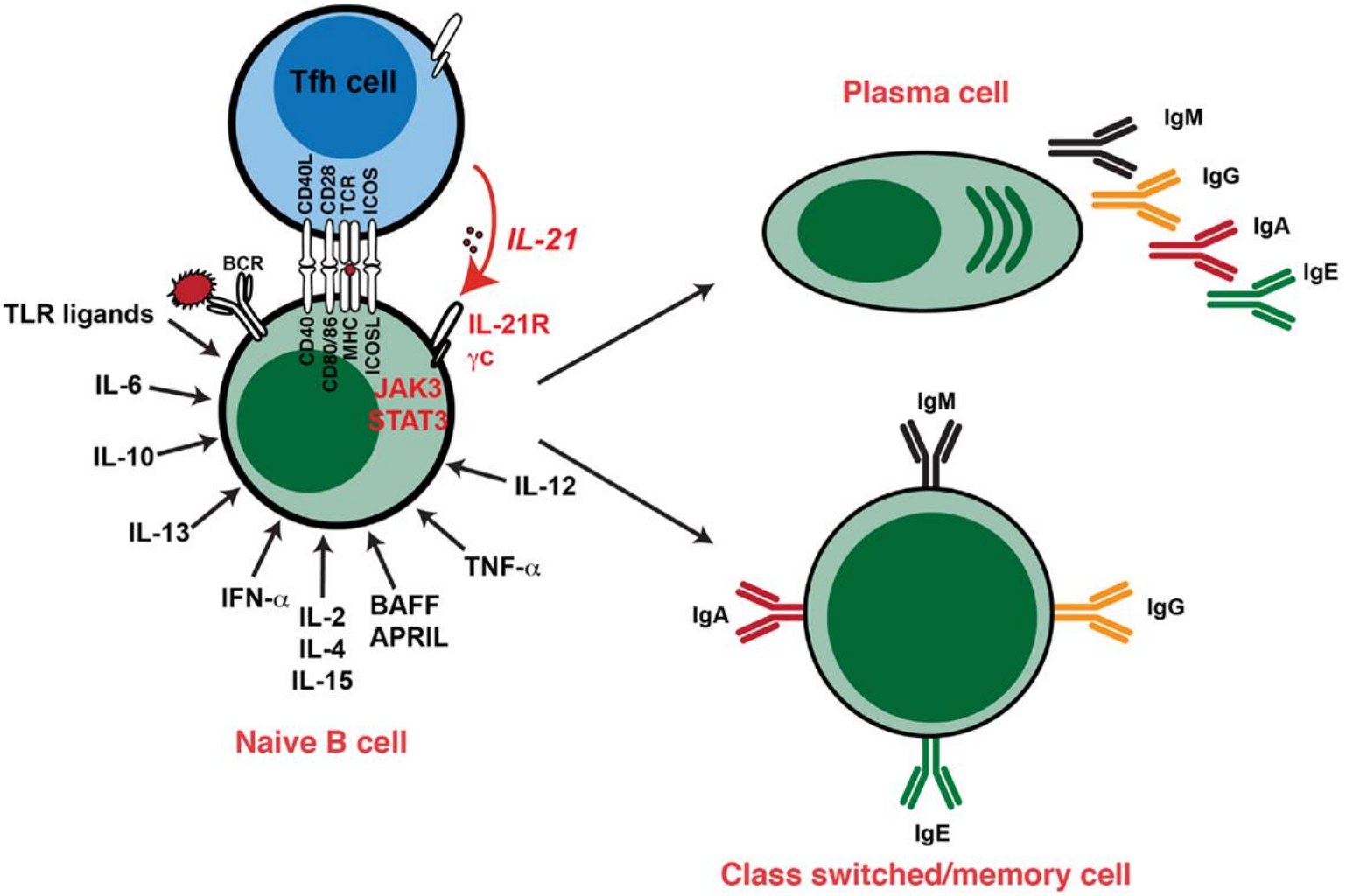


B cells recognize specific fragments of intact proteins via antibody receptors



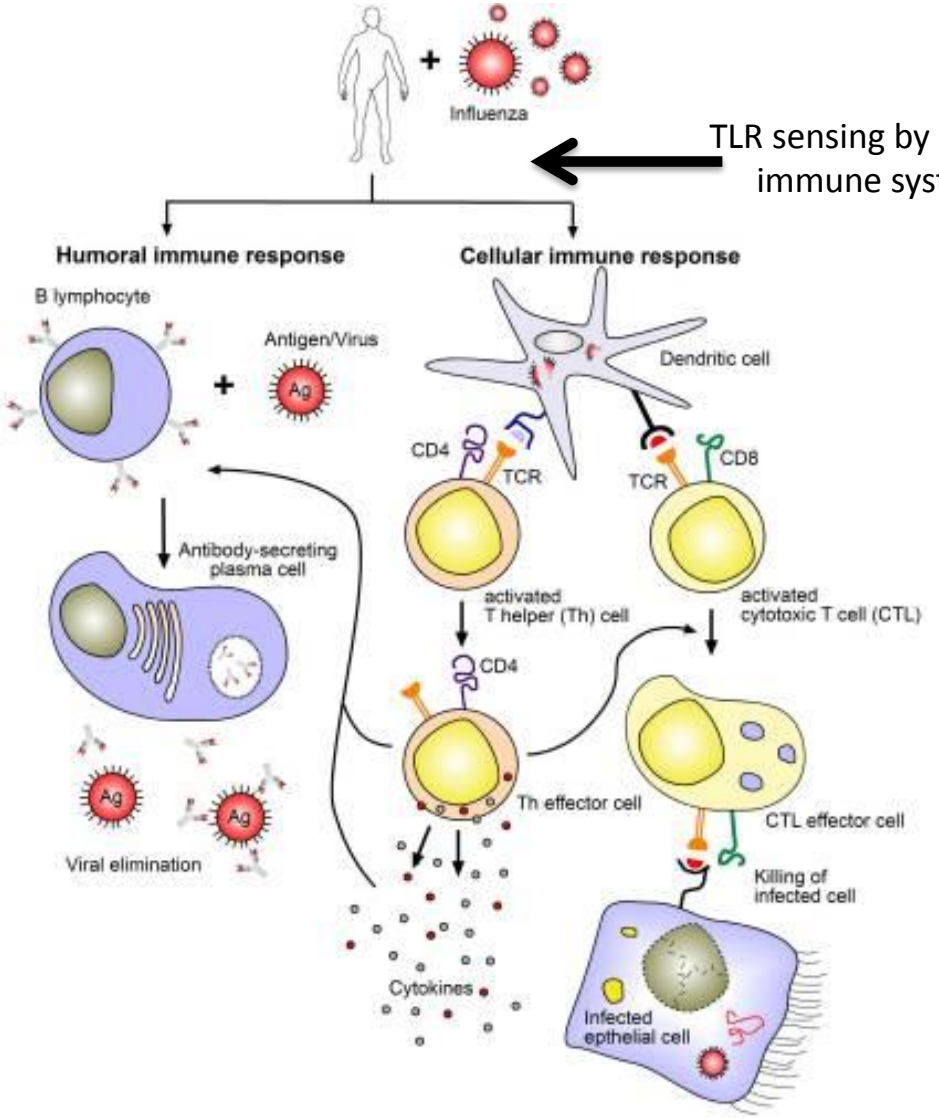
Adapated from Wikipedia Commons

Antibodies can be membrane-bound or secreted



Moens & Tangye, Cytokine-mediated regulation of plasma cell generation: IL-21 takes center stage. Frontiers in Immunology vol. 5 2014

The infection-immunity cycle



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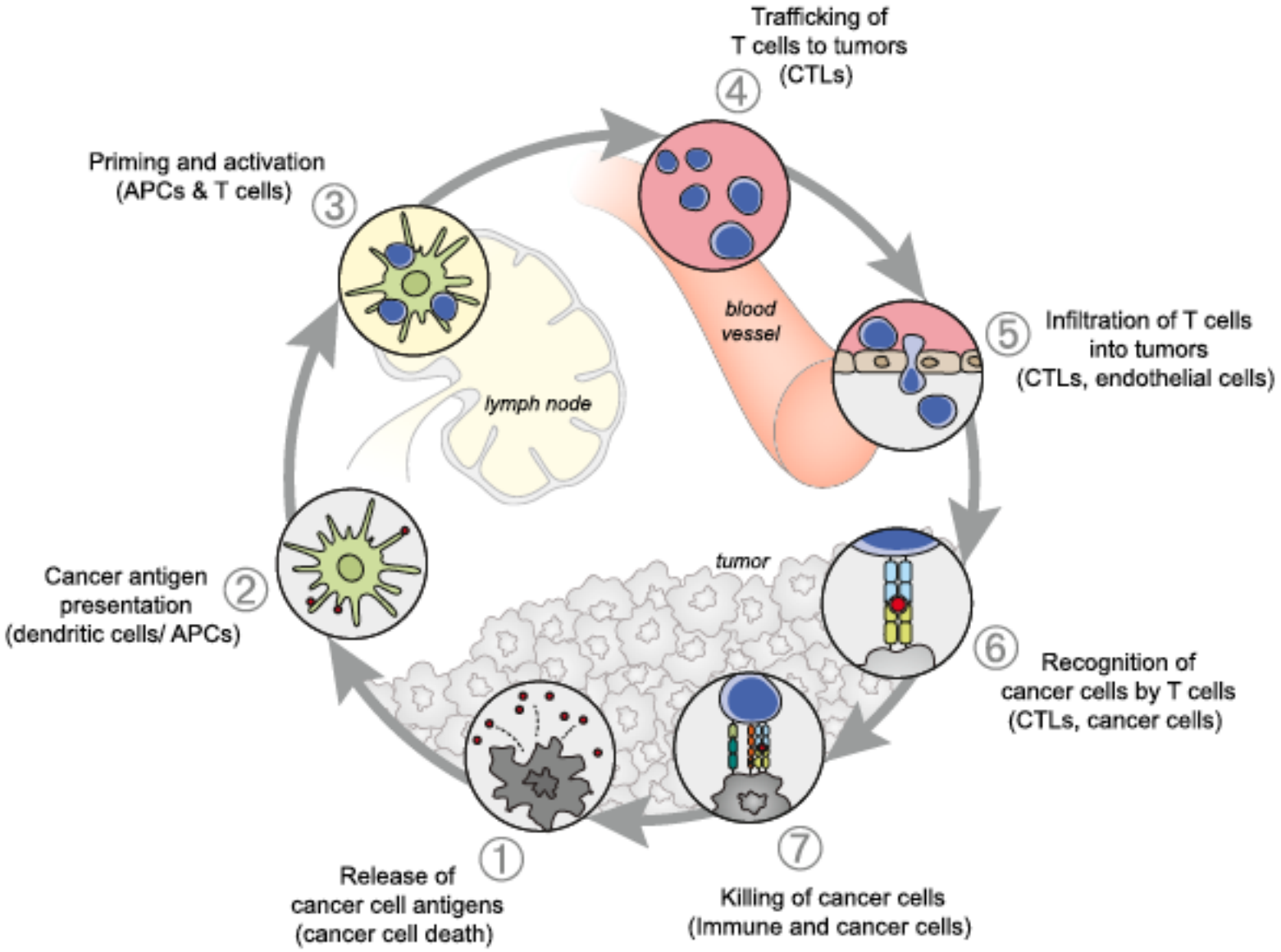
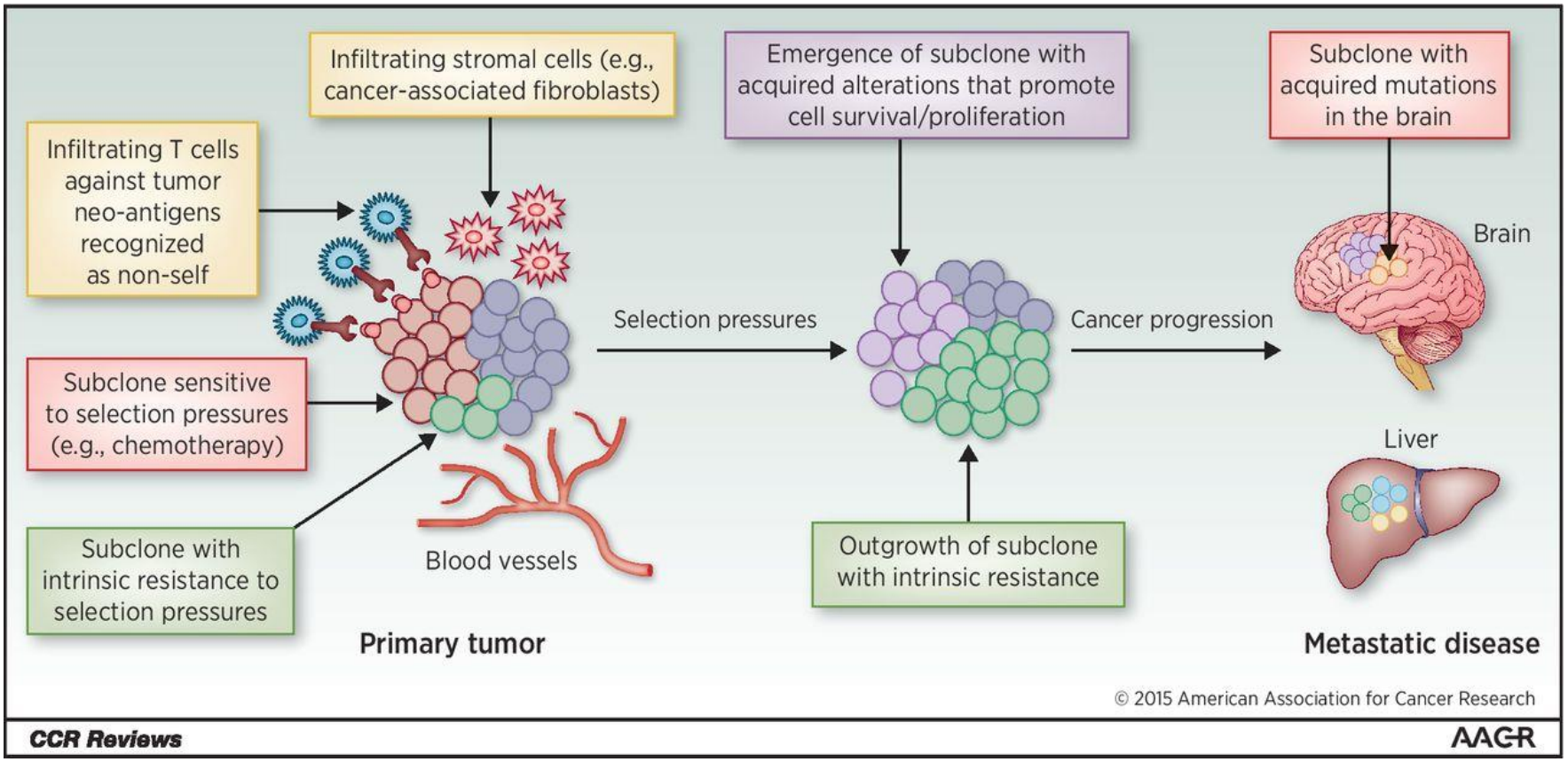
The cancer-immunity cycle

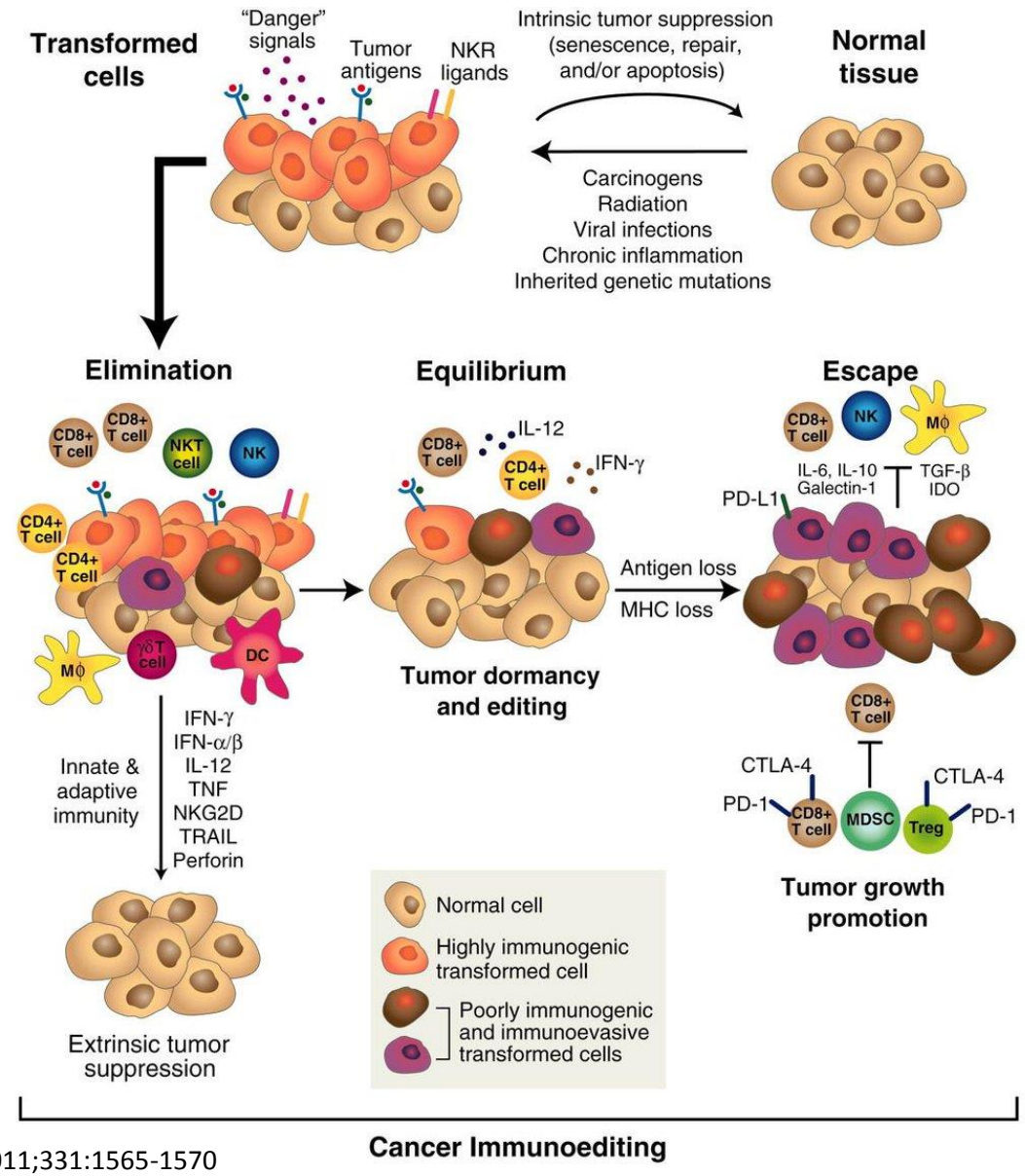


Tumors evolve, adapt, progress, and escape



Translational implications of tumor heterogeneity, Jamal-Hanjani et al, Clinical Cancer Research 2015

Tumors ‘edit’ the immune response to avoid destruction



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

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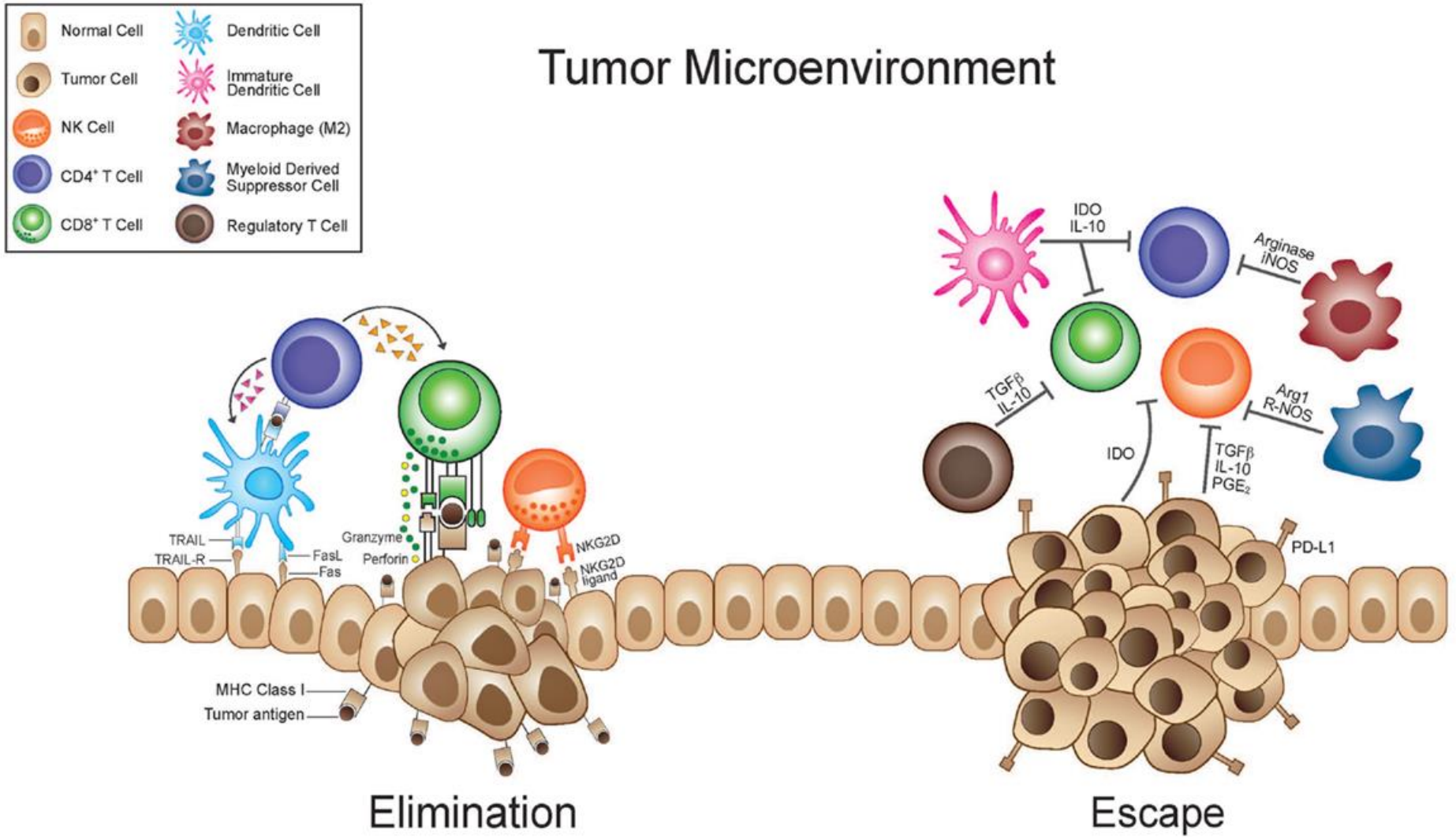

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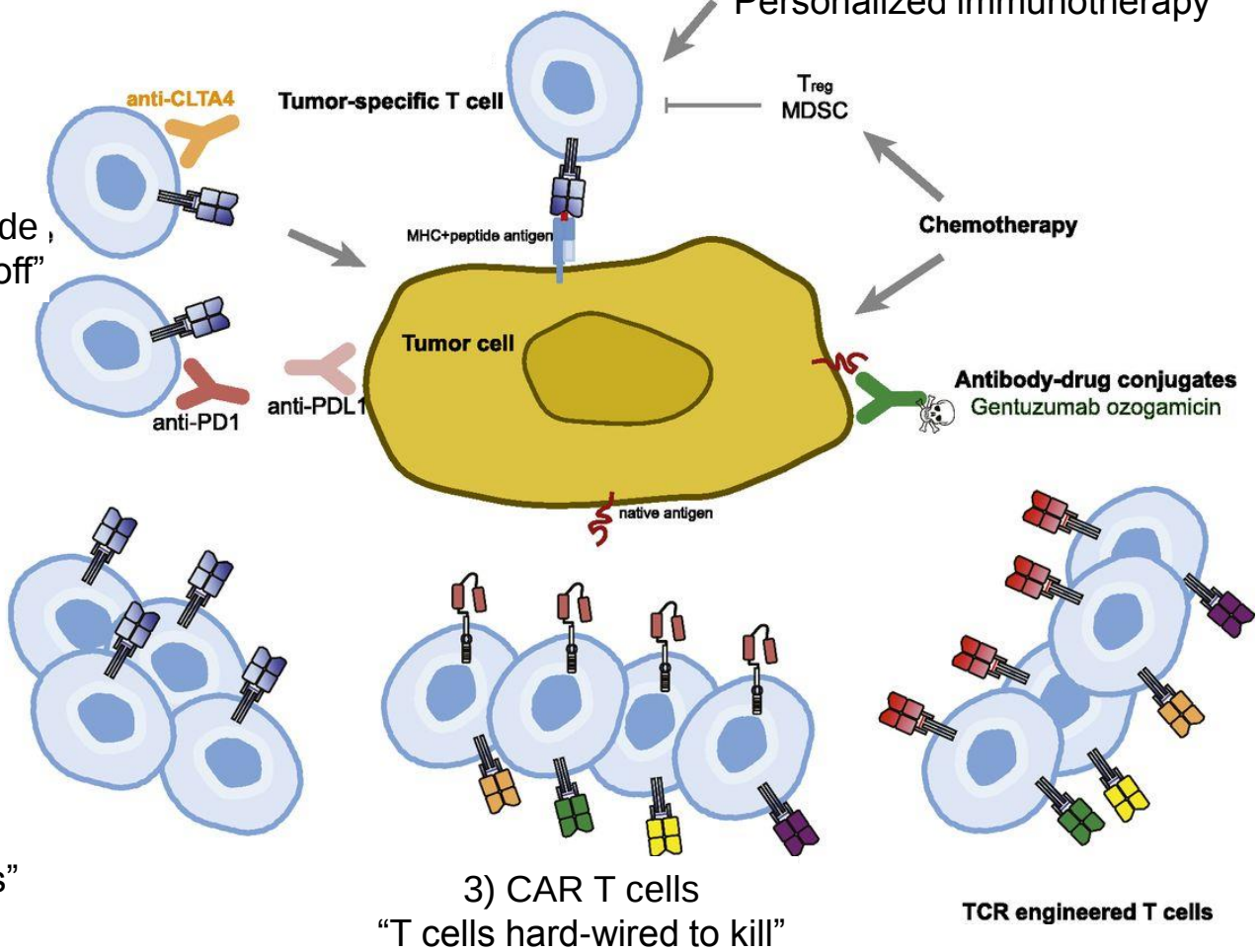
General approaches to cancer immunotherapy

4) Neoantigens
"Personalized immunotherapy"

1) Checkpoint Blockade ,
"taking the brakes off"



2) Tumor-infiltrating
Lymphocytes (TIL)
"An army of tumor-killers"

3) CAR T cells
"T cells hard-wired to kill"

Marcela V. Maus et al. Blood 2014;123:2625-2635

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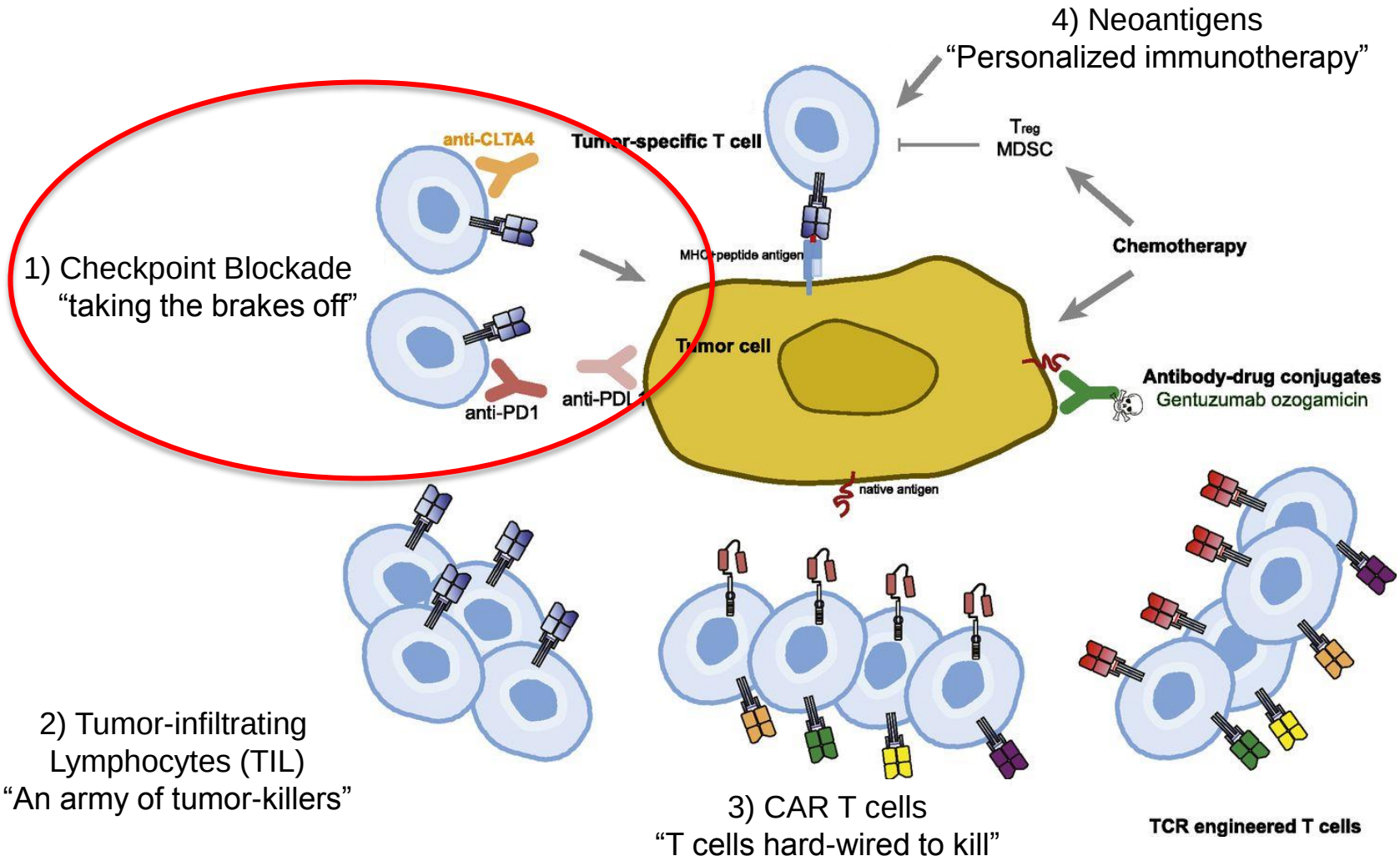

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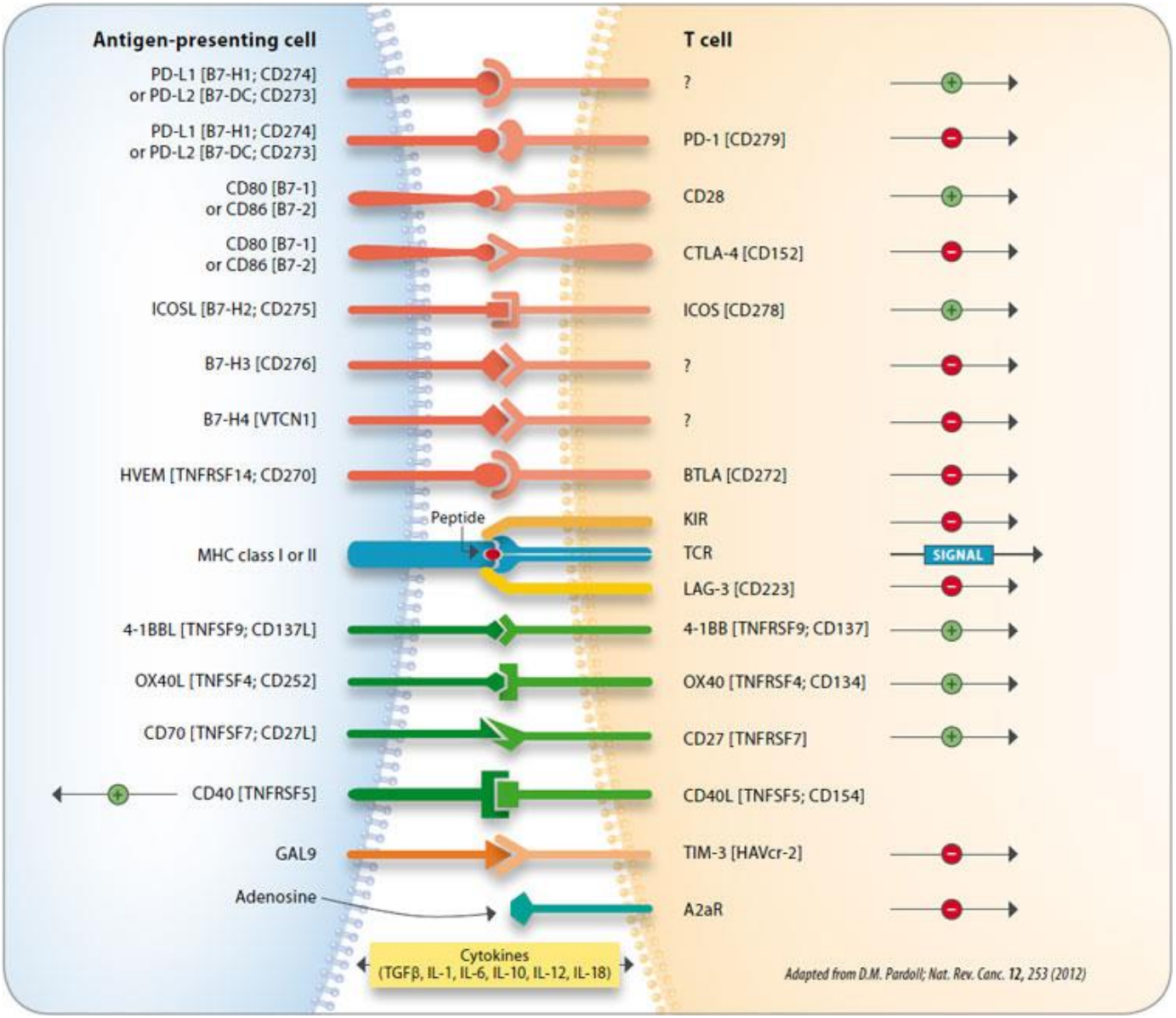
T cell responses are regulated by both positive and negative signals



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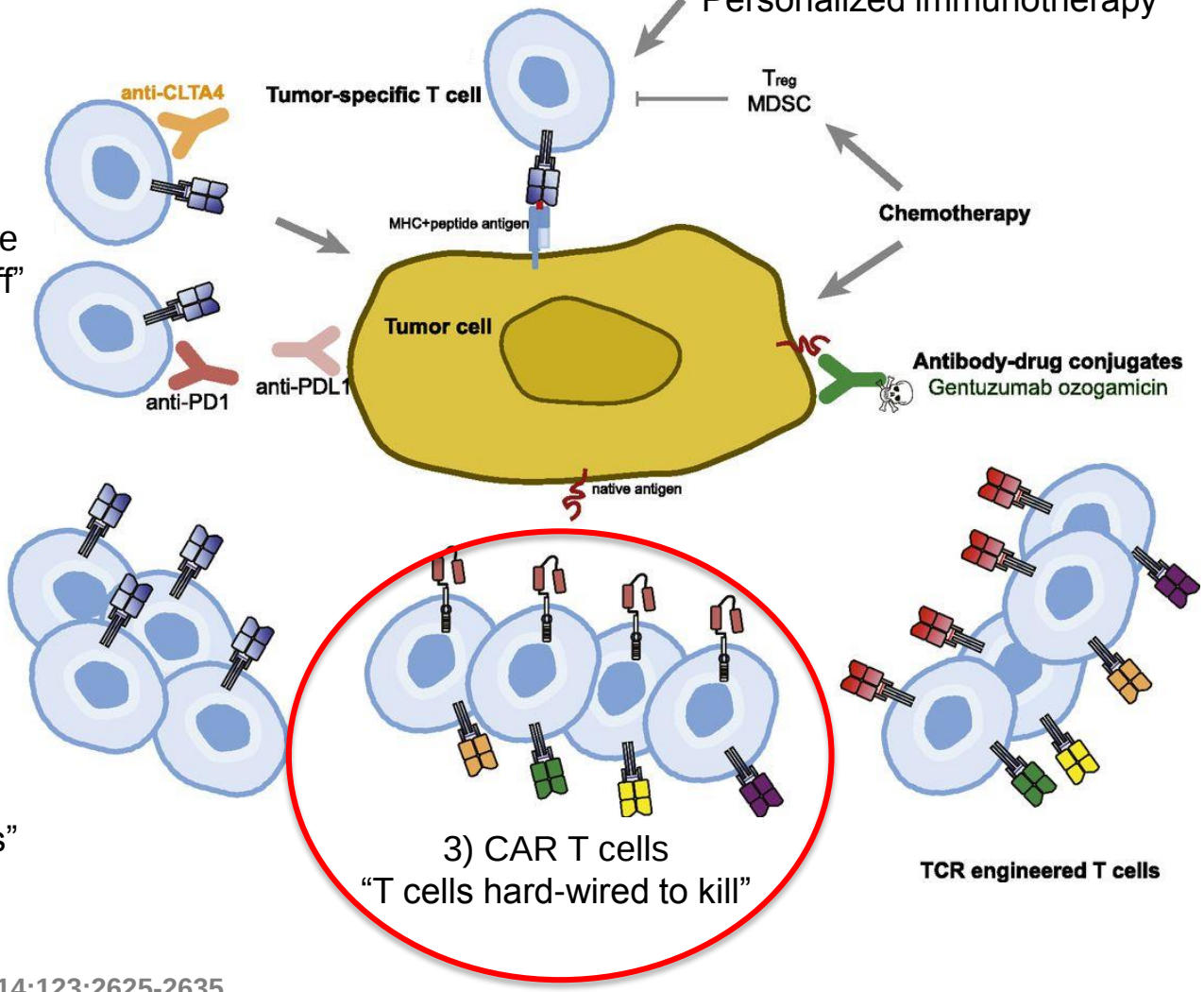

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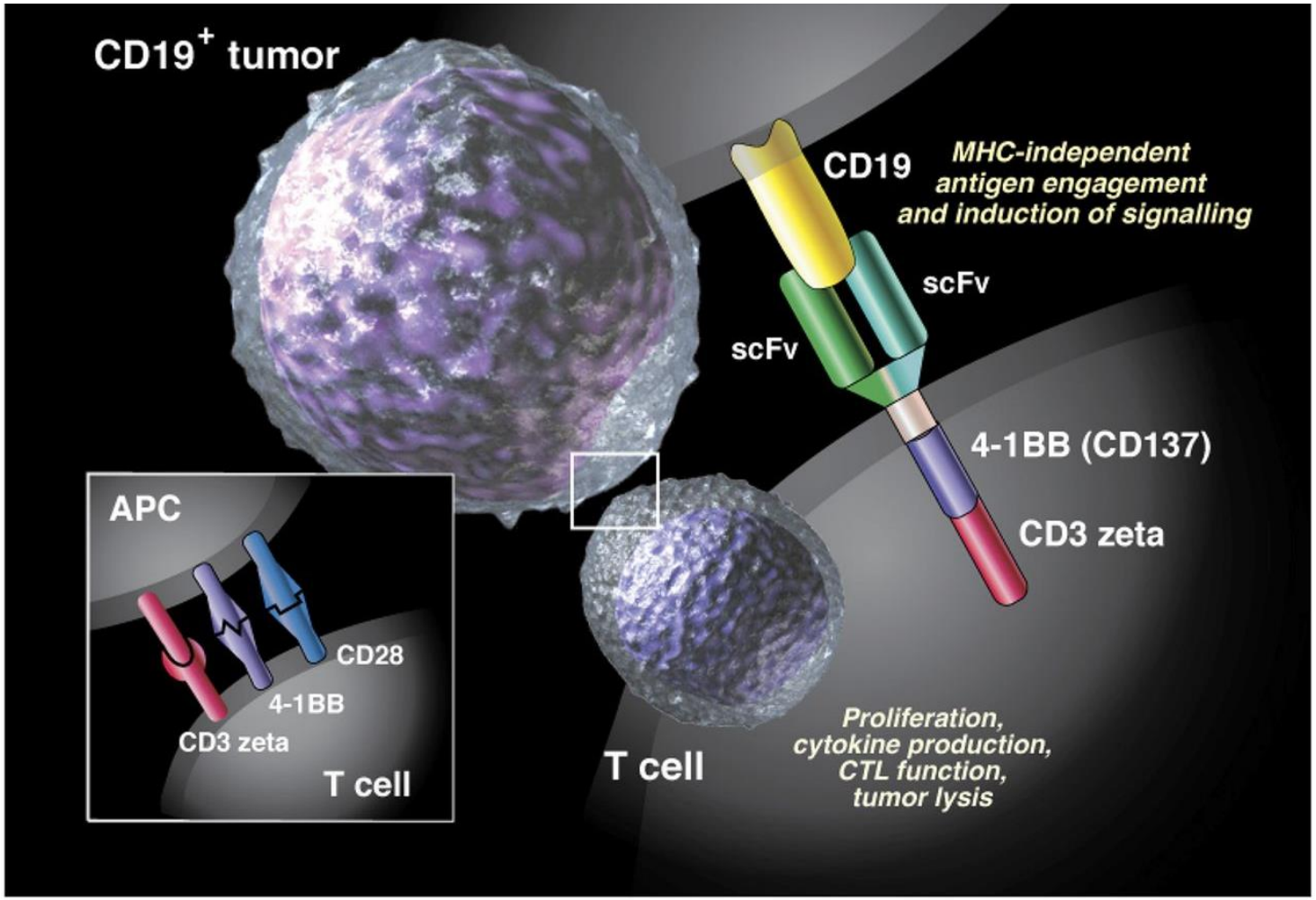
Chimeric Antigen Receptors (CAR) combine features of antibodies and T cell receptors



Adapted from Shannon L. Maude et al. Blood 2015;125:4017-4023

Conclusions

- The immune response to infection comprises both innate and adaptive arms.
- The T cells that recognize infected cells can also recognize and respond to the ‘altered self’ of tumors
- Tumors use multiple normal physiologic and adaptive mechanisms to avoid immune destruction
- Immunotherapy can involve general (i.e. checkpoint blockade or CAR-T) or specific (TIL therapy or personalized vaccines) approaches