

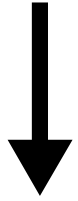
Principles of Immunotherapy - in GI tumors

Pierre Coulie
de Duve Institute
University of Louvain

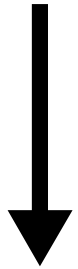
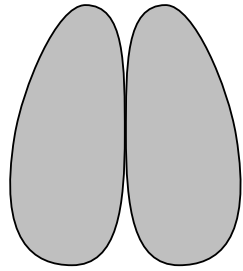
▶ T lymphocytes



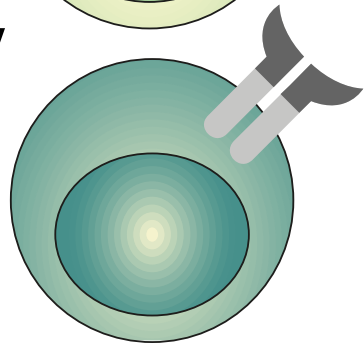
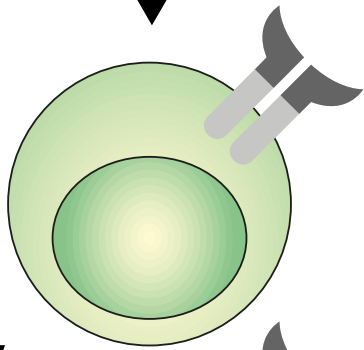
Bone marrow

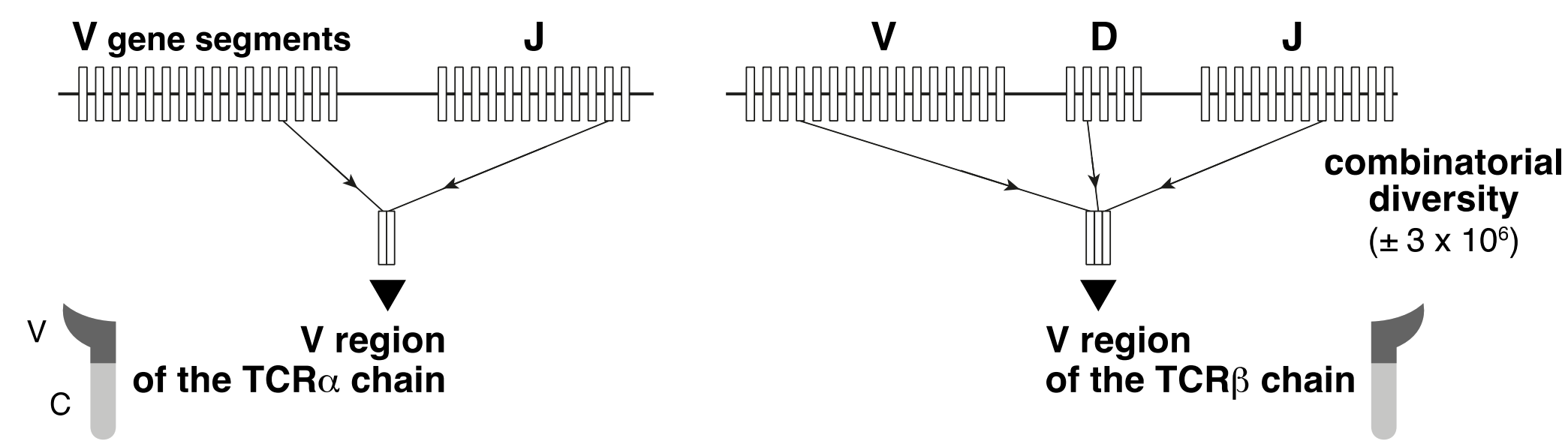
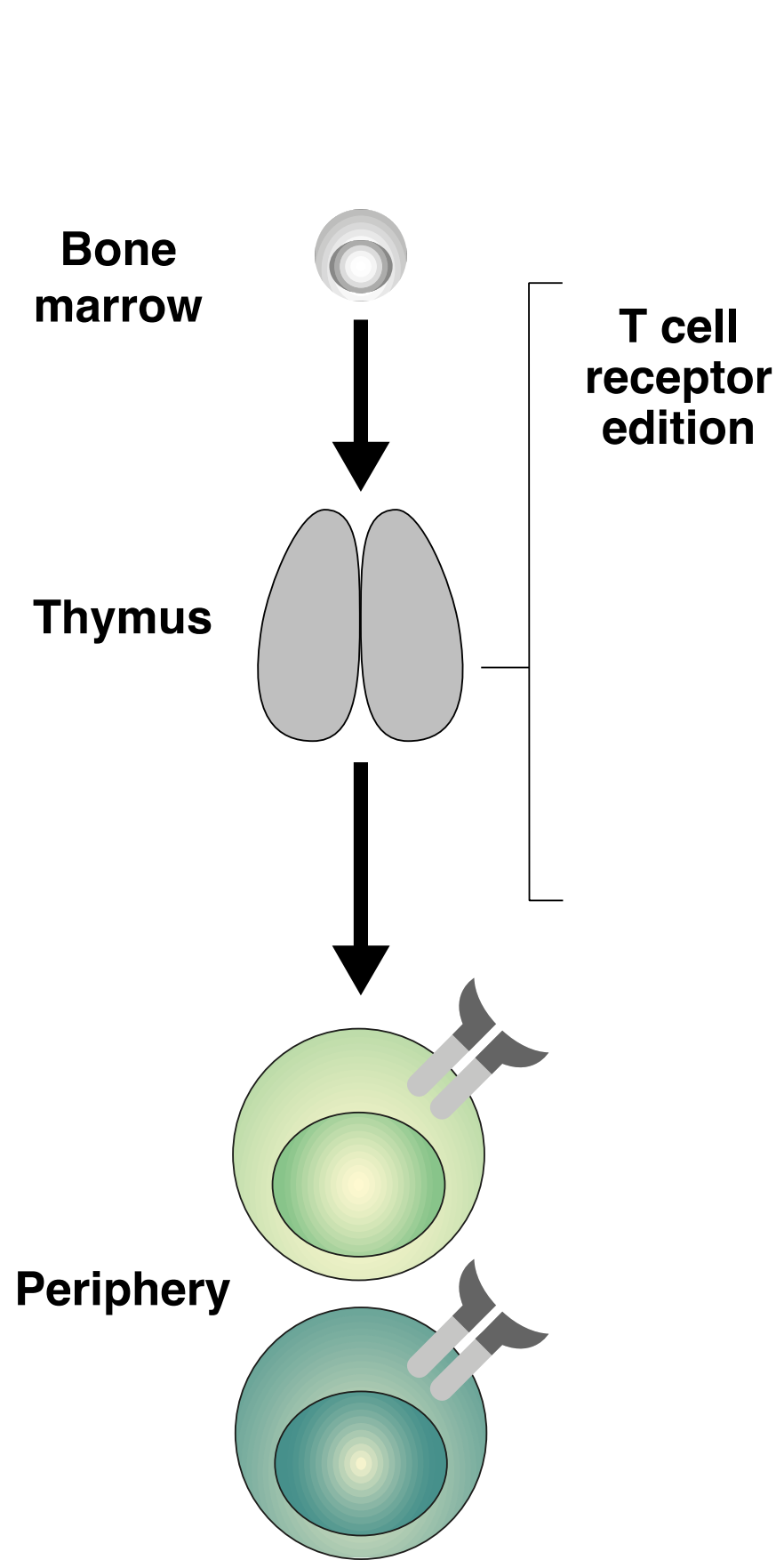


Thymus

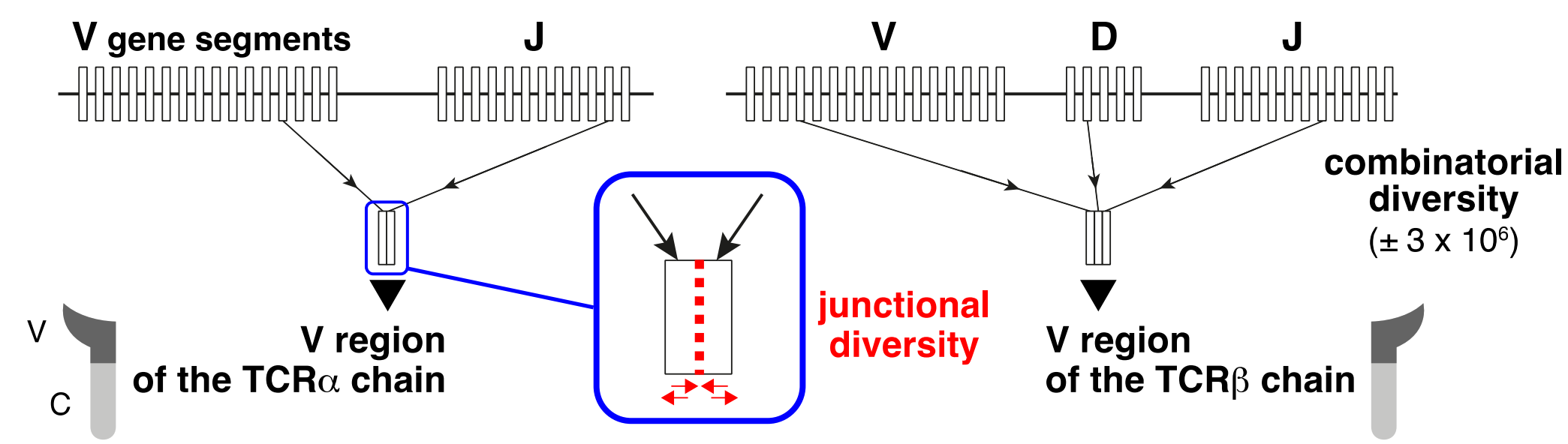
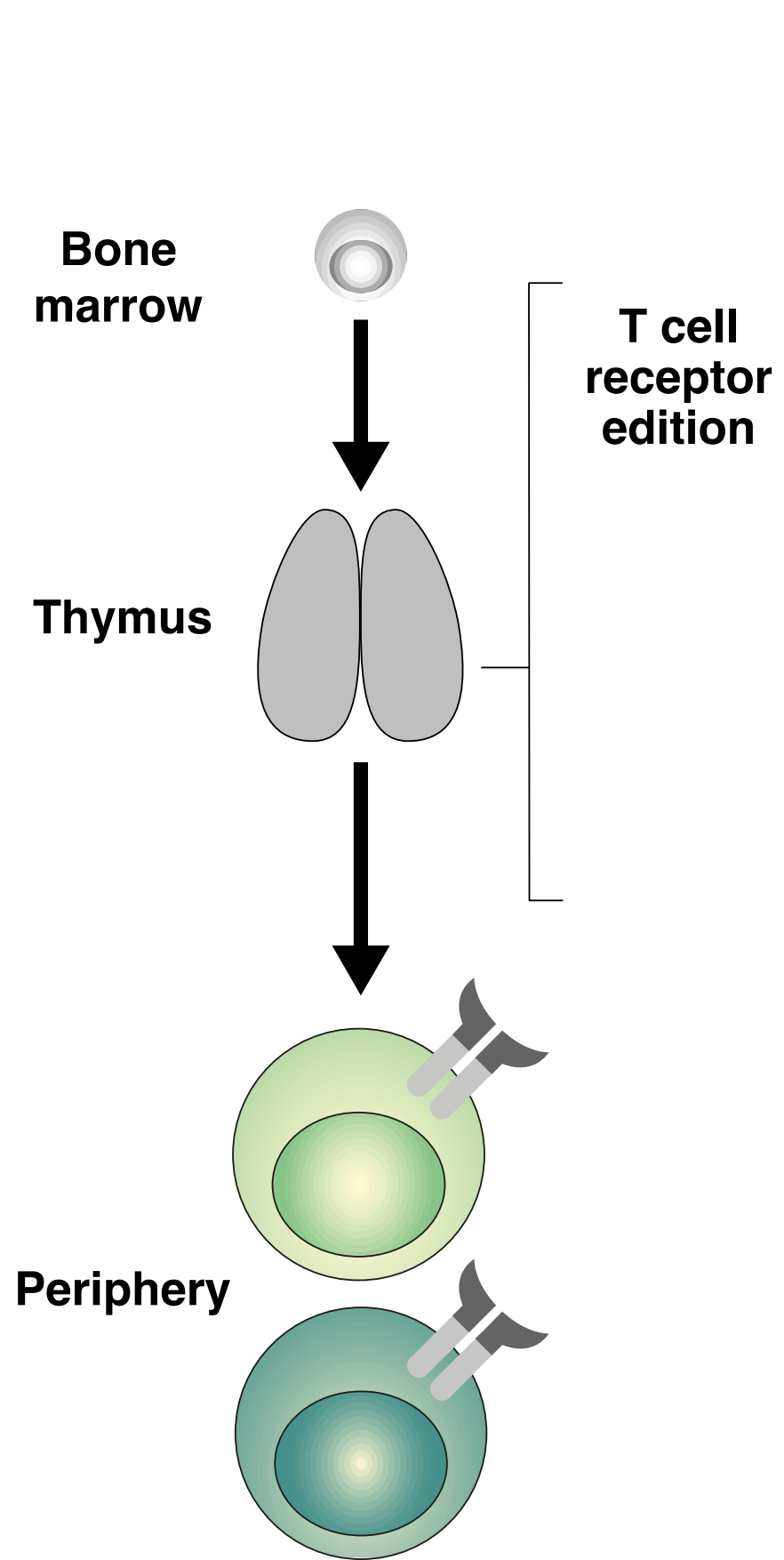


Periphery

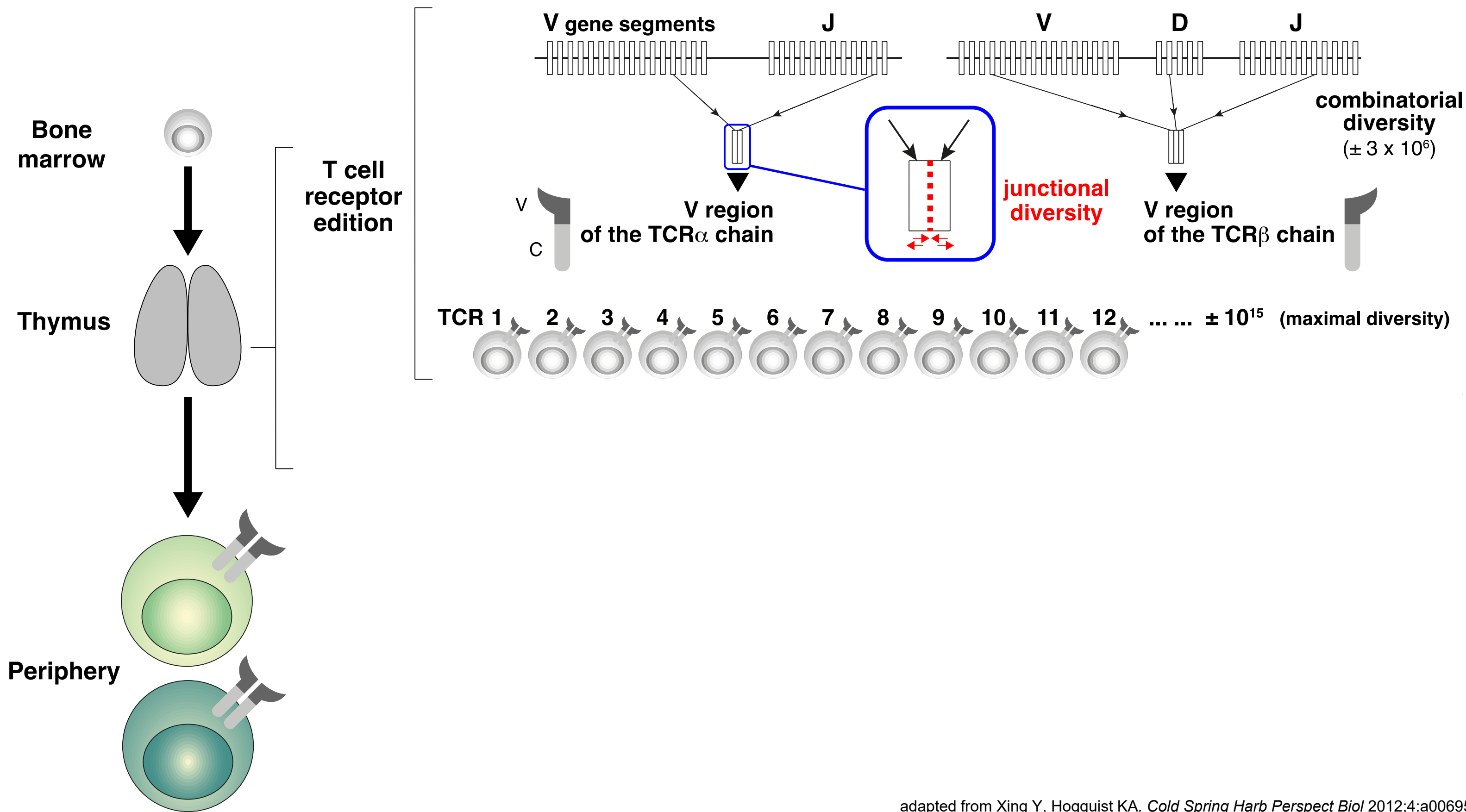




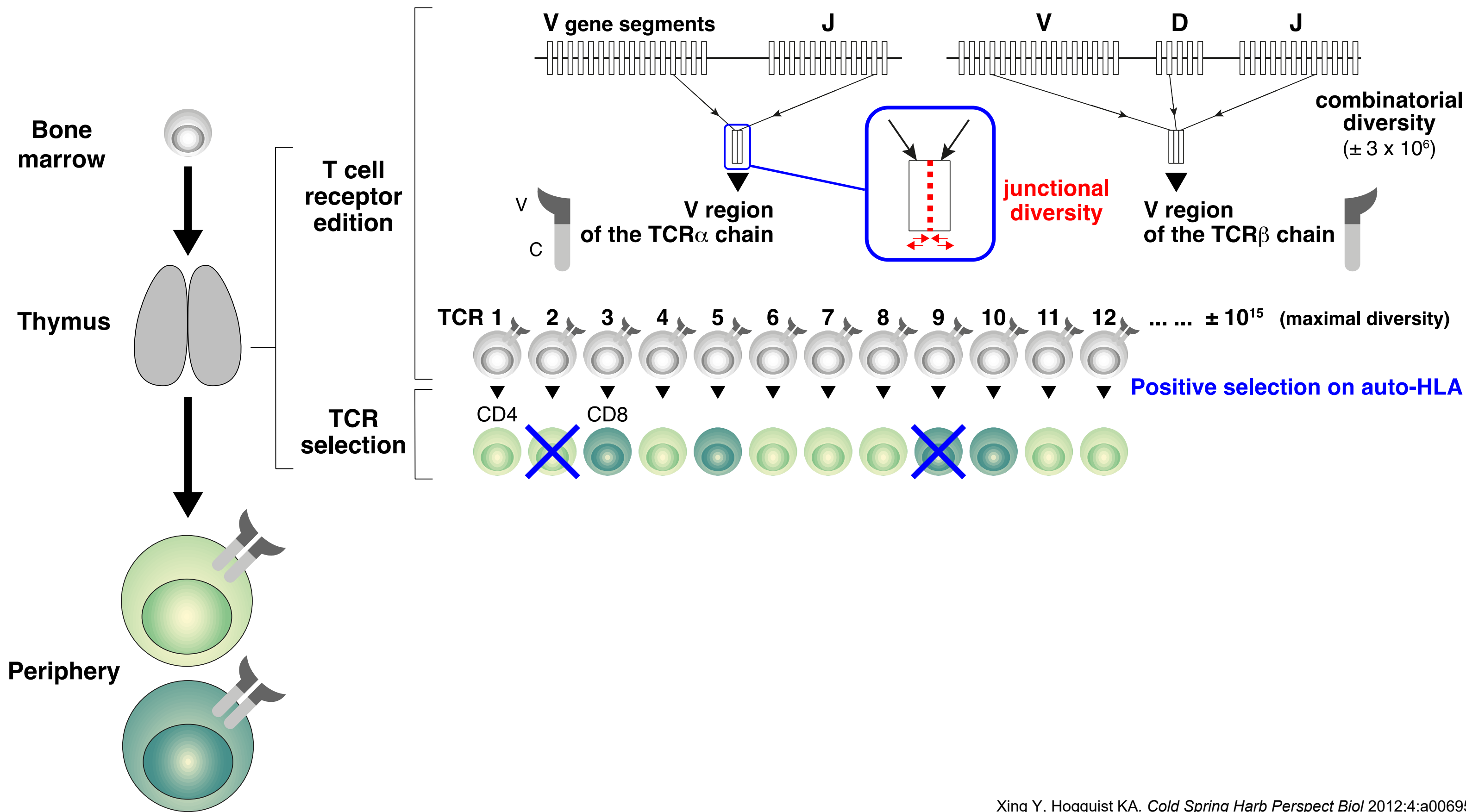
adapted from Xing Y, Hogquist KA. *Cold Spring Harb Perspect Biol* 2012;4:a006957.

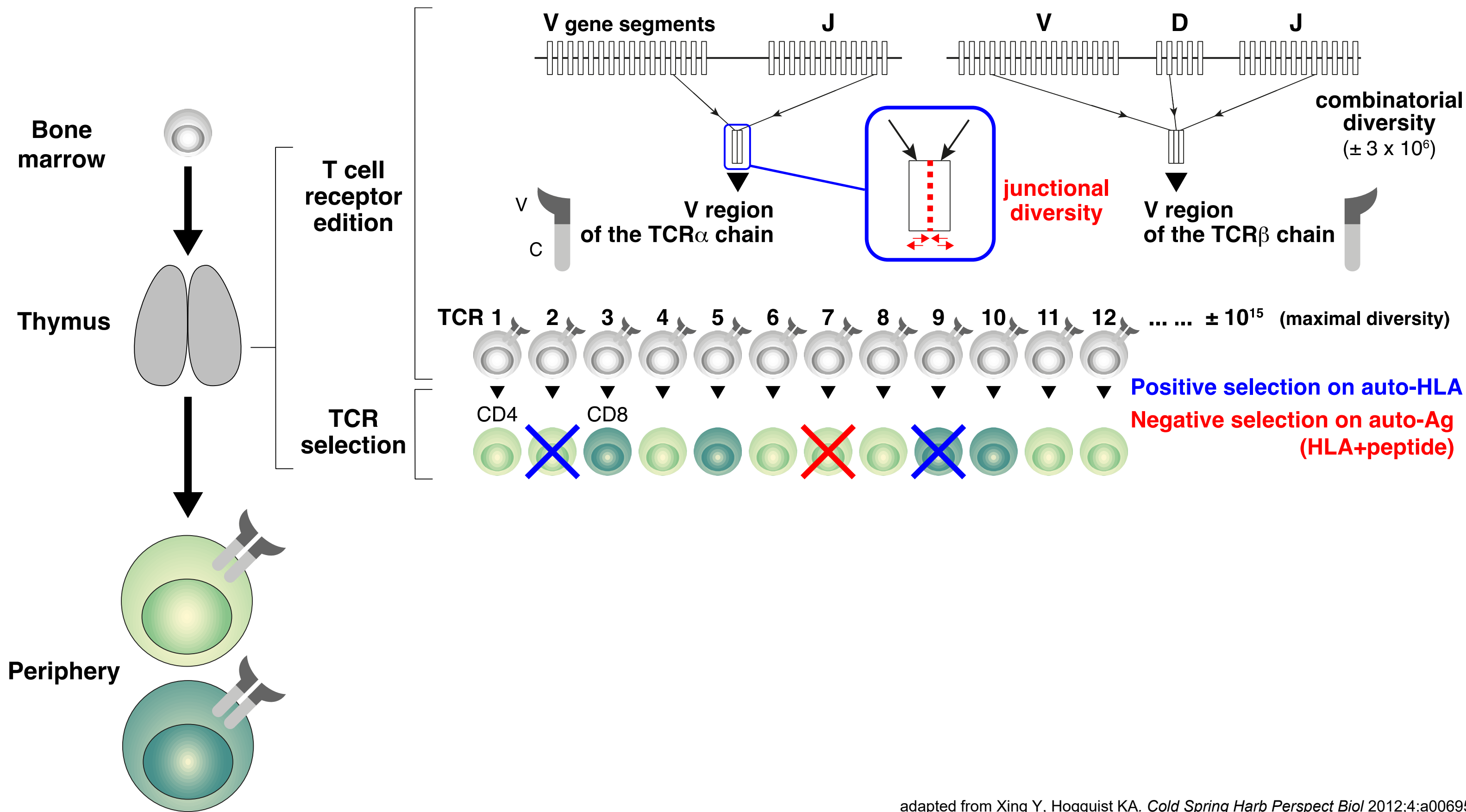


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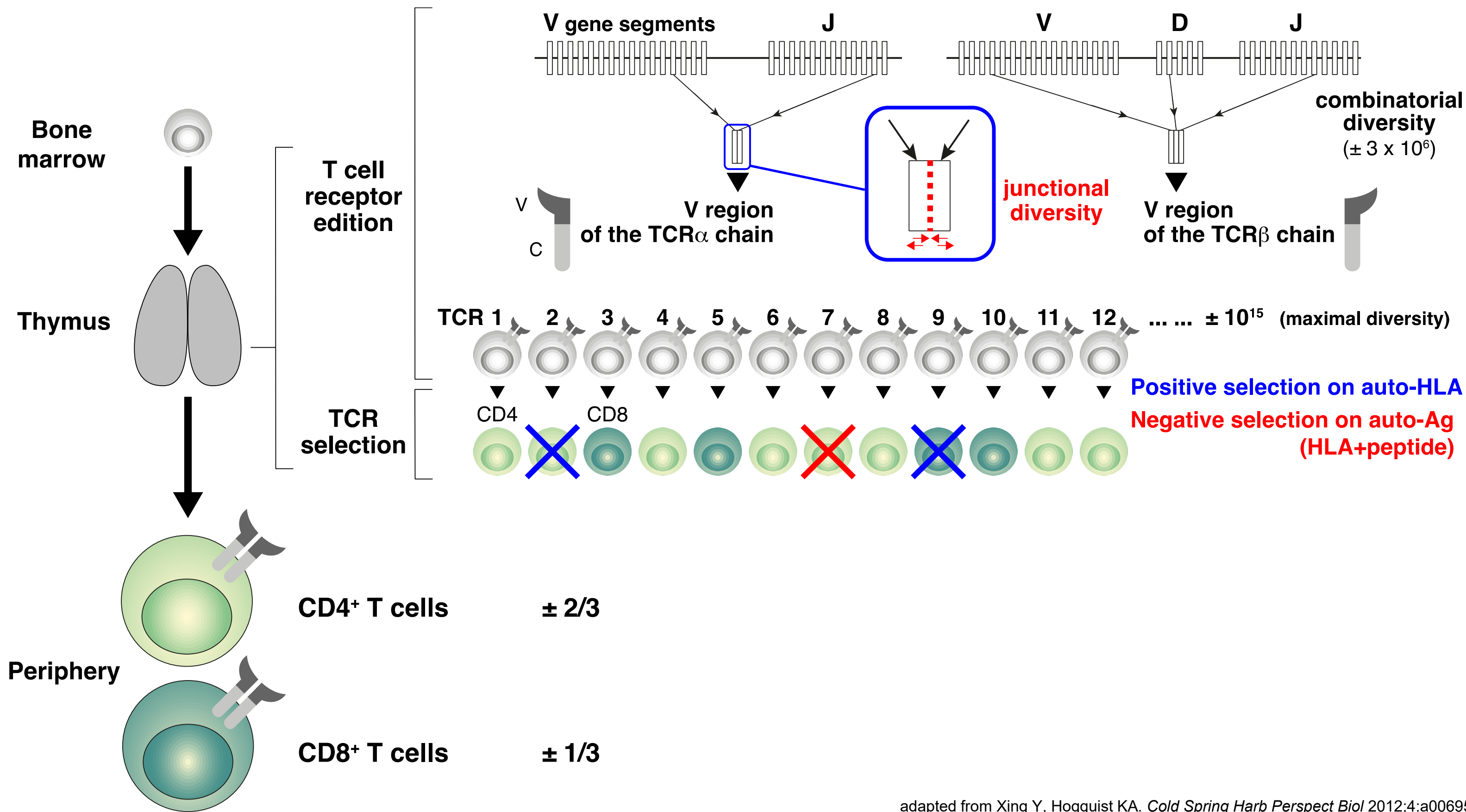


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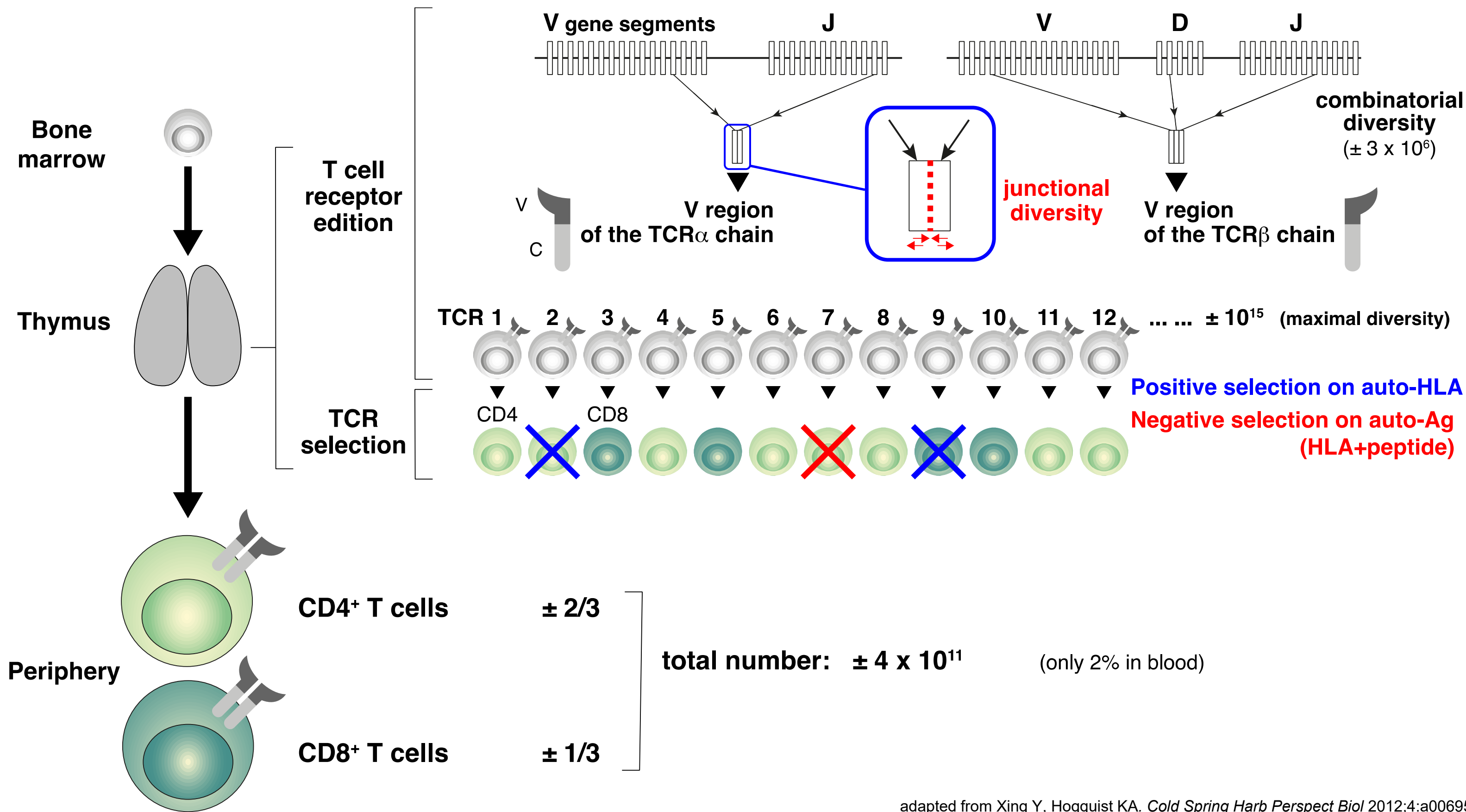




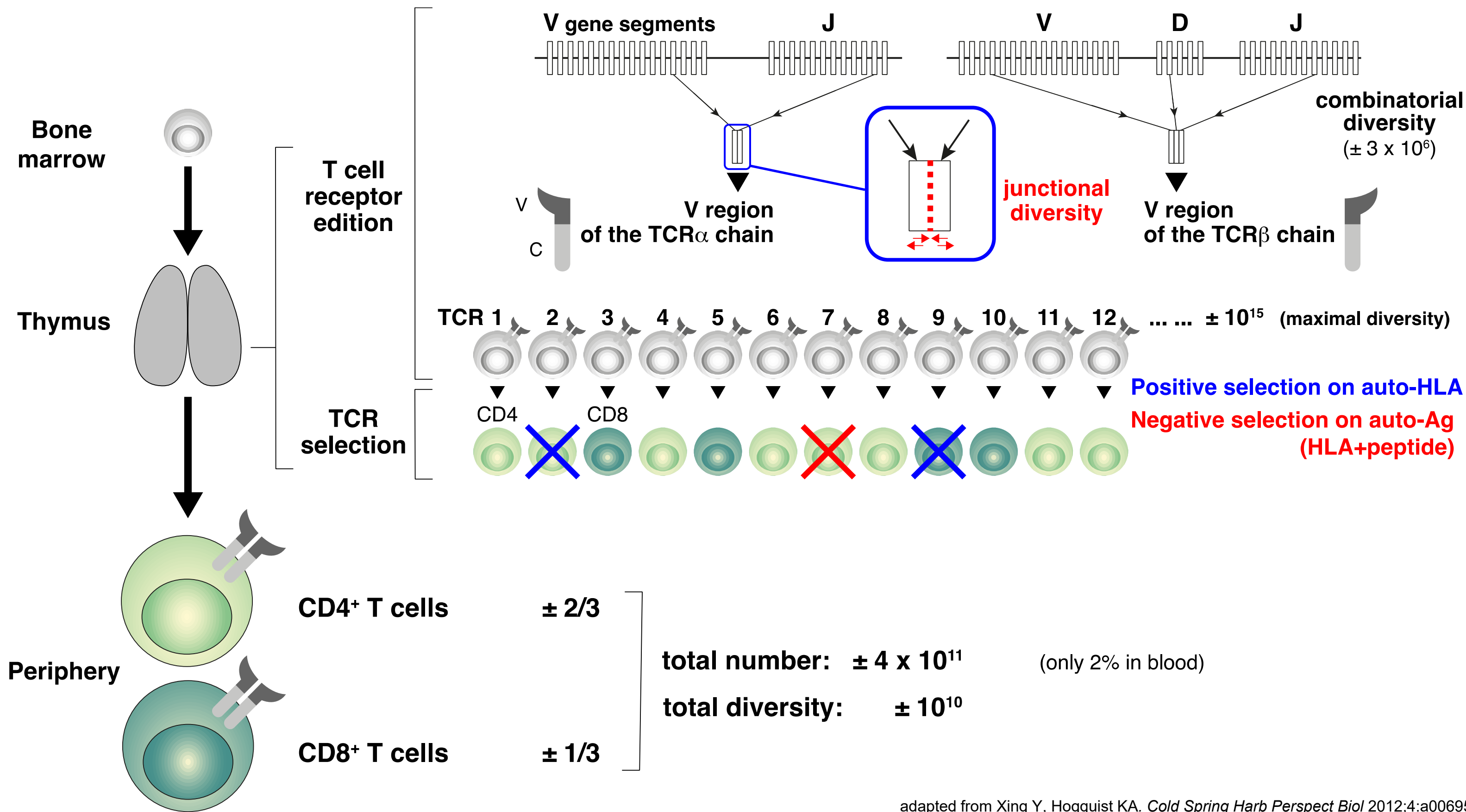
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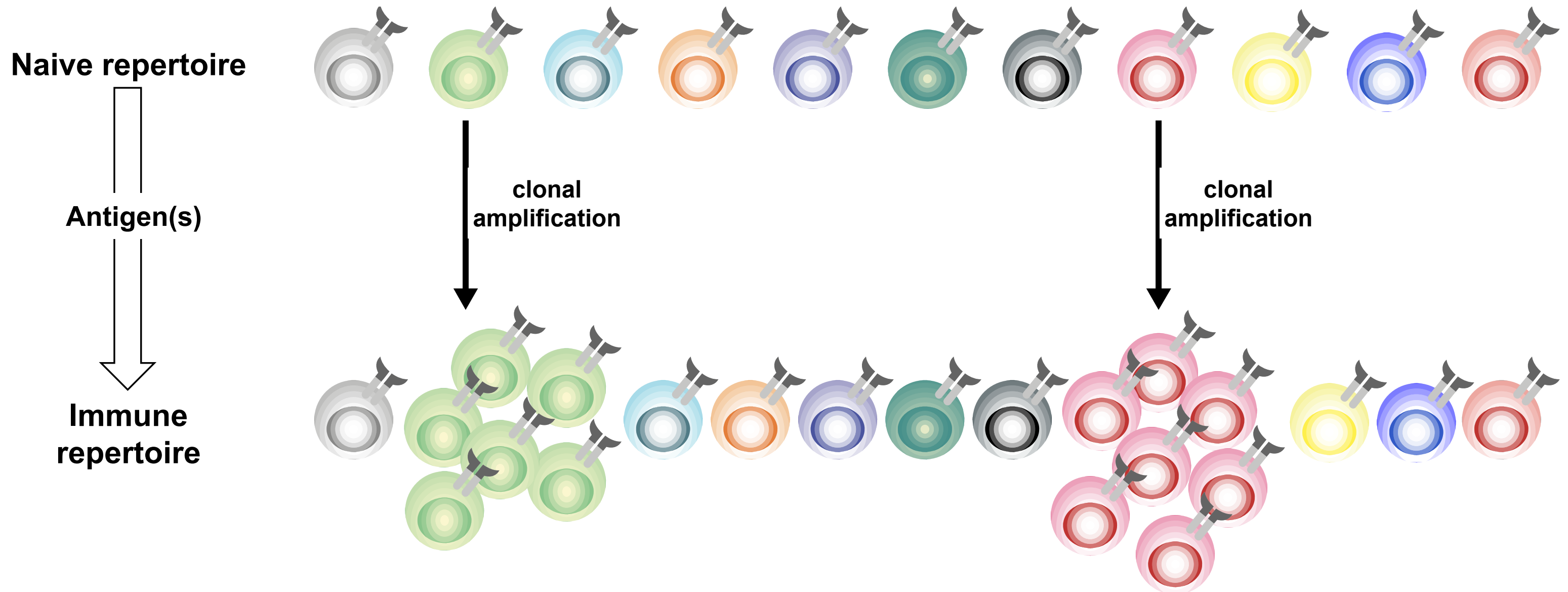


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'Adaptative' immunity: it's all about repertoire

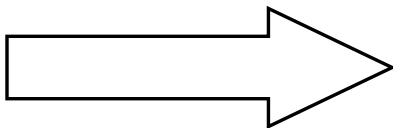


- ▶ CTLA-4 and PD-1: physiological inhibitors of T cell activation

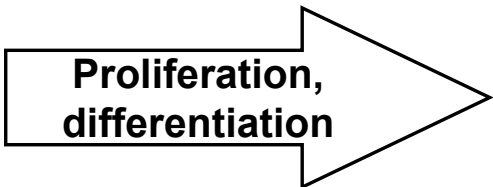


Antigenic stimulation: priming and activation via CD28/B7

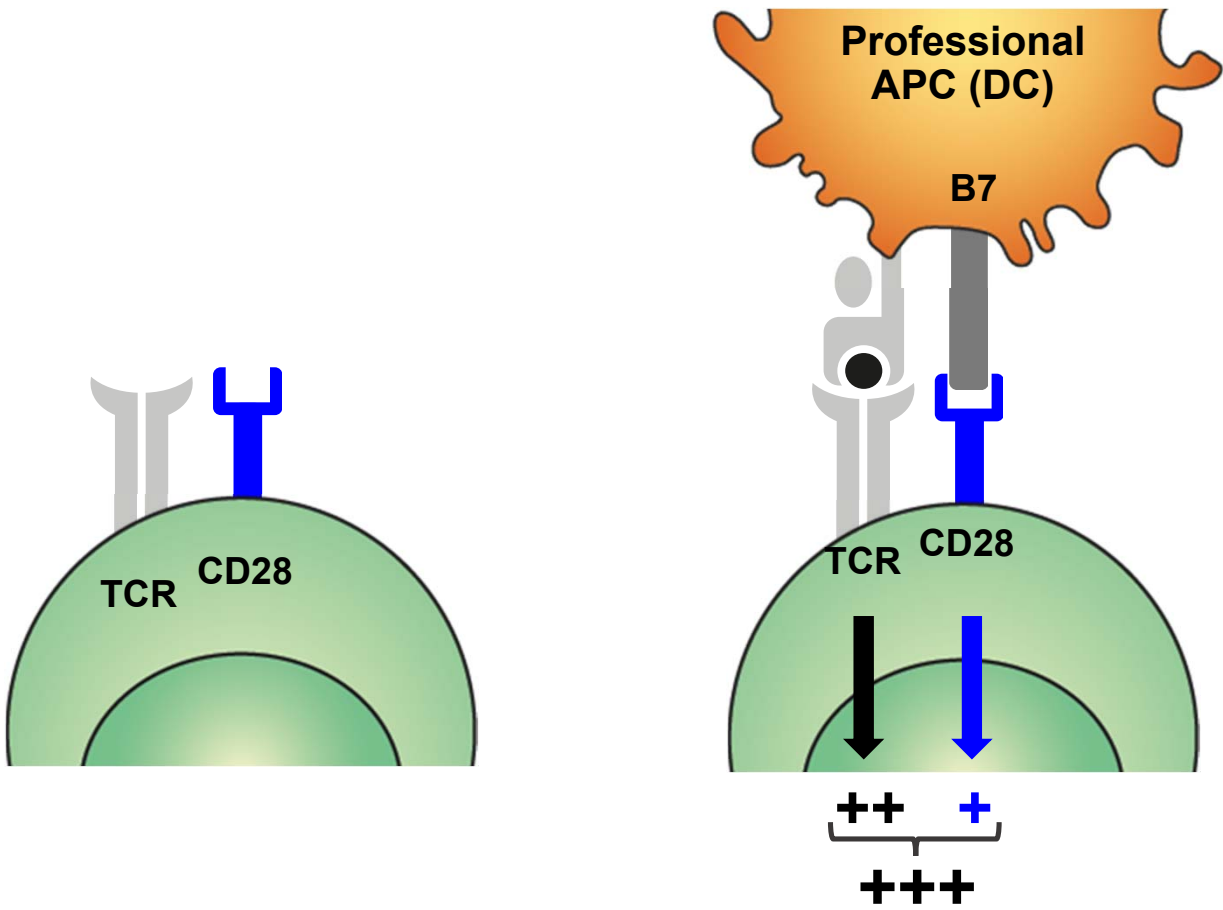
Naive T cell



Priming
(first activation)



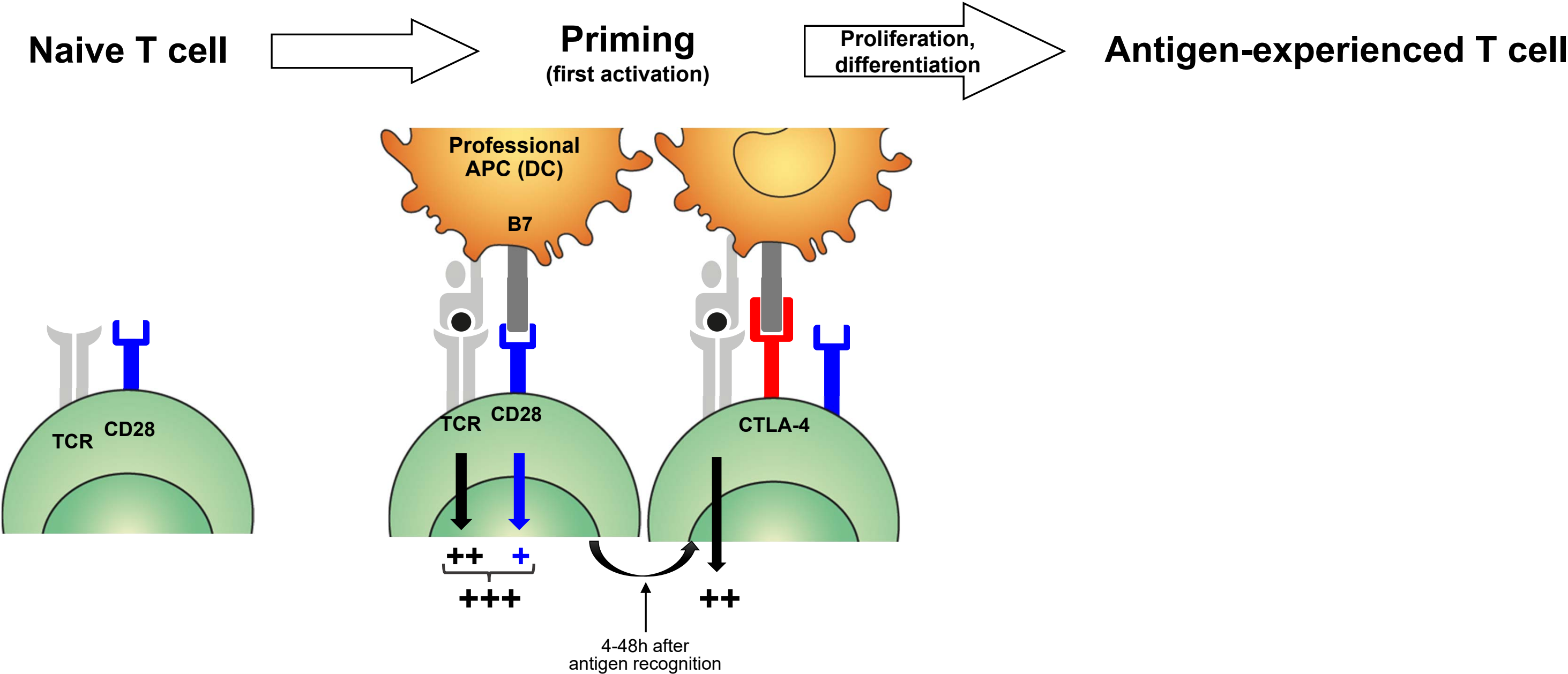
Antigen-experienced T cell



APC, antigen presenting cells; DC, dendritic cell.
Wei S, et al. Cancer Discovery 2018;8:1069–86; Chen D & Mellman I. Immunity 2013;39:1–10; Pardoll DM. Nat Rev Cancer 2012;12:252-264; Sharma P et al. Science 2015;348:56-61.



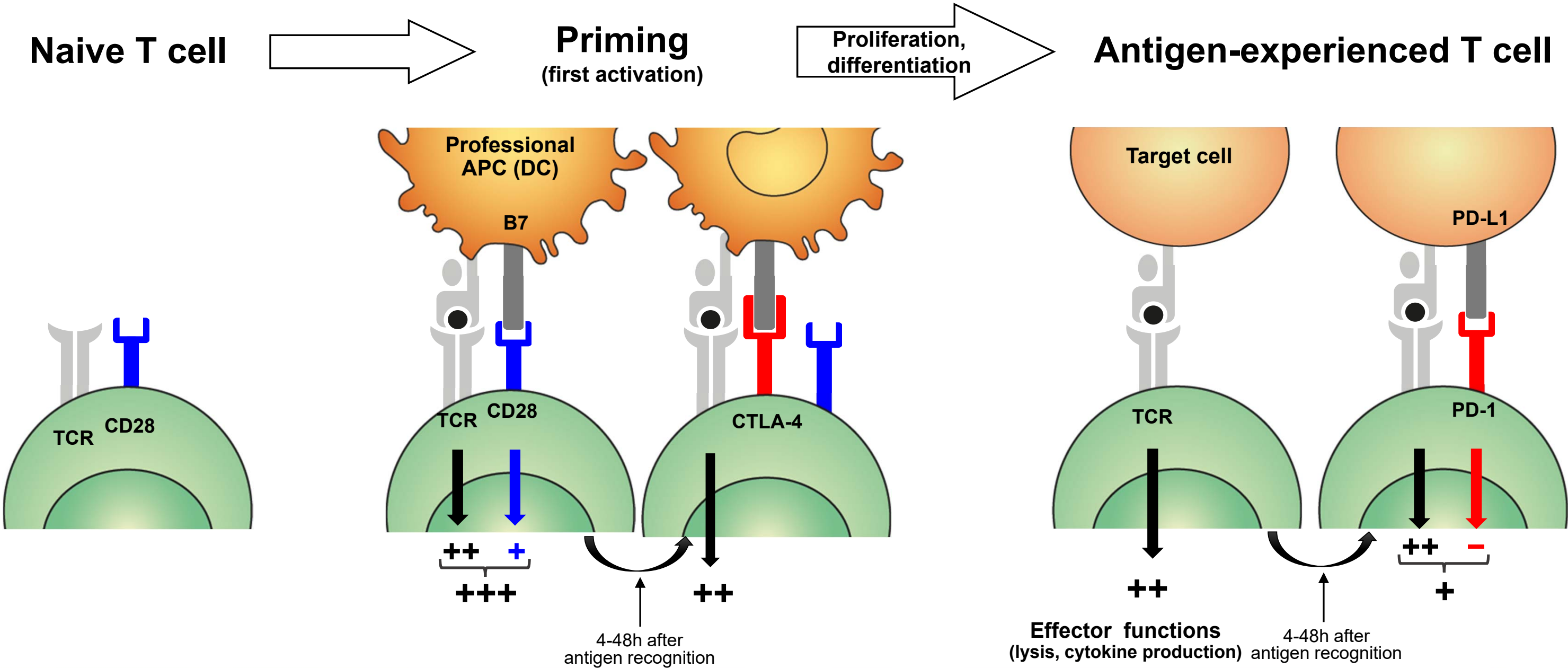
Antigenic stimulation: inhibition by CTLA-4



APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen 4; DC, dendritic cell.
Wei S, et al. Cancer Discovery 2018;8:1069–86; Chen D & Mellman I. Immunity 2013;39:1–10; Pardoll DM. Nat Rev Cancer 2012;12:252-264; Sharma P et al. Science 2015;348:56-61.



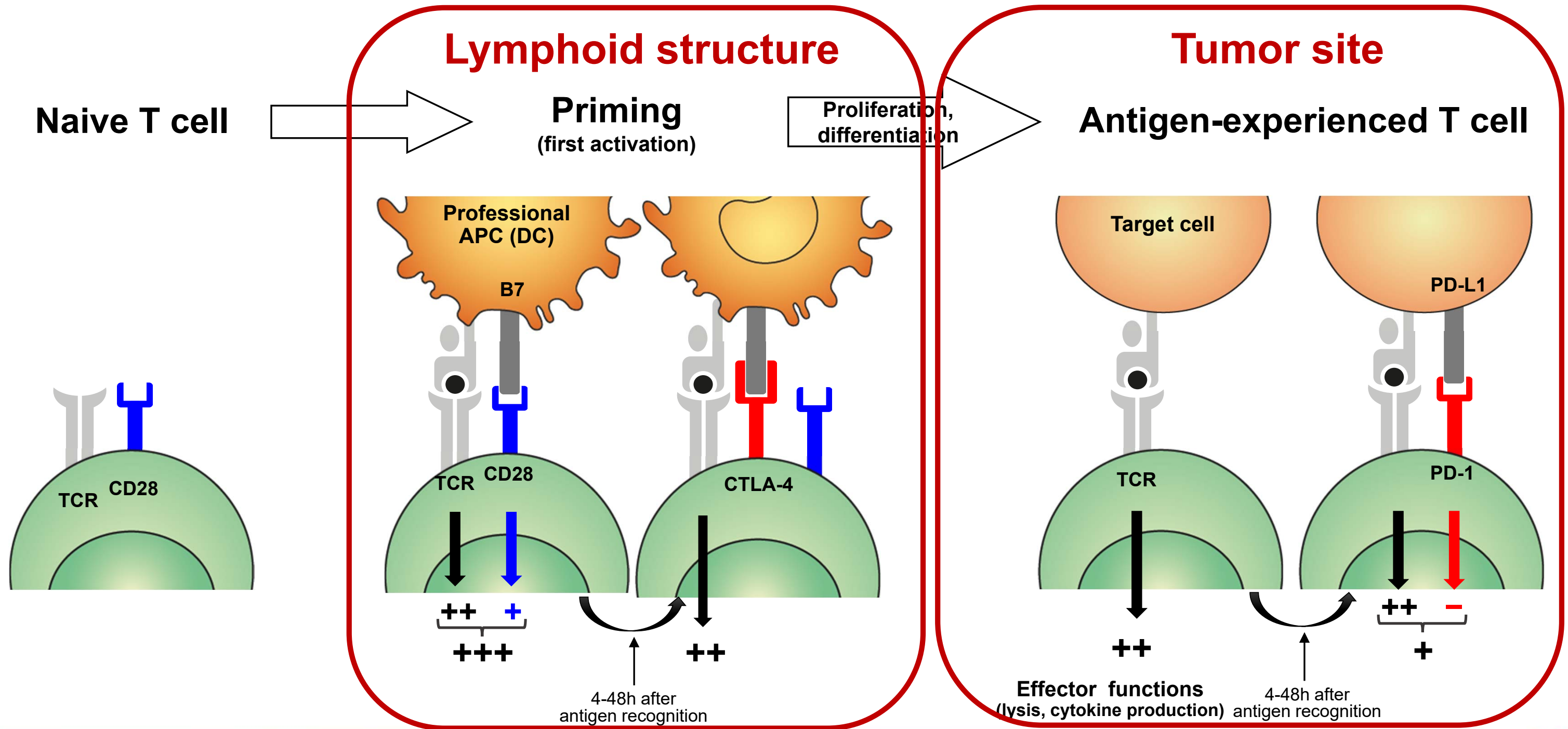
Antigenic stimulation: inhibition by PD-1



APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen 4; DC, dendritic cell; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.
 Wei S, et al. Cancer Discovery 2018;8:1069–86; Chen D & Mellman I. Immunity 2013;39:1–10; Pardoll DM. Nat Rev Cancer 2012;12:252-264; Sharma P et al. Science 2015;348:56-61.



Antigenic stimulation: CTLA-4 and PD-1 inhibitions at distinct locations



APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen 4; DC, dendritic cell; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.
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- ▶ Blocking the CTLA-4 and/or PD-1 pathways



Blocking the CTLA-4 and/or PD-1 pathways

Blocking the CTLA-4 inhibitory pathway

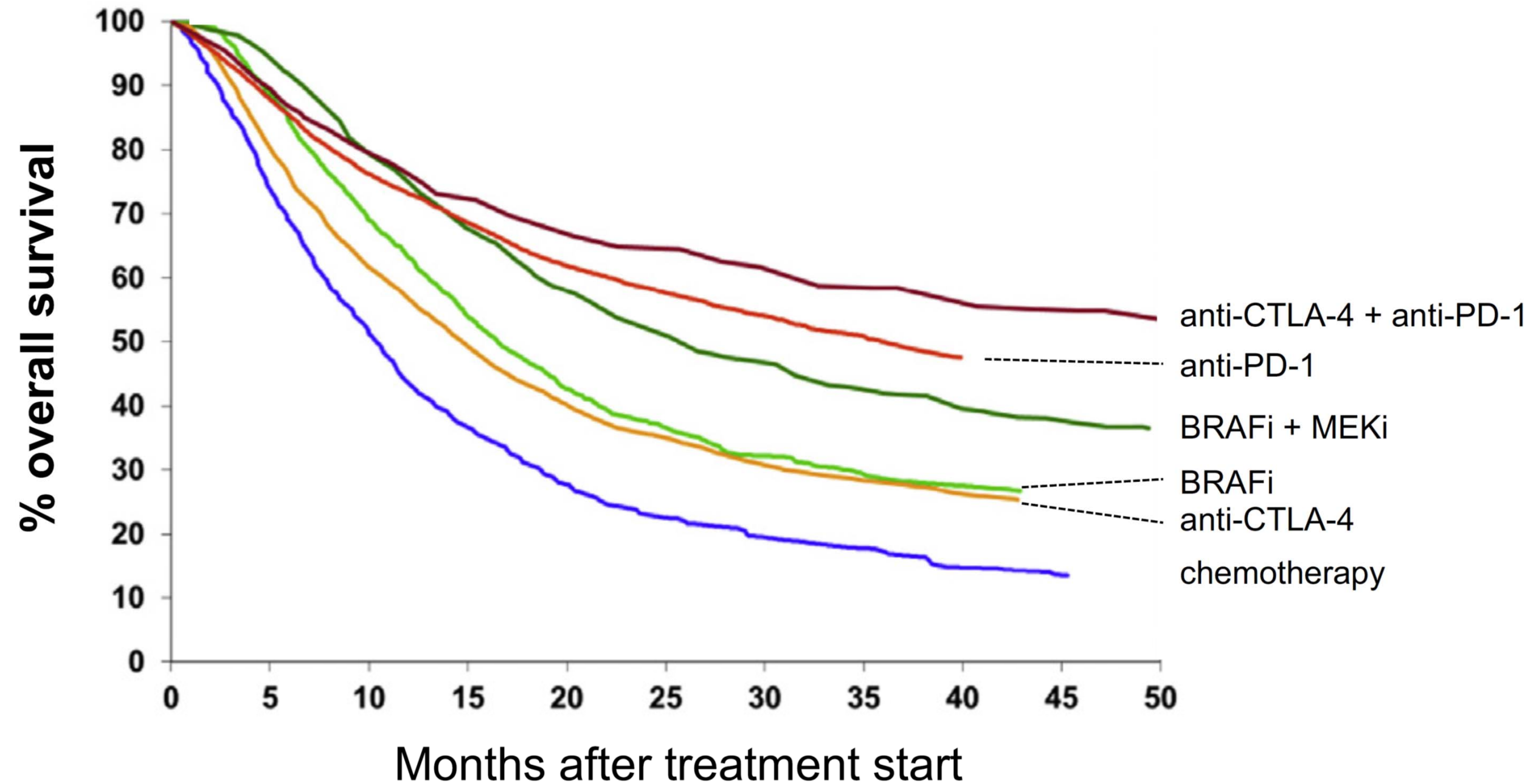
anti-CTLA-4:	ipilimumab	IgG1
	tremelimumab	IgG2

Blocking the PD-1 inhibitory pathway

anti-PD-1:	nivolumab	IgG4
	pembrolizumab	IgG4
anti-PD-L1:	atezolizumab	IgG1
	durvalumab	IgG1
	avelumab	IgG1



Therapeutic progresses for patients with advanced metastatic melanoma



BRAF, V-RAF murine sarcoma viral oncogene homolog B1; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-L1, programmed death-ligand 1.
Ugurel S, et al. *Eur J Cancer* 2020;130:126–130.

No adequate well-controlled head-to-head clinical trials are available



▶ Side effects



Side effects: irAEs

- ▶ Expected because *ctla4*^{-/-} or *pdc1*^{-/-} mice displayed autoimmunity and multiorgan lymphoproliferation¹
 - (more severe in *ctla4*^{-/-} than in *pdc1*^{-/-} animals)



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- ▶ T lymphocytes activated during administration of immunostimulatory antibodies, mainly by microbial antigens, will proliferate more, exerting more effector functions (cytokines, lysis, ...) for longer durations²⁻⁸



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- ▶ As CD4 helper T cells and Tregs control B cells, the above also applies to antibodies⁷

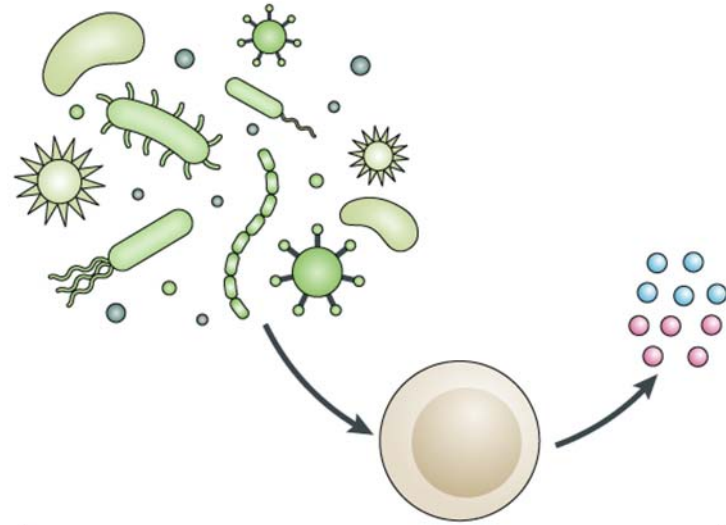
CTLA-4, cytotoxic T-lymphocyte antigen 4; irAE, immune-related adverse event; PD-L1, programmed death-ligand 1; Treg, regulatory T cells.

1. Chambers C et al. *Immunity* 1997;7:885-95; 2. Kvistborg P et al. *Sci Transl Med* 2014;176:254ra128; 3. Cha E et al. *Sci Transl Med* 2014;6:238ra70; 4. Wei et al. *Cancer Discov* 2018;8:1069-86; 5. Pedicord VA et al. *Proc Natl Acad Sci USA* 2011;108:266-71; 6. Schadendorf D et al. *J Clin Oncol* 2015;33:1898-94; 7. Pardoll DM et al. *Nat Rev Cancer* 2012;12:252-64; 8. Brahmer JR et al. *J Clin Oncol* 2013;31:1021-8.



Main immunopathogenic mechanisms proposed for irAE

Activation by the microbiome



- Pro-inflammatory lineage shifts
- Inflammatory cytokine production

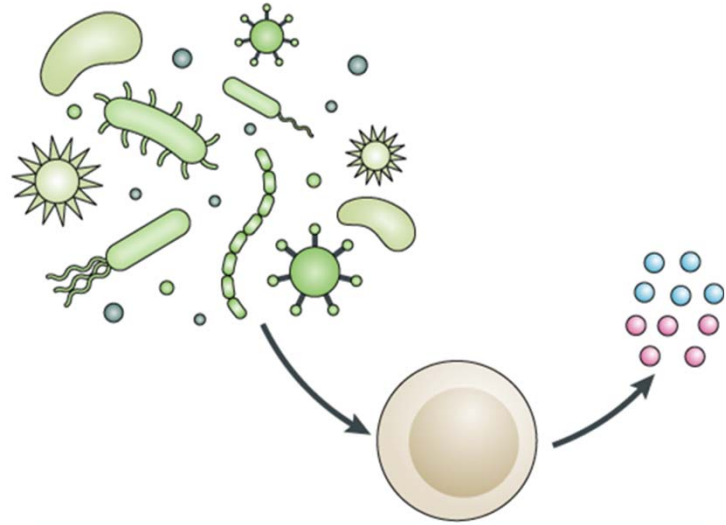
Immune checkpoint

Checkpoint inhibitor



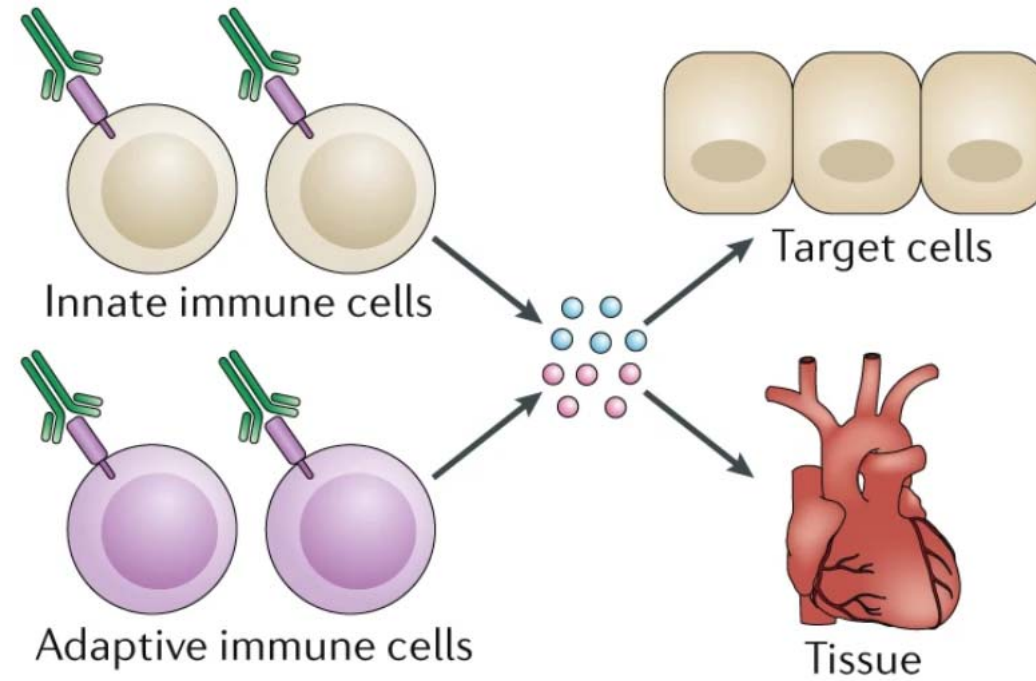
Main immunopathogenic mechanisms proposed for irAE

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- Inflammatory cytokine production

Effects of cytokines or chemokines



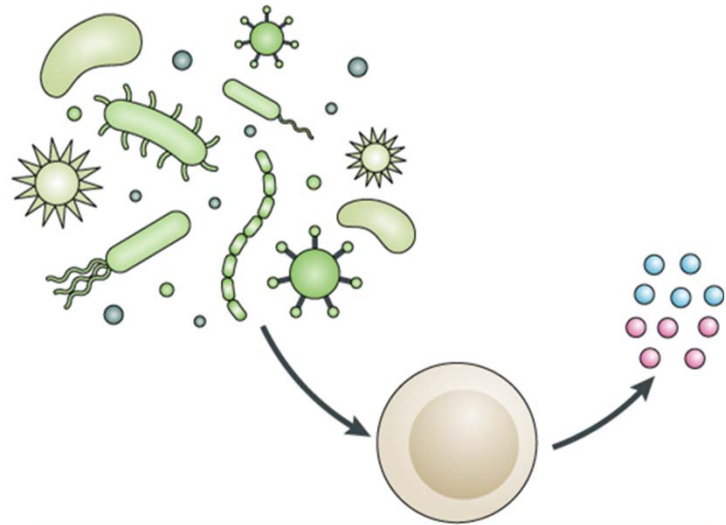
 Immune checkpoint

 Checkpoint inhibitor



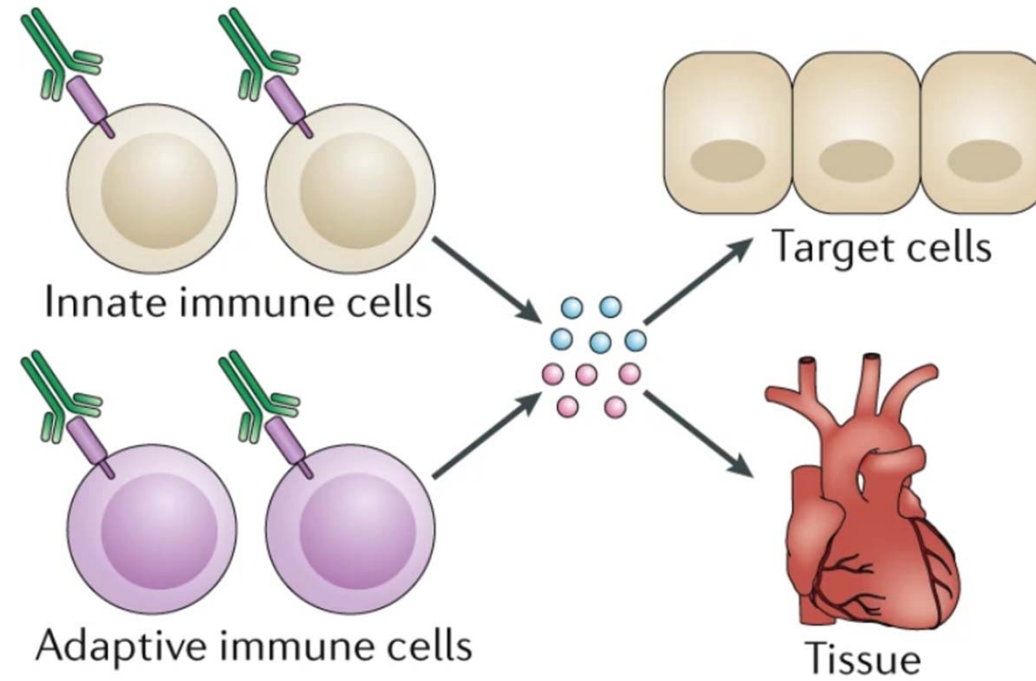
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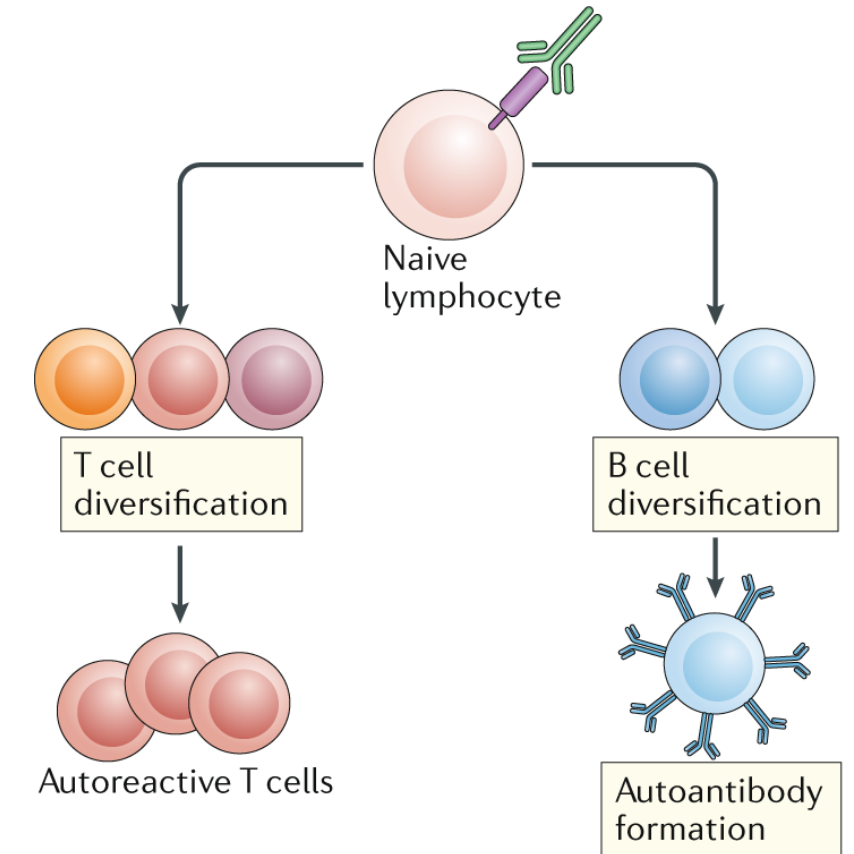


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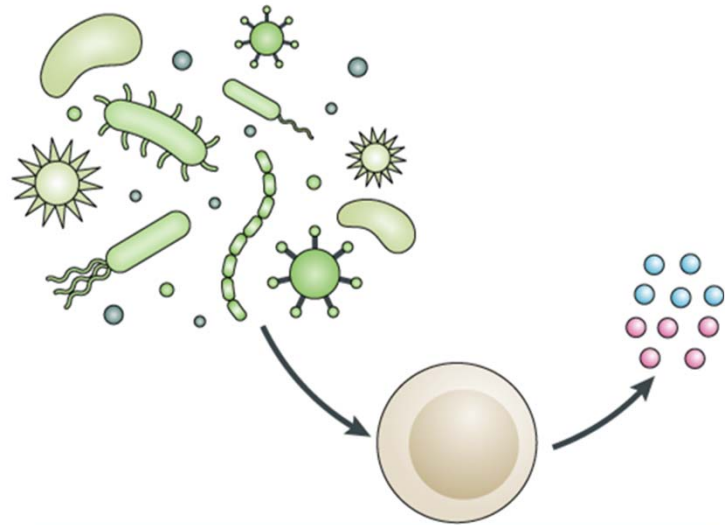


Breach of self-tolerance



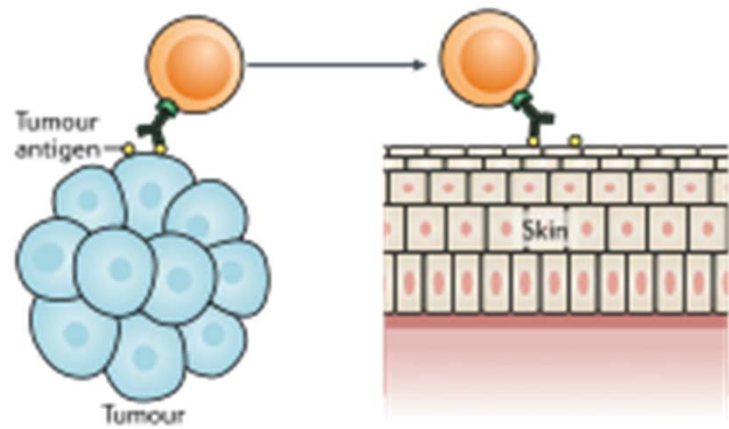
Main immunopathogenic mechanisms proposed for irAE

Activation by the microbiome

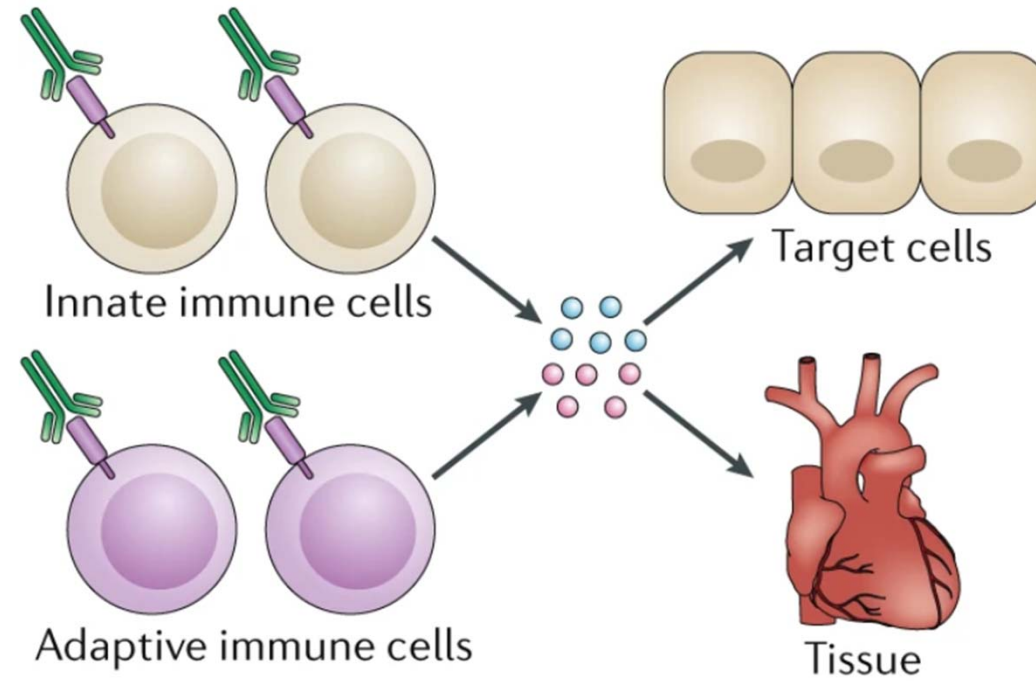


- Pro-inflammatory lineage shifts
- Inflammatory cytokine production

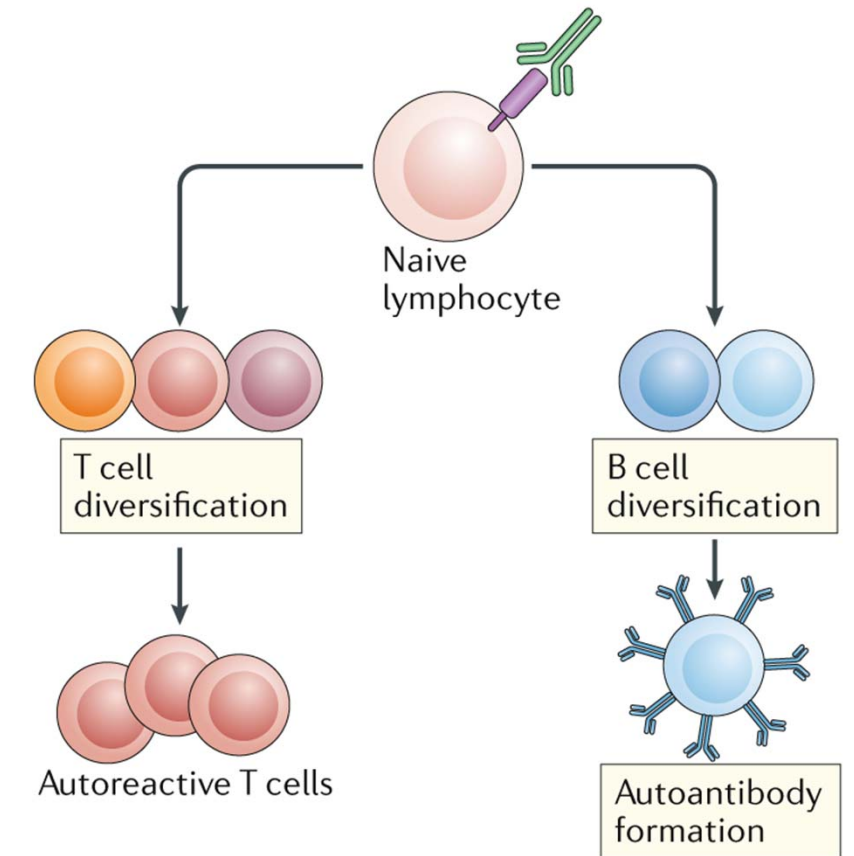
Cross-reactivity between self and tumor antigens



Effects of cytokines or chemokines



Breach of self-tolerance



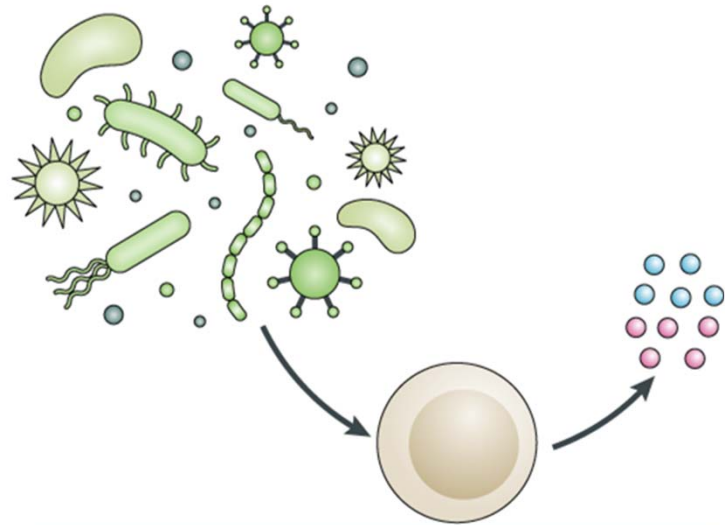
Immune checkpoint

Checkpoint inhibitor



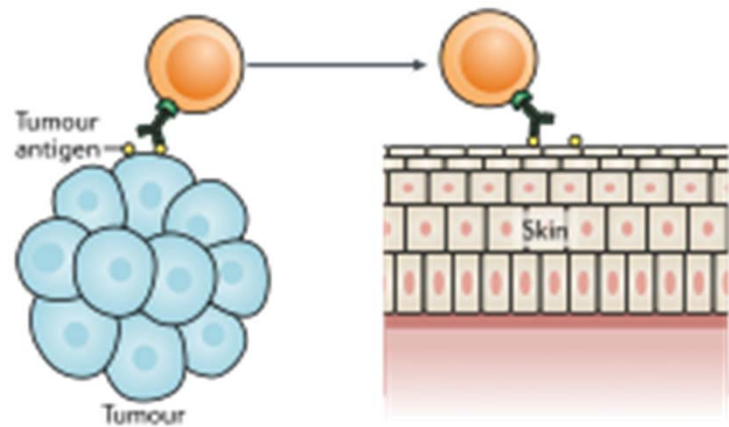
Main immunopathogenic mechanisms proposed for irAE

Activation by the microbiome

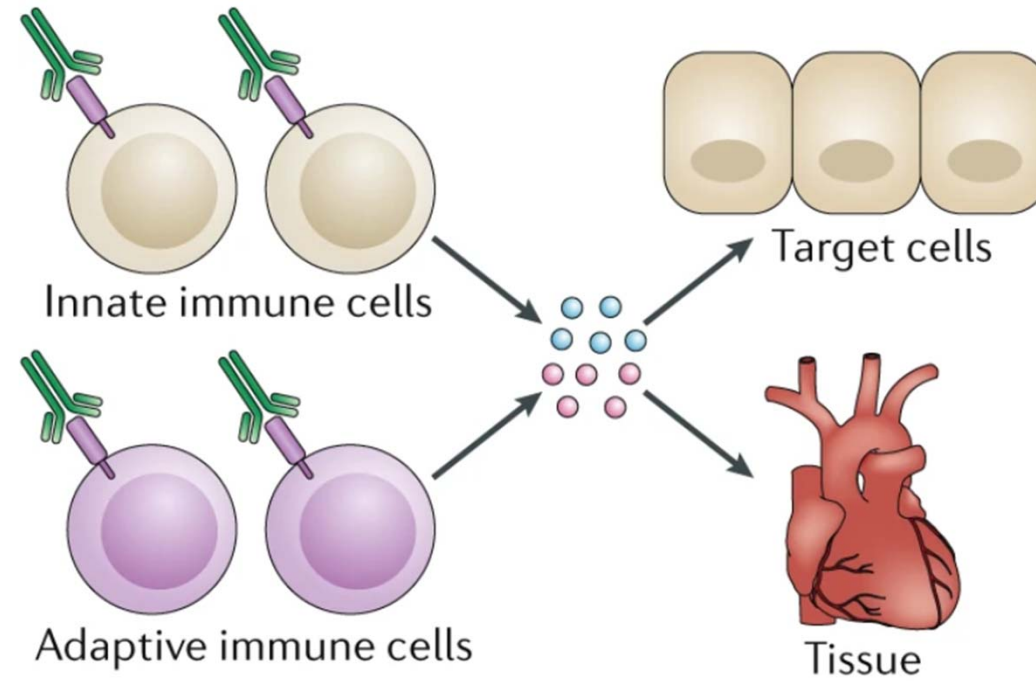


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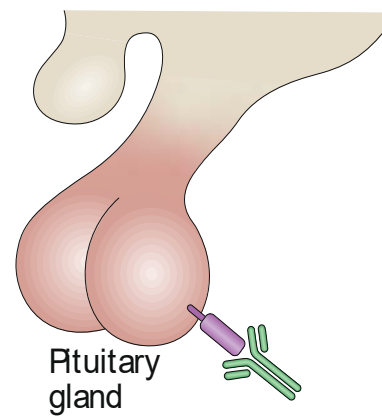
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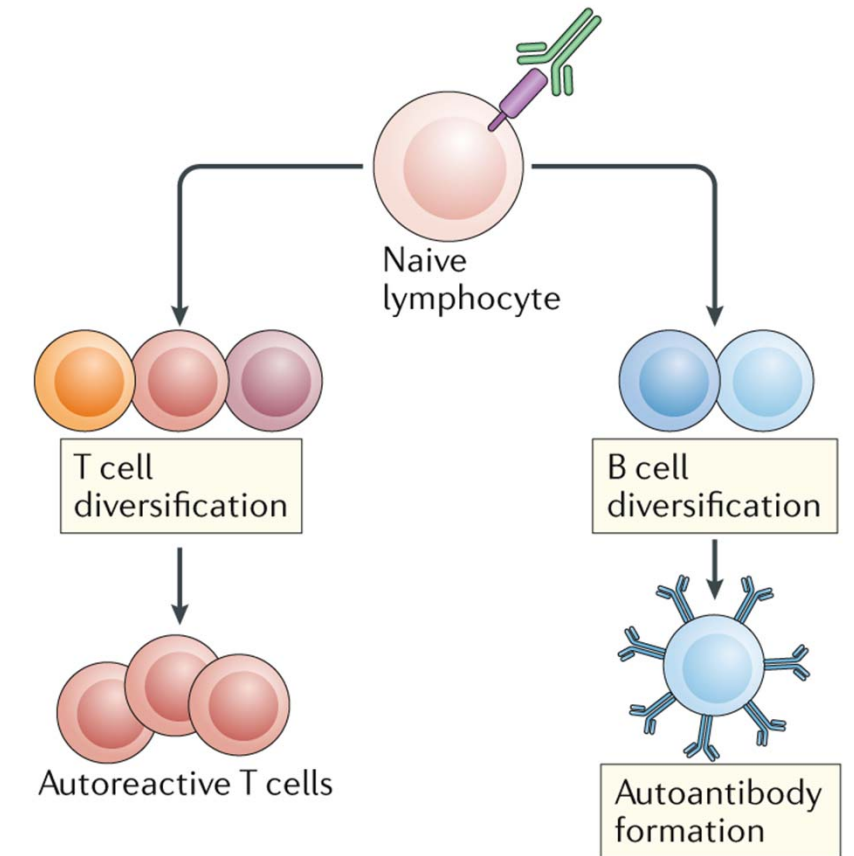
Effects of cytokines or chemokines




Off-target effects



Breach of self-tolerance



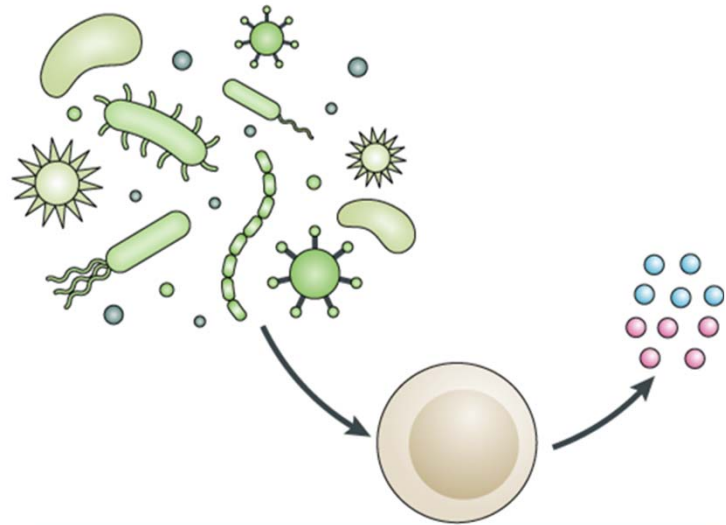
 Immune checkpoint

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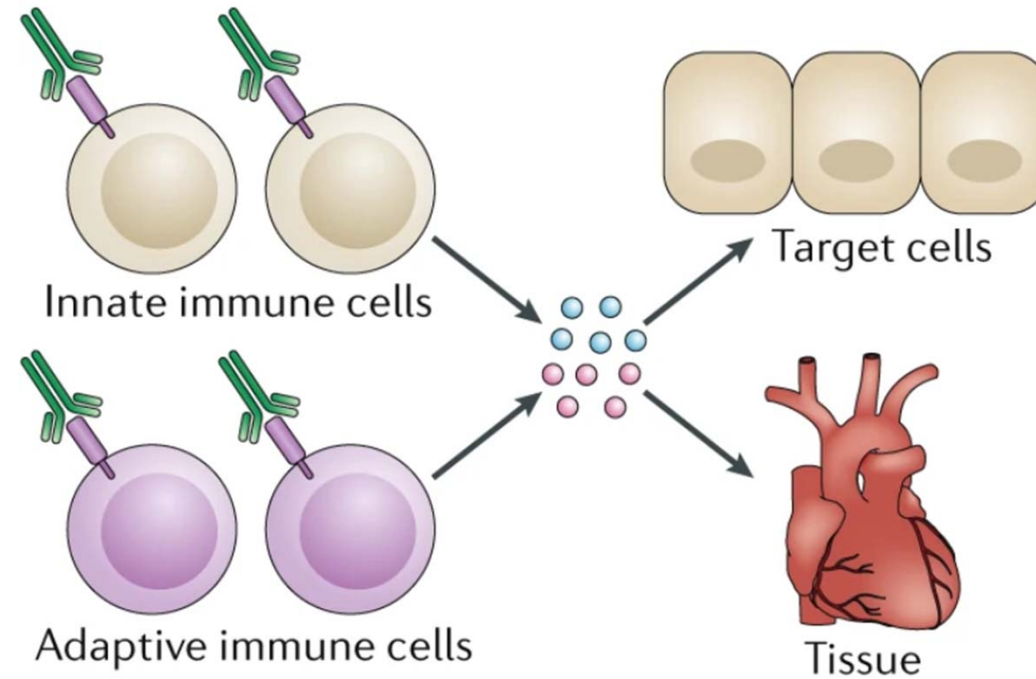
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Activation by the microbiome

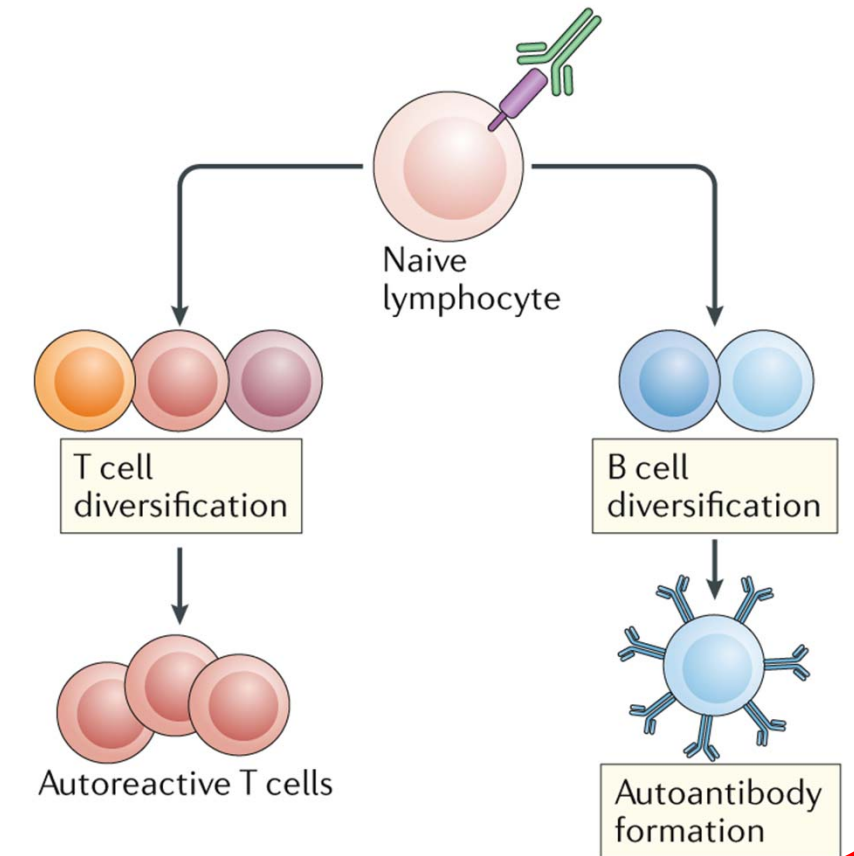


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Effects of cytokines or chemokines



Breach of self-tolerance

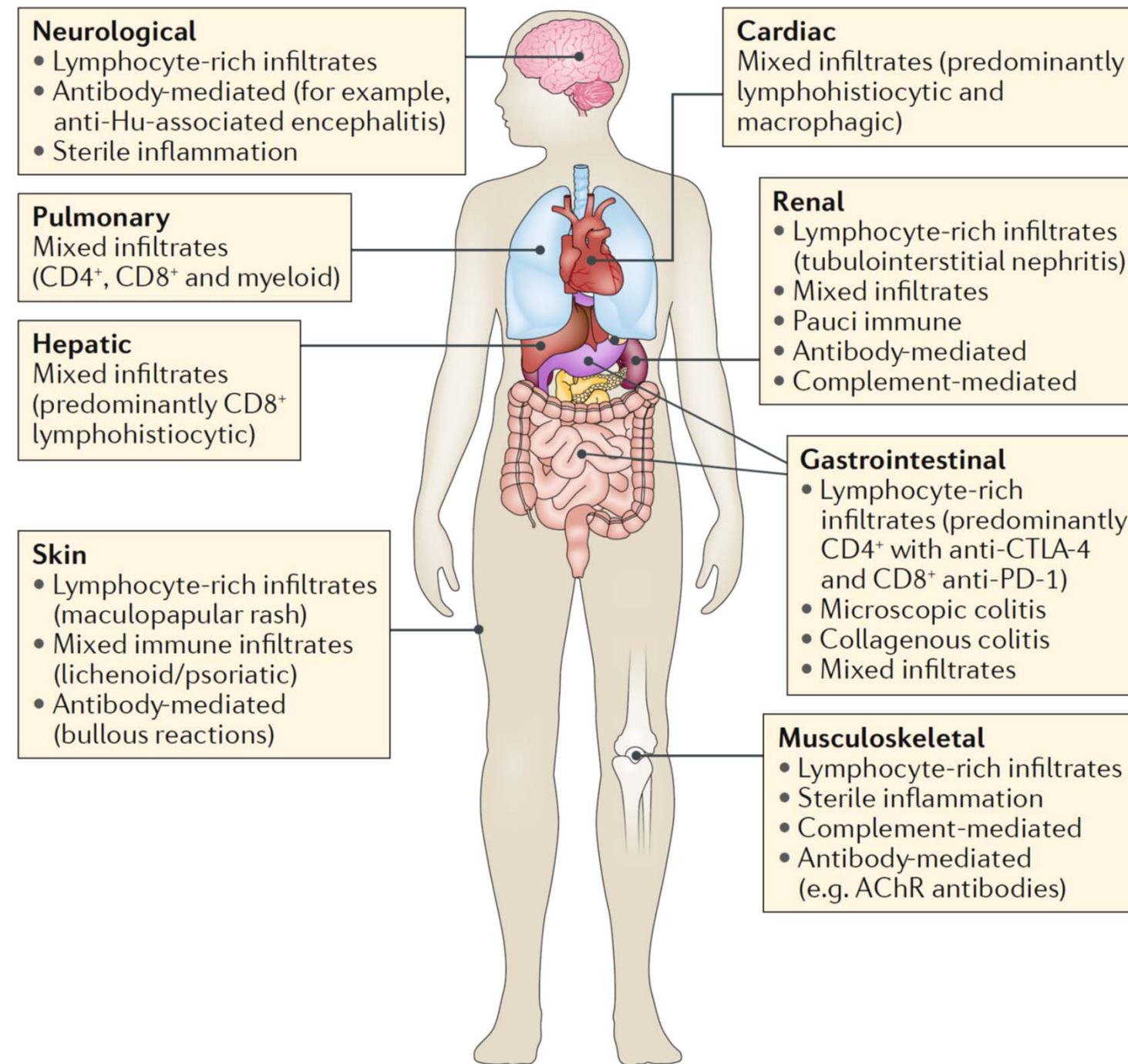


Important

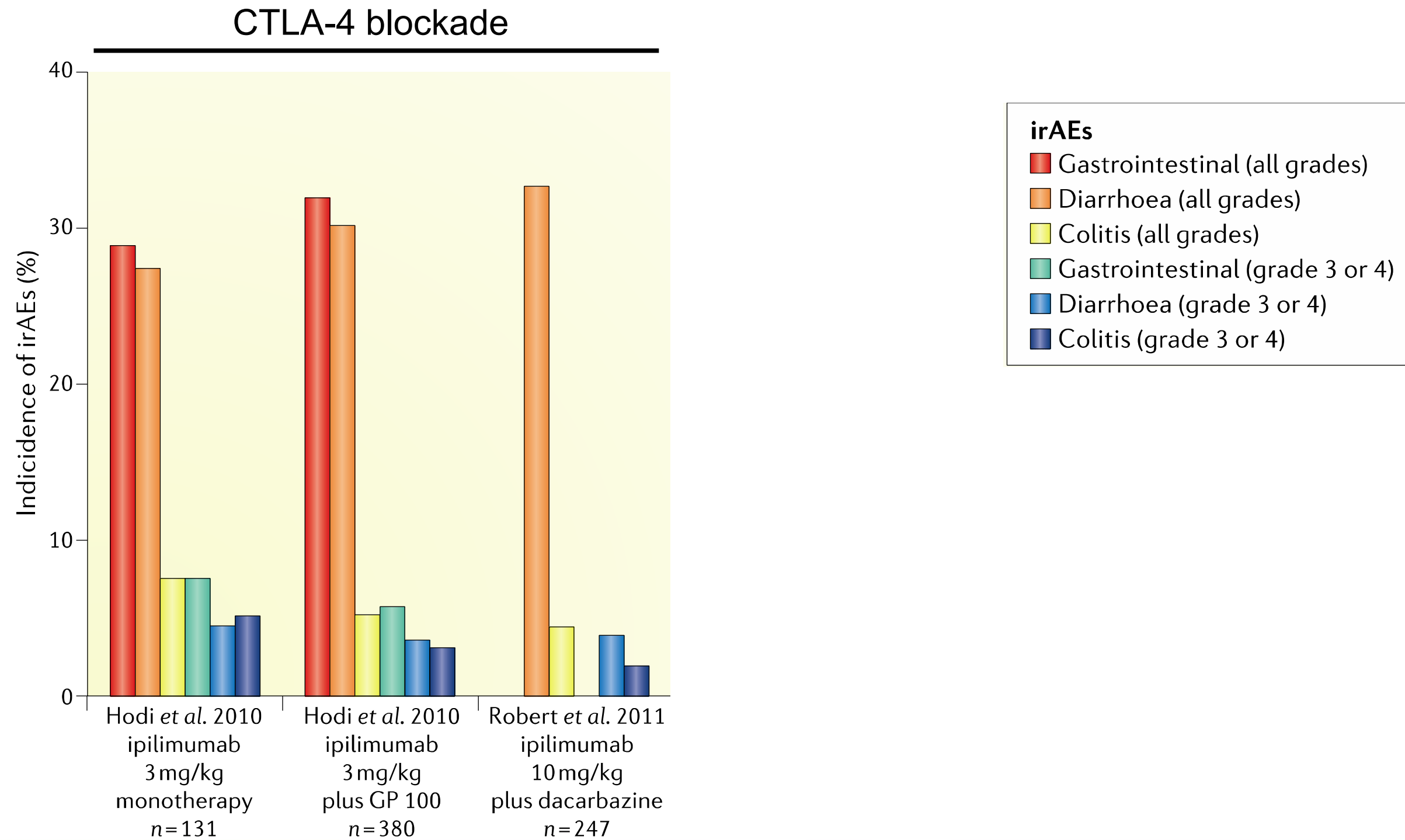
It is a mix of autoinflammation (mostly) and autoimmunity



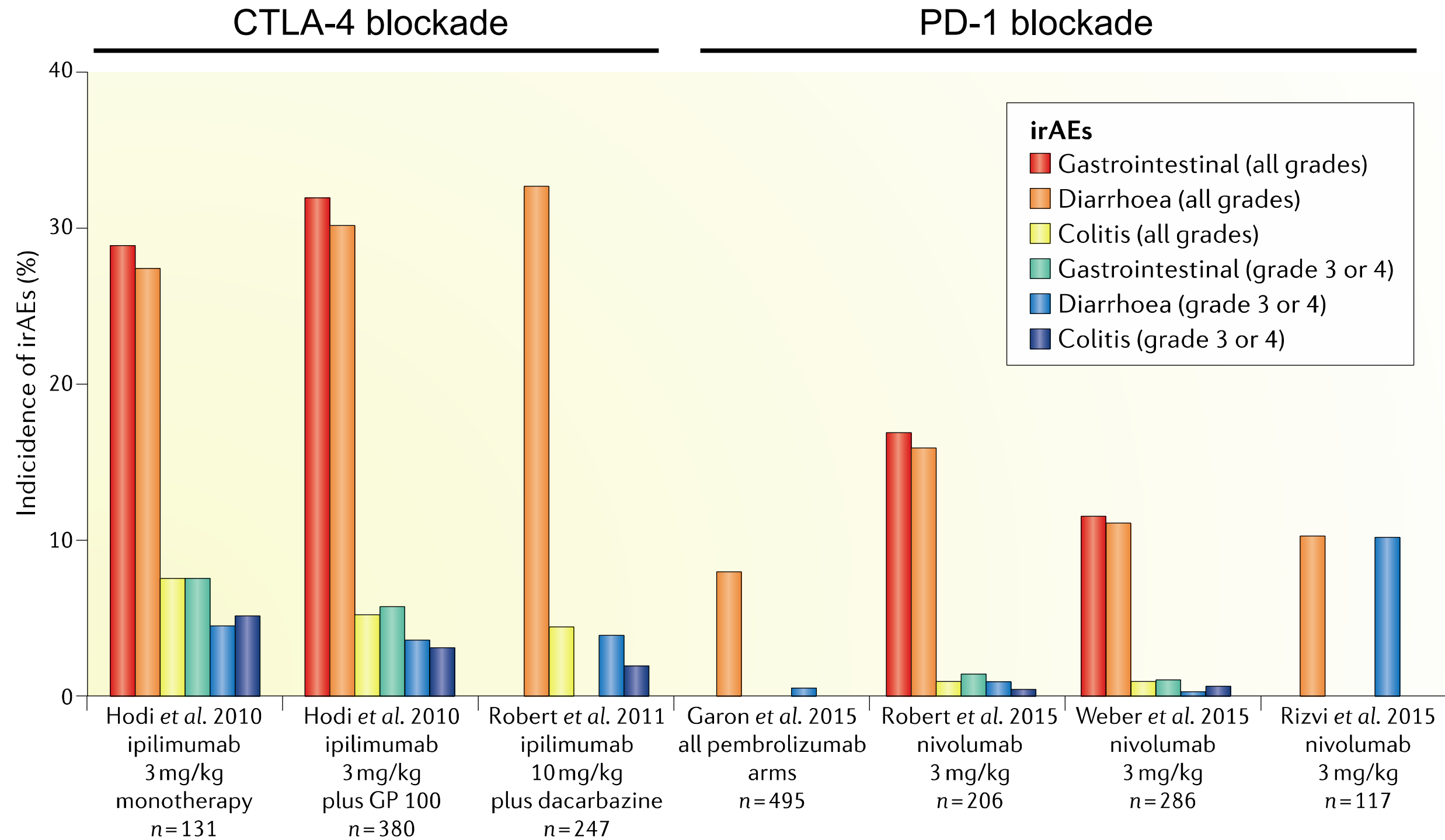
Most commonly observed affected organ systems



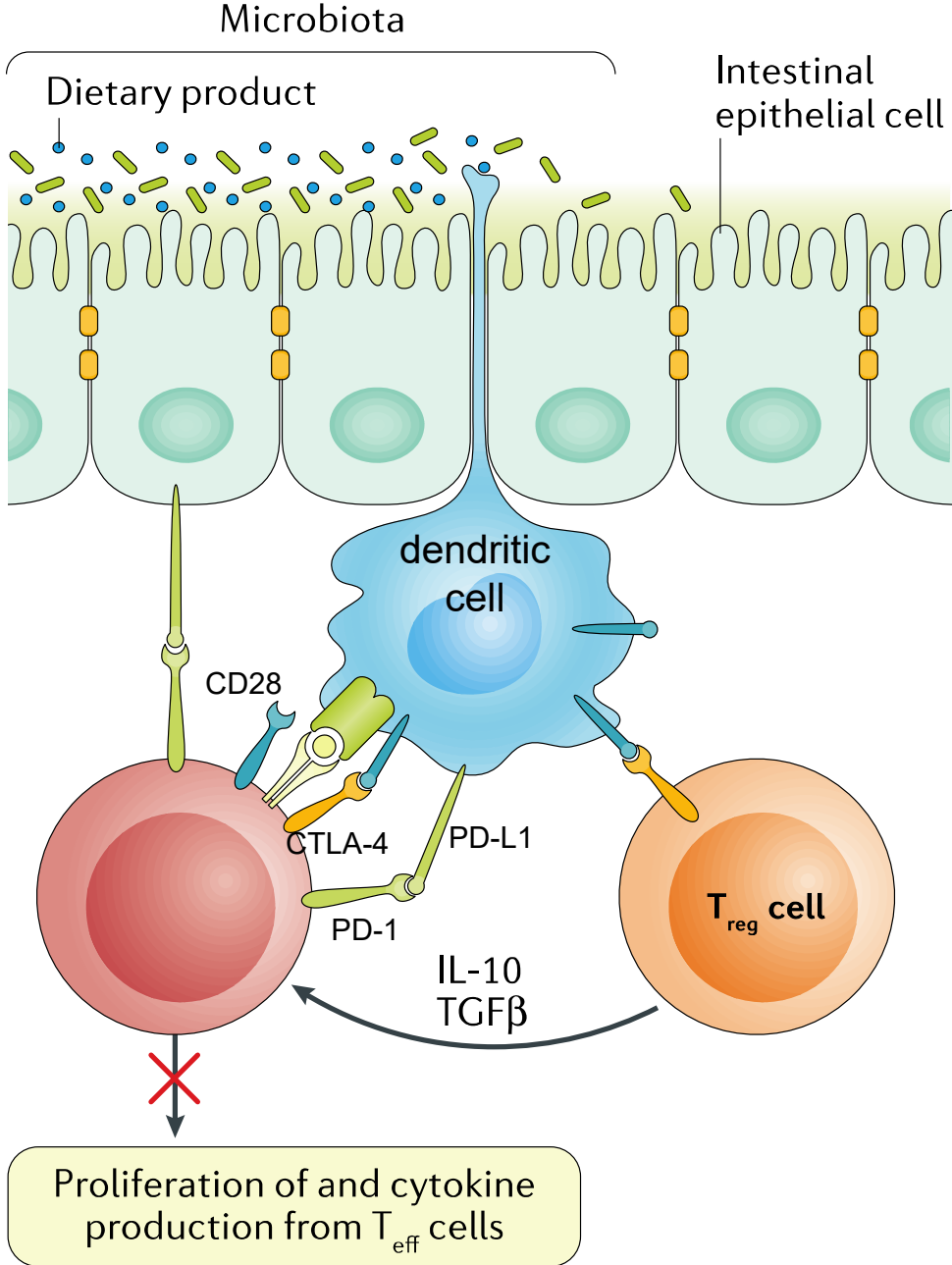
Gastrointestinal toxicity after CTLA-4 or PD-1 blockade



Gastrointestinal toxicity after CTLA-4 or PD-1 blockade



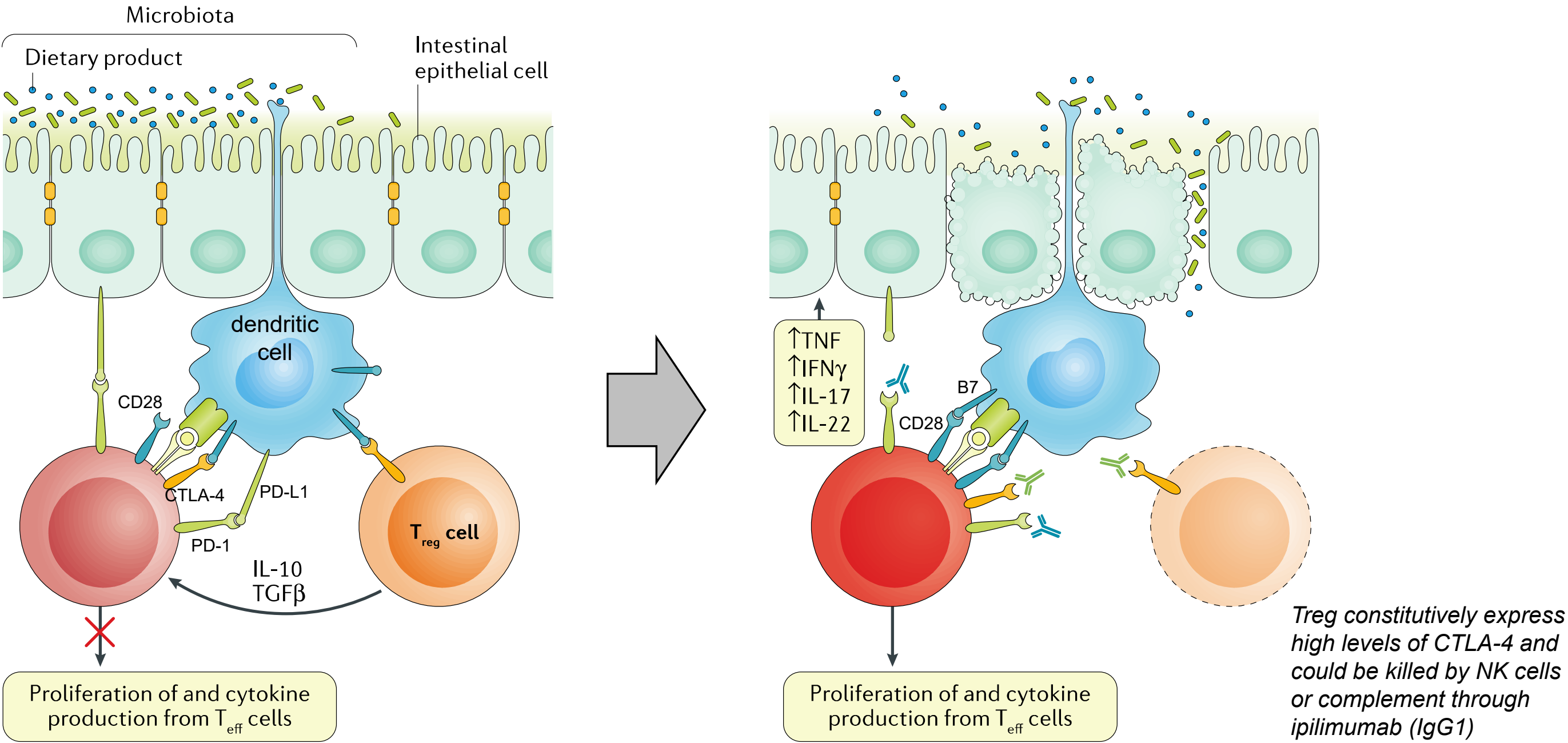
Possible mechanism of colitis during CTLA-4 or PD-1 blockade



Reproduced with permission from *Nat Rev Gastroenterol Hepatol*: Samaan MA et al. 2018;15:222–34.



Possible mechanism of colitis during CTLA-4 or PD-1 blockade



Reproduced with permission from *Nat Rev Gastroenterol Hepatol*: Samaan MA et al. 2018;15:222–34.



Summary

- ▶ Antibodies blocking the CTLA-4 or PD-1 inhibitory pathways increase the number and activity of T lymphocytes activated by their antigen
- ▶ CTLA-4 and PD-1 blockades act on tumor-specific but also on non tumor-specific T cells
- ▶ Immune-related adverse events are caused mostly by non tumor-specific T cells
- ▶ Among the latter, those recognizing gut microbiota are likely to cause GI toxicity

