ImmunoScience Academy
Partnering for Education & Optimizing Treatment in ImmunoScience

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de Duve INSTITUTE

Immunotherapy: from the lab to the clinic

Pr. Pierre Coulie MD, PhD
de Duve Institute
University of Louvain
Brussels, Belgium

Mercury number IOBE18NP04371-07
Date of preparation: December 2018

pierre.coulie@uclouvain.be

Cancer immunotherapy

From the lab

- Tumor antigens recognized by T cells
- Inhibitory and stimulatory coreceptors
- CAR technology

To the clinic

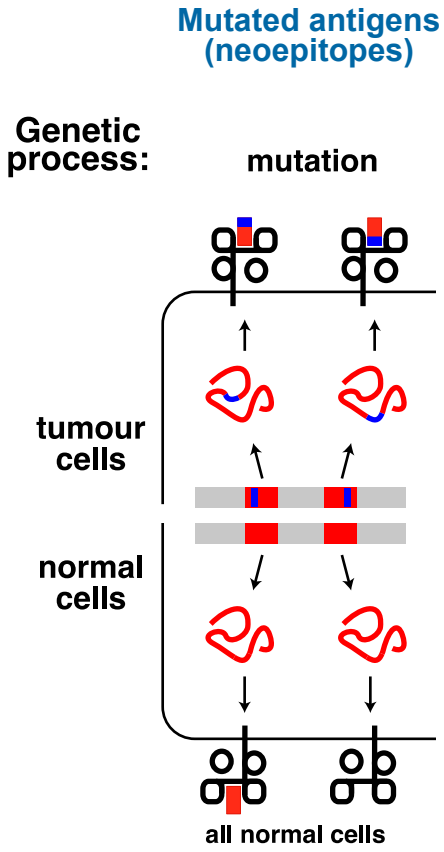
- 'Checkpoint blockade'
- Anti-CD19 CAR T cells

What's next?

- Combination therapies
- Counteract local resistance or immunosuppression
- Immunizations

CAR, chimeric antigen receptor.

Classes of tumor antigens recognized by T cells

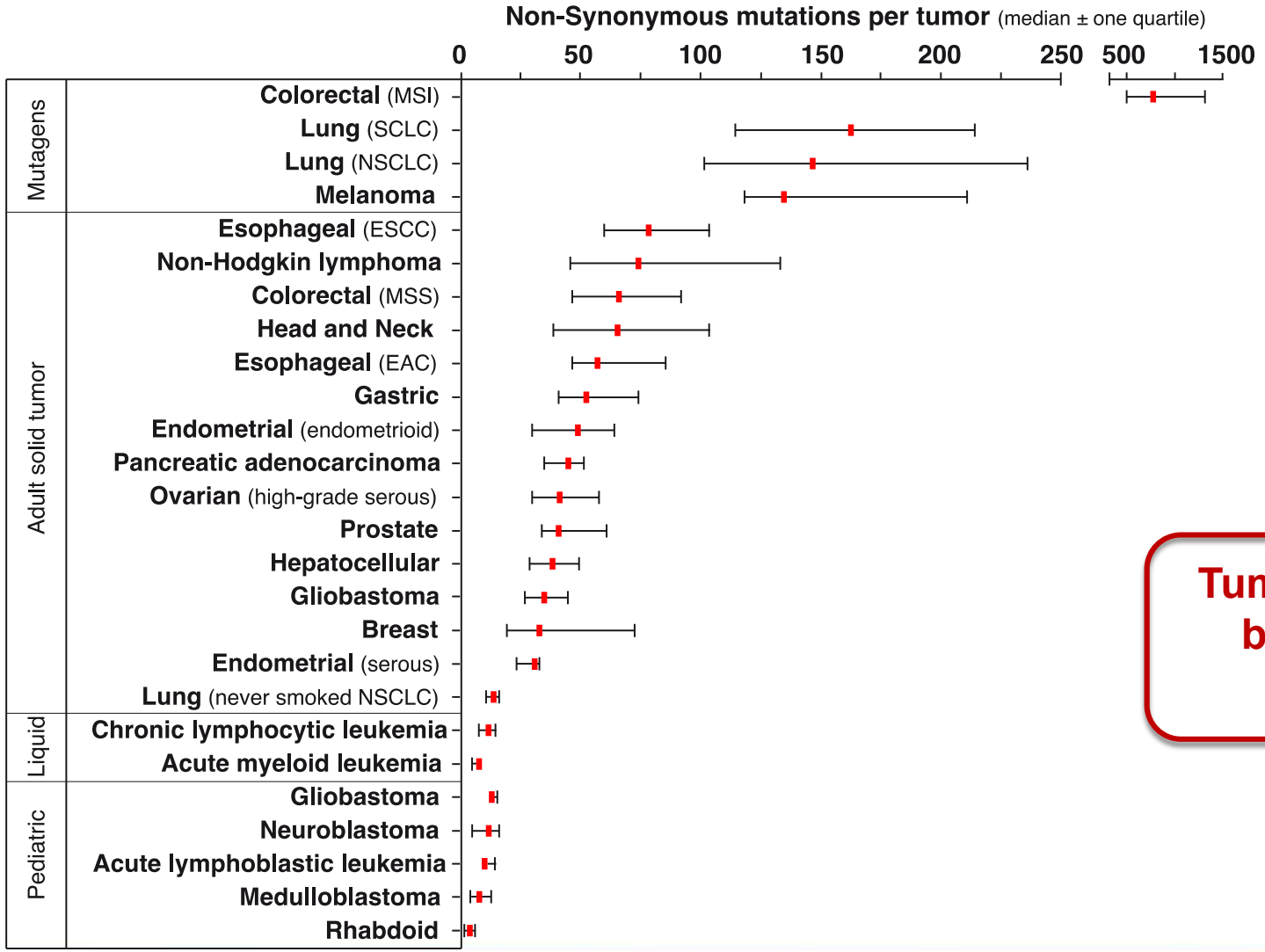


DNA mutations (mostly non synonymous single nucleotide variations)

- Amino acid change in a protein
- Mostly at random: passenger mutations
- A peptide containing a mutant amino acid can be presented by HLA molecules and recognized by T cells

HLA, human leukocyte antigen.
Coulie et al. Nat Rev Cancer 2014;14:135–46.

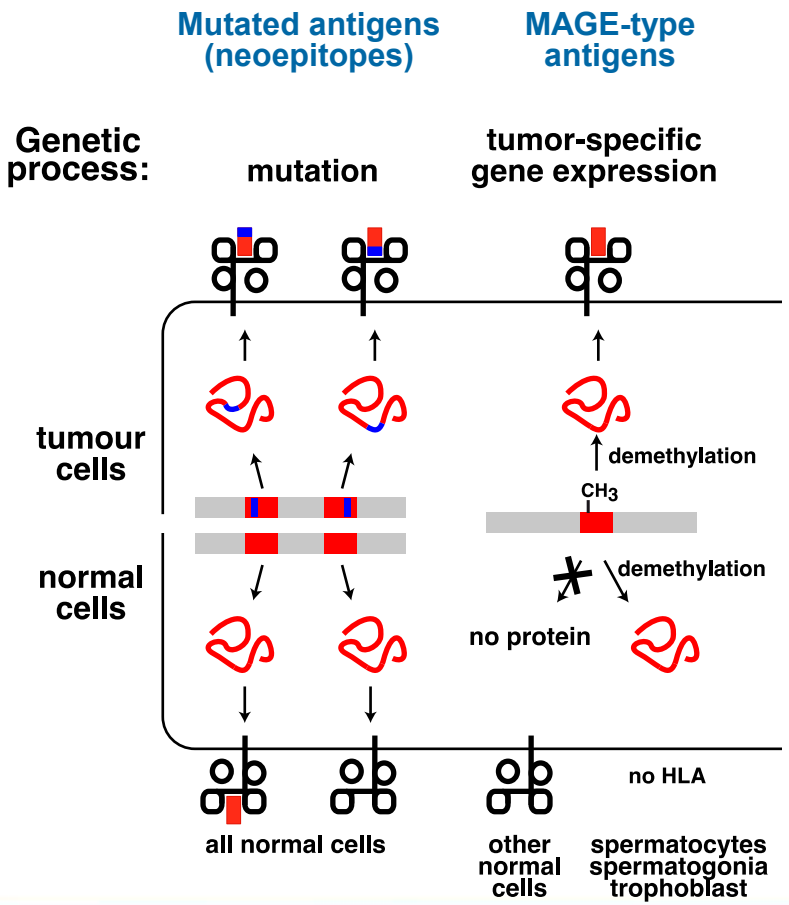
Antigens resulting from mutations (single nucleotide variations)



Tumor mutation burden is a predictive biomarker for clinical response to CTLA-4 or PD-1 blockade

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-L1, programmed cell death ligand 1.
Adapted from Vogelstein et al. Science 2013;339:1546–58.

Classes of tumor antigens recognized by T cells



Cancer-germline genes

- Expressed in tumors
- Silent in normal adult tissues except for germline cells (HLA-negative)
- Reason for this pattern of expression: DNA demethylation
- Examples:
  - *MAGEA1, -A2, -A3, ... -A12*
  - *MAGEC1, -C2*
  - *LAGE1 = NYESO1*
  - *BAGE, GAGE*
  - *SSX1, -2*
- Often erroneously referred to as ‘Cancer Testis Antigens’

HLA, human leukocyte antigen; MAGE, melanoma antigen gene; MAGE-A1, MAGE family member A1.
Coulie et al. Nat Rev Cancer 2014;14:135–46.

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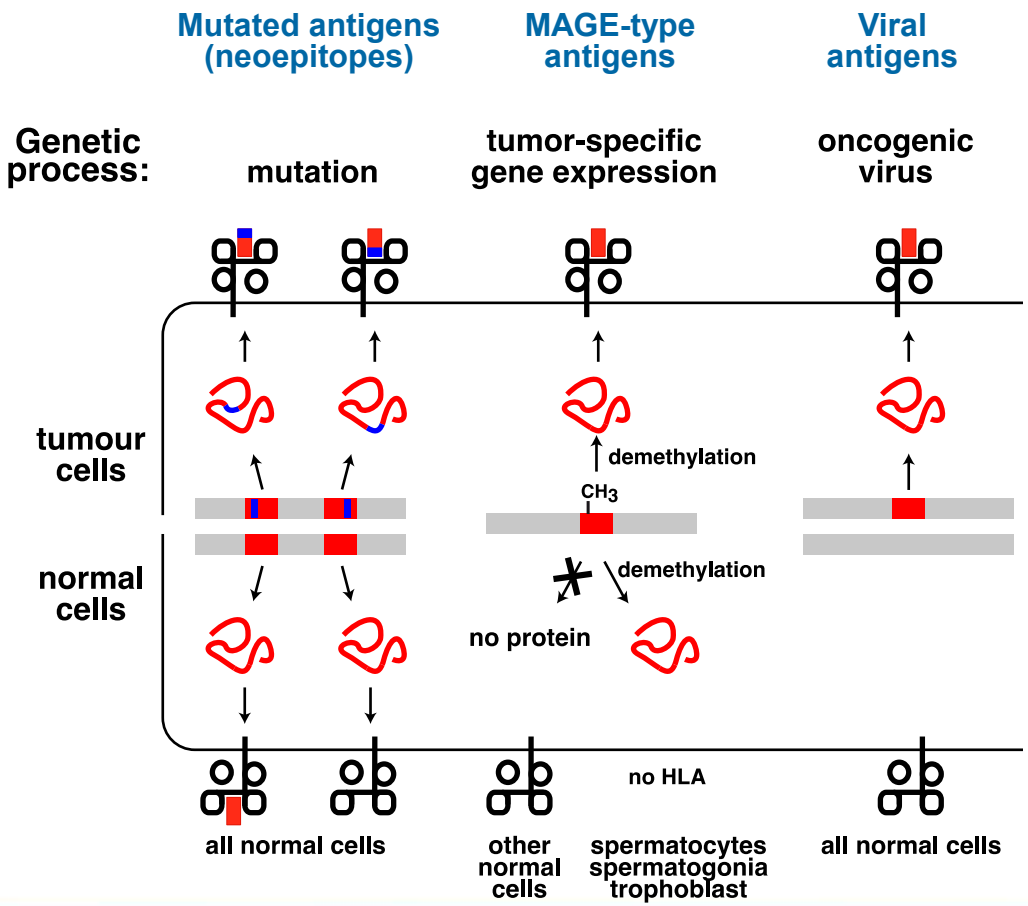

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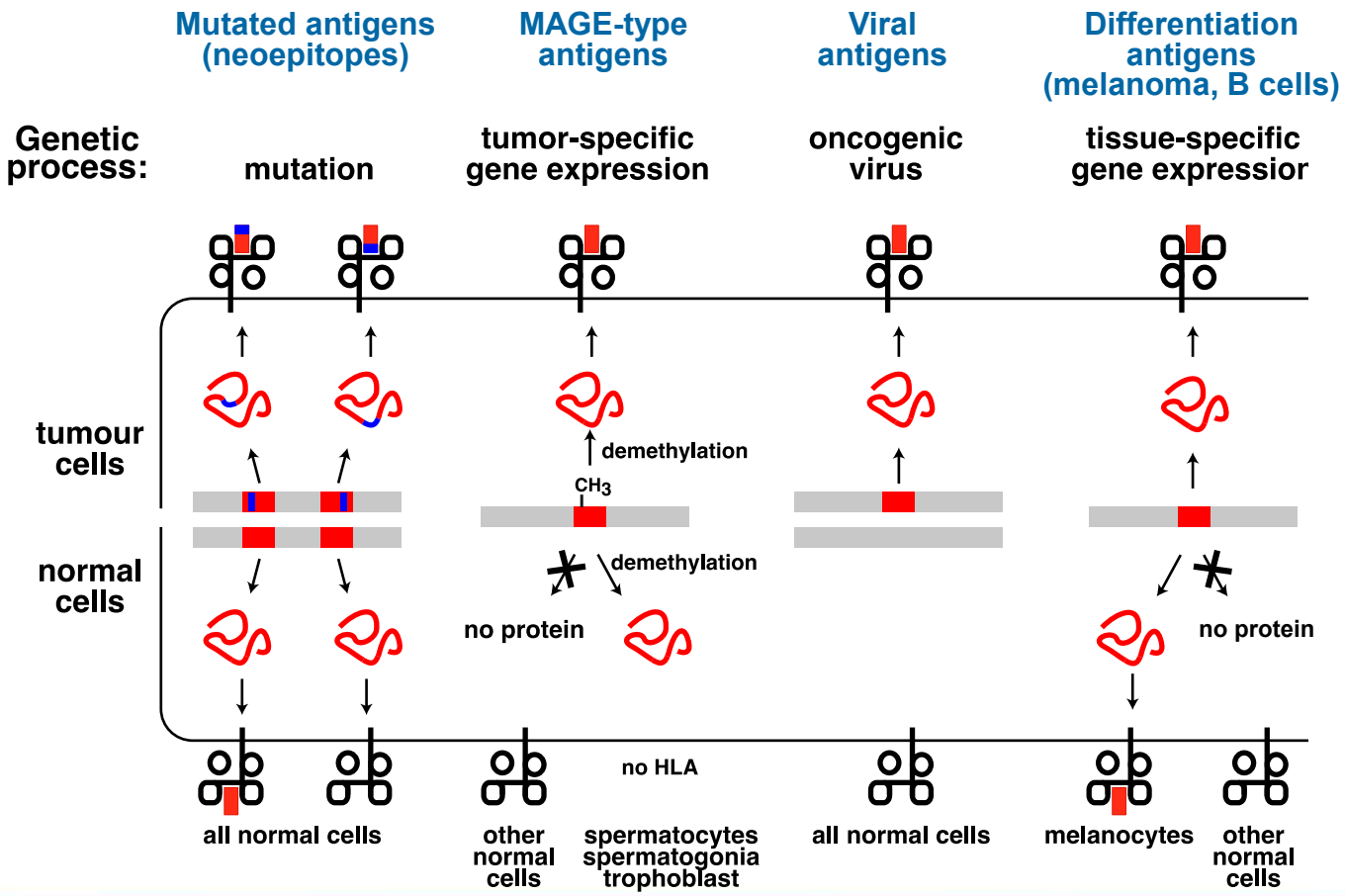

CEA, carcinoembryonic antigen; gp100, glycoprotein 100; HLA, human leukocyte antigen; MAGE, melanoma antigen gene; PSA, prostate-specific antigen.
Coulie et al. Nat Rev Cancer 2014;14:135–46.

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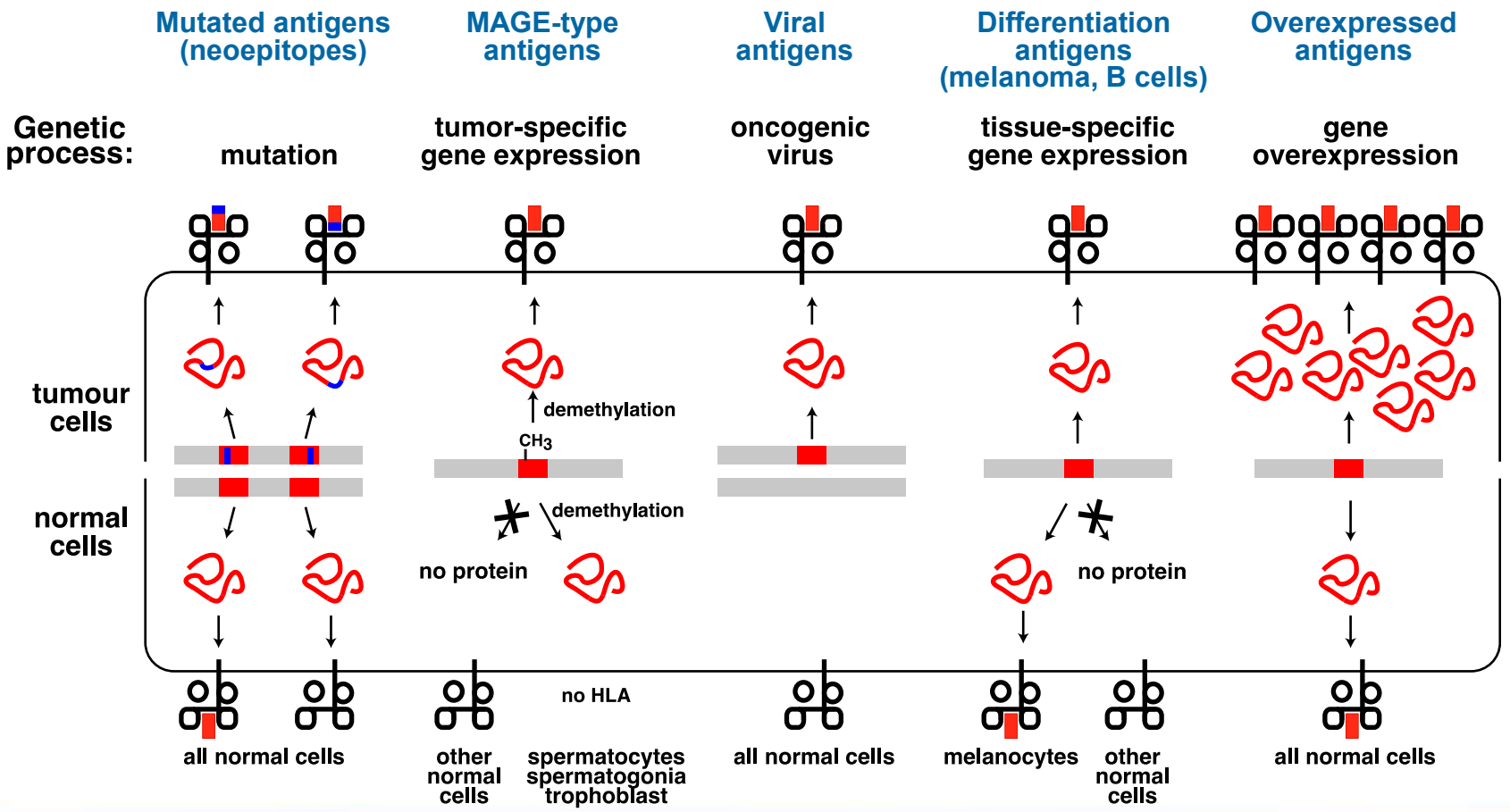

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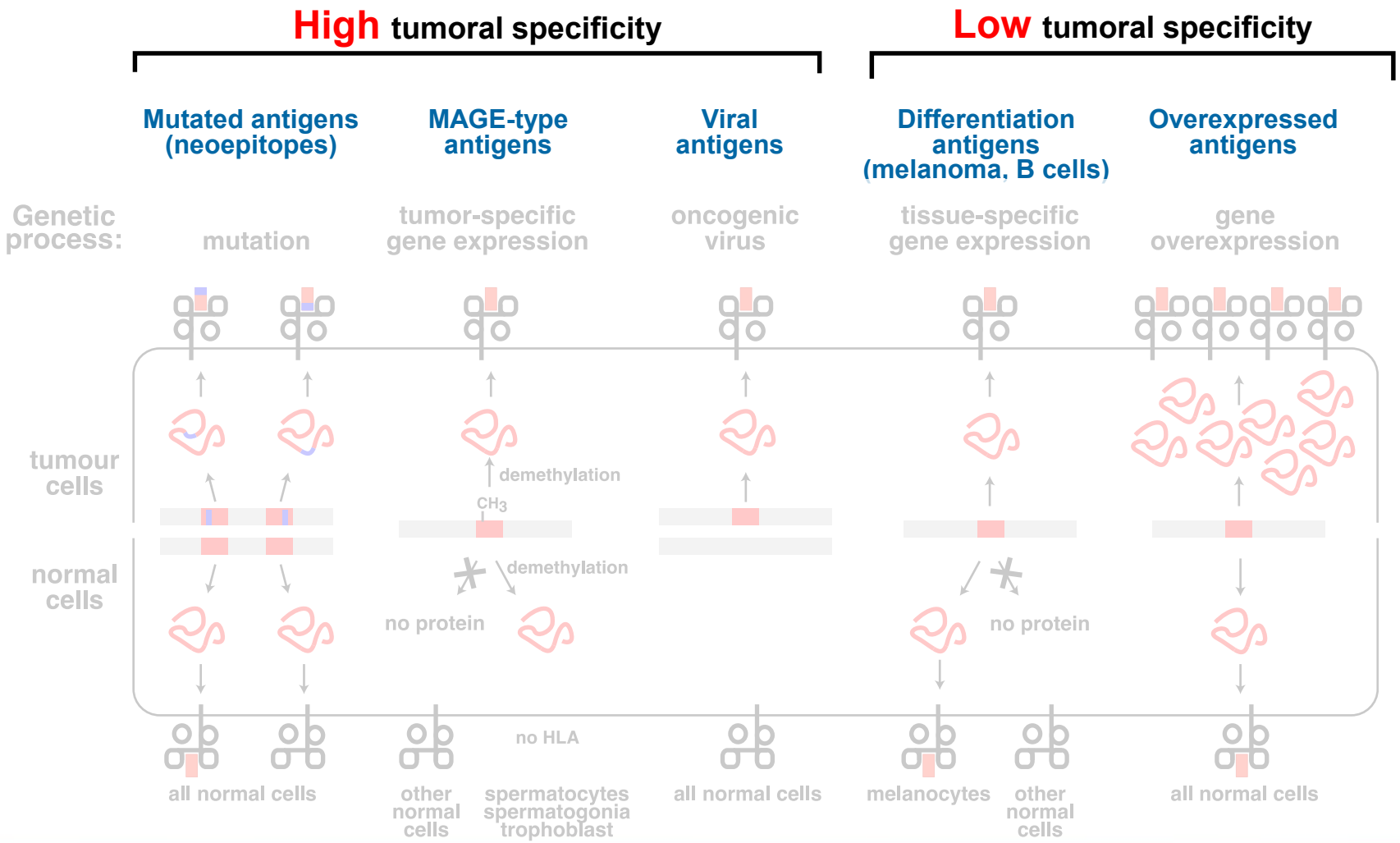

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Tumor antigens: conclusions

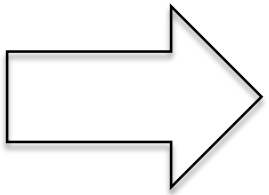
- Human tumors are antigenic to autologous T cells
- Some antigens are truly tumor-specific
- Tumors are also, at least in some patients, immunogenic
  - Autologous anti-tumor CTL are found in blood or tumors

Key properties of T-cells for cancer therapy

Killing capacities

Absolute tumor **specificity**

Memory



Unique therapeutic modality:

Long-lasting and **tumor-specific antitumor activity**

The antitumoral activity of all the other anticancer treatments stops together with the treatments.

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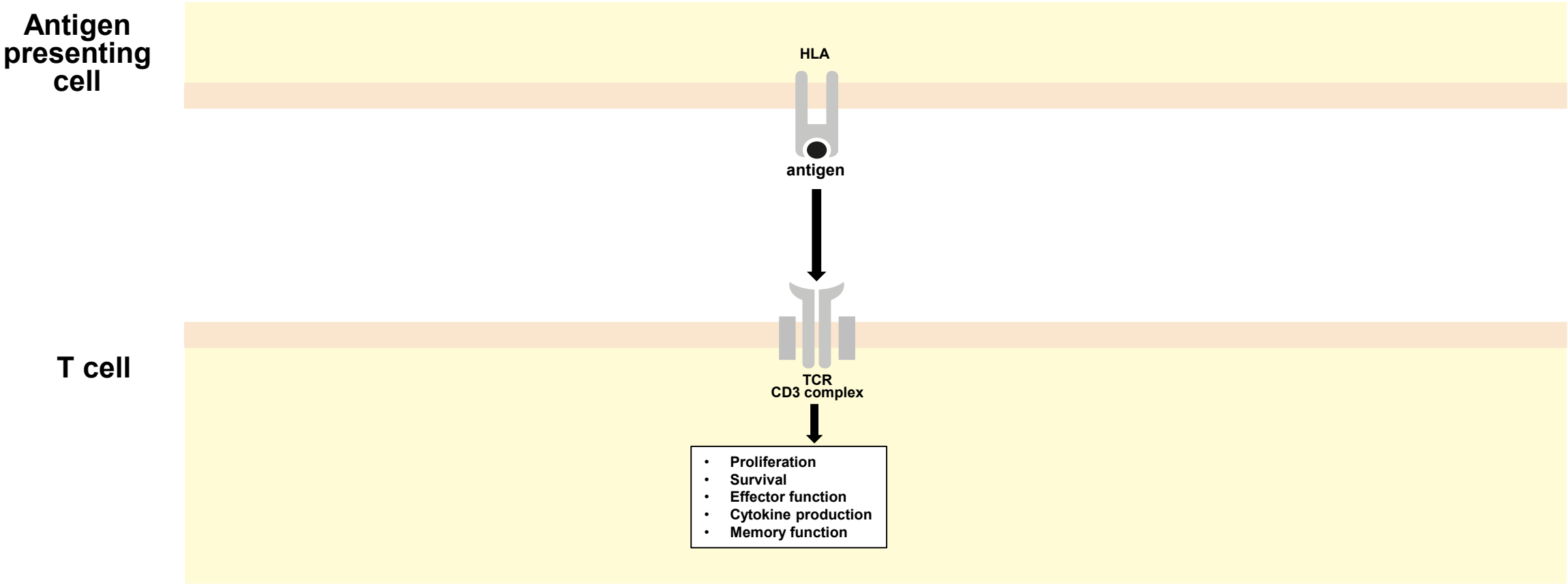
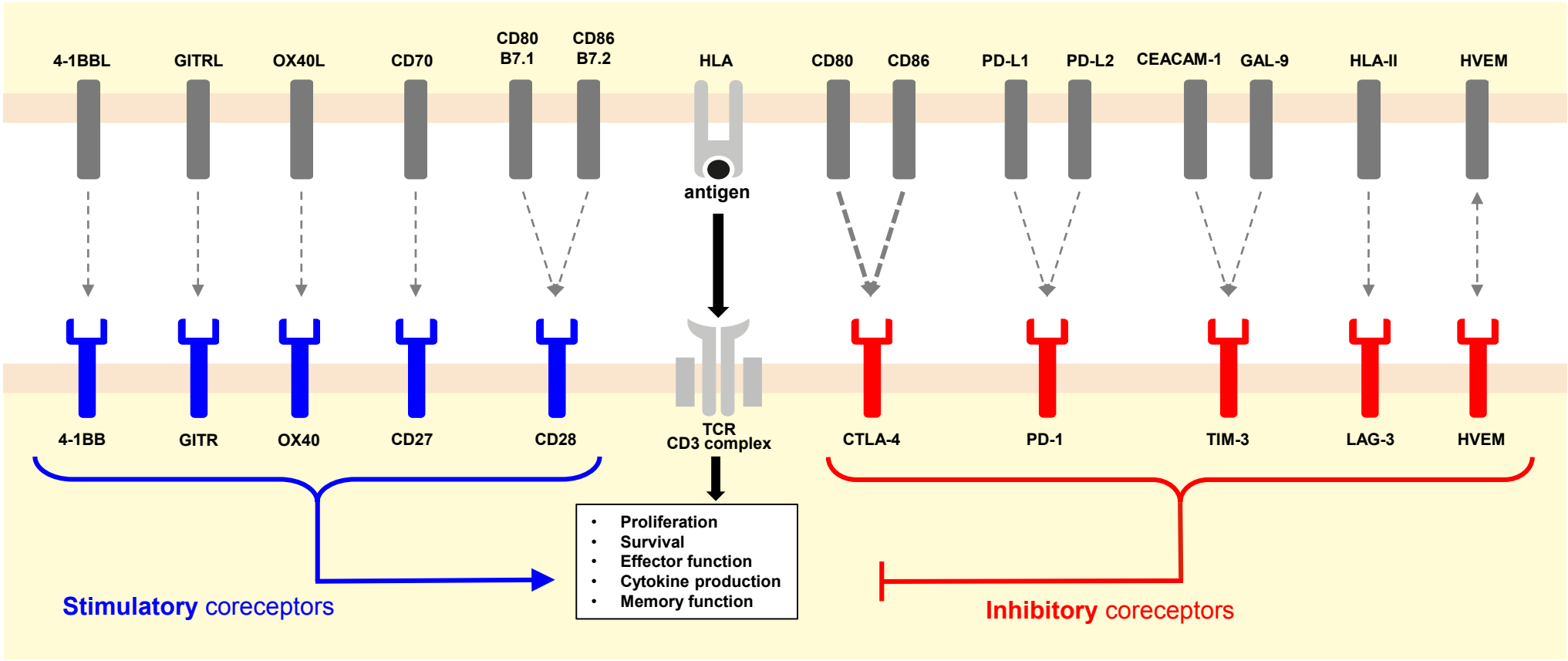
Stimulatory and inhibitory coreceptors



CD, cluster of differentiation; HLA, human leukocyte antigen; TCR, T-cell receptor;
Adapted from Kershaw et al. Nat Rev Cancer 2013;13:525–41.

Stimulatory and inhibitory coreceptors



Role: fine tuning of T-cell activation in time and space

CD, cluster of differentiation; CEACAM-1, carcinoembryonic antigen-related cell adhesion molecule 1; CTLA-4, cytotoxic T-lymphocyte associate protein 4; GAL-9, galectin 9; GITRL, glucocorticoid-induced TNF receptor ligand; HLA, human leukocyte antigen; HVEM, herpesvirus entry mediator; LAG-3, lymphocyte activating 3; PD-L1/2, programmed death-ligand 1/2; TCR, T-cell receptor; TIM-3, T cell immunoglobulin and mucin domain 3; TNF, tumor necrosis factor.
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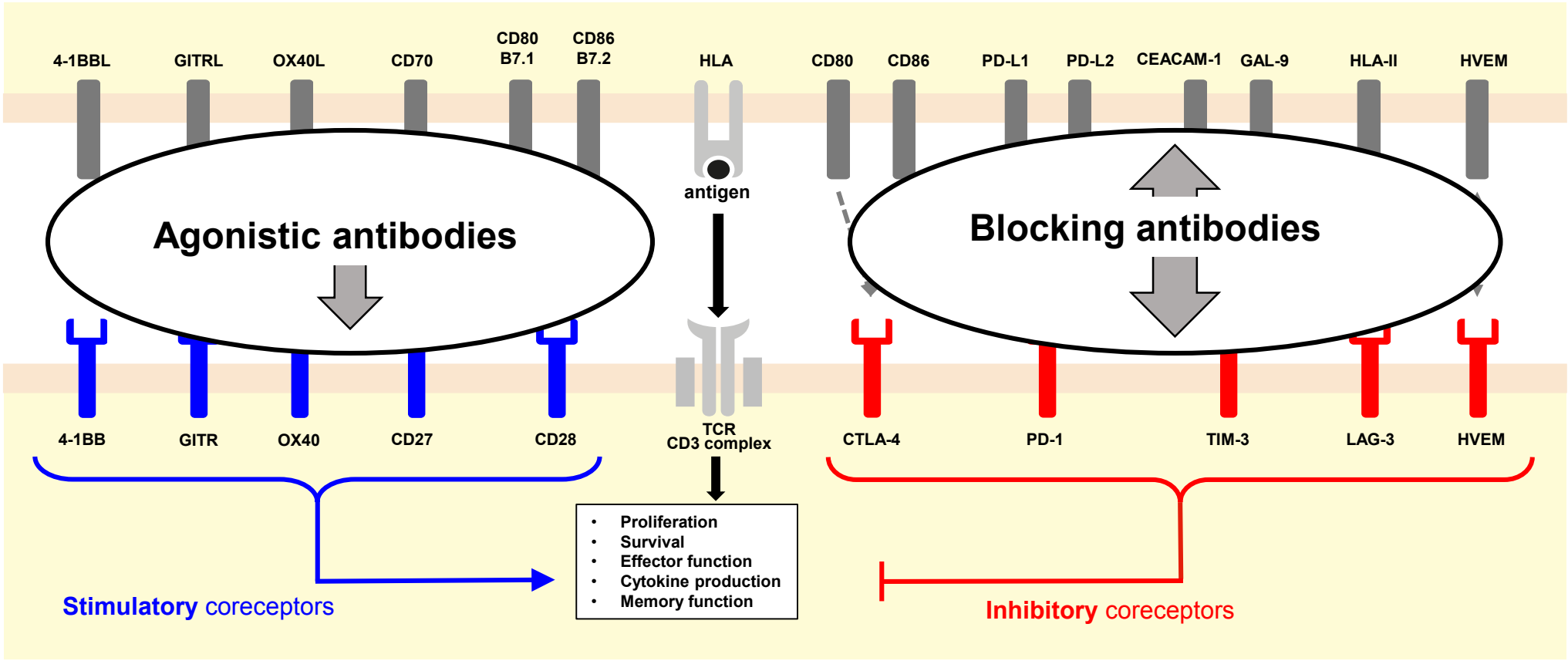

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Lessons from CTLA-4 or PD-1 blockade in cancer patients

- Durable tumor regressions or stabilizations
- Across many cancer histotypes

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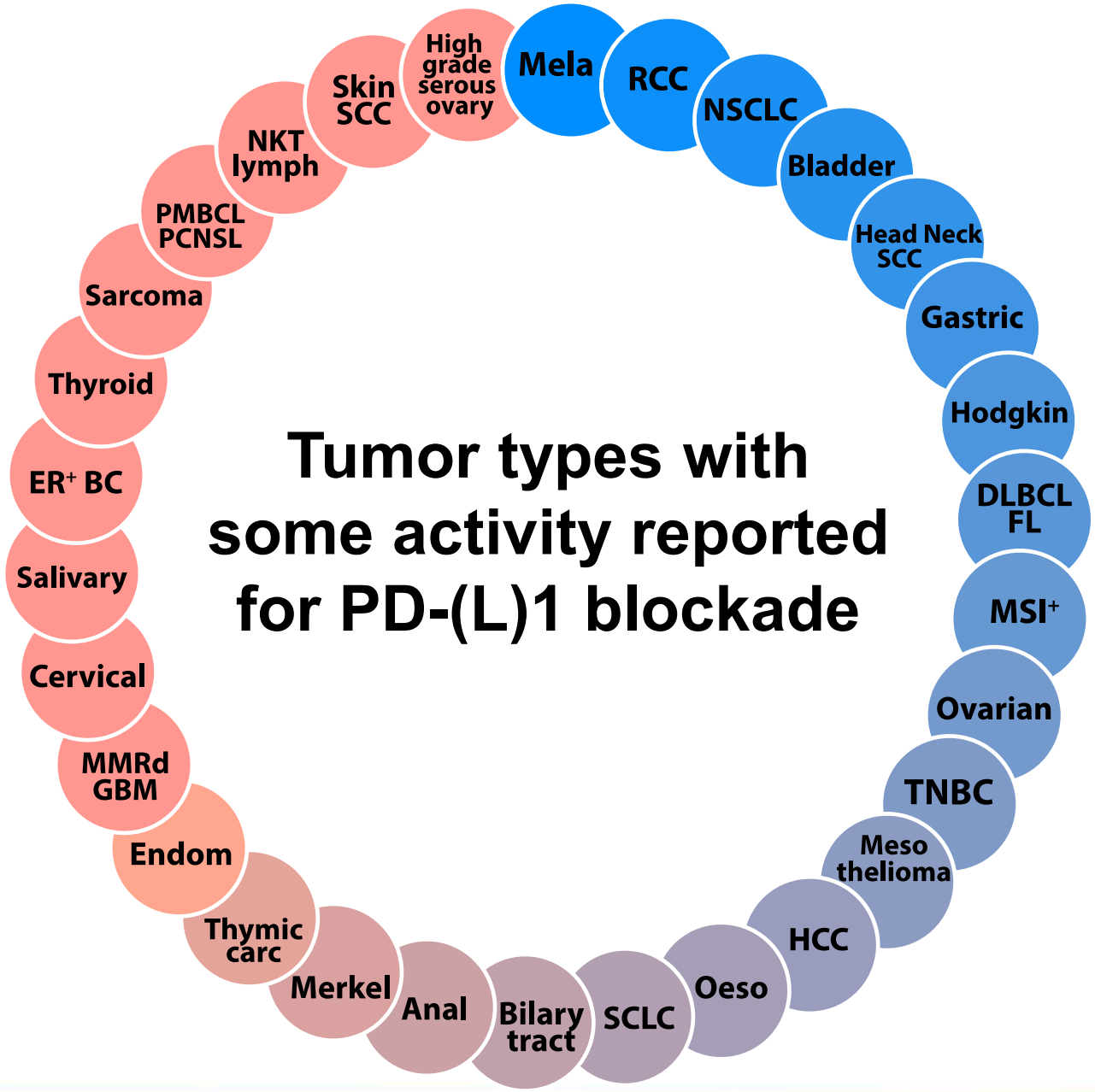
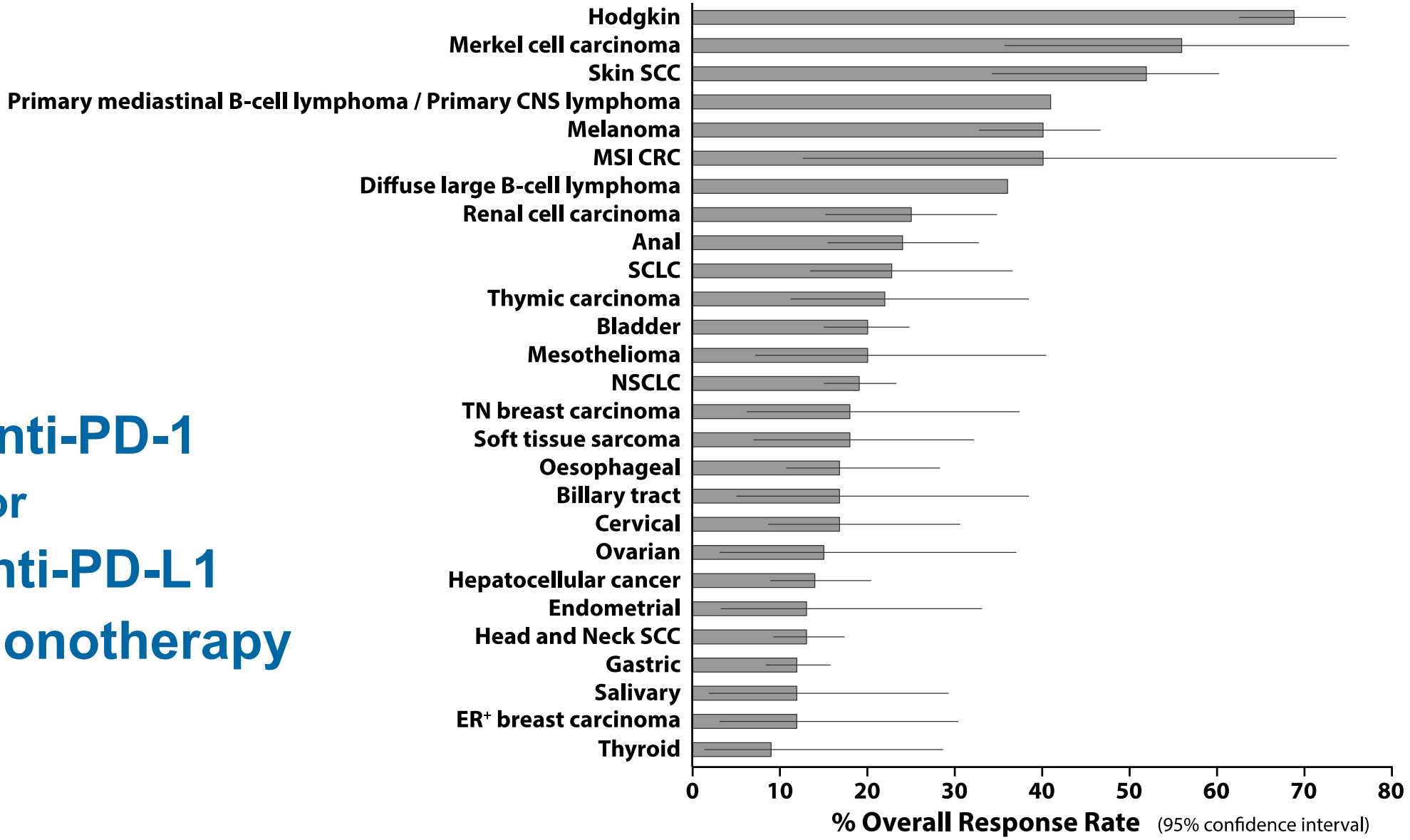


Adapted from Hirsch et al. Br J Cancer 2018; doi: 10.1038/s41416-018-0294-4. [Epub ahead of print].

Anti-PD-1 or anti-PD-L1 monotherapy



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- Not all patients....
- Serious but manageable toxicities, for most of them

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Lessons from CTLA-4 or PD-1 blockade in cancer patients

- Durable tumor regressions or stabilizations
- Across many cancer histotypes

- Not all patients....
- Serious but manageable toxicities, for most of them

- Predictive biomarkers (for PD-1 blockade)
  - PD-L1 expression: constitutive (Hodgkin) or induced (IFN-γ)
  - Patients who already mounted an antitumor T cell response are more likely to respond.
    - tumor mutational load, HLA (tumor's antigenicity)
    - TILs ('hot tumors')
    - various immune transcriptomic signatures, including IFN-γ → PD-L1
  - Gut microbiome ?

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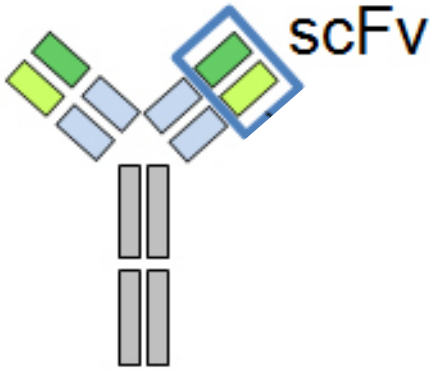
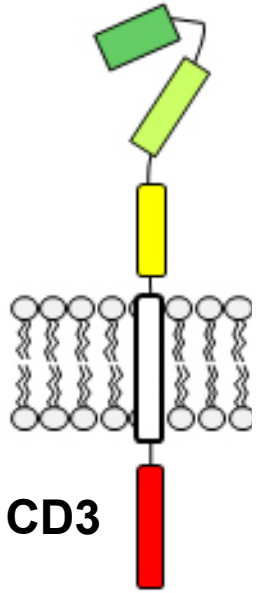
CAR (Chimeric Antigen Receptor) technology

Antibody



CAR



First clinical results of CD19 CAR therapy for ALL

		Complete remission rate
Brentjens et al. 2013, *Sci Transl Med*	5 adults	100%
Grupp et al. 2013, *N Engl J Med*	2 children	100%
Davila et al. 2014, *Sci Transl Med*	16 adults	88%
Lee et al. 2015 , *Lancet*	20 children	70%
Maude et al. 2014, *N Engl J Med*	25 children	90%
	5 adults	100%
Frey et al. 2014, ASH	12 adults	89%
Park et al. 2014, ASH	27 adults	89%

ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor
Adapted from Sadelain M. J Clin Invest 2015;125:3392–3400.

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Combination therapies (PD-1 blockade + x)[1]

- **Other immunostimulatory antibodies** (CTLA-4, TIM3, ICOS, NKG2A, CD40, CSF1R, CD47, ...)
- **Chemotherapy** → *Example:* *Pembrolizumab (anti-PD-1) + chemotherapy as first-line treatment in NSCLC (Gandhi et al - NEJM – 2018)[2]*
- **Radiotherapy**
- **Targeted therapy**
- **Pegylated cytokines (IL-2, IL-10)**
- **Proinflammatory signals (oncolytic viruses)**
- **Means to alleviate the intratumoral immunosuppressive environment**
- **Immunizations**

'Heat the cold tumors'

IDO, TGF-ß, A2AR, T_{reg}, MDSC (chemotherapy)

1. Pierre Coulie 2018. Personal communication. 2. Gandhi et al. N Engl J Med 2018;378:2078–92.

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