ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

www.immunoscienceacademy.be

Understanding immunoscience

A guide for specialists working with immunotherapies

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Module 1. Basic immunology

Click on a chapter below to start learning

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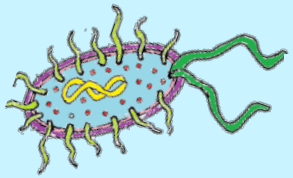
Introduction to the immune system

Module 1. Basic immunology

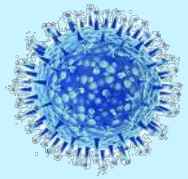
What is the immune system?

- A set of mechanisms that evolve to protect our organism against:

Pathogens



Bacteria

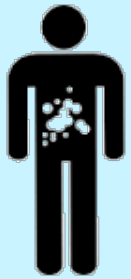


Viruses

Parasites

Harmful physical or chemical stimuli

Body's own cells during illness



- It comprises numerous sensors and effectors grouped into **innate** and **adaptive** immunity

PubMed Health 2019;4:11–22. Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072548/. Accessed October 2022.

Innate vs adaptive immunity

Feature[1–4]	Innate immunity	Adaptive immunity
Specificity	Broad, not fully specific to invading pathogen	Highly specific to the pathogen or threat
Memory	None	Yes, after exposure
Timing of response	Fast, acts within minutes	Slow, requires several days before becoming effective
Activation	Constitutionally active: present at birth, prior to any contact with antigen	Activated in each individual in response to pathogen presentation or antigen contact
Development	Fully functional at birth	Adapts over time, after contact with antigen

Effectors	- Physical barriers
	- Complement
	- Inflammation
	- Cells
	  - Granulocytes (neutrophils, basophils, eosinophils)
	  - Mast cells
	  - Natural killer cells
	  - Macrophages
	  - Dendritic cells
		- B lymphocytes, antibodies
		- T lymphocytes

1. Dranoff. Nat Rev Cancer 2004;4:11–22. 2. Janeway et al. Immunobiology, 5th edn, 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK27090/. Accessed October 2022 3. Moser & Leo. Vaccine 2010;28 Suppl. 3:C2–13. 4. Litman et al. Nat Rev Immunol 2010;10:543–53.

Interactions between innate and adaptive immunity

Chapter homepage

Innate immunity

Adaptive immunity

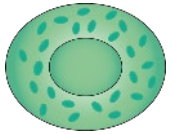
Complement

IgM or IgG antibodies bound to their antigen can activate complement

Antibodies

Learn more about antibodies

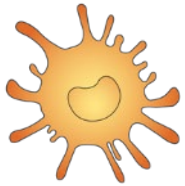
Mast cells



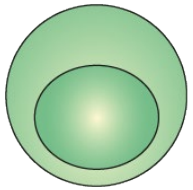
IgE antibodies bind to FcRs on mast cells; antigen recognition causes mast cell degranulation

Antibodies

Dendritic cells



Antigen presentation by DCs is required for T-cell priming (first activation)

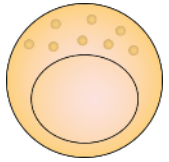


T lymphocytes

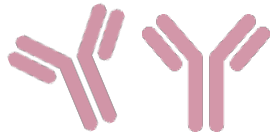
Learn more about dendritic cells

Learn more about T lymphocytes

Natural killer cells



Through their FcγRs, NK cells kill target cells recognized by IgG antibodies



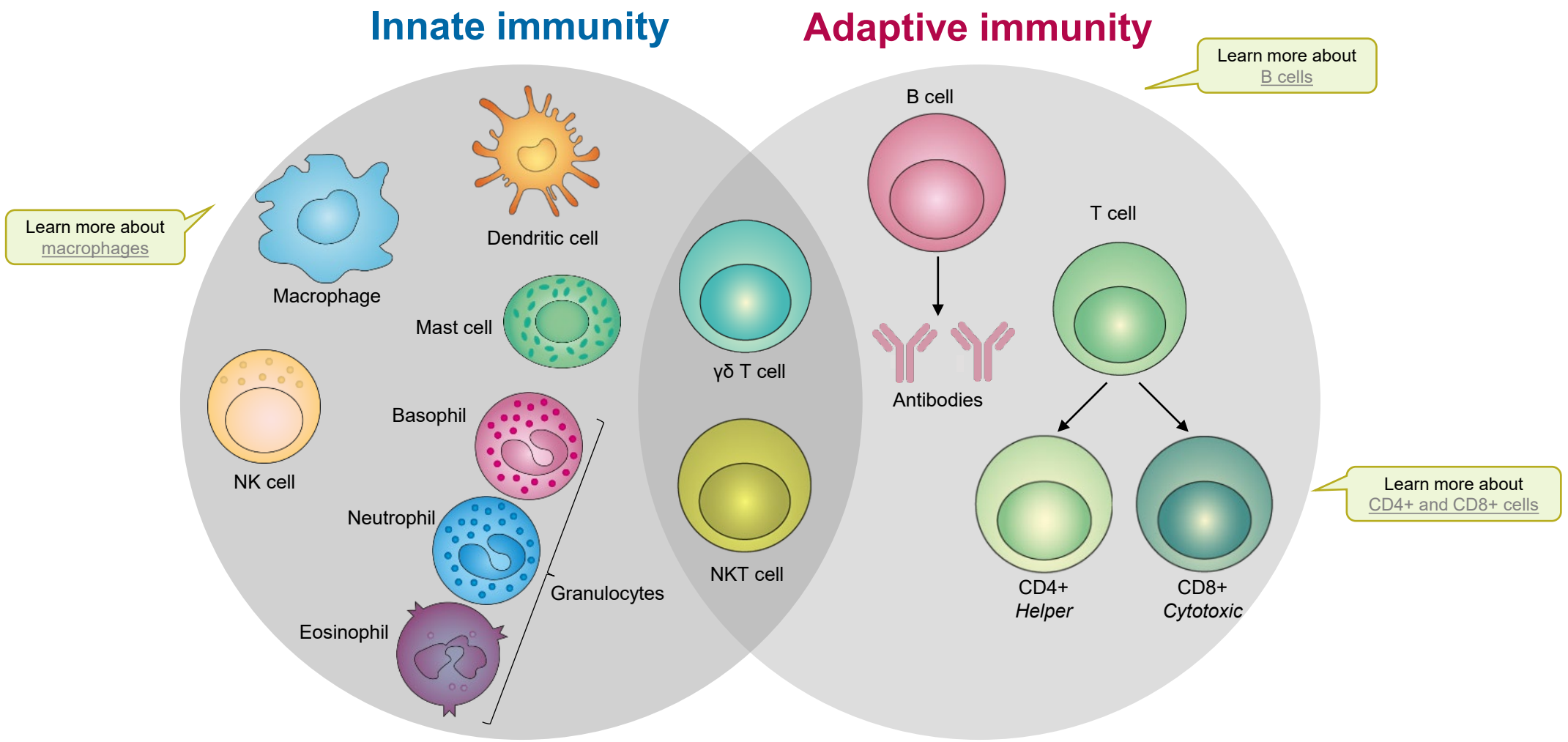
Antibodies

Learn more about NK cells

DC, dendritic cell; FcR, Fc receptor; FcγR, Fc receptor for IgG; Ig, immunoglobulin; NK, natural killer.
Professor P. Coulie, personal communication

Chapter homepage

Cells involved in innate and adaptive immunity

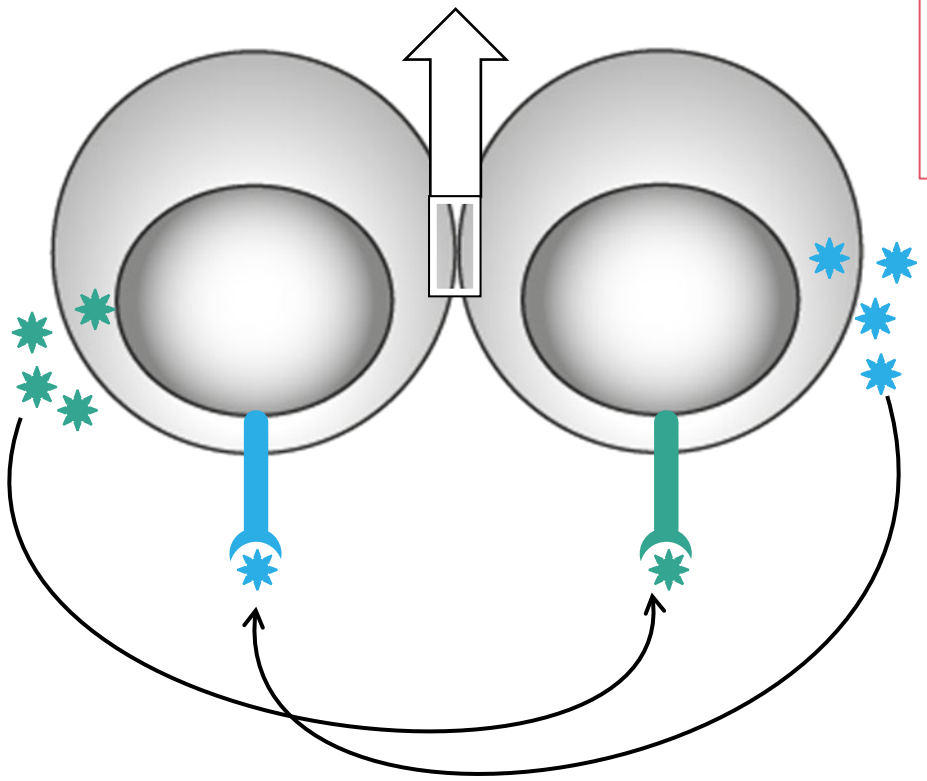


NK, natural killer; NKT, natural killer T.
Adapted from Dranoff. Nat Reviews Cancer 2004;4:11–22.

Communications between immune cells
and between immune and non-immune cells

Contact dependent

- Adhesion molecules (e.g. integrins)
- T-cell receptor > HLA-peptide
- Stimulatory coreceptors
- Inhibitory coreceptors
- Gap junctions

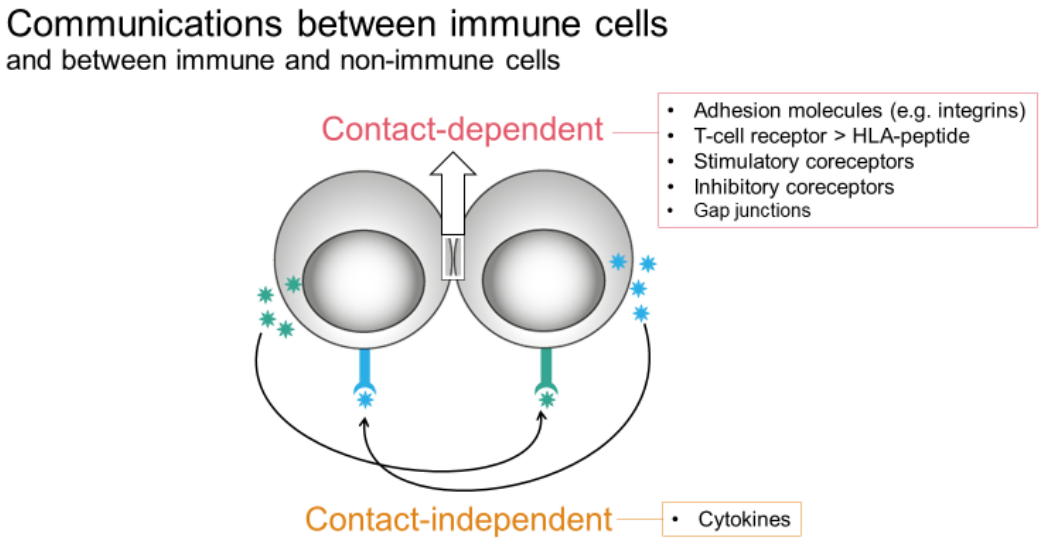


Contact independent

- Cytokines

HLA, human leukocyte antigen.
Professor P Coulie, personal communication 2017.

Clinical relevance
Communications between immune cells



- **Monoclonal antibodies that block integrin function on T cells are used therapeutically**
- **Natalizumab**
  - A humanized monoclonal anti-α4-integrin antibody (α4-integrin is a cell adhesion molecule)
  - It is indicated for the treatment of multiple sclerosis
  - Warning: natalizumab is associated with the rare neurological condition progressive multifocal leukoencephalopathy
- **Vedolizumab**
  - Humanized IgG1 monoclonal antibody that binds to the human $\alpha_4\beta_7$ integrin
  - It is indicated for the treatment of Crohn's disease and ulcerative colitis

HLA, human leukocyte antigen; IgG, immunoglobulin G; SmPC, summary of product characteristics.
Always refer to the SmPC. All product information listed is available in SmPCs. All SmPCs are available from http://www.ema.europa.eu/ema/.

Cytokines

- A group of over 100 small (5–20 kD) glycoproteins that are important in cell signaling[1]
- Bind to high-affinity receptors
- Act mostly on the cells that secrete them (autocrine effects) or on nearby cells (paracrine effects)
  - The IL-1 family are endocrine pyrogens[2]
- A single cytokine can have multiple biological actions (pleiotropy)[2]
- Similar functions can be stimulated by different cytokines (redundancy)[2]

Main types of cytokines[1]

Interleukins (n = 39)	Interferons	TNF family (n = 18)	Chemokines (n = 44)	TGF-β superfamily	Colony-stimulating factors
	• Type I: α, β, λ • Type II: IFN-γ	• TNFα • TNFβ (lymphotoxin α) • CD40L • FasL • CD70 • …etc.		• TGF-β1 • TGF-α • BMPs • GDNFs • …etc.	• Erythropoietin • Thrombopoietin • CSF1 (M-CSF) • CSF2 (GM-CSF) • CSF3 (G-CSF)

BMP, bone morphogenetic protein; CD40L, CD40 ligand; CSF, colony-stimulating factor; G-CSF, granulocyte CSF; GDNF, glial cell-derived neurotrophic factor; GM-CSF, granulocyte macrophage-CSF; IFN, interferon; IL, interleukin; M-CSF, macrophage CSF; TGF, transforming growth factor; TNF, tumor necrosis factor.

1. Professor P Coulie, personal communication. 2. Zhang & An. Int Anesthesiol Clin 2007;45:27–37.

Clinical relevance
Cytokines as therapeutic agents

Cytokines

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Zhang & An. Int Anesthesiol Clin 2007;45:27–37.

► Cytokines as therapeutic drugs

Therapeutic agent	Indications
IL-2 (aldesleukin)	Metastatic renal cell carcinoma
IL-11 (oprelvekin)	Severe thrombocytopenia prevention
G-CSF (e.g. filgrastim) and GM-CSF	Immunoreconstitution
IFNβ1α	Multiple sclerosis
IFNγ-1b	Chronic granulomatous disease and osteopetrosis
Epoetin-α	Anemia

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Clinical relevance

Cytokines: blocking the effects with monoclonal antibodies

Chapter homepage

Cytokines

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Zhang & An. Int Anesthesiol Clin 2007;45:27–37.

Monoclonal antibodies that inhibit cytokine effects

Target	Drug	Licensed indications
Anti-TNFα agents	Infliximab, adalimumab	Severe inflammatory conditions, e.g. rheumatoid arthritis and Crohn's disease
TNF receptor inhibitor	Etanercept	Severe inflammatory conditions, e.g. rheumatoid arthritis, psoriasis, ankylosing spondylitis
Anti-IL-1β	Canakinumab	Autoinflammatory periodic fever syndromes, Still's disease
IL-1 receptor antagonist	Anakinra	Rheumatoid arthritis, periodic fever syndromes, autoinflammatory diseases, Still's disease, COVID-19
Anti-IL-6 receptor	Tocilizumab	Rheumatoid arthritis, systemic juvenile idiopathic arthritis, cytokine release syndrome
Anti-IL-17A	Secukinumab, Ixekizumab	Plaque psoriasis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis
Anti-IL-17RA	Brodalumab	Plaque psoriasis
Anti-IL-12/23	Ustekinumab	Crohn's disease, ulcerative colitis

BMP, bone morphogenetic protein; CD40L, CD40 ligand; CSF, colony-stimulating factor; G-CSF, granulocyte CSF; GDNF, glial cell-derived neurotrophic factor; G-CSF, granulocyte CSF; GM-CSF, granulocyte macrophage-CSF; IFN, interferon; IL, interleukin; M-CSF, macrophage CSF; SmPC, summary of product characteristics; TGF, transforming growth factor; TNF, tumor necrosis factor.
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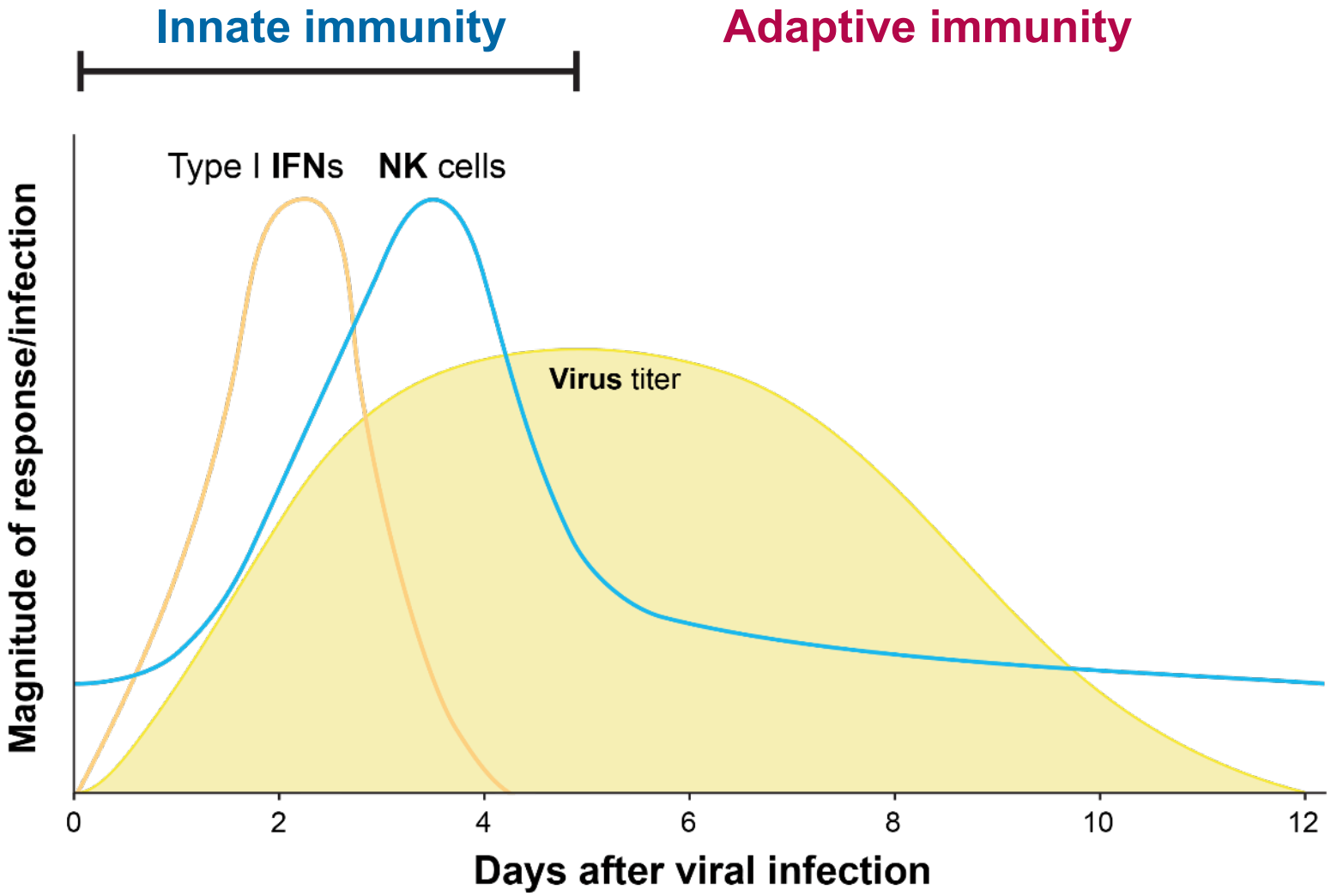
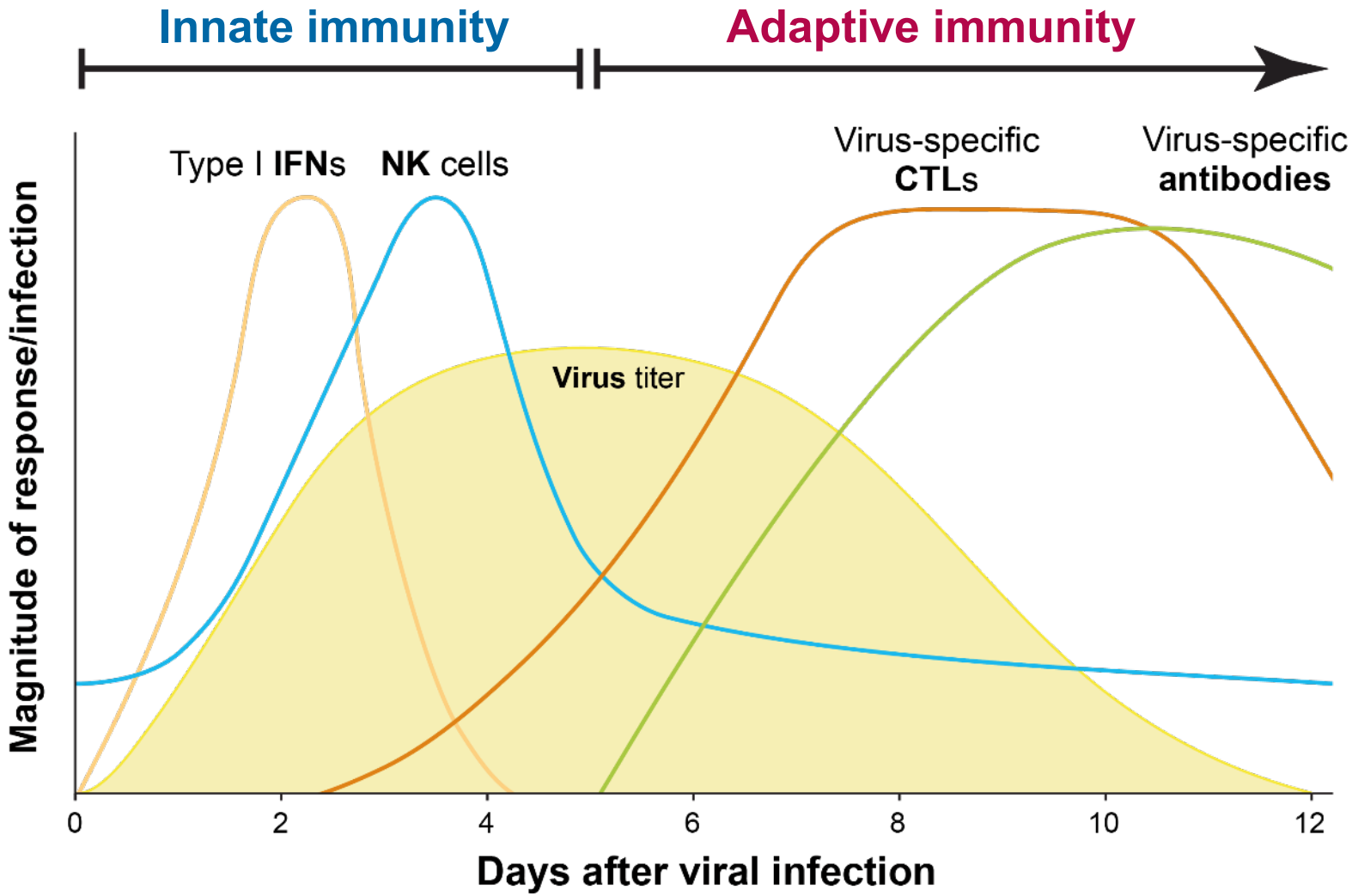
Timeline of a normal immune response to a virus



IFN, interferon; NK, natural killer.
Abbas et al. Cellular and Molecular Immunology, 8th edn, 2015.

Timeline of a normal immune response to a virus

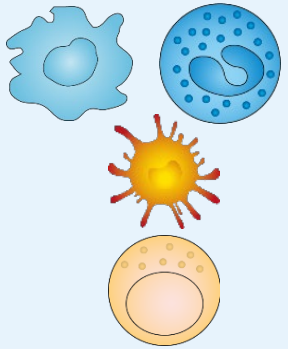


CTL, cytotoxic T lymphocyte; IFN, interferon; NK, natural killer.
Abbas et al. Cellular and Molecular Immunology, 8th edn, 2015.

Innate immunity

Module 1. Basic immunology

The innate immune response

Overview of the key players	
Physical and chemical barriers epithelia, mucus, defensins...	
Cells phagocytic cells (macrophages, neutrophils) dendritic cells natural killer cells	
Sensors on cells, inside cells and in blood, to detect microbes or 'danger'	
Blood proteins complement cytokines inflammatory mediators	

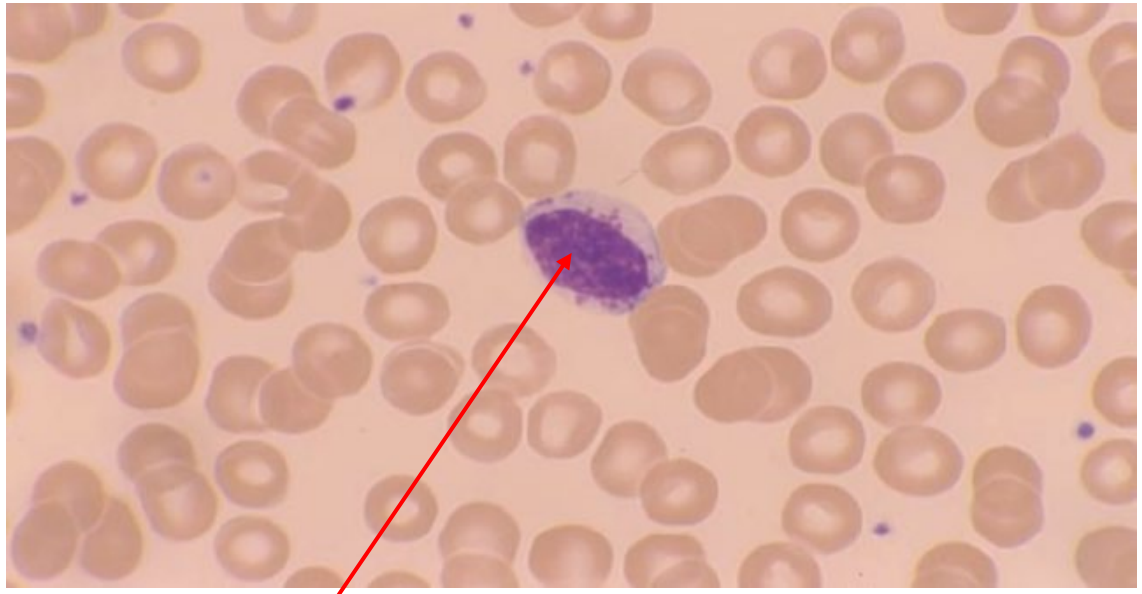
Main form of defense

1. Adapted from Dranoff. Nat Reviews Cancer 2004;4:11–22.Lowell 2. Lowell presentation Available from: https://immunox.ucsf.edu/sites/immunox.ucsf.edu/files/pdf/Innate%20Immunity%20%231.2_2018.pdf Accessed October 2022. 3. Rathinam and Fitzgerald. Virology 2011;411:153–162. 4. Mogensen et al. Retrovirology 2010;7:54.

The innate immune response: natural killer cells

Chapter homepage
Back to introduction

- 10% of peripheral blood mononuclear cells are NK cells[1]
- NK cells can be activated by target cells, which they lyse[1]
- NK cell activation depends on an array of activating and inhibitory receptors[1]
- KIR-HLA has an important role in the development and activity of NK cells[2]



Large granular lymphocyte = NK cell

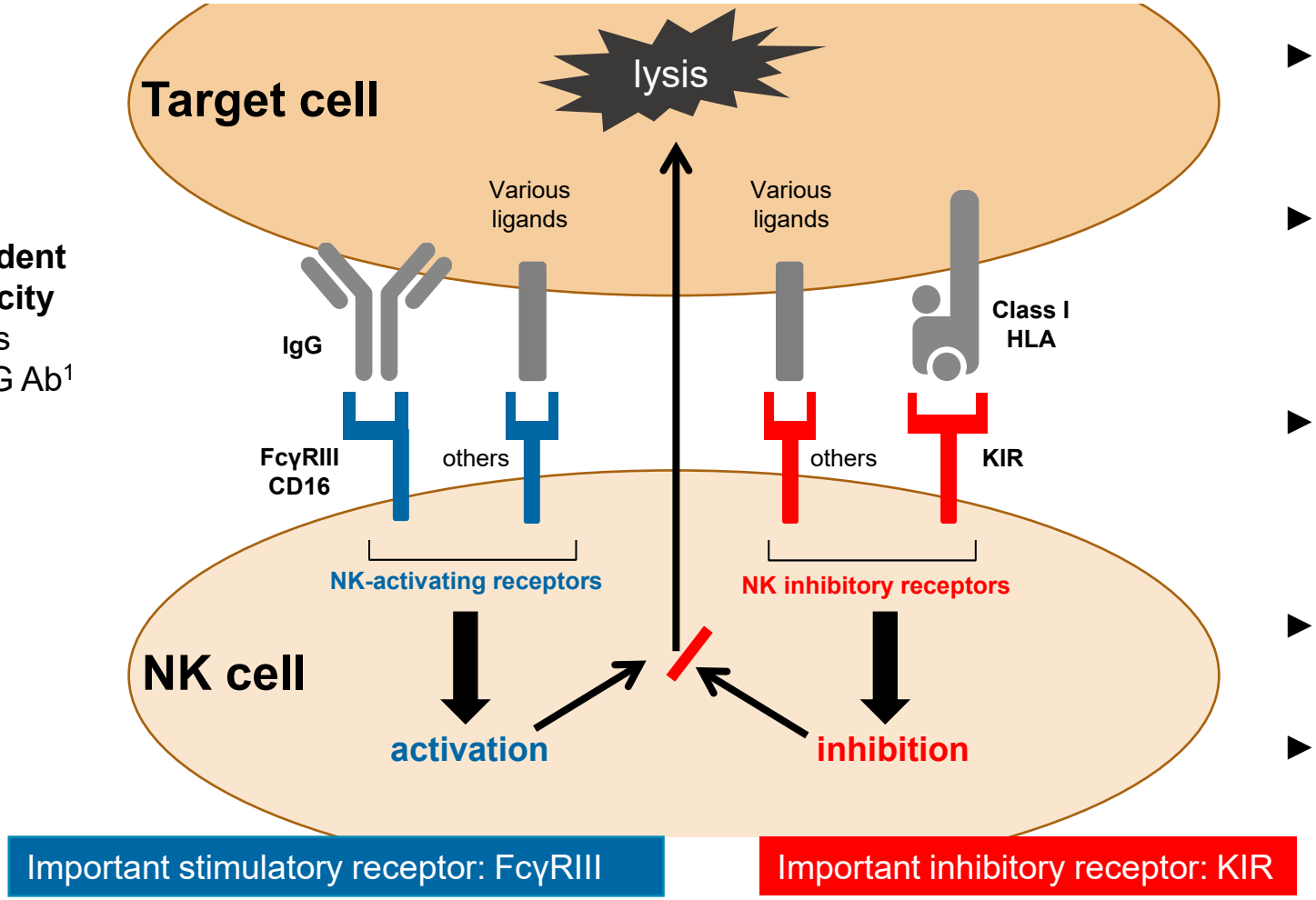
HLA, human leukocyte antigen; KIR, killer immunoglobulin-like receptor; NK, natural killer.

1. Mandal & Viswanathan. Hematol Oncol Stem Cell Ther 2015;8:47–55. 2. de Smith AJ et al. Blood 2014;123:2494–503. Large granular lymphocyte image from: Kern. PDQ Hematology, 2002:7.

The innate immune response: controlling NK cell activation

Chapter homepage

- **Antibody-dependent cellular cytotoxicity**
- NK cells lyse cells recognized by IgG Ab[1]



- NK cells and CTLs have complementary roles in immune responses
- CTLs recognize peptides that are derived from **tumor** and **virus** antigens presented by HLA class I molecules
- In tumor and microbe-infected cells, **expression of HLA class I** on the cell surface is often **downregulated**
- These cells are thereby able to **escape CTL killing**
- However, NK cells are able to recognize and kill these cells[2]

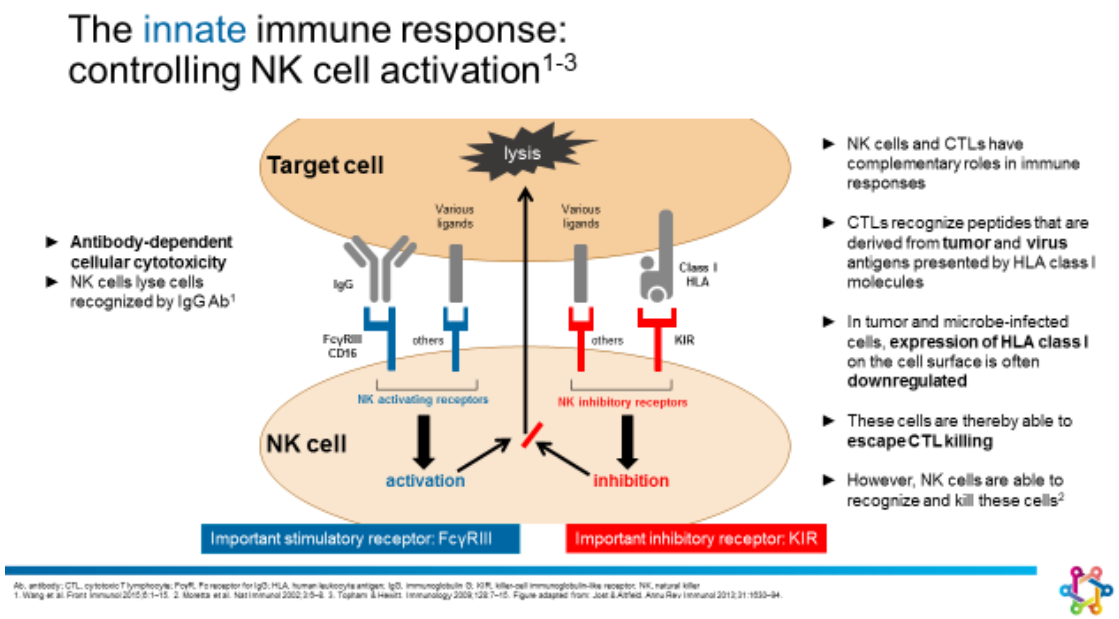
Ab, antibody; CTL, cytotoxic T lymphocyte; FcγR, Fc receptor for IgG; HLA, human leukocyte antigen; IgG, immunoglobulin G; KIR, killer-cell immunoglobulin-like receptor; NK, natural killer

1. Wang et al. Front Immunol 2015;6:1–15. 2. Moretta et al. Nat Immunol 2002;3:6–8. 3. Topham & Hewitt. Immunology 2009;128:7–15. Figure adapted from: Jost & Altfeld. Annu Rev Immunol 2013;31:1630–94.

Clinical relevance

Chapter homepage

The innate immune response: controlling NK cell activation



- **Monoclonal antibodies that promote cell lysis are used therapeutically**
- **Rituximab**
  - A humanized monoclonal anti-CD20 antibody (IgG1); CD20 is a B-cell-specific surface molecule
  - It is indicated for the treatment of B-cell malignancies (CLL and NHL), rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and pemphigus vulgaris
  - It has several mechanisms of action, including ADCC, CD20-mediated signaling and cell death, complement activation and ADCP[1]
  - FcγRIII polymorphisms (158V instead of 158F) with higher affinity for IgG1 are associated with better clinical responses[2]
- **Monoclonal antibodies that block KIRs and are expected to increase NK cell lytic activity against tumor cells are being evaluated in patients with cancer**

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CLL, chronic lymphocytic leukemia; FcγR, Fc receptor for immunoglobulin G; KIR, killer-cell immunoglobulin-like receptor; NHL, Non-Hodgkin's lymphoma; NK, natural killer; SmPC, summary of product characteristics.

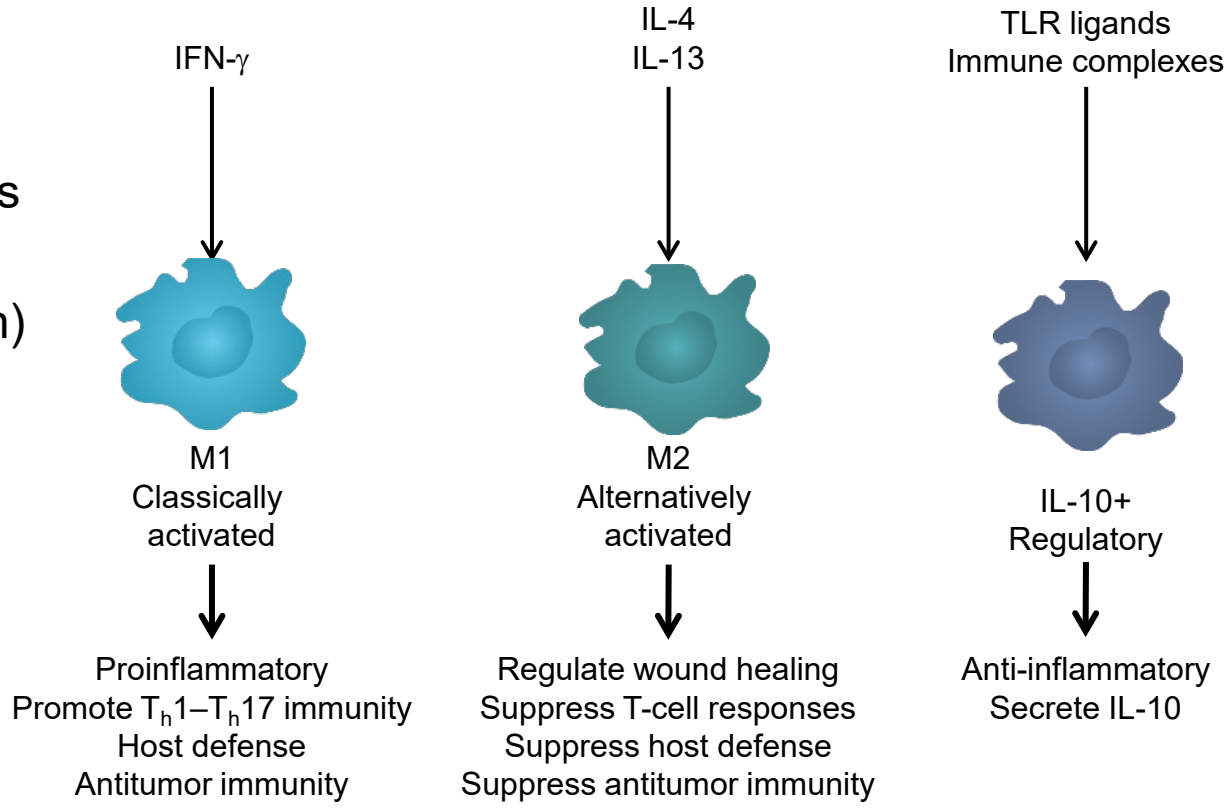
1. Dalakas. Nat Clin Pract Neurol 2008;4:557–67. 2. Wang et al. Front Immunol 2015;6:1–15. Always refer to the SmPC. All SmPCs available from http://www.ema.europa.eu/ema/

The innate immune response: macrophages

Chapter homepage
Back to introduction

- Macrophages are phagocytic cells found in all tissues[1]
- Macrophages are involved in antiviral responses via[1,2]
  - Phagocytosis and destruction of pathogens
  - Destruction of infected cells
  - Production of soluble factors (inflammation)
  - Presentation of microbial antigens to T and B lymphocytes as part of the adaptive immune response

Macrophages have multiple activation phenotypes, driven by environmental signals



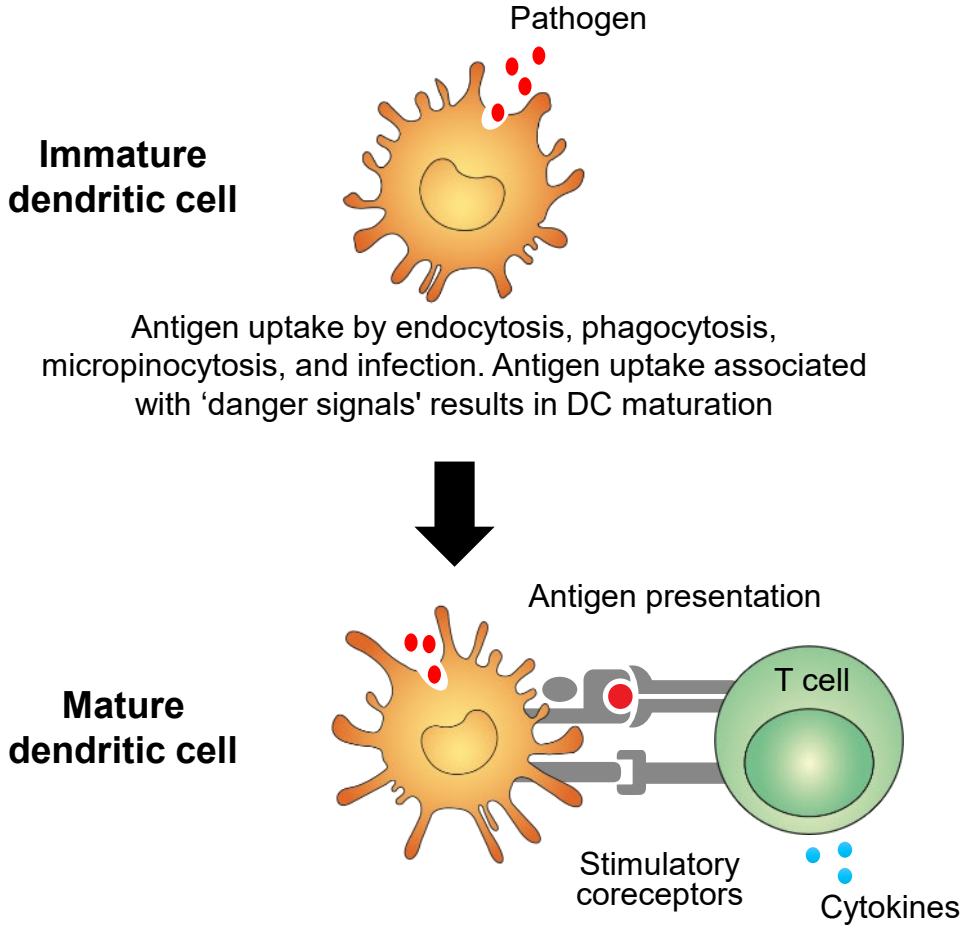
IFN, interferon; IL, interleukin; T_h, T helper; TLR, Toll-like receptor.

1. Elhelu. J Natl Med Assoc 1983;75:314–7. 2. Klimpel. In: Medical Microbiology, 4th edn, 1996. Available from: http://www.ncbi.nlm.nih.gov/books/NBK8423/. Accessed October 2022. Figure adapted from Galli et al. Nature Immunol 2011;12:1035–44.

The innate immune response: dendritic cells

Chapter homepage
Back to introduction

- Dendritic cells are typically located in tissues exposed to external environments, e.g. the respiratory system and gastrointestinal mucosae[1]
- They are recruited to sites of infection by chemokines[1]
- Pathogen recognition via Toll-like receptors triggers antiviral responses[1,2]
  - Phagocytosis
  - Secretion of inflammatory cytokines and interferons
  - Migration to lymph nodes (attracted by chemokines)
  - Processing of antigenic peptides and presentation to CD4+ and CD8+ T cells (DCs can 'prime' T cells)



Antigen presentation and activation of T cells

DC, dendritic cell.

1. Wen et al. J Leukocyte Biol 2008;83:439–46. 2. Martín-Fontecha et al. Dendritic Cells. In: Handbook of Experimental Pharmacology 2009:188. Figure adapted from Szatmari et al. EMBO J 2008;27:2353–62.

Sensors in innate immunity: pattern recognition receptors

Chapter homepage

- PRRs are a collection of receptors that can be present[1,2]
  - on cells
  - inside cells (cytoplasm, endosomes)
  - in plasma
- They recognize two classes of molecules, which are absent from 'normal' cells:

PAMPs

Pathogen-associated molecular patterns

- These are molecules associated with classes of microbes
  - Examples include lipopolysaccharide from Gram-negative bacteria and dsRNA from viruses

DAMPs

Danger-associated molecular patterns

- These are molecules present or released after cell damage (e.g. through UV, irradiation, heat) or death
  - Examples include HMGb1, heat shock proteins, and purine metabolites, such as ATP12 and uric acid13

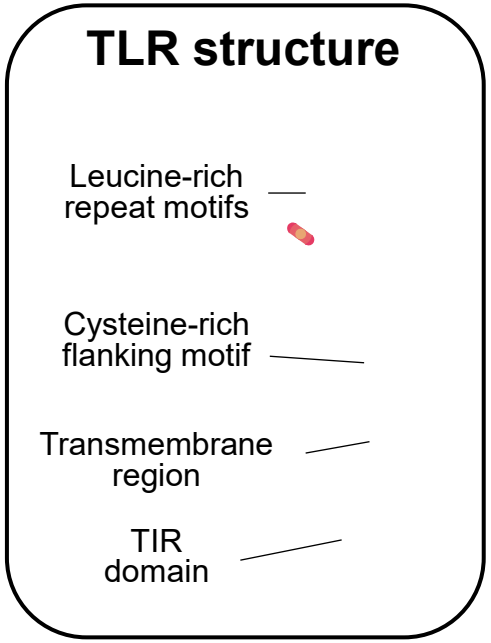
- Signaling PRRs induce **inflammation**; endocytic PRRs promote **phagocytosis**

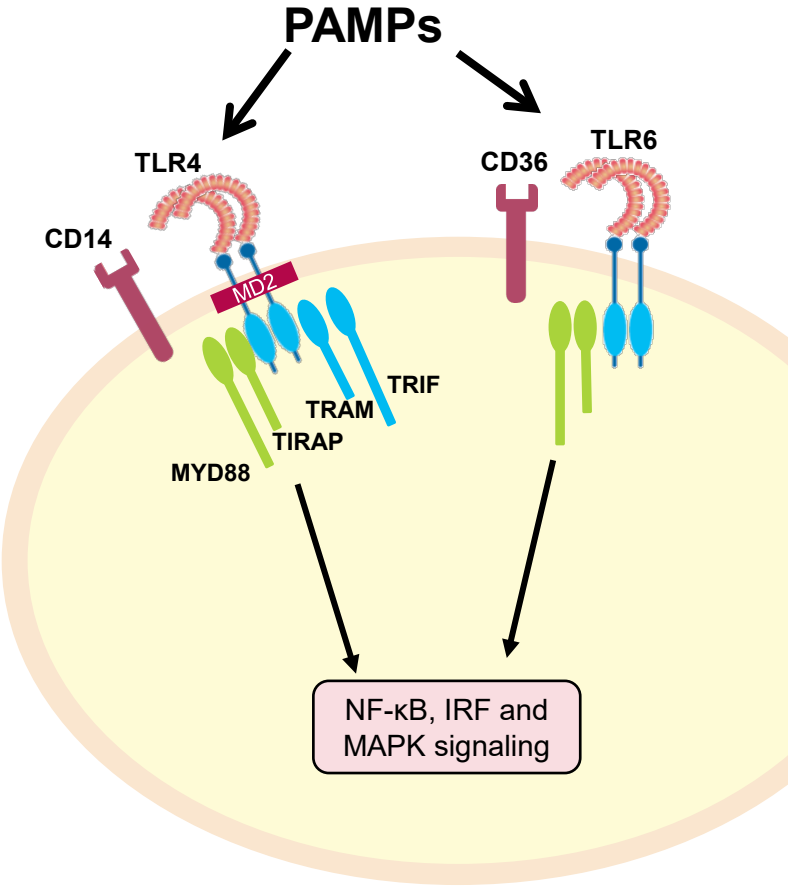
DAMP, danger-associated molecular pattern; dsRNA, double-stranded RNA; HMGB1, high mobility group box 1 protein; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; TAP, transporter associated with antigen processing; UV, ultraviolet.

Seong & Matzinger. Nat Rev Immunol 2004;4:469–78. 2. Chen & Nunez. Nat Rev Immunol 2010;10:826–37.

Toll-like receptors: a family of PRRs

- TLRs are a family of dimeric transmembrane receptors[1] (some TLRs need coreceptors)
- TLRs are present on many cell types, including sentinel cells of the immune system[2] and in endosomes within such cells[3]
- They recognize specific PAMPs on pathogens and initiate a cell signaling cascade via NF-κB, IRF and MAPK[2,3]
- Different TLRs bind to different ligands[4,5]

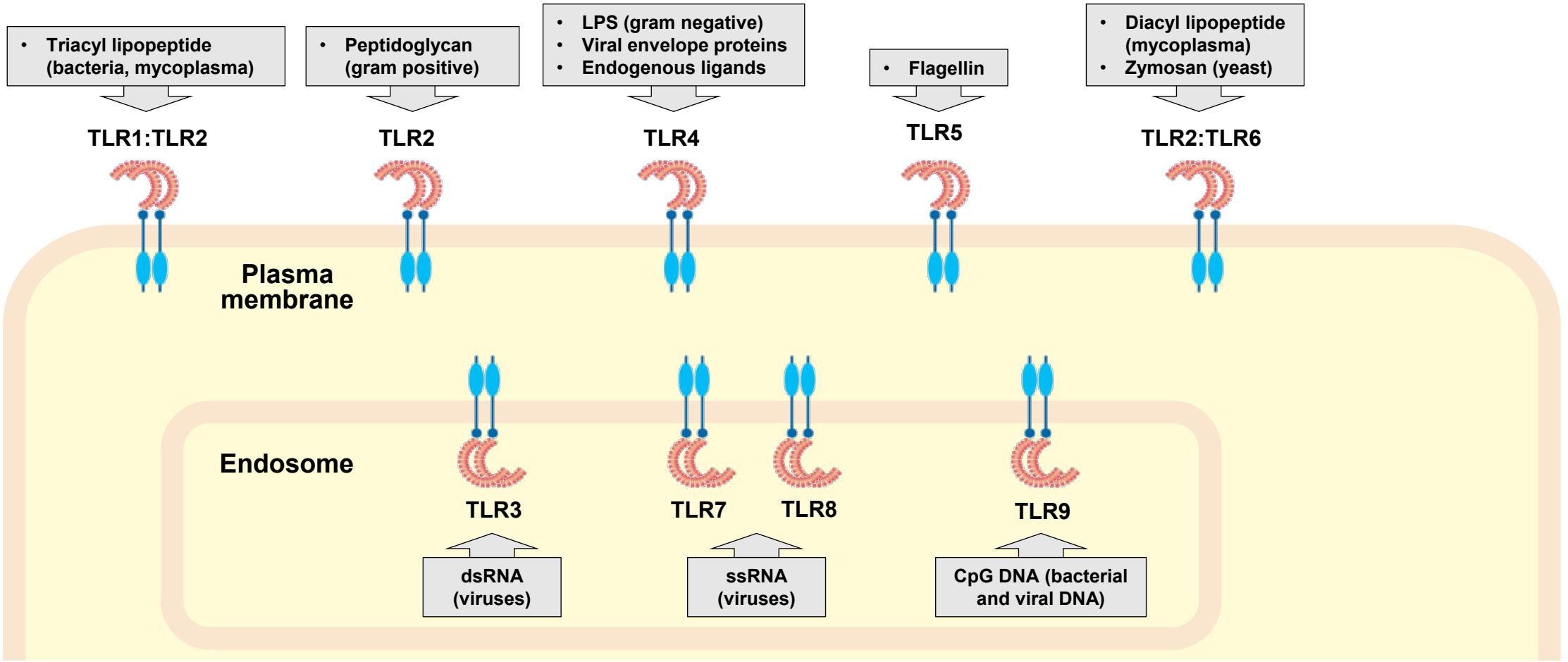




IRF, interferon regulatory factor; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; PAMP, pathogen-associated molecular pattern; TIR, Toll/interleukin-1 receptor; TIRAP, TIR domain-containing adaptor protein; TLR, Toll-like receptor; TRAM, TRIF-related adaptor molecule; TRIF, TIR-domain-containing adaptor protein inducing interferon beta.

1. Armant & Fenton. Genome Biol 2002;3:3011. 2. Netea et al. Nature Immunol 2012;13:535–42. 3. Mogensen et al. Retrovirology 2010;7:54. 4. Abbas et al. Cellular and Molecular Immunology, 7th edn, 2011. 5. Medzhitov. Nat Rev Immunol 2001;1:135–45. Figure adapted from references 4 and 5.

Different TLRs bind to different PAMPs

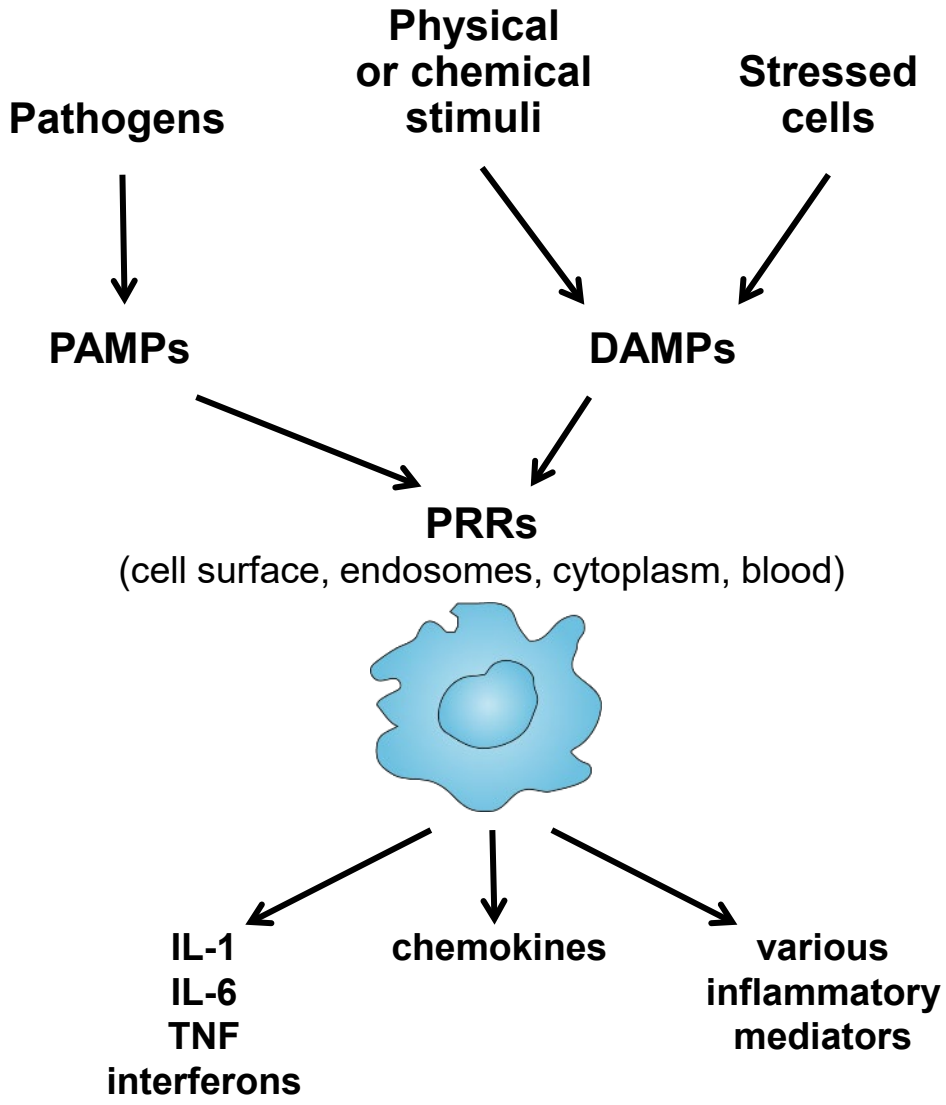


dsRNA, double-stranded RNA; LPS, lipopolysaccharide; PAMP, pathogen-associated molecular pattern; ssRNA, single-stranded RNA; TLR, Toll-like receptor.

1. Netea et al. Nat Immunol 2012;13:535–42. 2. Armant & Fenton, Genome Biol 2002;3:3011. 3. Mogensen et al. Retrovirology 2010;7:54. Figure adapted from 4. Abbas et al. Cellular and Molecular Immunology, 7th edn. 5. Leulier F and Lemaitre B, Nat Rev Gen 2008:9:165-178

The innate immune response: inflammation

- Inflammation is a biological response of the immune system to harmful stimuli, such as pathogens, damaged cells, toxic compounds, or irradiation[1]
- Recognition of PAMPs by PPRs (e.g. on macrophages, dendritic cells) triggers signaling cascades that culminate in the production of cytokines, including chemokines and interferons, and other inflammatory mediators[2]
- This cascade of signals leads to the recruitment of inflammatory cells (phagocytic and immune cells) and tissue and wound repair, and participates in the induction of adaptive immune responses[3]



DAMP, danger-associated molecular pattern; IL, interleukin; PAMP, pathogen-associated molecular pattern; PPR, pathogen recognition receptor; TNF, tumor necrosis factor.

1 Chen et al. Oncotarget 2018;9:7204–7218. 2. Liu & Cao. Cell Mol Immunol 2016;13:711–14. 3. Chen et al. Nat Rev Immunol 2010;10:826–37. Image adapted from Chen et al. Nat Rev Immunol 2010;10:826–37.

Adaptive immunity

Module 1. Basic immunology

The adaptive immune response: hallmarks of adaptive immunity

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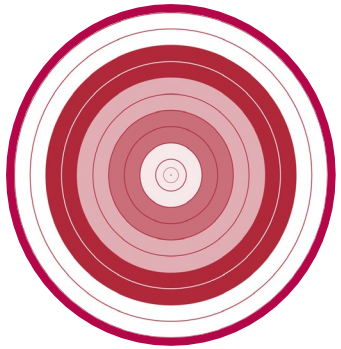


Specificity

- B and T lymphocytes have diverse surface receptors (immunoglobulins and TCRs, respectively) that recognize antigens
- These receptors are very specific to each antigen

Memory

- Immune memory: a better (faster, stronger) B or T cell response compared with first contact with antigen
- Result of the long-term persistence of a fraction of antigen-specific B or T cells

TCR, T-cell receptor

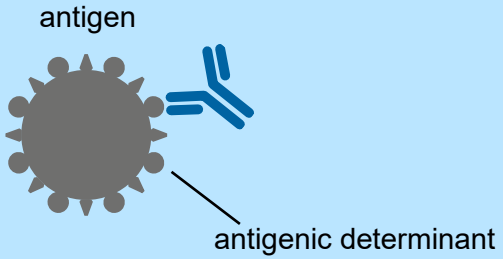
Janeway et al. In: Immunobiology: The Immune System in Health and Disease, 5th edn, 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK27090/ and https://www.ncbi.nlm.nih.gov/books/NBK27092/. Accessed October 2022.

The adaptive immune response: antigens

Chapter homepage

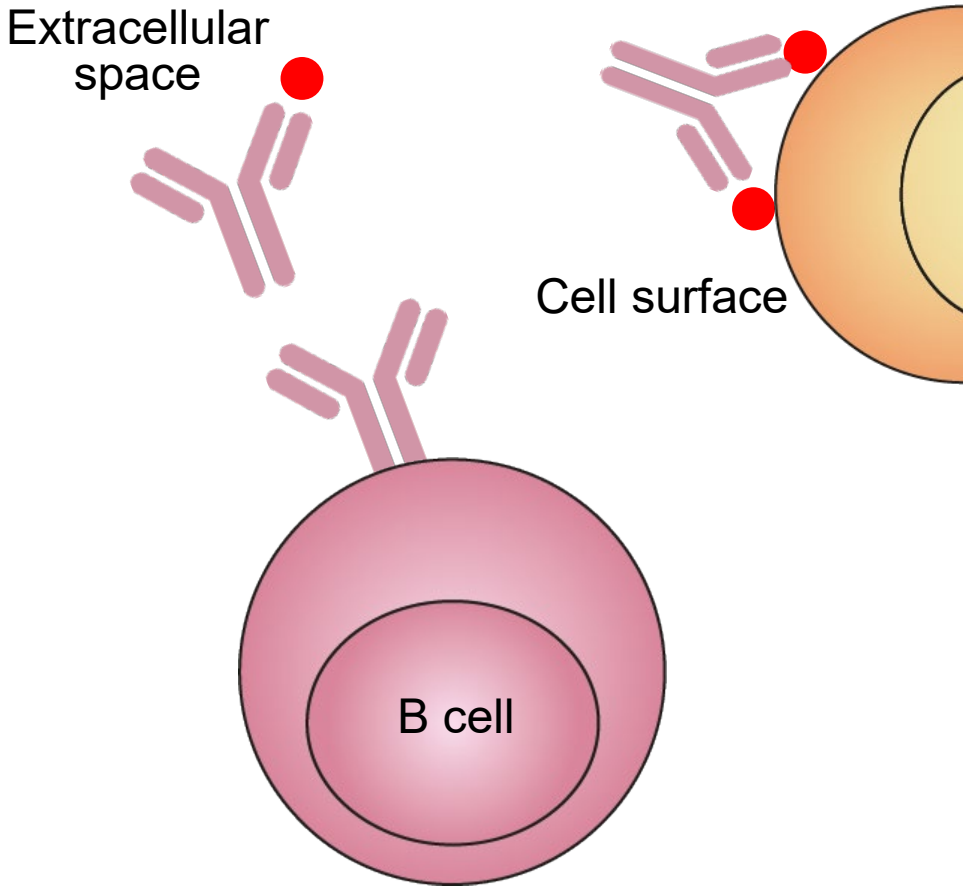
- An antigen is a substance, usually from the external environment of an organism (= 'non-self'), that can be specifically recognized by either antibodies or T lymphocytes
- An antigen does not necessarily induce a specific immune response; when it does so, the antigen is an immunogen (all immunogens are antigens, but all antigens are not immunogens)
- Antigens may have various sizes

Cell:	10,000 nm
Bacterium:	1000 nm
Virus:	50 nm
Protein:	5 nm
Drug:	< 1 nm

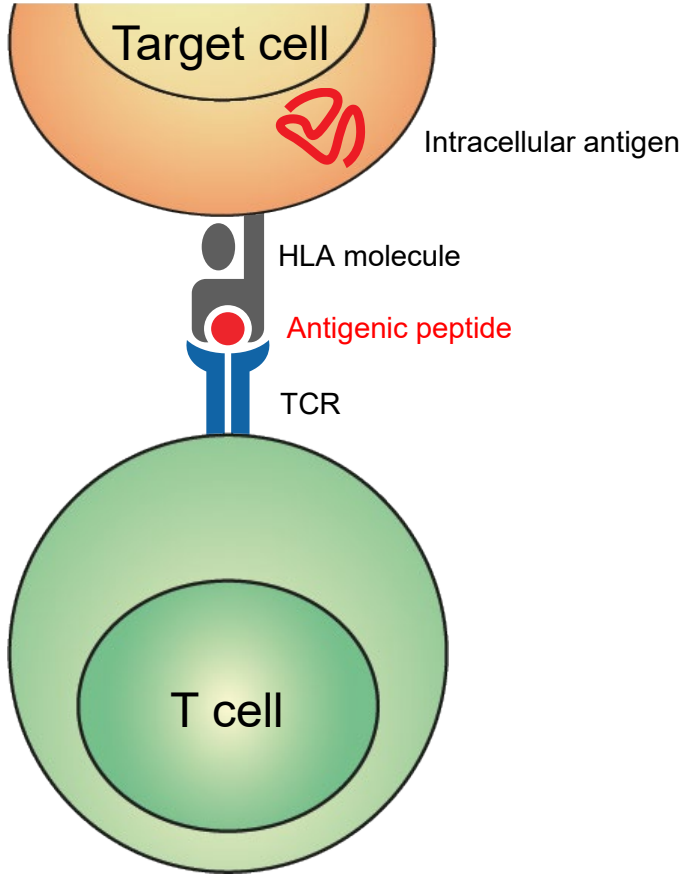


- The part of the antigen that is actually recognized is the antigenic determinant (epitope)
- Most common antigens have many antigenic determinants

Antigen recognition in adaptive immunity



Direct recognition of **extracellular** antigens by antibodies[1]



Recognition of **intracellular** antigens by TCRs via the HLA-peptide complex[2]

HLA, human leukocyte antigen; TCR, T-cell receptor.

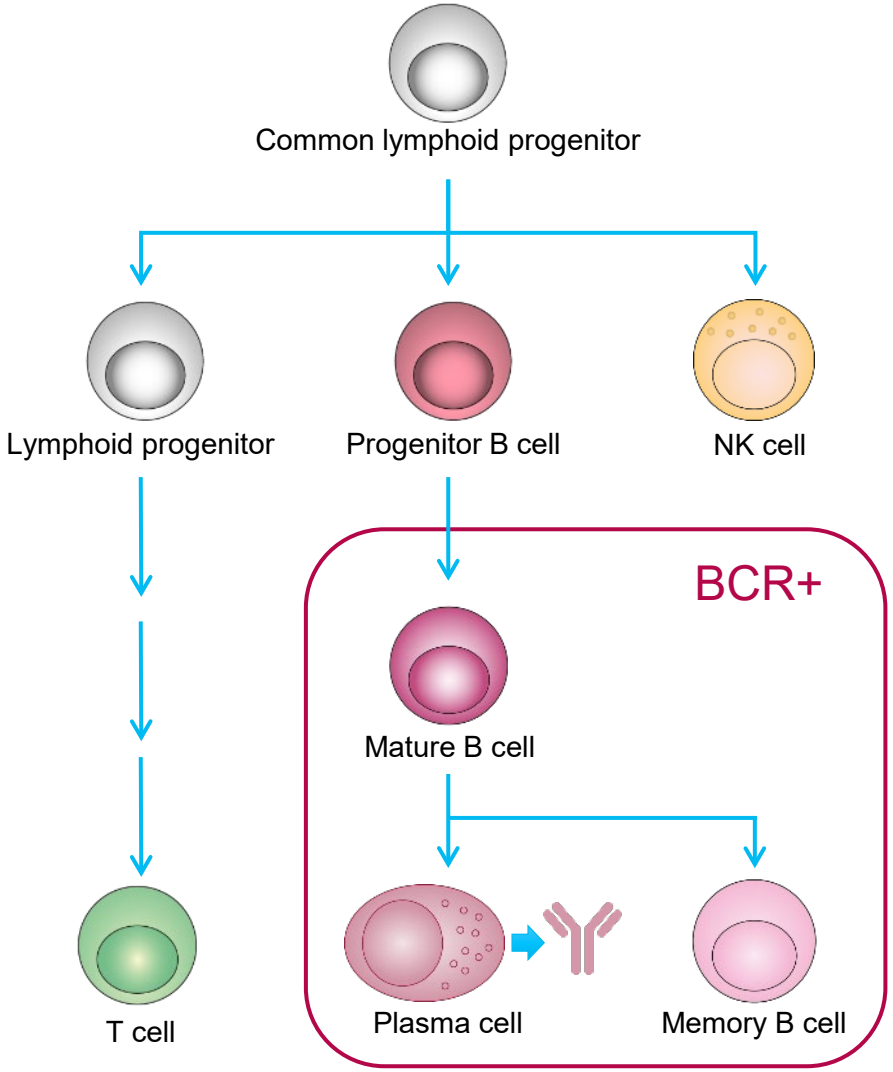
1. Alberts et al. Molecular Biology of the Cell, 4th edn, 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26884/. Accessed October 2022. 2. Heath & Carbone. Nat Rev Immunol 2001;1:126–35.

Adaptive immunity: B cells

Module 1. Basic immunology

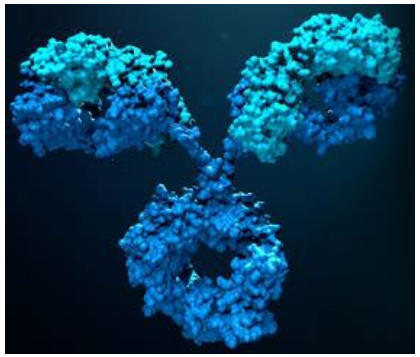
The adaptive immune response: B lymphocytes and antibodies

- B lymphocytes, or B cells, originate from the same lymphoid precursor as T cells
- Immature B cells are formed in the bone marrow, whereas mature B cells circulate in the blood and lymphatic systems
- B cells can be distinguished from other lymphocytes by the presence of an antigen-binding BCR (antibody) on the cell surface
- Only plasma cells secrete antibodies

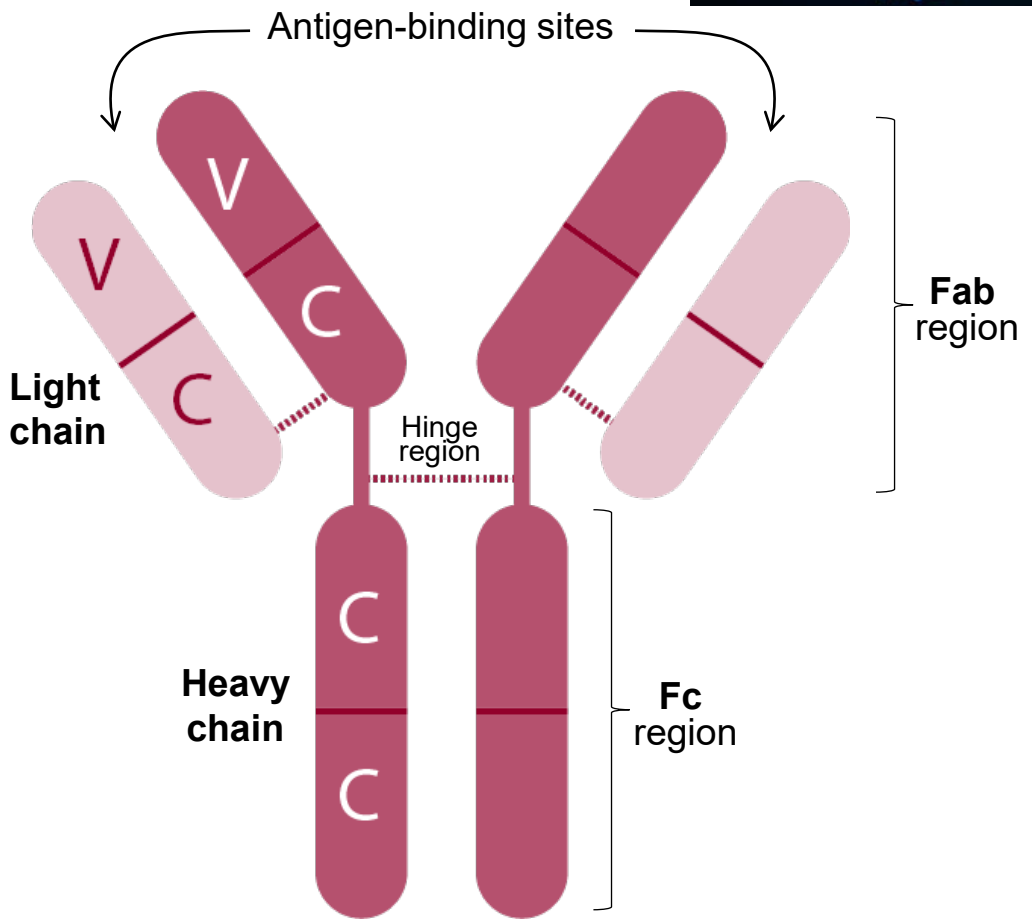


BCR, B-cell receptor; NK, natural killer.
Male et al. Immunology, 7th edn, 2001.

Antibody (immunoglobulin) structure



- All antibodies all are built from the same basic units
- Heavy and light chains
  - Antibodies comprise two identical light chains (approx. 25 kD) and two identical heavy chains (approx. 50 kD)
  - Heavy and light chains linked by disulfide bonds
- Variable (V) and constant (C) regions
  - Both heavy and light chains can be divided into two regions based on variability in amino acid sequences
- Hinge region
  - The region at which the arms of the molecule forms a Y-shape
- The antibody molecule is folded (see inset) into globular regions called immunoglobulin domains
  - Light chain: two domains
  - Heavy chain: four (or five) domains



C, constant; Fab, antigen-binding fragment; Fc, crystallizable fragment; V, variable.
Janeway et al. Immunobiology, 5th edn, 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK27144/. Accessed October 2022.

Antibody effector functions

Antibodies perform different functions in different regions of their structure[1–3]

Through Fab region

- **Neutralization:** antibodies prevent pathogens from binding their receptors
- **B-cell activation:** antibodies serve as B-cell surface antigen receptors

Through Fc region

- **Complement-dependent cytotoxicity:** activates complement system (IgM, IgG)

Functions that occur through Fc receptors

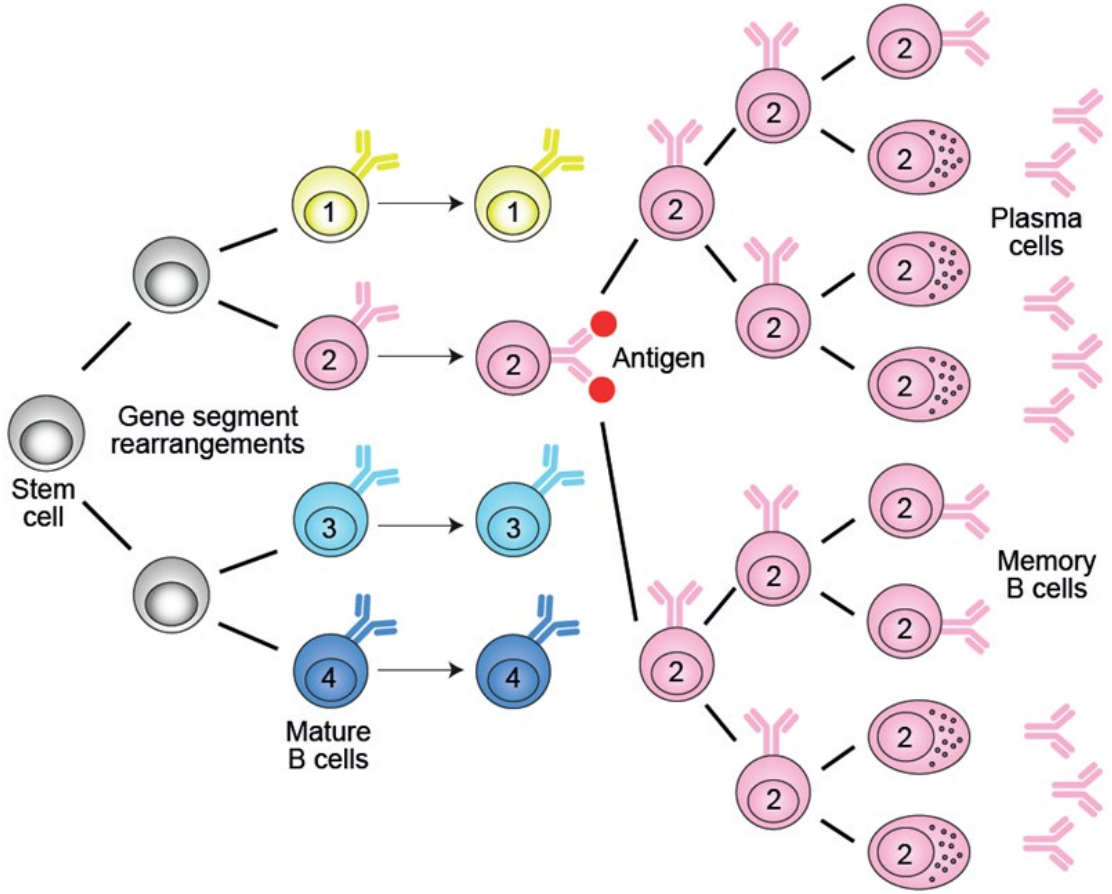
- **Opsonization:** antibody-tagged pathogen is consumed by phagocytes (IgG, IgA)
- **Degranulation:** of mast cells or basophils (IgE)
- **ADCC:** antibody-coated cells lysed by NK cells (IgG)
- **Tissue distribution:** occurs according to classes
  e.g. IgG → fetus via FcRn; IgA → mucosae via pIgR

ADCC, antibody-dependent cellular cytotoxicity; Fab, antigen-binding fragment; Fc, crystallizable fragment; FcRn, neonatal Fc receptor; Ig, immunoglobulin; NK, natural killer.

1. Boundless Anatomy and Physiology. Available from https://courses.lumenlearning.com/boundless-ap/chapter/humoral-immune-response/. Accessed October 2022. 2. Absolute antibody. Available from: http://absoluteantibody.com/antibody-resources/antibody-overview/antibody-effector-functions/. Accessed October 2022. 3. Alberts et al. Molecular Biology of the Cell, 4th edn, 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26884/. Accessed October 2022.

The adaptive immune response: clonal expansion of activated B cells

- Activated B cells are driven to divide and differentiate into plasma and memory cells
  - Plasma cells produce antibodies for neutralizing pathogens or labeling them for destruction
  - Memory cells have long lifespans and respond quickly upon reinfection with the same pathogen
- These cells have the same antigen specificity (same BCR) as the original B cell



Maturation into B cells that are antigenetically committed

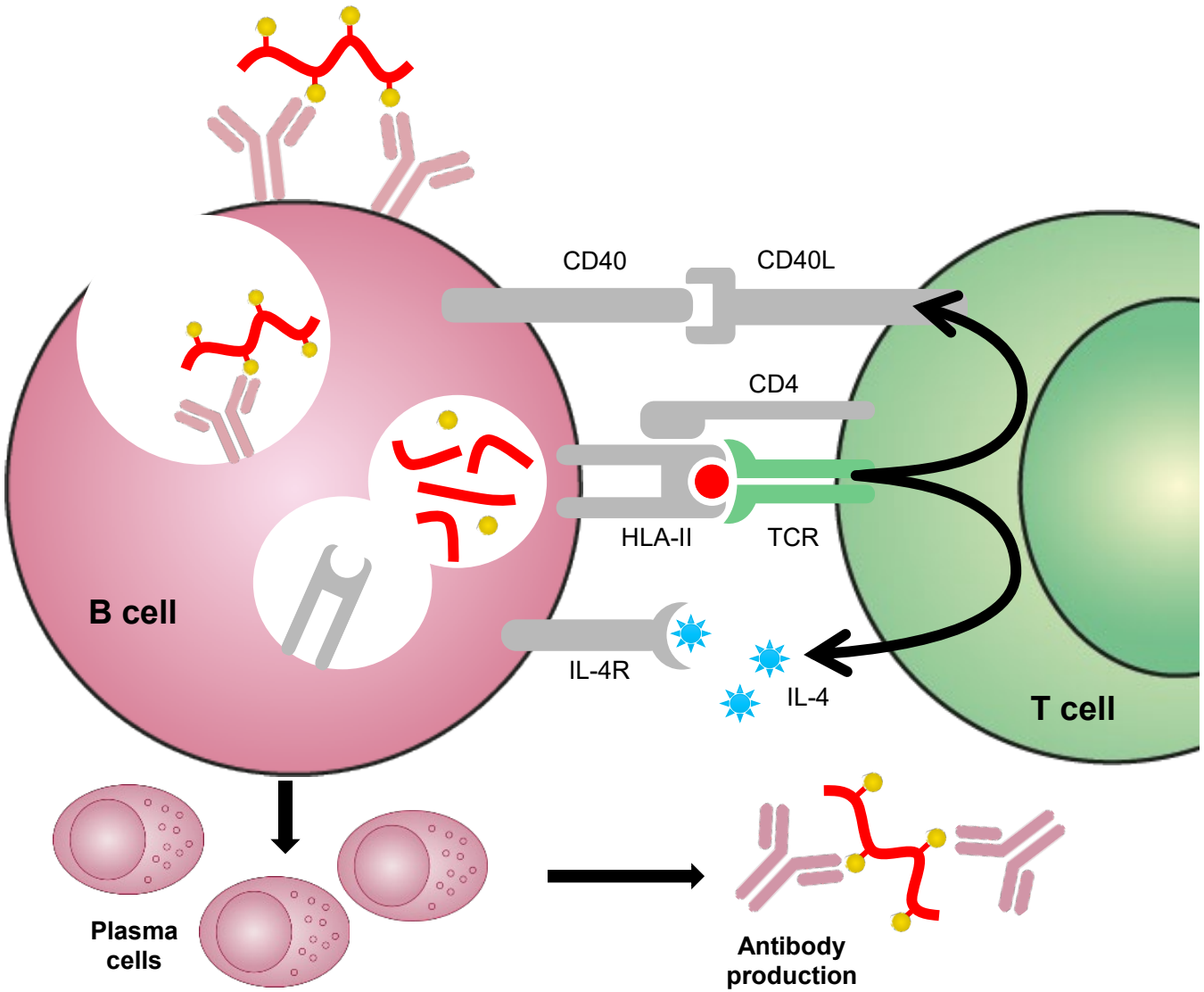
Antigen-dependent proliferation and differentiation into plasma and memory cells

BCR, B-cell receptor.

Male et al. Immunology, 7th edn, 2001. Image adapted from: Owen & Punt. Kuby Immunology, 7th edn, 2012.

T-cell-dependent B-cell activation (T–B collaboration)[1,2]

- The surface immunoglobulin that serves as the BCR has two roles in B-cell activation:
  - BCR binds antigen (a hapten-carrier complex), leading directly to the intracellular signaling cascade[1,2]
  - BCR delivers the antigen to intracellular sites where it is degraded and returned to the B-cell surface as peptides bound to HLA class II molecules[1]
- The peptide:HLA class II complex is recognized by helper T cells, stimulating them to express CD40L and secrete IL-4, which stimulates B-cell proliferation and differentiation into Ab-secreting cells[1]



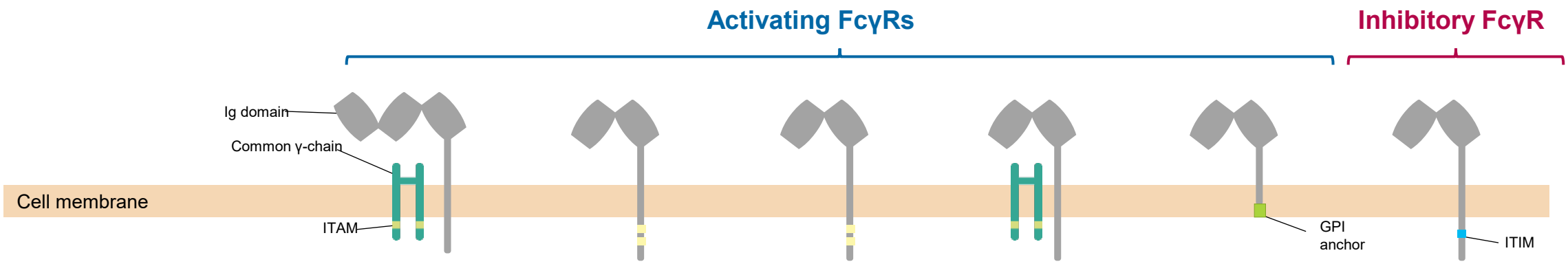
Ab, antibody; BCR, B-cell antigen receptor; CD40L, CD40 ligand; HLA, human leukocyte antigen; IL-4R, interleukin-4 receptor; TCR, T-cell receptor.

1. Janeway et al. Immunobiology: The Immune System in Health and Disease, 5th edn, 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK27142/. Accessed October 2022. 2. Alberts et al. Molecular Biology of the Cell. 4th edn, 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK21054/. Accessed October 2022.

Structure, cellular distribution and affinities of human activating and inhibitory Fcγ receptors

Chapter homepage

Human FcγRs differ in function, affinity for the Fc fragment of antibody and cellular distribution[1]



		FcγRI CD64	FcγRIIA CD32a	FcγRIIC CD32c	FcγRIIIA CD16	FcγRIIIB CD16	FcγRIIB CD32b
Expression	**Lymphoid**	–	–	NK cell	NK cell	–	B cell, plasma cell
	Myeloid	Monocyte, DC and macrophage	Monocyte, DC and macrophage	–	Monocyte, DC and macrophage	–	Monocyte, DC and macrophage
	Granulocyte	Neutrophil and eosinophil	Neutrophil	–	–	Neutrophil, mast cell and eosinophil	Neutrophil, basophil and mast cell
IgG subclasses binding affinity		1 >>> 2, 3 and 4	1 and 3 >> 2 > 4	1 > 3 >> 4 > 2	1 >> 2 and 3 > 4	1 and 3 >> 2 and 4	1 > 3 >> 4 > 2

DC, dendritic cell; Fc, crystallizable fragment; FcγR, Fc receptor for IgG; GPI, glycosylphosphatidylinositol; IgG, immunoglobulin G; ITAM, immunoreceptor tyrosine-based activating motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; NK, natural killer; (–) not expressed.

Adapted from 1. Smith & Clatworthy. Nat Rev Immunol 2010;10:328–43. 2. Nimmerjahn et al. Nat Rev Immunol 2008;8:34–47.

Adaptive immunity: T cells

Module 1. Basic immunology

The adaptive immune response: T lymphocytes

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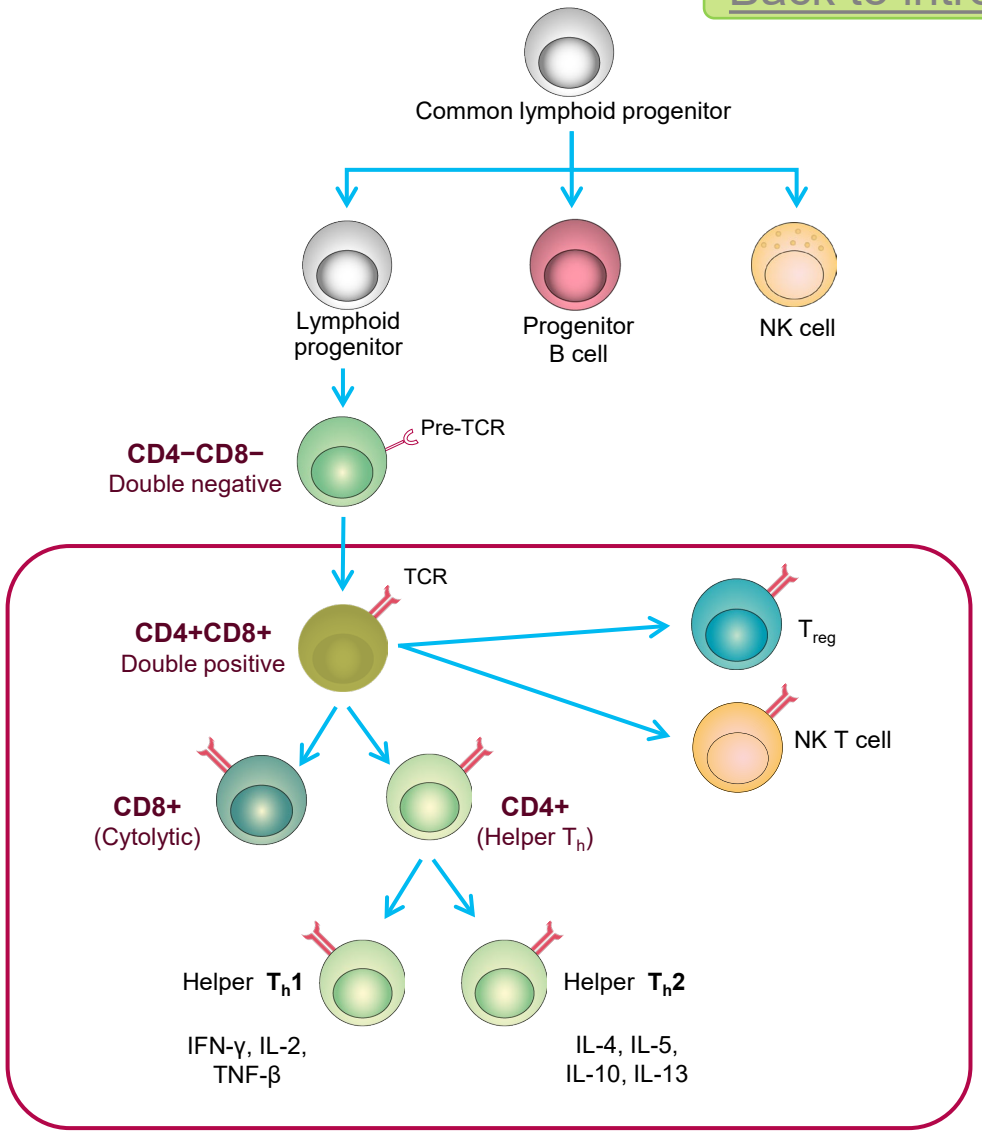
- T cells originate from lymphoid precursors in the bone marrow and develop in the thymus[1]
- T cells can be distinguished from other lymphocytes (e.g. B cells and NK cells) by the presence of an antigen-binding TCR on the cell surface[1]
- T cells differentiate into a number of subtypes
  - Cytolytic T cells (CD8+)
  - Helper T cells (CD4+: T_h1, T_h2 and T_h17)
  - T_{regs} (CD4+)
  - NK T cells

The main function of T lymphocytes is to recognize intracellular microbes that are inaccessible to antibodies[2]



IFN, interferon; IL, interleukin; NK, natural killer; TCR, T-cell receptor; T_h, T helper; TNF, tumor necrosis factor; T_{reg}, regulatory T cell.

1. Andersen. J Invest Dermatol 092006;126:32–41. 2. Janeway et al. Immunobiology: The Immune System in Health and Disease, 5th edn, 2001. Available from: http://www.ncbi.nlm.nih.gov/books/NBK27092/ and https://www.ncbi.nlm.nih.gov/books/NBK26827/. Accessed October 2022. Image adapted from Janeway et al. Immunobiology: The Immune System in Health and Disease, 5th edn, 2001 and Germain RN. Nat Rev Immuno 2002;2:3-322

Distinct functions of CD4 vs CD8 and HLA class I versus class II molecules

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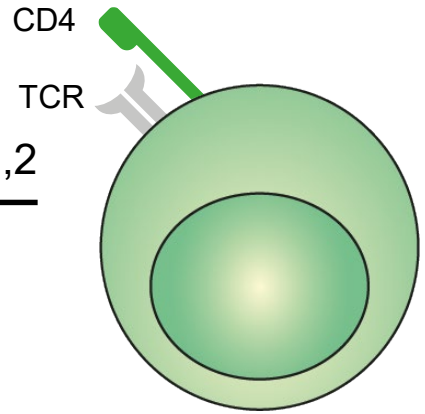
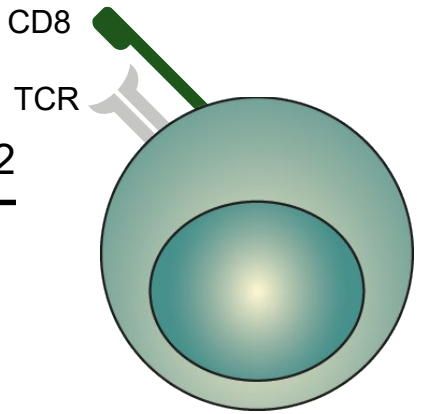
CD4+ T lymphocytes[1,2]



- T **helper** (T_h)
- Recognition of peptides derived from **extracellular** proteins (phagocytosis, endocytosis)
- Recognition of peptides presented by HLA **class II** molecules only
- These T cells are 'HLA class II-restricted'

CD8+ T lymphocytes[1,2]

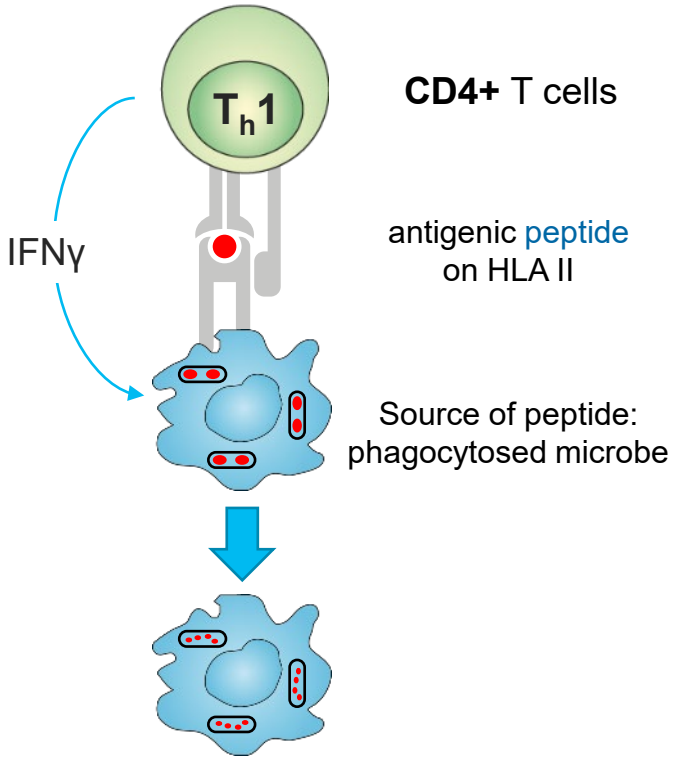


- **CTL: cytolytic**
- Recognition of peptides derived from **intracellular** proteins (i.e. those produced within the cells)
- Recognition of peptides presented by HLA **class I** molecules only
- These T cells are 'HLA class I-restricted'

CTL, cytotoxic T lymphocyte. HLA, human leukocyte antigen; TCR, T-cell receptor.

1. Blum et al. Annu Rev Immunol 2013;31:443–73. 2. Woodworth & Behar. Crit Rev Immunol 2006;26:317–52

Major T-cell functions against pathogens[1-5]



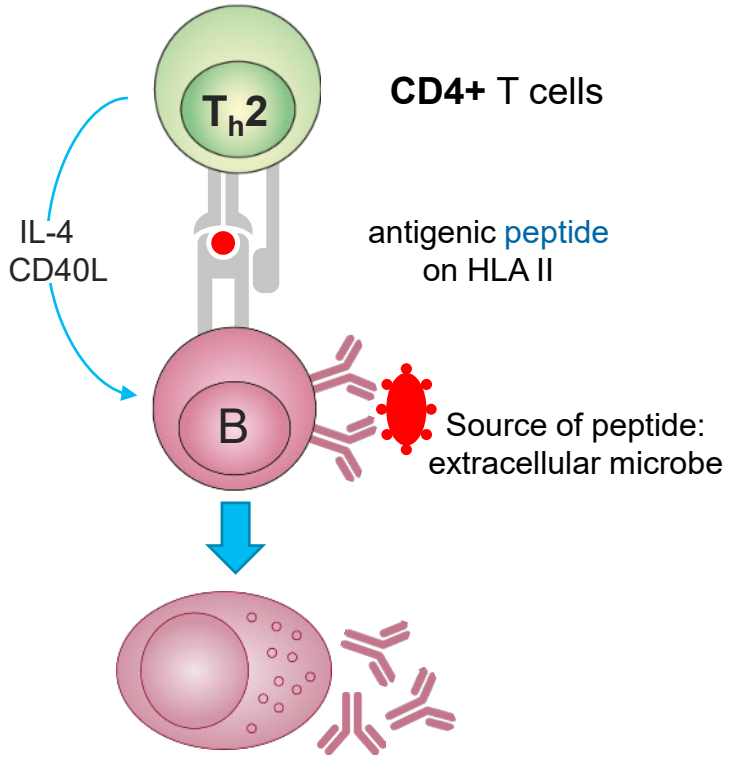
CD4+ T cells

antigenic peptide on HLA II

Source of peptide: phagocytosed microbe

T_h1 cells produce high amounts of IFNγ, which activates macrophages to kill phagocytosed bacteria

Function: macrophage activation



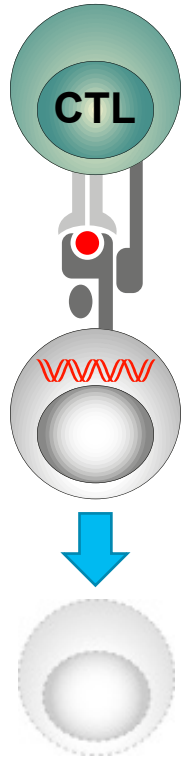
CD4+ T cells

antigenic peptide on HLA II

Source of peptide: extracellular microbe

B cells activated by antigen and T cells produce antibodies of high affinities and of IgG, IgA or IgE isotypes (instead of IgM)

Function: B-cell differentiation



CD8+ T cells

antigenic peptide on HLA I

Source of peptide: DNA/RNA of intracellular microbe

An activated CTL can kill infected cells through
- Production and release of **cytotoxic granules**
- **FasL** (on CTL)/Fas (on target) interactions
- Secretion of cytokines such as **TNF-α**

Function: target cell apoptosis

CD40L, CD40 ligand; CTL, cytotoxic T lymphocyte; FasL, Fas ligand; HLA, human leukocyte antigen; IFN, interferon; Ig, immunoglobulin; IL-4, interleukin 4; Th, T helper; TNF, tumor necrosis factor.

1. Janeway et al. Immunobiology: The Immune System in Health and Disease, 5th edn, 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK27149/. Accessed October 2022. 2. Bell. Available from: https://www.immunology.org/public-information/bitesized-immunology/cells/cd4-t-cells. Accessed October 2022. 3. Wissinger. Available from: https://www.immunology.org/public-information/bitesized-immunology/cells/cd8-t-cells. Accessed October 2022. 4. Andersen. J Invest Dermatol 2006;126:32–41. 5. Mosser & Zhang. Curr Protoc Immunol 2008;Chapter 14:Unit 14.2.

Major histocompatibility complex

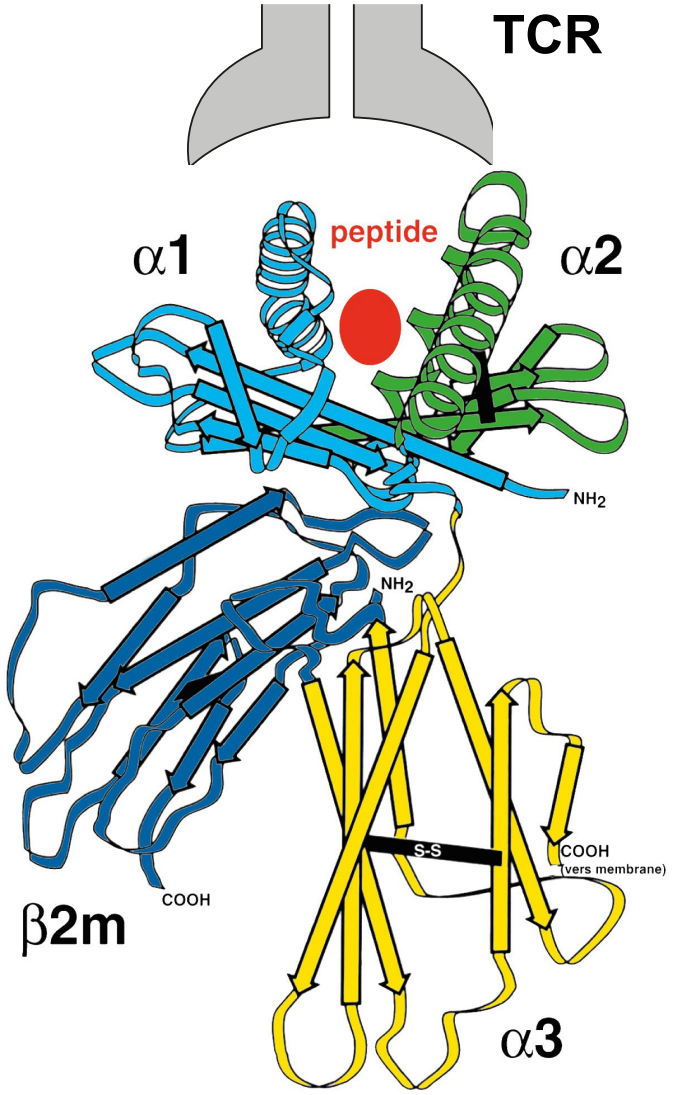
- The MHC is a set of genes identified in mice that determines graft rejection/ acceptance (histocompatibility)
- The MHC genes code for the MHC molecule
- In humans, the MHC genes/molecules were discovered on white blood cells and are therefore named the human leukocyte antigen (HLA) genes/molecules
  - Three genes encode the HLA class I molecules: *HLA-A*, *HLA-B*, *HLA-C*
  - Six genes encode the HLA class II molecules: *HLA-DR*, *HLA-DP*, *HLA-DQ* (two chains)
- The HLA genes are highly polymorphic (many alleles)
- The function of the HLA molecules is presentation of antigenic peptides to T lymphocytes

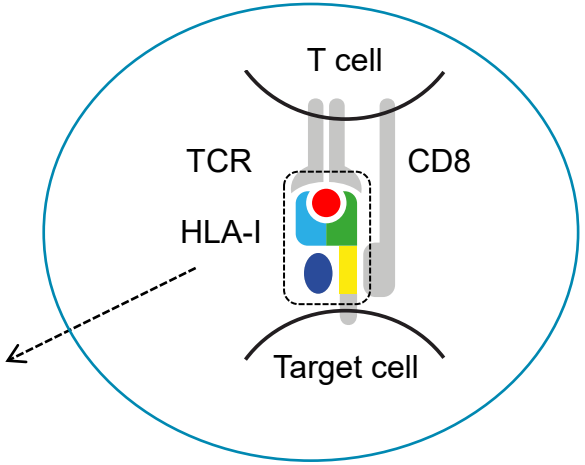
HLA, human leukocyte antigen; MHC, major histocompatibility complex.

Janeway et al. Immunobiology: The Immune System in Health and Disease, 5th edn, 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK27156/. Accessed October 2022.

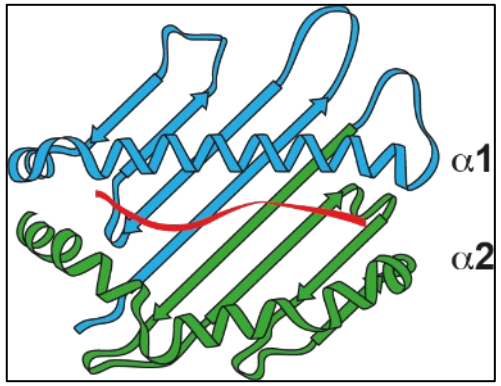
Crystal structure of HLA class I molecules

- The TCR recognizes a complex between a class I or class II HLA molecule and an antigenic peptide
- The HLA class I molecule is a heterodimer with a heavy chain, containing the α_1, α_2 and α_3 domains, and $ß_2$microglobulin
- The TCR interacts with the antigenic peptide presented in a groove on top of the HLA molecule, between the α_1 and α_2 domains
- The TCR contacts both the antigenic peptide itself and residues of the α_1 and α_2 domains of the presenting HLA molecule





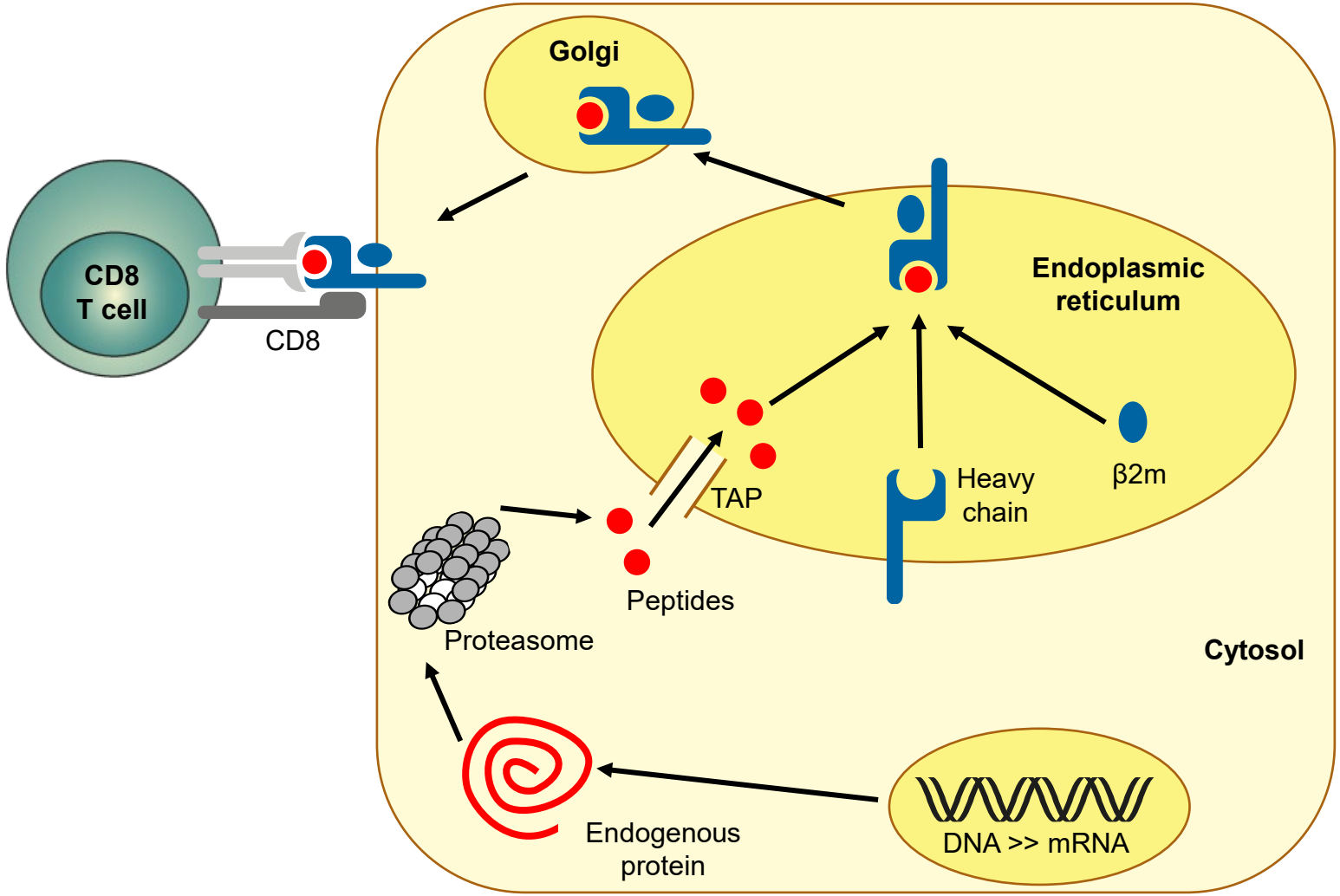
Top view



ß2m, beta$_2$ microglobulin; HLA, human leukocyte antigen; TCR, T-cell receptor.
Bjorkman et al. J Immunol 2005;174:13–9.

Canonical HLA class I antigen processing pathway

- Proteins are degraded by the proteasome
- Next, the resultant peptides are translocated by TAP into the ER lumen and loaded onto HLA class I molecules
- The peptide–HLA class I complexes are then released from the ER and transported via the Golgi to the plasma membrane
- The antigenic peptide is presented to CD8+ T cells



ß2m, beta$_2$ microglobulin; ER, endoplasmic reticulum; HLA, human leukocyte antigen; TAP, transporter associated with antigen presentation.

1. Neefjes et al. Nat Rev Immunol 2011;11:823–36.

Canonical HLA class II antigen processing pathway

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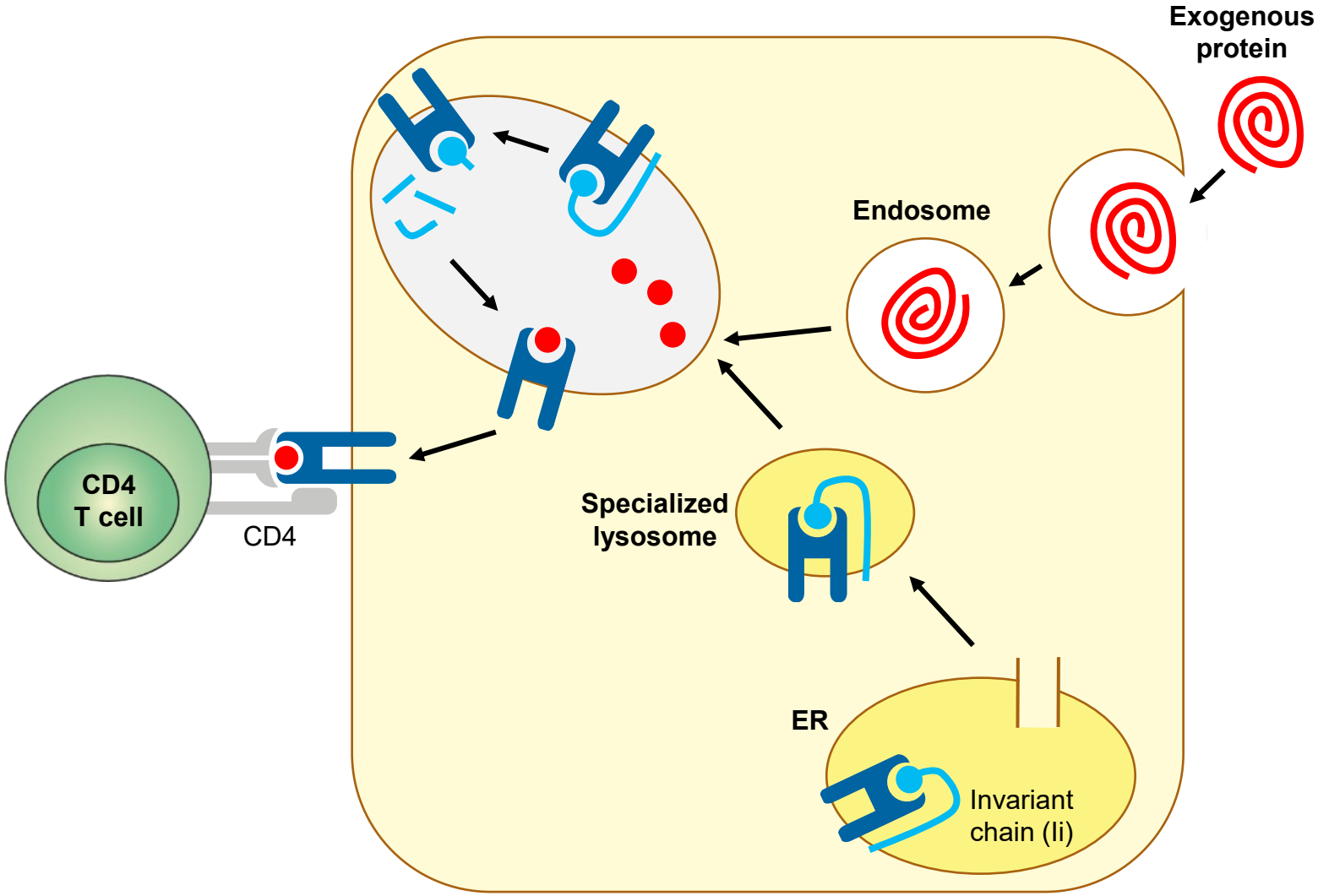
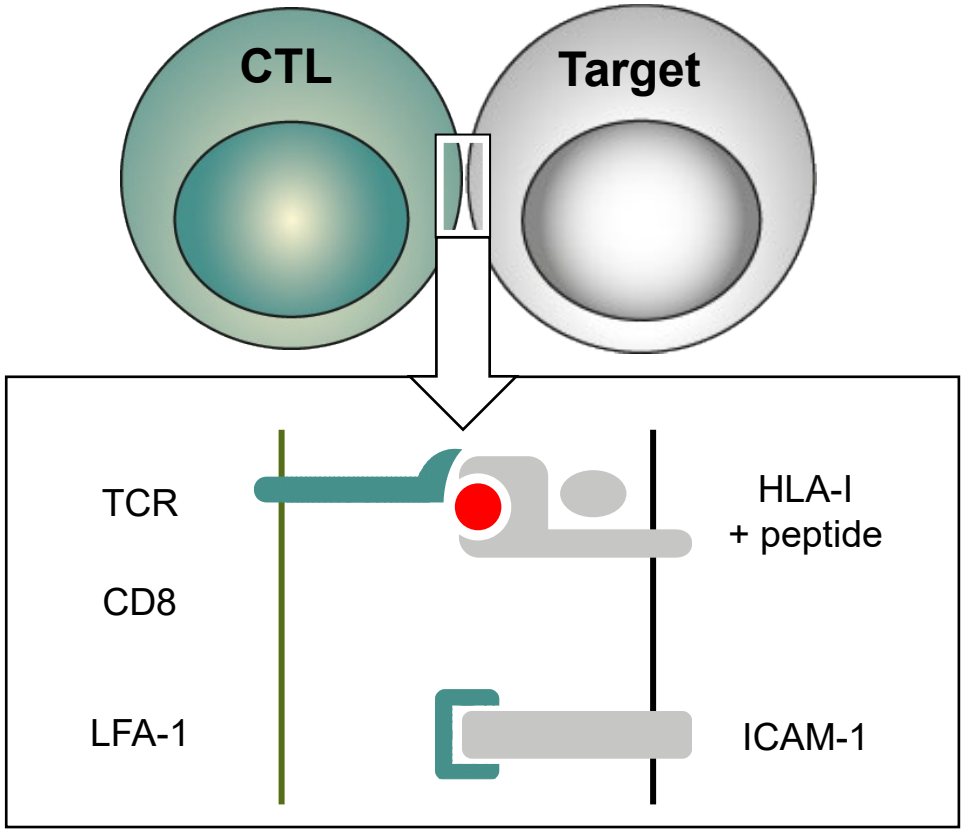
- HLA class II α- and β-chains assemble in the ER and form a complex with the invariant chain
- The heterotrimer is transported through the Golgi to the HLA class II compartment
- Endocytosed proteins and Ii are degraded by resident proteases
- The Ii fragment in the peptide-binding groove is exchanged for an antigenic peptide
- HLA class II molecules are transported to the plasma membrane to present antigenic peptides to CD4+ T cells



ER, endoplasmic reticulum; HLA, human leukocyte antigen; Ii, invariant chain; TAP, transporter associated with antigen presentation.
Neefjes et al. Nat Rev Immunol 2011;11:823–36.

Interactions that regulate the immune response occur in the nanoscale gap between T cells and APCs[1]

- The specificity of the interaction between a T cell and an APC depends on the TCR and HLA-peptide complexes
- ICAM-1 is an adhesion molecule that forms a link to LFA-1, an integrin that mediates adhesion between T cells and APCs[1,2]
- Adhesion molecules are needed to allow T cells to bind to APCs long enough for them to become activated[2]
- Once the TCR has been triggered, it can further enhance the activity of LFA-1 and promote formation of an immunological synapse[3]



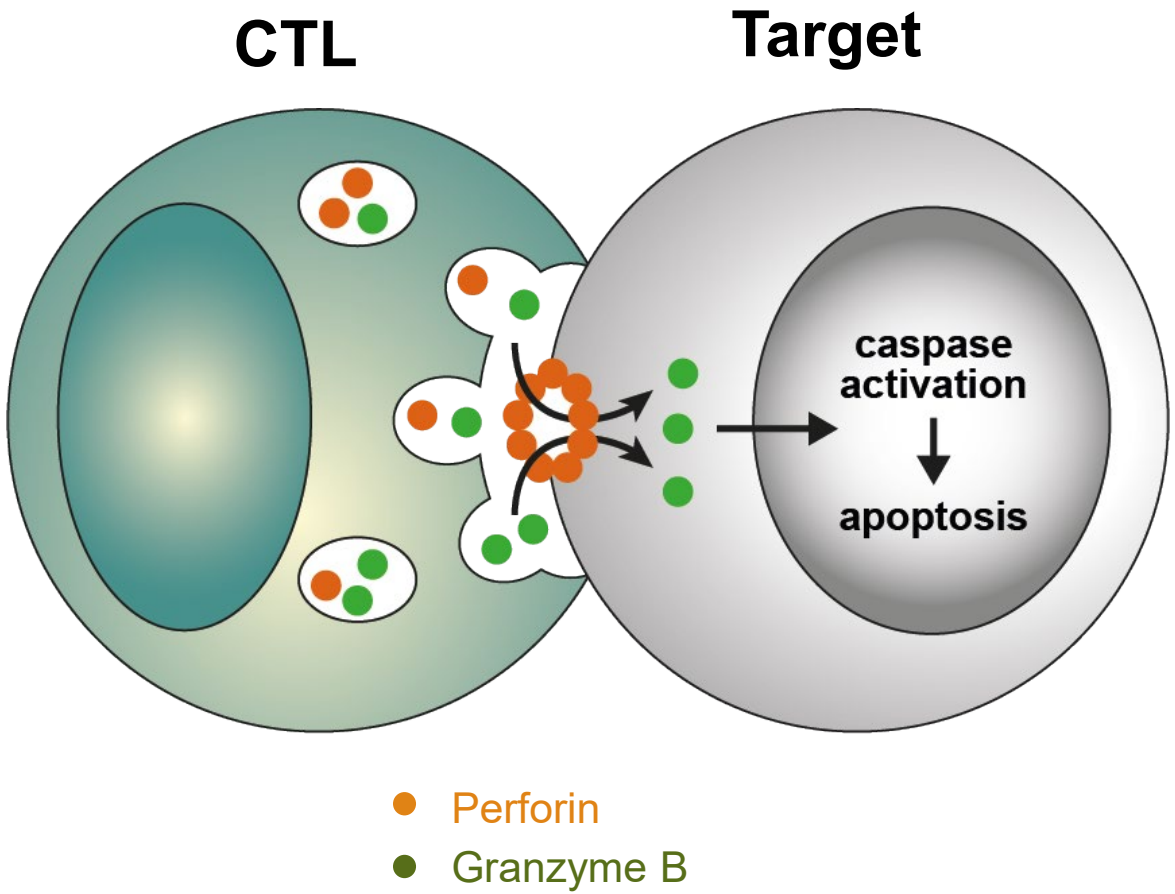
'Immunological synapse'
antigen recognition + adherence molecules

APC, antigen-presenting cell; HLA, human leukocyte antigen; ICAM, intercellular adhesion molecule; LFA, leukocyte function-associated antigen; TCR, T-cell receptor.

1. Shimizu. Nat Immunol 2003;4:1052–4. 2. Alberts et al. Molecular Biology of the Cell, 4th edn, 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26827/. Accessed October 2022. 3. Dustin. Cancer Immunol Res 2014;11:1023–33.

Granule-mediated cytolysis by CTLs

- Once bound to its target cell, a CTL can use different strategies to kill the target cell
- By killing the infected cell, the CTL can release **perforin**
- **Perforin** is stored in CTLs within secretory vesicles, which also contain serine proteases such as **granzyme B**
- **Perforin**, a pore-forming protein, polymerizes in the plasma membrane of the target cell, forming transmembrane channels
- **Granzyme B** cleaves and activates members of the caspase family that mediate apoptosis
- NK cells use the same lytic machinery as CTLs



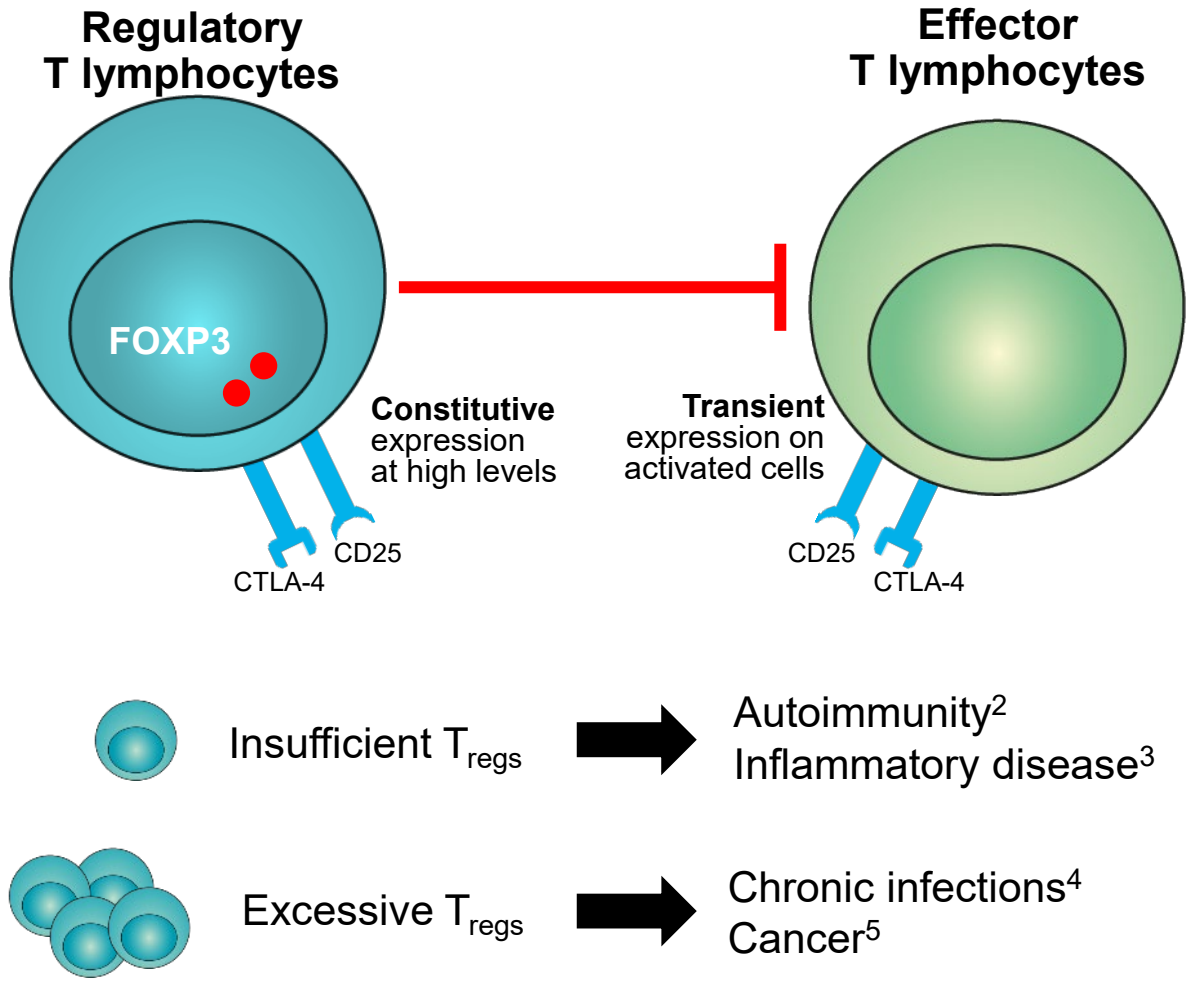
CTL, cytotoxic T lymphocyte; NK, natural killer.

Alberts et al. Molecular Biology of the Cell, 4th edn, 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26926/. Accessed October 2022.

Regulatory T cells are vital to immune homeostasis

Chapter homepage

- T_{reg} differentiation and immunosuppressive activity depend on transcription factor FOXP3 (*Foxp3*$^{-/-}$ mice die from autoimmunity at an early age)
- T_{regs} maintain tolerance to self-antigens and prevent autoimmune disease
- Human T_{regs} do not bear a unique surface marker. They constitutively express high levels of CD25 and CTLA-4
- T_{regs} are immunosuppressive through various mechanisms and generally suppress or downregulate induction and proliferation of effector T cells[1]

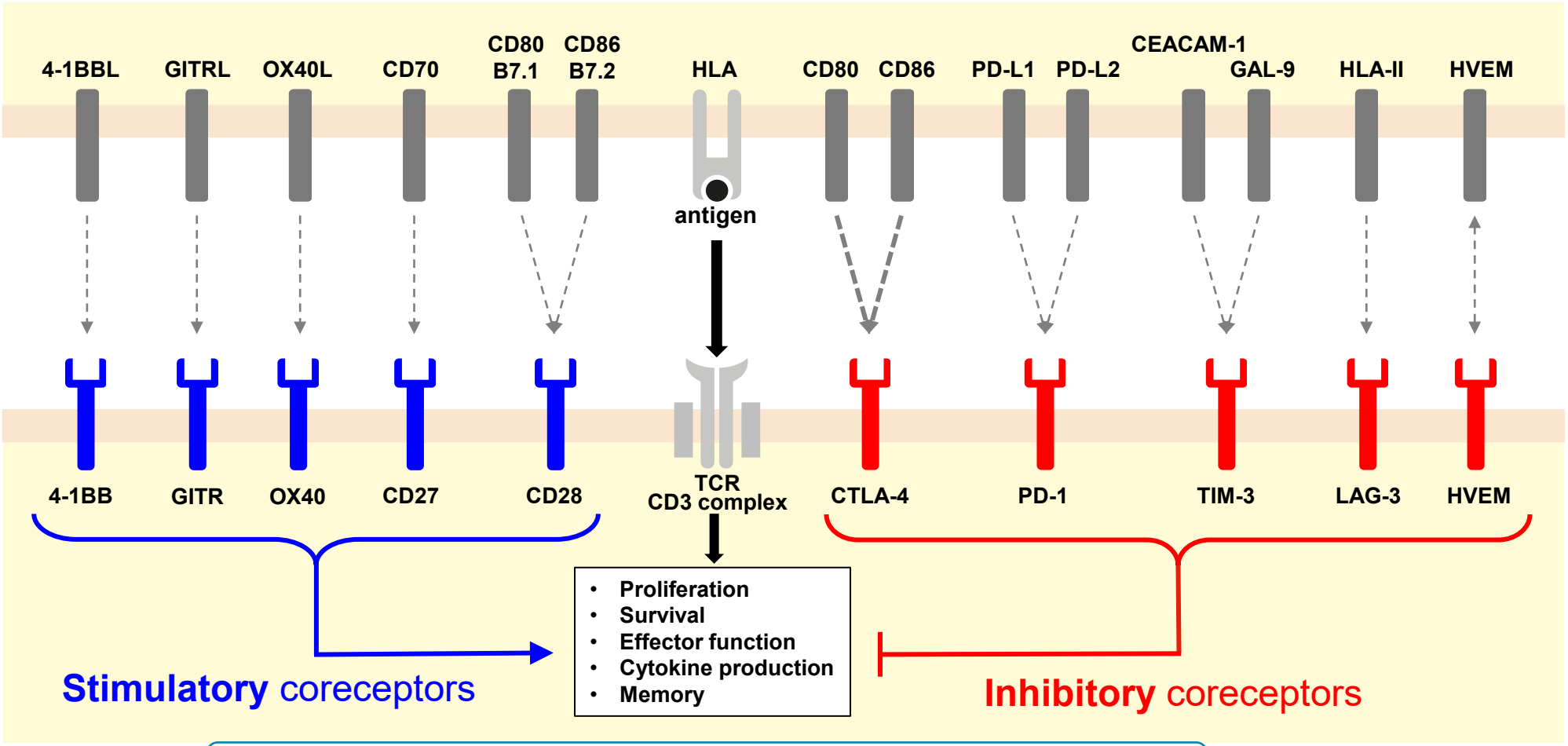


CTLA-4, cytotoxic T lymphocyte-associated protein 4; FOXP3, forkhead box P3; T_{reg}, regulatory T cell.

1. Chevalier et al. J Immunol 2014;193:4845–58. 2. Komatsu et al. Nat Med 2014;20:62–70. 3. Thorburn & Hansbro. Am J Respir Cell Mol Biol 2010;43:511–9. 4. Sanchez & Yang. Immunol Res 2011;49:124–34. 5. Smigiel et al. Immunol Rev 2014;259:40–59.

T-cell regulation: stimulatory and inhibitory coreceptors

Chapter homepage



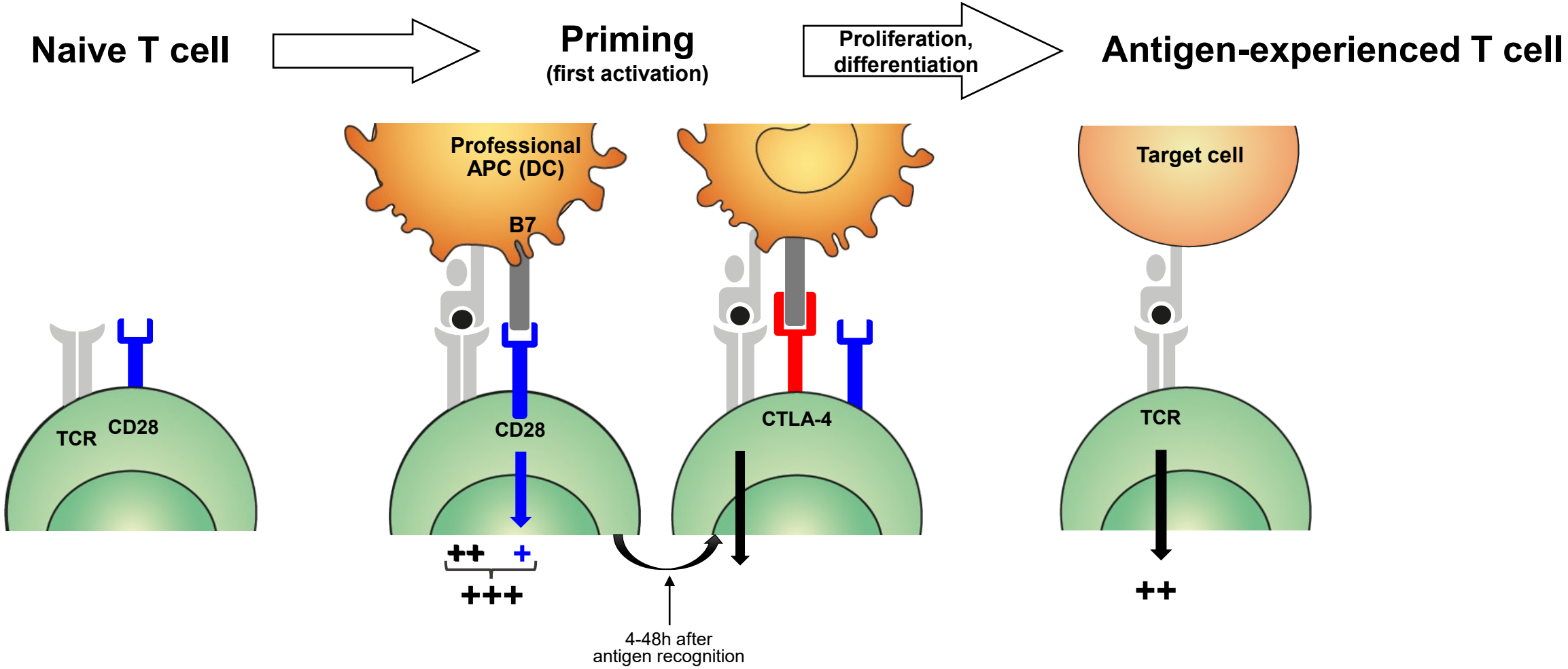
Function: fine-tuning of T-cell activation in time and space

APC, antigen-presenting cell; HLA, human leukocyte antigen; TCR, T-cell receptor.

Adapted from Kershaw et al. Nat Rev Cancer 2013;13:525–41. doi:10.1038/nrc3565 2. Dustin. Cancer Immunol Res 2014;11:1023–33. 3. Le Mercier et al. Front Immunol 2015; 6:1-15.

Stimulatory and inhibitory coreceptors fine tune T-cell activity

Chapter homepage

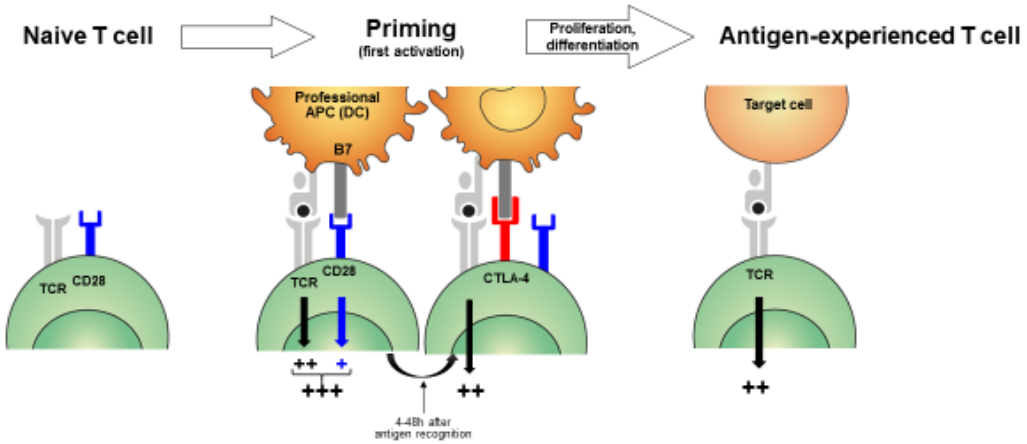


APC, antigen-presenting cell; CTLA-4, cytolytic T-lymphocyte-associated protein 4; DC, dendritic cell; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.

Alberts et al. Molecular Biology of the Cell, 4th edn, 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26827/. Accessed October2022.

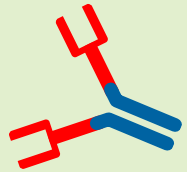
Clinical relevance
Modulation of T-cell activity (1)

Stimulatory and inhibitory coreceptors fine tune T-cell activity



APC, antigen-presenting cell; CTLA-4, cytolytic T-lymphocyte-associated protein 4; DC, dendritic cell; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.
Alberts et al. Molecular Biology of the Cell: T Cells and MHC Proteins. 4th edn. 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26827/. Accessed May 2017.

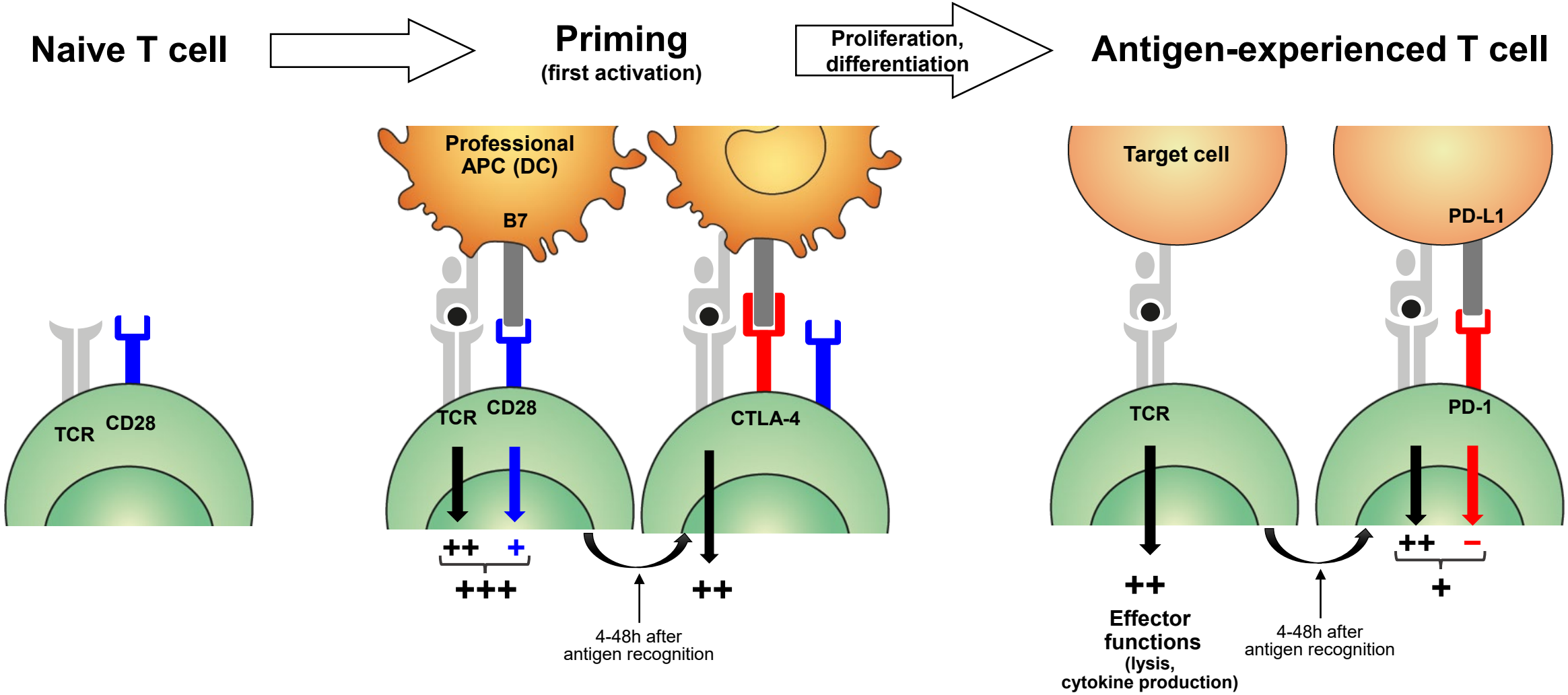
- **Agents that target T-cell coreceptors to modulate T-cell activity are used therapeutically**

	Abatacept	Belatacept
Structure	A fusion protein that consists of the extracellular domain of human CTLA-4 linked to a modified Fc portion of human IgG1 	
Mechanism of action	Binds to B7 (CD80/CD86) ligands and prevents T-cell costimulation by CD28	
Therapeutic indications	Rheumatoid arthritis, psoriatic arthritis, polyarticular juvenile idiopathic arthritis	Prophylaxis of graft rejection in adult recipients of a renal transplant

APC, antigen-presenting cell; CTLA-4, cytolytic T-lymphocyte-associated protein 4; DC, dendritic cell; Fc, crystallizable fragment; IgG, immunoglobulin G; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; SmPC, summary of product characteristics; TCR, T-cell receptor.
Always refer to the SmPC. All SmPCs are available from http://www.ema.europa.eu/ema/.

Stimulatory and inhibitory coreceptors fine tune T-cell activity

Chapter homepage

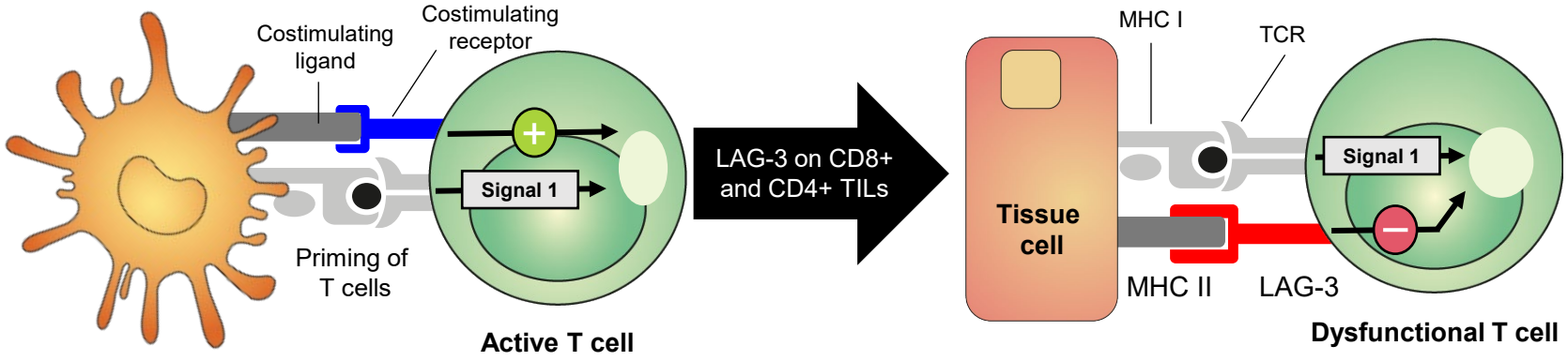


APC, antigen-presenting cell; CTLA-4, cytolytic T-lymphocyte-associated protein 4; DC, dendritic cell; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.
Adapted from 1. Alberts et al. Molecular Biology of the Cell, 4th edn, 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26827/. Accessed October 2022. and 2. Riley. Immunol Rev. 2009; 229:114–125.

Stimulatory and inhibitory coreceptors fine tune T-cell activity

- LAG-3 is a cell-surface molecule expressed on T cells and other immune cells that has diverse inhibitory biologic effects on the function of T cells[1,2]

LAG-3



Increased expression of LAG-3 on CD8+ and CD4+ TILs, especially in the context of PD-1 expression, inhibits effector T-cell function[1,3-5]

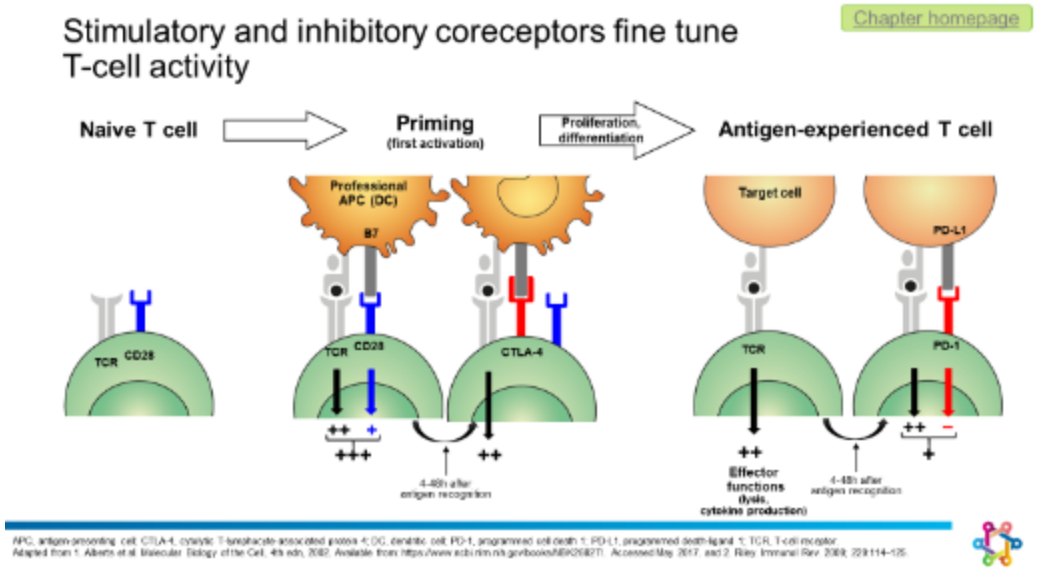
Interaction of LAG-3 with its ligands triggers inhibitory activity that reduces the function of effector T cells, leading to an impaired ability to fight tumor cells and an increased potential for tumor growth[1,5]

Ligands for LAG-3 are distinct from the ligands of other inhibitory immune checkpoints such as PD-1 or CTLA-4. Among its ligands, the most well established is MCH II; others are emerging, including FGL1[1,5–7]

APC, antigen-presenting cell; CTLA-4, cytotoxic T lymphocyte antigen 4; FGL1, fibrinogen-like protein 1; LAG-3, lymphocyte-activation gene 3; PD-1, programmed death-1; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

1. Long L, et al. Genes Cancer 2018;9:176-189; 2. Grosso JF, et al. J Clin Invest 2007;117:3383-3392; 3. Workman CJ, et al. J Immunol 2004;172:5450-5455; 4. Woo SR, et al. Cancer Res 2012;74:917-927;
5. Wang J, et al. Cell 2019;176:334-347.e12.; 6. Huang R-Y, et al. Oncoimmunology 2017;6:e1249561; 7. Maçon-lemaître L, Triebel F. Immunology 2005;115:170-178.

Clinical relevance
Modulation of T-cell activity (2)



Checkpoint inhibitors

Monoclonal antibodies that block T-cell inhibitory coreceptors to increase T-cell activity and are used in oncology

- **Anti-CTLA-4 antibodies**
  - Ipilimumab, indicated for melanoma, RCC, NSCLC, CRC, MPM and ESCC
- **Anti-PD-1 antibodies**
  - Nivolumab, indicated for melanoma, NSCLC, MPM, RCC, cHL, SCCHN, CRC, ESCC, gastric adenocarcinoma and urothelial carcinoma
  - Pembrolizumab, indicated for melanoma, NSCLC, cHL, urothelial carcinoma, SCCHN, ESCC, CRC, breast cancer, cervical cancer and RCC
- **PD-L1 antibodies**
  - Atezolizumab, indicated for urothelial carcinoma, NSCLC, SCLC, HCC and breast cancer
  - Durvalumab, indicated for urothelial carcinoma (FDA), NSCLC and SCLC
- **Anti-LAG-3 antibodies**
  - Relatlimab, indicated for melanoma (in combination with nivolumab; FDA)

cHL, classical Hodgkin lymphoma; CRC, colorectal cancer; CTLA-4, cytolytic T-lymphocyte-associated protein 4; HCC, hepatocellular carcinoma; MPM, malignant pleural mesothelioma; NSCLC, non-small-cell lung cancer; ESCC, esophageal squamous cell carcinoma; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; PI, prescribing information. RCC, renal cell carcinoma; SCCHN, squamous cell cancer of the head and neck; SCLC, small-cell lung cancer. Always refer to the SmPC or PI. All SmPCs are available from http://www.ema.europa.eu/ema/. PIs are available from https://www.fda.gov/drugs/. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home. Accessed October 2022.

Module 1: Summary and key takeaways

- The immune system is a vital source of protection against pathogens, harmful substances and the body's own cells during illness
- While the innate immune system is broad, the adaptive immune system is highly specific to the pathogen or threat
- In innate immunity, key players include macrophages, which are important in antibacterial responses, and NK cells, which can kill HLA class I-deficient cells not detected by CTLs
- In adaptive immunity, T and B cells have vital roles:
  - B cells can be activated by T-cell-dependent pathways, leading to the production of antibodies, which are involved in pathogen elimination
  - The main function of T lymphocytes is to recognize intracellular microbes that are inaccessible to antibodies, along with other specialized functions
- Changes to the balance of the immune system are associated with various diseases, which can be targeted with immunotherapy

CTL, cytotoxic T lymphocyte; HLA, human leukocyte antigen; NK, natural killer.

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Types of immunotherapy

Types of immunotherapy

Click on a chapter below to start learning

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Click on the ISA logo of a slide to return to the chapter homepage

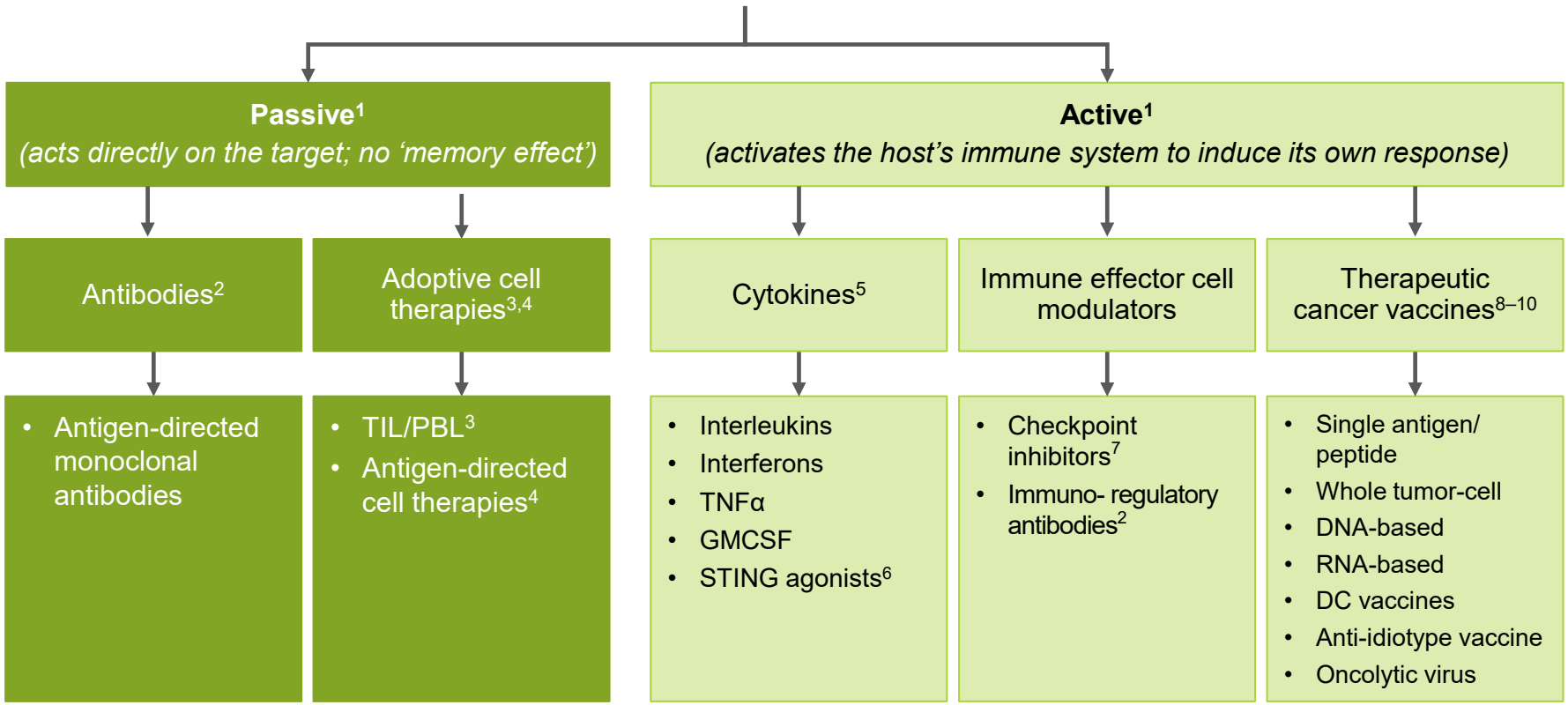
Introduction

Types of immunotherapy

What is immunotherapy?

Immunotherapy is a treatment that either **induces, enhances or suppresses** immune mechanisms

Immunotherapies encompass a wide variety of different classes

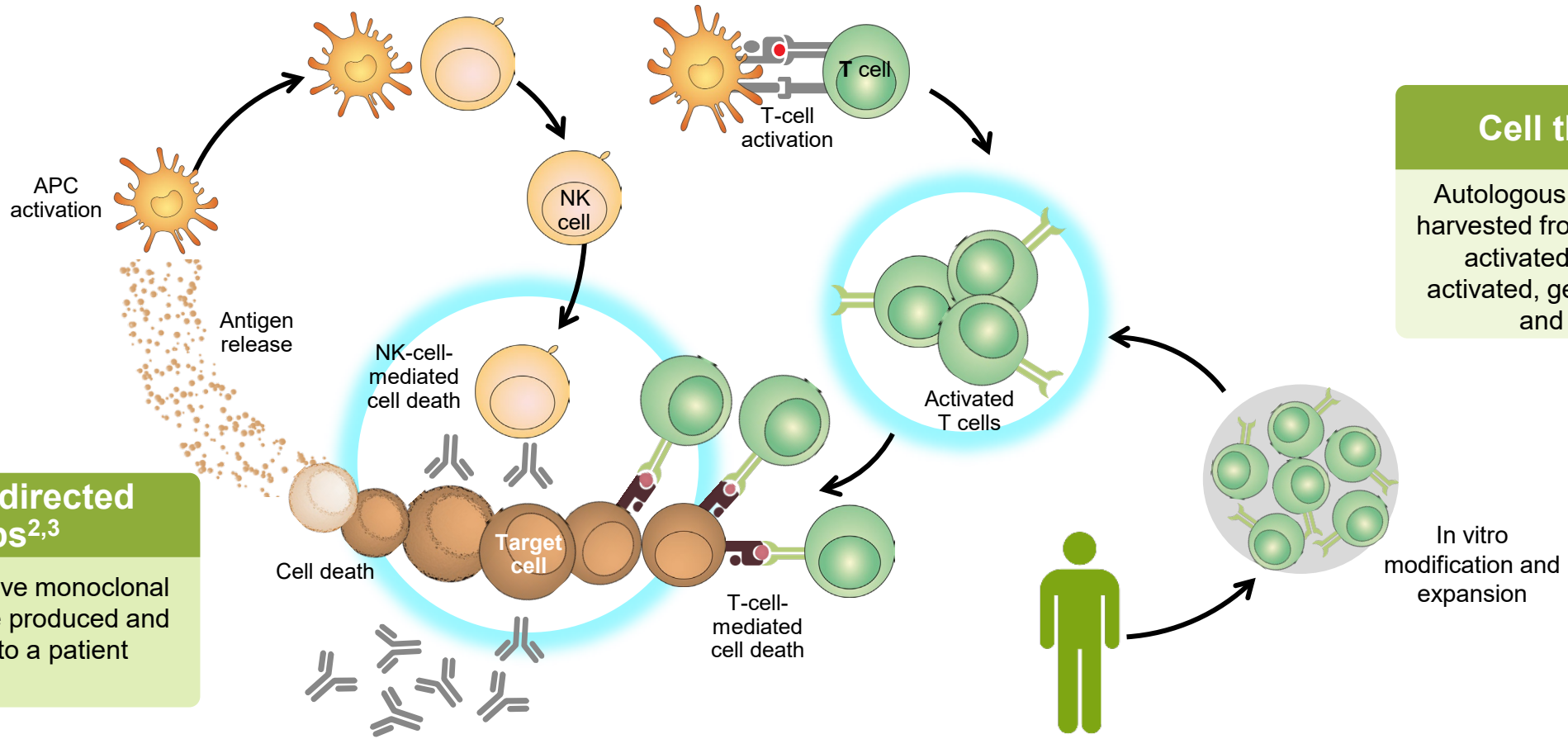


DC, dendritic cell; GMCSF, granulocyte-macrophage colony-stimulating factor; PBL, peripheral blood lymphocytes; STING, stimulator of interferon genes; TIL, tumor infiltrating T cells; TNF, tumor necrosis factor.

1. Finn. Ann Oncol 2012;23(suppl 8):viii6–9. 2. Redman et al. Mol Immunol 2015;67:28–45. 3. Dudley. J Cancer 2011;2:360–2. 4. Yu et al. J Hematol Oncol 2017;10:1–13. 5. List & Neri. Clin Pharmacol 2013;5:29–45. 6. Iurescia et al. Front Immunol 2018;9:711. 7. Pardoll. Nat Rev Cancer 2012;12:252–64. 8. Maithreye 2015. Available from https://www.slideshare.net/sunitamaithreye999/cancer-vaccine [Accessed October 2022]. 9. Guo et al. Adv Cancer Res 2013;119:421–475; 10. NCI. Cancer Treatment Vaccines. Available at: https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/cancer-treatment-vaccines [Accessed October 2022].

For full information of individual agents, always refer to the Summary of Product Characteristics

Passive immunotherapy does not require the patient's immune system to initiate the response[1–3,a]



Antigen-directed mAbs[2,3]

Antigen-reactive monoclonal antibodies are produced and injected into a patient

Cell therapies[4]

Autologous immune cells are harvested from the patient, then activated then selected, activated, genetically modified and expanded

[a]However, passive immunotherapies for cancer do depend on the patient's immune system for long-term tumor control or complete tumor elimination. Despite different classifications, some overlap between active and passive immunotherapies does exist.

APC, antigen-presenting cell; mAb, monoclonal antibody; NK, natural killer.

1. Finn. Ann Oncol 2012;23(suppl 8):viii6–9. 2. Rescigno et al. Biochim Biophys Acta 2007;1776:108–23. 3. Mellman et al. Nature 2011;480:480–9. 4. Rosenberg. Sci Transl Med 2012;4(127ps8):1–5.

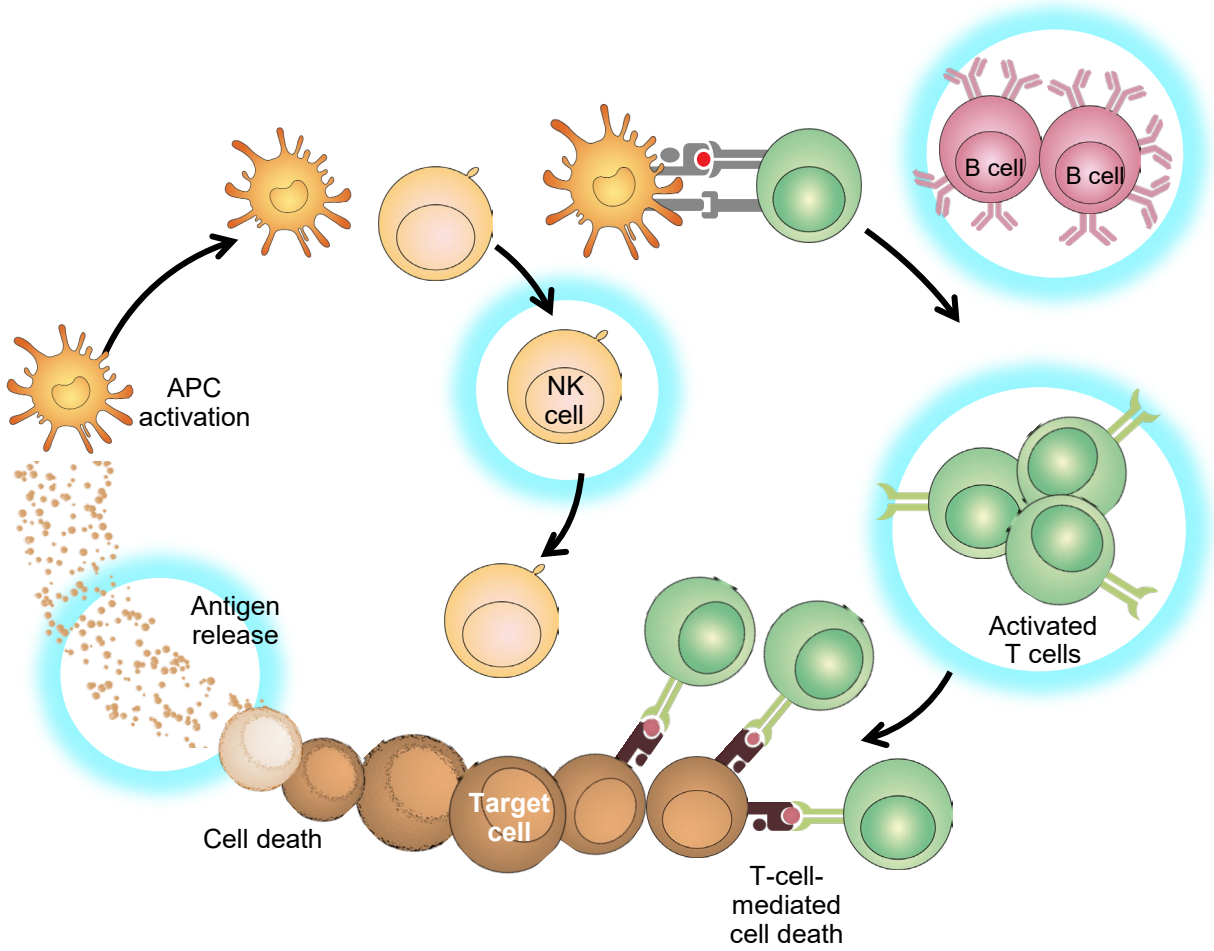
Active immunotherapy stimulates the immune system to elicit an immune response[1,2,a]

Therapeutic vaccines[2,3,5]

Therapeutic vaccines may prime the immune system to attack target cells in the body by introducing immune cells to one or more antigens

Cytokines[6]

Cytokines are small proteins that modulate the effector functions of immune cells, thereby influencing the immune response



Immunoregulatory antibodies[3,4]

Immunoregulatory monoclonal antibodies either act to enhance the immune response (in the treatment of cancer or infections) or suppress the immune response (in the treatment of autoimmunity or inflammatory diseases)

Checkpoint inhibitors[7,8]

Immune checkpoints refer to a set of 'control' pathways within the immune system. Overcoming checkpoint inhibition using antibodies or recombinant forms of the ligands or receptors enhances T-cell activity

[a]Despite different classifications, some overlap between active and passive immunotherapies does exist.

NK, natural killer.

1. Finn. Ann Oncol 2012;23(suppl 8):viii6–9. 2. Rescigno et al. Biochim Biophys Acta 2007;1776:108–23. 3. Mellman et al. Nature 2011;480:480–9. 4. Redman et al. Mol Immunol 2015;67:28–45. 5. Guo et al. Adv Cancer Res 2013;119:421–75. 6. List & Neri. Clin Pharmacol 2013;5(suppl):29–45. 7. Pardoll. Nat Rev Cancer 2012;12:252–64. 8. Thallinger et al. Wien Klin Wochenschr 2018;130:85–91.

Immunotherapy is either stimulatory or inhibitory

- Immunotherapy either activates or dampens the immune response; the choice of immunotherapy depends on the target disease

Tumors and infections

Autoimmunity and inflammatory diseases

‘Stimulatory’ immunotherapies

- Adoptive cell therapy[1]
- Antigen-directed monoclonal antibodies[2,3]
- Cytokines[4]
- Checkpoint inhibitors[5,6]
- Immunoregulatory monoclonal antibodies[3]

‘Suppressing’ immunotherapies[a]

- Immunoregulatory monoclonal antibodies[7,8]
- Allergen-specific immunotherapy[9]

[a]Other types of immunosuppressive therapy also exist (e.g. corticoids , immunoglobulins, tacrolimus) but are not covered in this module.

1. Rosenberg. Sci Transl Med. 2012;4:1–5. 2. Rescigno et al. Biochim Biophys Acta 2007;1776:108–23. 3. Mellman et al. Nature 2011;480:480–9. 4. List & Neri. Clin Pharmacol 2013;5(suppl):29–45. 5. Pardoll. Nat Rev Cancer 2012;12:252–64. 6. Thallinger et al. Wien Klin Wochenschr 2018;130:85–91. 7. Redman et al. Mol Immunol 2015;67:28–45. 8. Kalden. Rheumatol Ther 2016;3:31–42. 9. Viswanathan & Busse. Chest 2012;141:1303–14.

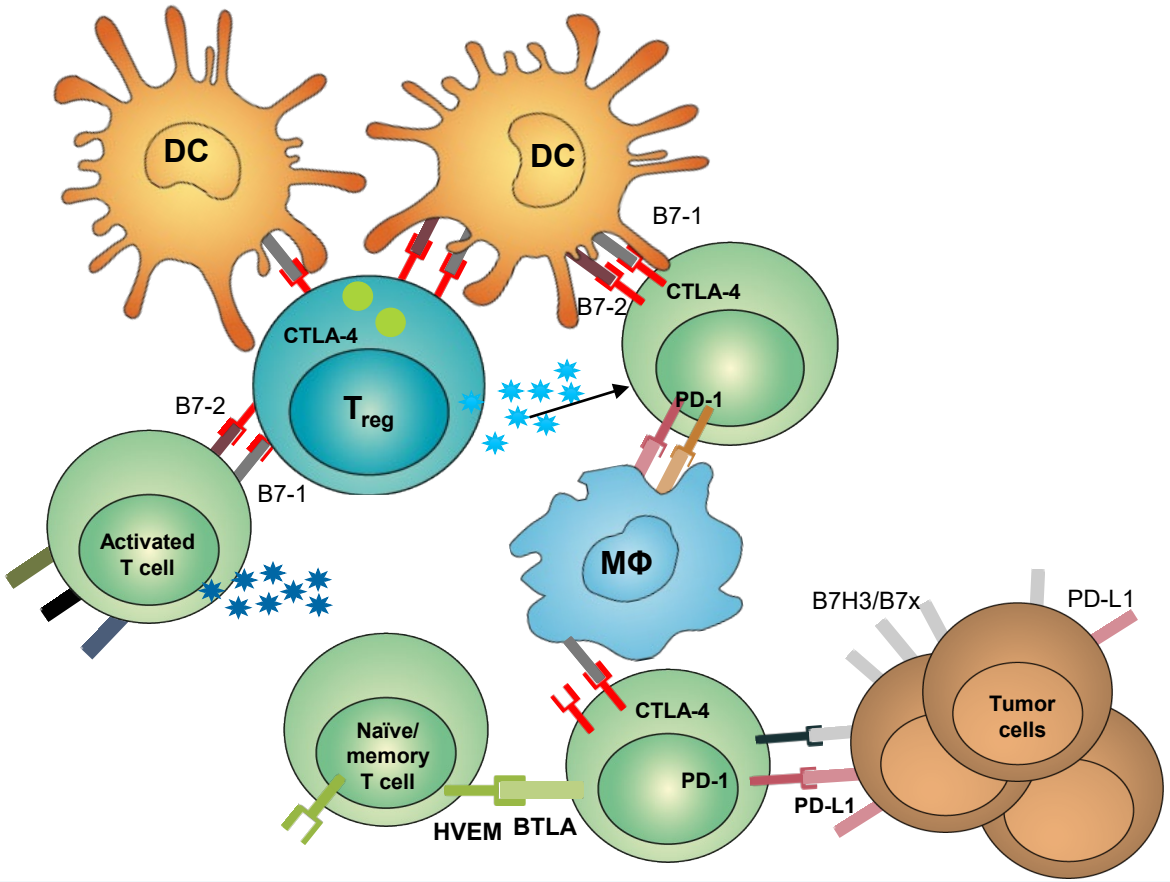
Checkpoint inhibitors

Types of immunotherapy

Inhibitory checkpoints of immune regulation

- Inhibitory signaling pathways, also termed immune checkpoints, are key to the immune response[1]
- They are vital to maintaining self-tolerance and limiting or modulating immune responses, and are initiated by ligand–receptor interactions[2]

Studies have shown that immune-checkpoint receptors are expressed during tolerance to self-antigens and chronic infection, and during inflammation[2,3]



Key players

CTLA-4 is expressed only on T cells and regulates the early stages of T-cell activation[2]

The main role of **PD-1** is to limit T-cell activity during an inflammatory response to infection and to limit autoimmunity[2,3]

PD-L1 is a ligand for PD-1. It is the major PD-1 ligand expressed on cells from solid tumors[2,3]

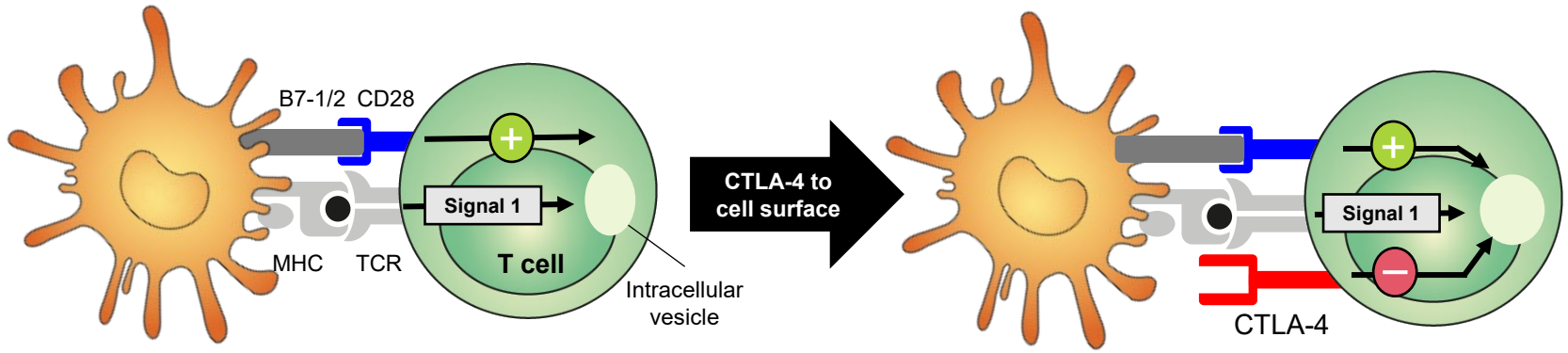
BTLA, B- and T-lymphocyte attenuator; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DC, dendritic cell; HVEM, herpesvirus entry mediator; MΦ, macrophage; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; Treg, regulatory T cell.

1. Wolchok & Saenger. Oncologist 2008;13:2–9. 2. Pardoll. Nat Rev Cancer 2012;12;252–64. 3. Thallinger et al. Wien Klin Wochenschr 2018;130:85–91.

Inhibitory checkpoints of immune regulation: potential targets for therapeutic intervention

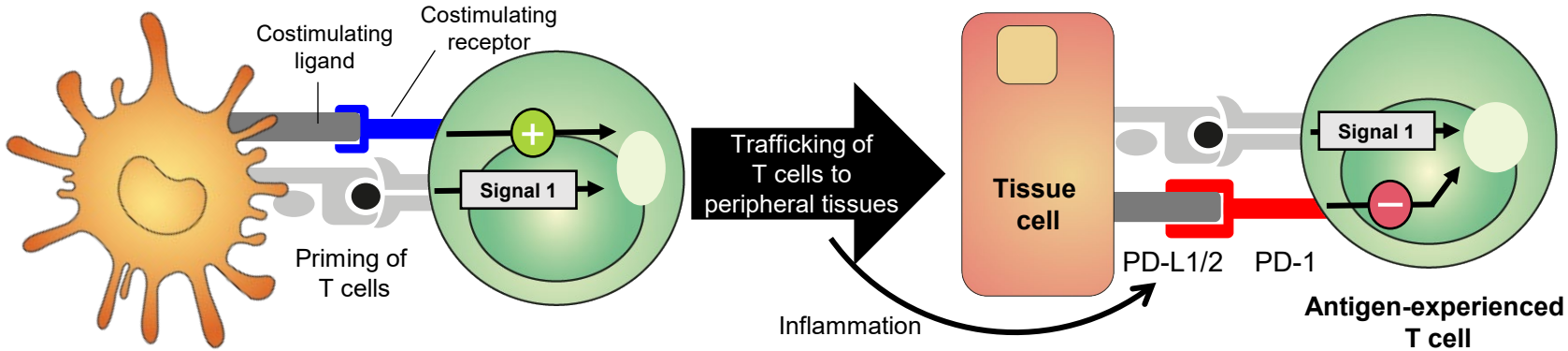
- Treatment with immune-checkpoint inhibitors currently involves the antibodies generated against CTLA-4, PD-1, or PD-L1[1]
- These checkpoint inhibitors are the targets of several therapies. Inhibitors of other immune checkpoints are also currently in development[2]

CTLA-4



CTLA-4 expression is induced in T cells upon initial response to the antigen

PD-1



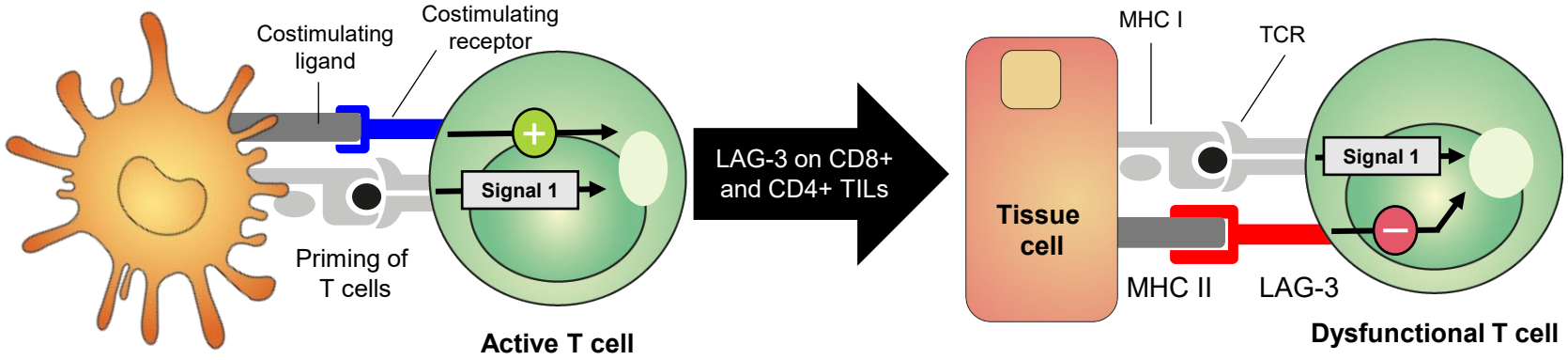
The PD-1 pathway regulates the inflammatory response by effector T cells

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DC, dendritic cell; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1/2, programmed cell death ligand 1/2; TCR, T-cell receptor.
1. Adapted from Pardoll. Nat Rev Cancer 2012;12;252–64; 2. Qin S, et al. *Mol Cancer* 2019;18:155.

Inhibitory checkpoints of immune regulation: potential targets for therapeutic intervention

- LAG-3 is a cell-surface molecule expressed on T cells and other immune cells that has diverse inhibitory biologic effects on the function of T cells[1,2]

LAG-3



Increased expression of LAG-3 on CD8+ and CD4+ TILs, especially in the context of PD-1 expression, inhibits effector T-cell function[1,3-5]

Interaction of LAG-3 with its ligands triggers inhibitory activity that reduces the function of effector T cells, leading to an impaired ability to fight tumor cells and an increased potential for tumor growth[1,5]

Ligands for LAG-3 are distinct from the ligands of other inhibitory immune checkpoints such as PD-1 or CTLA-4. Among its ligands, the most well established is MCH II; others are emerging, including FGL1[1,5–7]

APC, antigen-presenting cell; CTLA-4, cytotoxic T lymphocyte antigen 4; FGL1, fibrinogen-like protein 1; LAG-3, lymphocyte-activation gene 3; PD-1, programmed death-1; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

1. Long L, et al. Genes Cancer 2018;9:176-189; 2. Grosso JF, et al. J Clin Invest 2007;117:3383-3392; 3. Workman CJ, et al. J Immunol 2004;172:5450-5455; 4. Woo SR, et al. Cancer Res 2012;74:917-927; 5. Wang J, et al. Cell 2019;176:334-347.e12.; 6. Huang R-Y, et al. Oncoimmunology 2017;6:e1249561; 7. Maçon-lemaître L, Triebel F. Immunology 2005;115:170-178.

Checkpoint inhibitors 1: CTLA-4 inhibitors

Types of immunotherapy

CTLA-4 checkpoint inhibitors: the role of CTLA-4

CTLA-4 stops potentially autoreactive T cells during the first stage of naive T-cell activation and so can be considered the ‘frontrunner’ of the immune-checkpoint inhibitors[1]

What does CTLA-4 do?

- Inhibitory coreceptor expressed on activated T cells intended to prevent a physiological immune response (i.e. to an infection) getting out of control or continuing beyond the necessary time of response[1,2]
- It has a higher affinity than CD28 for ligands B7-1 (CD80) and B7-2 (CD86); however, unlike CD28, CTLA-4 binding to B7 ligands does not produce a stimulatory signal[1]
- Thus, CTLA-4 binding to B7 is a negative regulator of T-cell activation, preventing T-cell proliferation, survival, and differentiation[1]
- In the TME, CTLA-4 inhibits the proper immune response and promotes tumour cell survival[1,3]

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; TME, tumor microenvironment.

1. Buchbinder & Desai. Am J Clin Oncol 2016;39:98–106. 2. Parry et al. Mol Cell Biol 2005;25:9543–53. 3. Leach et al. Science 1996;271:1734–6.

Back to other mAbs

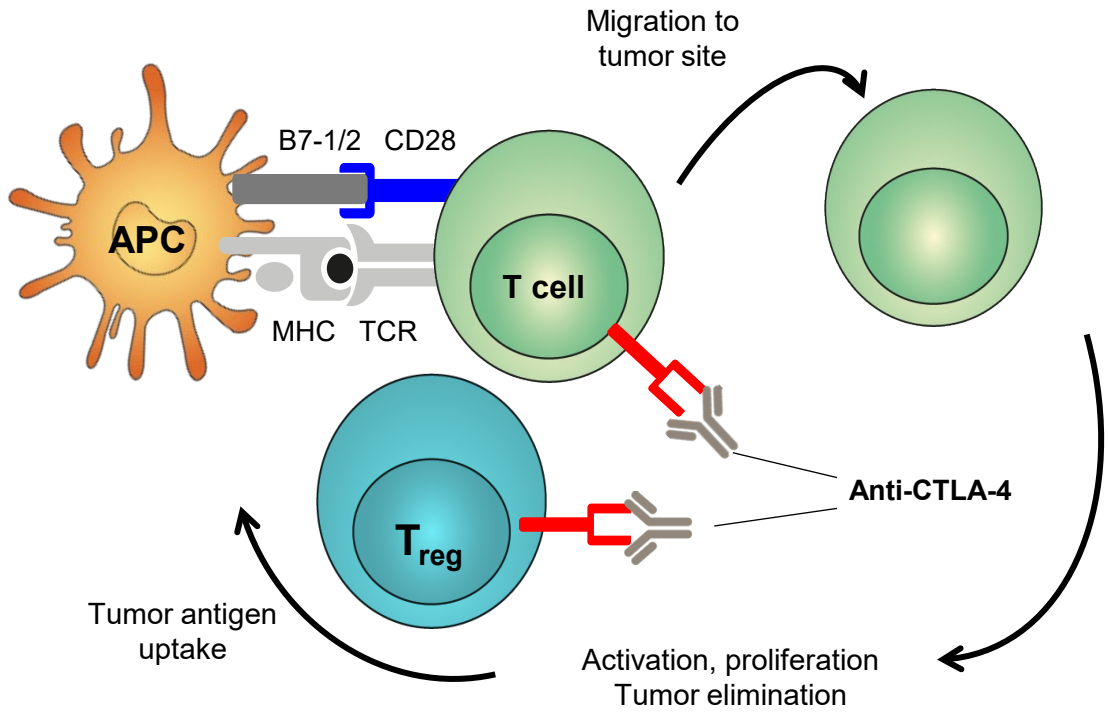
CTLA-4 checkpoint inhibitors: targeting CTLA-4

Targeting CTLA-4

- Preventing CTLA-4 from binding to its ligands can disrupt immune-checkpoint signaling, and this is the premise for immune-checkpoint inhibitors[1]
- CTLA-4 blockade can also reduce T_{reg} function, which may contribute to an antitumor immune response[1]
- Blockade of immune-checkpoint pathways can yield durable disease regression in a broad range of malignancies[2]

CTLA-4 inhibitors: mechanism of action[1]

- Inhibiting CTLA-4 allows more T-cell clones to activate and proliferate and reduces T_{reg}-mediated immunosuppression[1]
- Ipilimumab is a CTLA-4 immune-checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells that mobilize to mount a direct T-cell immune attack against tumor cells[3]



APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; MHC, major histocompatibility complex; TCR, T-cell receptor; T_{reg}, regulatory T cell.

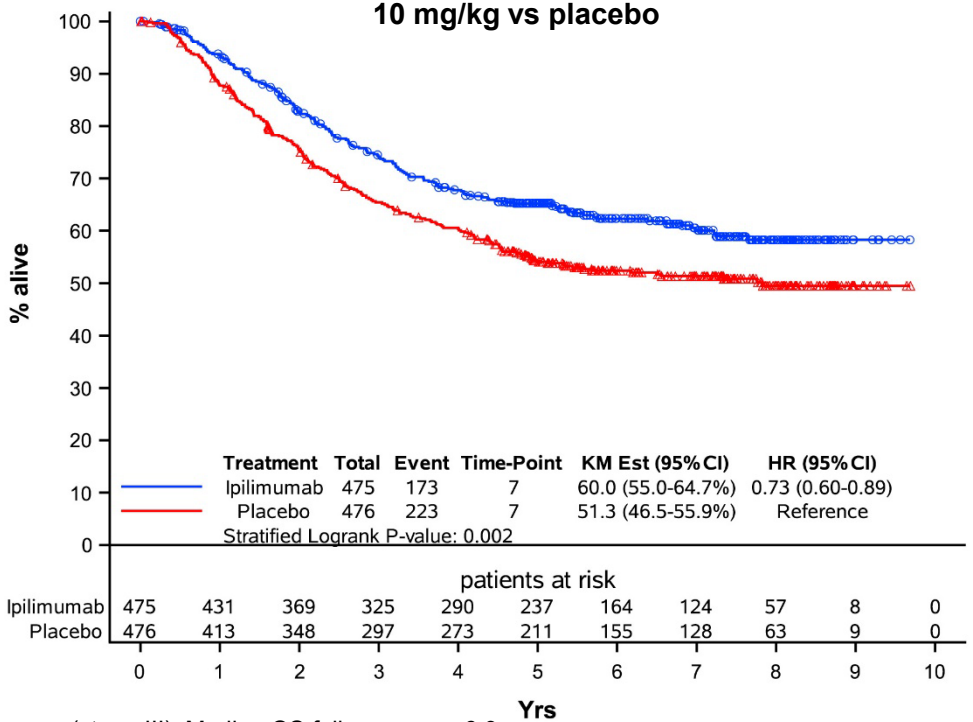
1. Buchbinder & Desai. Am J Clin Oncol 2016;39:98–106. 2. Callahan et al. Immunity 2016;44:1069–78. 3. Yervoy SmPC 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/yervoy-epar-product-information_en.pdf. Accessed October 2022.

CTLA-4 checkpoint inhibitors: clinical overview

- The CTLA-4 inhibitor ipilimumab improves OS in patients with advanced melanoma[1]

Significantly higher rates of RFS, OS, and distant metastasis–free survival[a] vs placebo[2]

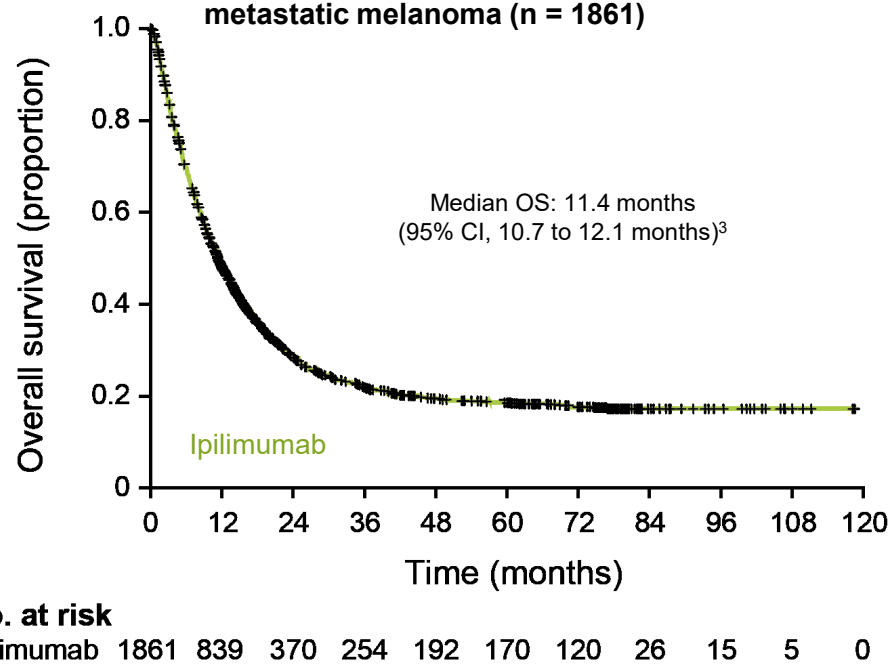
Kaplan–Meier estimate of OS in patients treated with ipilimumab 10 mg/kg vs placebo



[a]As adjuvant therapy (stage III). Median OS follow-up was 6.9 years.

Long-term survival for ipilimumab-treated patients with advanced melanoma[3]

Primary pooled analysis of OS data from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1861)



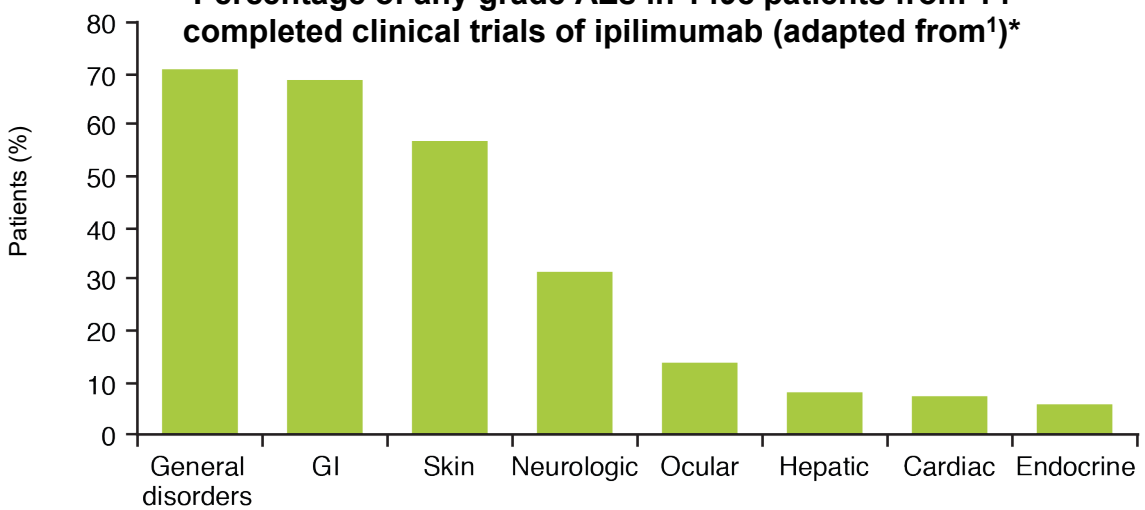
CI, confidence interval; OS, overall survival; RFS, recurrence-free survival.

1. Yervoy SmPC 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/yervoy-epar-product-information_en.pdf. Accessed October 2022. 2. Eggermont et al. Eur J Cancer 2019;119:1-10. 3. Schadendorf et al. J Clin Oncol 2015;33:1889–94.

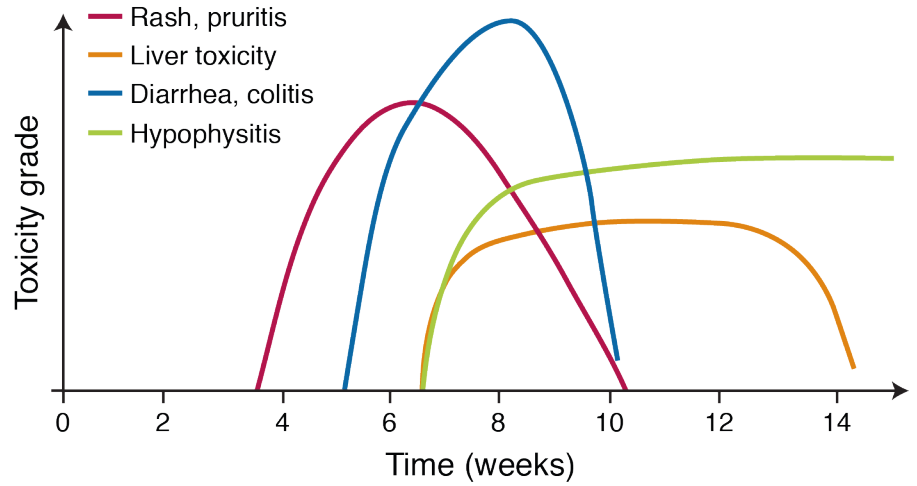
CTLA-4 checkpoint inhibitors: adverse events

- Owing to the immune-stimulatory action, CTLA-4 inhibitors, such as ipilimumab, are associated with a range of inflammatory- and immune-related AEs[1]
- These include dermatologic, gastrointestinal, endocrine, hepatic, immune system, infections, metabolic, musculoskeletal/connective tissue, nervous system, renal and respiratory toxicities[1,2]

Percentage of any-grade AEs in 1498 patients from 14 completed clinical trials of ipilimumab (adapted from[1])*



Timing of occurrence of irAEs following ipilimumab treatment[3]



Published guidance on the management of checkpoint-inhibitor toxicities is available[3–10]

*AEs were categorized by organ system. AEs were included regardless of causality.
Patients may have experienced more than one event.

AE, adverse event; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; GI, gastrointestinal; irAE, immune-related adverse event. 1. Camacho. Cancer Med 2015;4:661–72. 2. Almutairi A, et al. Front Oncol 2020;10:91. 3. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv42. 4. Puzanov et al. J Immunother Cancer 2017;5:95. 5. Davies & Duffield. Immunotargets Ther 2017:6:51–71. 6. Brahmer et al. J Clin Oncol 2018; 36:1714–68. 7. Aspeslagh et al. BMSO ImmunoManager. Available from https://www.bsmo.be/immunomanager/. Accessed October 2022. 8. NCCN Clinical Practice Guidelines. Management of Immunotherapy-Related Toxicities. Version 1.2022 — February 28, 2022. Accessed October 2022. To view the most recent and complete version of the guideline, go online to NCCN.org . 9. Castinetti F et al. French Endocrine Society Guidance on endocrine side effects of immunotherapy, Endocrine-Related Cancer (2019) 26, G1–G18. 10. Champiat S, et al. Ann Oncol 2016;27:559–74.

Checkpoint inhibitors 2: PD-1/PD-L1 inhibitors

Types of immunotherapy

PD-1/L1 checkpoint inhibitors: the role of PD-1 and PD-L1

PD-1 is a checkpoint protein on T cells. It normally acts as a type of “off switch” that helps keep the T cells from attacking other cells in the body. It does this when it attaches to PD-L1, a protein on some normal (and cancer) cells[1]

What do PD-1 and PD-L1 do?[2]

- PD-1 induces T-cell tolerance and inhibits the TCR signaling pathway through SHP-2
- When bound to its ligand (PD-L1 or PD-L2), PD-1 is able to suppress the function of T cells by recruiting SHP-2
- The key and instant outcome of stimulation via PD-1 is the inhibition of T-cell growth and cytokine secretion
- PD-1 serves an important role in tumor immune escape[3]

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1/2, programmed cell death ligand 1/2; SHP-2, Src homology-2 domain containing phosphatase; TCR, T-cell receptor.

1. American Cancer Society. Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html. Accessed October 2022. 2. Okazaki et al. Nat Immunol 2013;14:1212–8. 3. Rosenblatt & Avigan. Blood 2017;129:275–9.

PD-1/L1 checkpoint inhibitors: targeting PD-1 and PD-L1

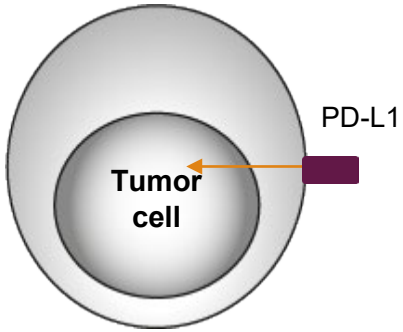
Targeting PD-1/PD-L1[1]

- In a pathologic setting, signaling via this pathway results in the emergence of an exhausted T-cell phenotype and the inability to mount protective immunologic responses
- In a malignant setting, upregulation of this pathway prevents the activation of tumor-reactive T cells, contributing to immune escape and growth of the tumor
- Therefore, blockade of this pathway is a viable therapeutic strategy

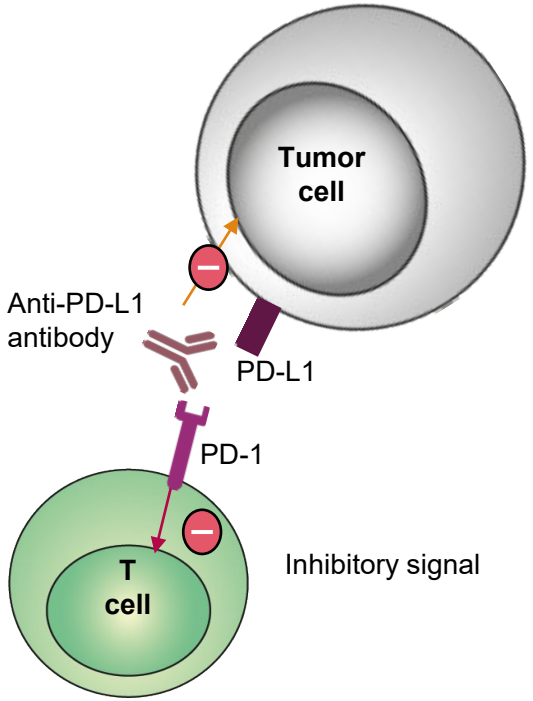
PD-1/L1 inhibitors: mechanism of action[2]

- Like anti-CTLA-4 antibodies, anti-PD-1 antibodies reverse the inhibitory signals sent to T cells to allow their metabolic reprogramming
- Thus, administration of anti-PD-1/PD-L1 antibodies results in activation of the immune system
- Only antibody isotypes activating FC receptors (on NK cells, and macrophages) can mediate ADCC

Reverse signaling via PD-L1 favors tumor growth and anti-apoptotic processes



Reinvigoration of T cells alter inhibition of the interaction of PD-1 with PD-L1



ADCC, antibody-dependent cell-mediated cytotoxicity; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1/2, programmed cell death ligand 1/2; SHP-2, Src homology-2 domain containing phosphatase; TCR, T-cell receptor.

1. Rosenblatt & Avigan. Blood 2017;129:275–9. 2. Granier et al. ESMO Open 2017;2:e000213.

Back to other mAbs

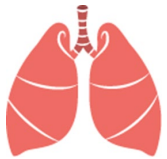
PD-1 and PD-L1 inhibitors

- PD-1 and PD-L1 inhibitors have been found to be efficacious in the treatment of several malignant diseases,[1–3] including advanced/refractory cancers[4]

Key

PD-1 inhibitor

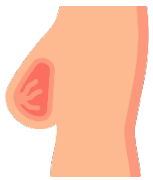
PD-L1 inhibitor



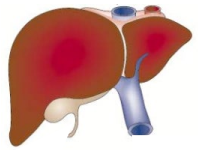
- Pembrolizumab
- Nivolumab
- Cemiplimab
- Atezolizumab
- Durvalumab

- Pembrolizumab
- Nivolumab

- Pembrolizumab
- Nivolumab
- Atezolizumab
- Avelumab



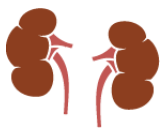
- Atezolizumab
- Pembrolizumab



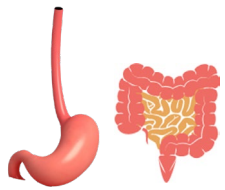
- Atezolizumab

- Pembrolizumab
- Nivolumab
- Avelumab
- Cemiplimab

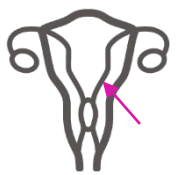
- Pembrolizumab
- Nivolumab



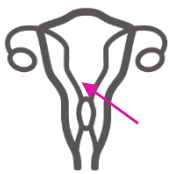
- Pembrolizumab
- Nivolumab
- Avelumab



- Pembrolizumab
- Nivolumab



- Pembrolizumab
- Dostarlimab



- Pembrolizumab

Licensed products for malignant indications only are shown. Non-malignant indications are not covered by this module

Images are not related to specific indications, but a broad category of disease types. PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

1. Shoushtari et al. Cancer 2016; 122:3354–62. 2. Jia et al. J Thorac Dis 2015;7:455–61. 3. Cancer Research Institute. Available at: https://www.cancerresearch.org/scientists/immuno-oncology-landscape/pd-1-pd-l1-landscape [Accessed October 2022]. 4. Zhang et al. Oncotarget. 2016;7:73068–79.

For full information of individual agents, always refer to the Summary of Product Characteristics

PD-1 inhibitors: clinical overview and selected key data (1)

Nivolumab: licensed indications[1]

Melanoma: monotherapy or in combination with ipilimumab; advanced (unresectable or metastatic)
Adjuvant melanoma: monotherapy; undergone complete resection
- Significant increase in RFS vs ipilimumab: HR 0.66, p < 0.0001; n = 906

NSCLC: monotherapy after prior chemotherapy; locally advanced or metastatic
- Increase in OS vs docetaxel (squamous; min follow-up 62.6 months): HR 0.62 (95% CI 0.48–0.79); n = 272
- Increase in OS vs docetaxel (non-squamous; min follow-up 62.7 months): HR 0.70 (95% CI 0.58–0.83); n = 582

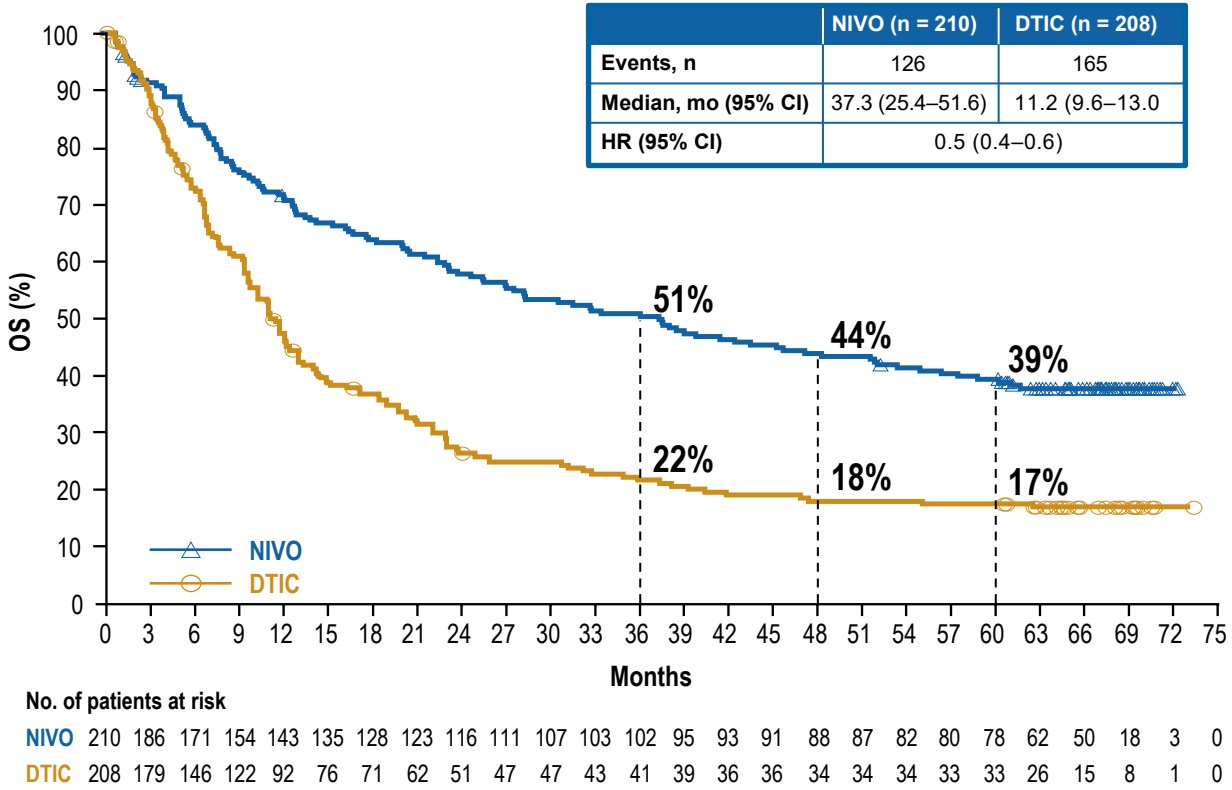
NSCLC: in combination with ipilimumab and 2 cycles of platinum-based chemotherapy first-line, tumors having no sensitizing EGFR mutation or ALK translocation.
MPM: in combination with ipilimumab; unresectable
RCC: monotherapy after prior chemotherapy, or first-line in combination with ipilimumab, or first-line in combination with cabozantinib; advanced
- Significant increase as monotherapy in OS vs everolimus: HR 0.73, p = 0.0018; n = 821
- Significant increase as combination in OS vs sunitinib: HR 0.63, p < 0.0001; n = 847

SCCHN: monotherapy after platinum-based therapy; recurrent or metastatic
- Significant increase in OS vs everolimus: HR 0.71, p = 0.0048; n = 361

cHL: monotherapy; relapsed or refractory
Urothelial carcinoma: monotherapy after failure of prior platinum-containing therapy; advanced unresectable or metastatic
Adjuvant urothelial carcinoma: monotherapy; MIUC with tumor PD-L1≥1%; high risk of recurrence
ESCC: monotherapy after prior fluoropyrimidine- and platinum-based combination chemotherapy, or in combination with ipilimumab first-line (with tumor PD-L1≥1%), or in combination with fluoropyrimidine- and platinum-based combination chemotherapy (with tumor PD-L1≥1%); unresectable advanced, recurrent or metastatic
Adjuvant EC or GEJC: monotherapy; residual pathologic disease following prior neoadjuvant chemoradiotherapy
Gastric, GEJ or esophageal adenocarcinoma: in combination with fluoropyrimidine- and platinum-based combination chemotherapy; HER2-negative advanced or metastatic; tumors express PD-L1 with a combined positive score (CPS) ≥ 5
dMMR/MSI-H CRC: in combination with ipilimumab after prior fluoropyrimidine-based combination chemotherapy

Survival outcomes in CheckMate 066 at 5 years[2a]

	NIVO (n = 210)	DTIC (n = 208)
Events, n	126	165
Median, mo (95% CI)	37.3 (25.4–51.6)	11.2 (9.6–13.0
HR (95% CI)	0.5 (0.4–0.6)	



No. of patients at risk

NIVO	210	186	171	154	143	135	128	123	116	111	107	103	102	95	93	91	88	87	82	80	78	62	50	18	3	0
DTIC	208	179	146	122	92	76	71	62	51	47	47	43	41	39	36	36	34	34	34	33	33	26	15	8	1	0

[a]minimum follow-up was 60 months from the last patient randomly assigned. With a median follow-up of 32.0 months for nivolumab and 10.9 months for dacarbazine (database lock April 9, 2019).

cHL, classical Hodgkin lymphoma; CRC, colorectal cancer; dMMR, mismatch repair deficient; DTIC, dacarbazine; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; GEJC, gastro-esophageal junction cancer; HR, hazard ratio; MIUC, muscle-invasive urothelial carcinoma; MPM, malignant pleural mesothelioma; MSI-H, microsatellite instability-high; NIVO, nivolumab; NSCLC, non-small-cell lung cancer; OS, overall survival; RCC, renal cell carcinoma; SCCHN, squamous cell cancer of the head and neck. 1. Opdivo SmPC 2022. Available fromhttps://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf [Accessed October 2022]. 2. Robert C, et al. J Clin Oncol 2020;38:3937–46.

For full information of individual agents, always refer to the Summary of Product Characteristics

PD-1 inhibitors: clinical overview and selected key data (2)

Pembrolizumab licensed indications[1]

Melanoma: monotherapy; advanced (unresectable or metastatic)
Adjuvant melanoma: monotherapy; undergone complete resection
- Higher RFS at 18 months vs placebo: 72% vs 54%

NSCLC:
Monotherapy; first-line metastatic and after prior chemotherapy
- First-line significant increase in OS vs chemotherapy: HR 0.63, p = 0.002; n = 305
- After prior chemotherapy significant increase for 2 mg/kg and 10 mg/kg vs chemotherapy (n = 1,033)
  - TPS ≥ 1% OS: HR 0.77, p = 0.00128 (n = 687); HR 0.61, p < 0.001 (n = 689), respectively
  - TPS ≥ 50% OS: HR 0.56, p < 0.001 (n = 291); HR 0.50, p < 0.001 (n = 303)

Combination; first-line metastatic
- Combination with pemetrexed and platinum chemotherapy significant increase in OS vs placebo with pemetrexed and platinum chemotherapy: HR 0.49, p < 0.00001 (n = 616)
- Combination with carboplatin and either paclitaxel or nab-paclitaxel significant increase in OS vs placebo with carboplatin and either paclitaxel or nab-paclitaxel: HR 0.64, P = 0.0008; n = 559

cHL: monotherapy; relapsed or refractory
- ORR = 69% (pembrolizumab 200 mg every 3 weeks (n = 210)

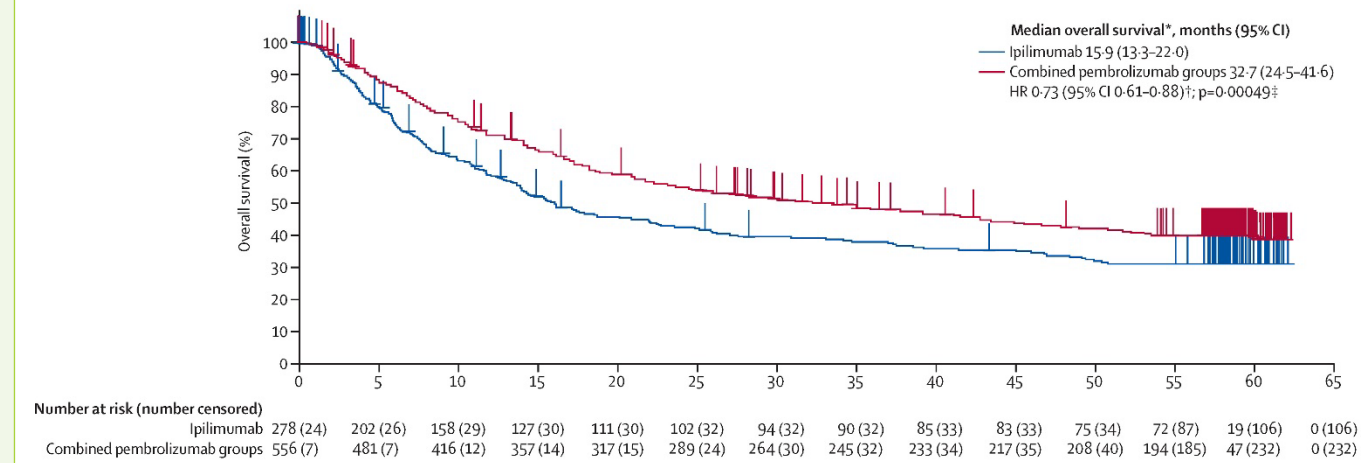
Urothelial carcinoma: monotherapy after prior chemotherapy and in patients who are not eligible for chemotherapy; locally advanced or metastatic
- After prior chemotherapy: significant increase in OS vs chemotherapy: HR 0.70, p < 0.001; n = 542
- Ineligible for chemotherapy: median OS (95% CI) 11.3 (9.7–13.1) months (n = 370)

HNSCC: monotherapy, or in combination with chemotherapy first-line; metastatic or unresectable. Monotherapy progressing on or after chemotherapy; recurrent or metastatic
- Significant increase in OS as monotherapy vs standard treatment: HR 0.74, p = 0.00133 (n = 512)
- Significant increase in OS as combination vs standard treatment: HR 0.65, p = 0.00002 (n = 477)
- Significant increase in OS as monotherapy after chemotherapy: HR 0.53, p = 0.001 (n = 129)

RCC: combination; first-line; advanced
- Significant increase in OS vs sunitinib: HR 0.53, p = 0.00005 (n = 861)

Adjuvant RCC: monotherapy; increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions
dMMR/MSI-H CRC: monotherapy, first-line (metastatic) or after previous fluoropyrimidine-based combination therapy (unresectable or metastatic)
dMMR/MSI-H non-CRC: monotherapy; following prior treatment with a platinum-containing therapy (advanced or recurrent) or following at least one prior therapy (unresectable or metastatic)
ESCC: combination; first-line; advanced unresectable or metastatic or HER-2 negative gastroesophageal junction adenocarcinoma, (PD-L1 CPS ≥ 10)
TNBC: combination as neoadjuvant followed by monotherapy as adjuvant (locally advanced, or early-stage), or combination (locally recurrent unresectable or metastatic)
EC: combination following prior treatment; advanced or recurrent
Cervical cancer: combination; persistent, recurrent, or metastatic

Overall survival in the total study population: post-hoc 5-year results[2]



cHL, classical Hodgkin lymphoma; CI, confidence interval; CRC, colorectal cancer; dMMR, mismatch repair deficient; EC, endometrial carcinoma; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

1. Keytruda SmPC 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf [accessed October 2022]. 2. Robert C, et al. Lancet Oncol 2019;20:1239-51.

PD-L1 inhibitors: clinical overview and selected key data

PD-L1 inhibitors: licensed indications

Avelumab[1]

- **Merkel cell carcinoma**: monotherapy; metastatic
- **Urothelial carcinoma**: monotherapy first-line; locally advanced. Monotherapy; metastatic & progression-free following platinum-based chemotherapy
- **RCC:** in combination with axitinib for the first-line treatment; advanced

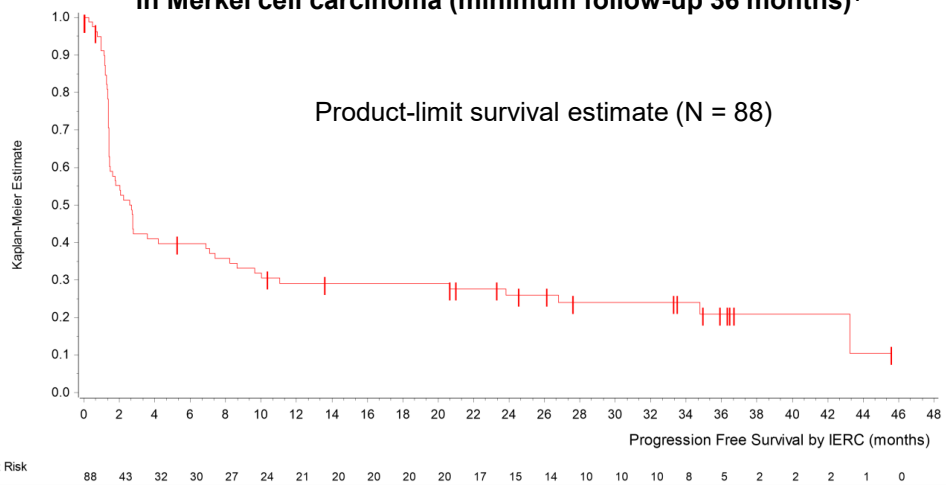
Atezolizumab[2]

- **Urothelial carcinoma**: monotherapy; locally advanced or metastatic; after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression ≥ 5%
- **Early-stage NSCLC:** monotherapy; adjuvant treatment following complete resection and platinum-based chemotherapy
- **NSCLC:** monotherapy; locally advanced or metastatic after prior chemotherapy. Monotherapy; first-line; in patients whose tumors have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells and do not have EGFR mutant or ALK-positive. Combination with bevacizumab, paclitaxel and carboplatin as first-line in metastatic non-squamous, and following failure of targeted therapies in patients with EGFR-mutant or ALK-positive. Combination with nab-paclitaxel and carboplatin; first-line; metastatic non-squamous patients who do not have EGFR mutant or ALK-positive
- **SCLC:** first-line in combination with carboplatin and etoposide; extensive stage
- **TNBC:** combination with nab-paclitaxel
- **HCC:** first-line in combination with bevacizumab; advanced or unresectable

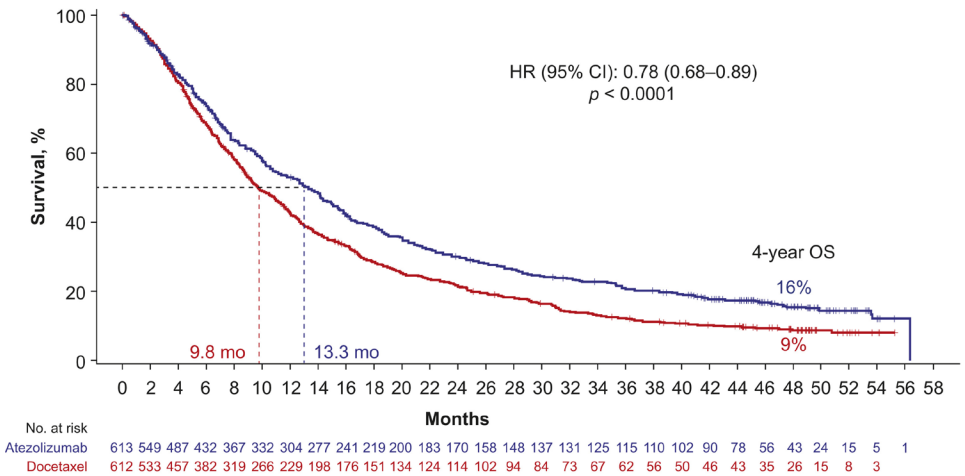
Durvalumab[3]

- **NSCLC:** monotherapy in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy; locally advanced, unresectable
- **ES-SCLC**: in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer

Kaplan-Meier estimates of PFS per RECIST v1.1, IERC for avelumab in Merkel cell carcinoma (minimum follow-up 36 months)[1]



4-year OS with atezolizumab vs docetaxel in NSCLC[4]



Data cutoff, January 9, 2019. Median follow-up: 47.7 months

CI, confidence interval; EMA, European Medicines Agency; HCC, hepatocellular carcinoma; IERC, Independent Endpoint Review Committee; MAA, Marketing Authorization Application; MCC, Merkel cell carcinoma; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

1. Bavencio SmPC 2022. 2. Tecentrc SmPC 2022. 3. Imfinzi SmPC 2022. All SmPCs available from: http://www.ema.europa.eu. 4. Mazieres J, et al. J Thorac Oncol 2021;16:140-50.

For full information of individual agents, always refer to the Summary of Product Characteristics

PD-1/PD-L1 checkpoint inhibitors: selected adverse events

- Owing to the immune-stimulatory action, PD-1/PD-L1 inhibitors are associated with a range of inflammatory- and immune-related AEs[1]
- These include dermatologic, gastrointestinal, endocrine, hepatic, immune system, infections, metabolic, musculoskeletal/connective tissue, nervous system, renal and respiratory toxicities[2–4]

Frequency of any-grade AEs reported with PD-1/PD-L1 inhibitors[5]

		PD-1 inhibitors (%)	PD-L1 inhibitors (%)
Dermatologic[4]	Rash and/or pruritus	~34	Not reported
Gastrointestinal[4]	Diarrhea, nausea or vomiting, colitis	Few data available	Few data available
Endocrine[4]	Hypophysitis	Very rare	Very rare
	Thyroid dysfunction	5–10	5–10
Hepatic[4]	Hepatitis	5–10 (single agent) Up to 30 (in combination with CTLA-4 blockade)	5–10 (single agent) Up to 30 (in combination with CTLA-4 blockade)
Other[4]	Fatigue	16–37	12–24
Pulmonary	Cough, dyspnea[4]	20–40	20–40
	Pneumonitis[5]	3.6	1.3
Other reported rare (≤ 1%) toxicities include neurologic, cardiac, hematologic, ocular, and renal toxicities[3]			

Published guidance on the management of checkpoint-inhibitor toxicities is available[5–12]

AE, adverse event; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

1. Pillai et al. Cancer 2018;271–7. 2. Gelao et al. Toxins 2014;6:914–33. 3. Villadolid Amin A. Transl Lung Cancer Res 2015;4:560–75. 4. Almutairi A, et al. Front Oncol 2020;10:91. 5.Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–42. 6. Khunger et al. Chest 2017;152:271–81. 7. Puzanov et al. J Immunother Cancer 2017;5:95. 8. Davies & Duffield. Immunotargets Ther 2017;6:51–71. 9. Brahmer et al. J Clin Oncol 2018;JCO2017776385 (Epub ahead of print). 10. Aspeslagh et al. BMSO ImmunoManager. Available from: https://www.bsmo.be/immunomanager/. Accessed October 2022. 11. NCCN Clinical Practice Guidelines. Management of Immunotherapy-Related Toxicities. Version 1.2022 — February 28, 2022. Accessed Aug 2022. 12. Castinetti F et al. French Endocrine Society Guidance on endocrine side effects of immunotherapy, Endocrine-Related Cancer (2019) 26, G1–G18

Checkpoint inhibitors 2: LAG-3 inhibitors

Types of immunotherapy

LAG-3 checkpoint inhibitors: the role of LAG-3

LAG-3 is a cell-surface molecule expressed on T cells and other immune cells. It regulates an inhibitory immune checkpoint pathway that limits the activity of T cells[1,2]

What does LAG-3 do?

- Increased expression of LAG-3 on CD8+ and CD4+ TILs, especially in the context of PD-1 expression, inhibits effector T-cell function[1,3–5]
- LAG-3 activity results in reduced T-cell activation and proliferation, and attenuates proinflammatory cytokine responses, such as IFN-γ, IL-2, and TNF-α[1,6,7]
- Activation of the LAG-3 pathway, which occurs when LAG-3 interacts with its ligands, triggers inhibitory activity that reduces the function of effector T cells, leading to an impaired ability to attack tumor cells and an increased potential for tumor growth[1,5]

LAG-3, lymphocyte-activation gene 3; TILs, tumor–infiltrating lymphocytes.

1. Long L, et al. Genes Cancer 2018;9:176–89; 2. Grosso JF, et al. J Clin Invest 2007;117:3383–92; 3. Workman CJ, et al. J Immunol 2004;172:5450-55; 4. Woo SR, et al. Cancer Res 2012;72:917-27; 5. Andrews LP, et al. Sci Immunol 2020;5:eabc2728; 6. Huang RY, et al. Oncoimmunology 2017;6:e1249561; 7. Maçon-Lemaître L, Triebel F. Immunology 2005;115:170–8

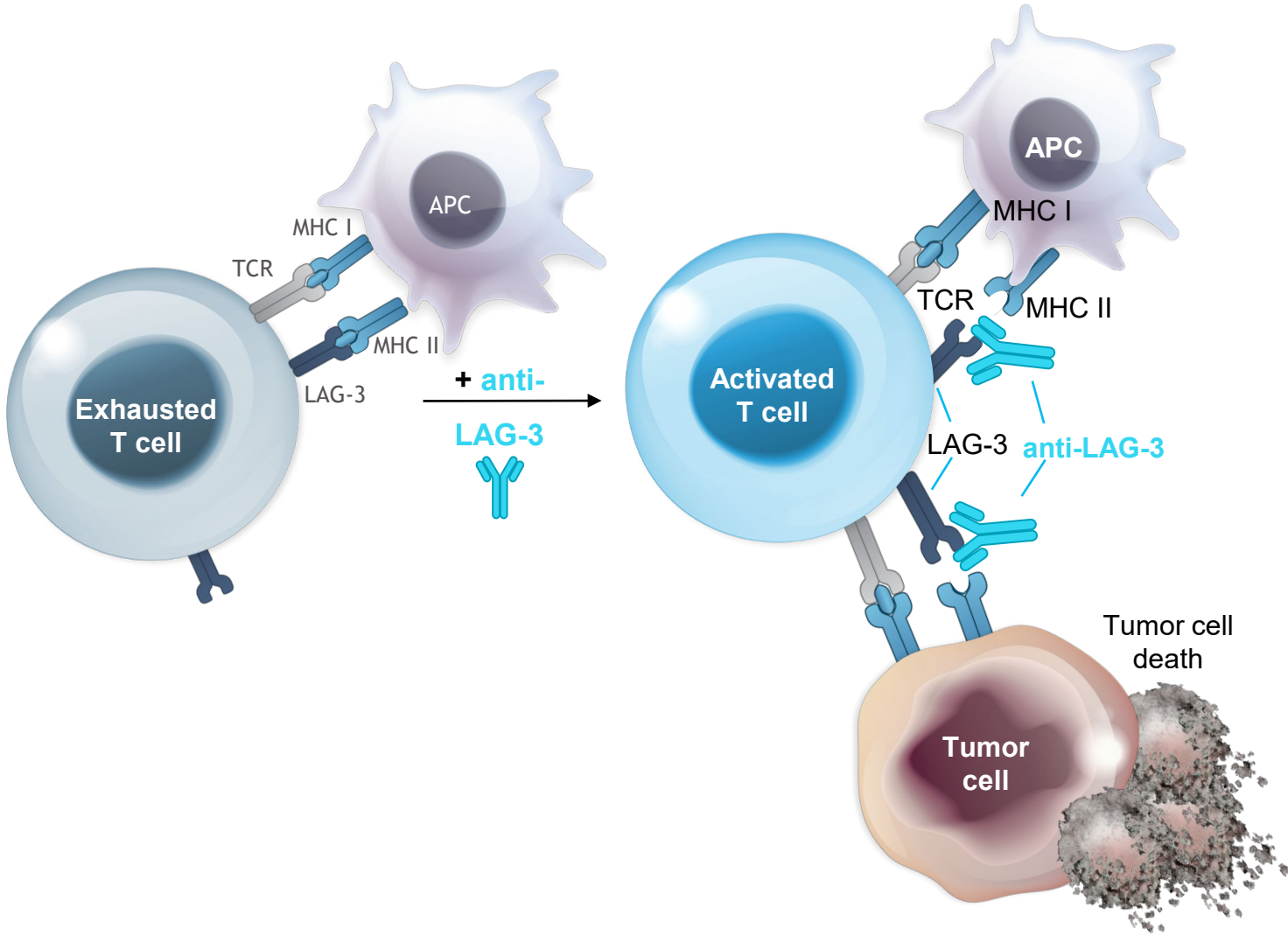
LAG-3 checkpoint inhibitors: targeting LAG-3

Targeting LAG-3[1–4]

- The interaction of LAG-3 with its ligands triggers inhibitory activity. Ligands for LAG-3 are distinct from the ligands of other inhibitory immune checkpoints such as PD-1 or CTLA-4. Among its ligands, the most well-established is MHC II; others are emerging, including FGL1

LAG-3 inhibitors: mechanism of action[1,5–9]

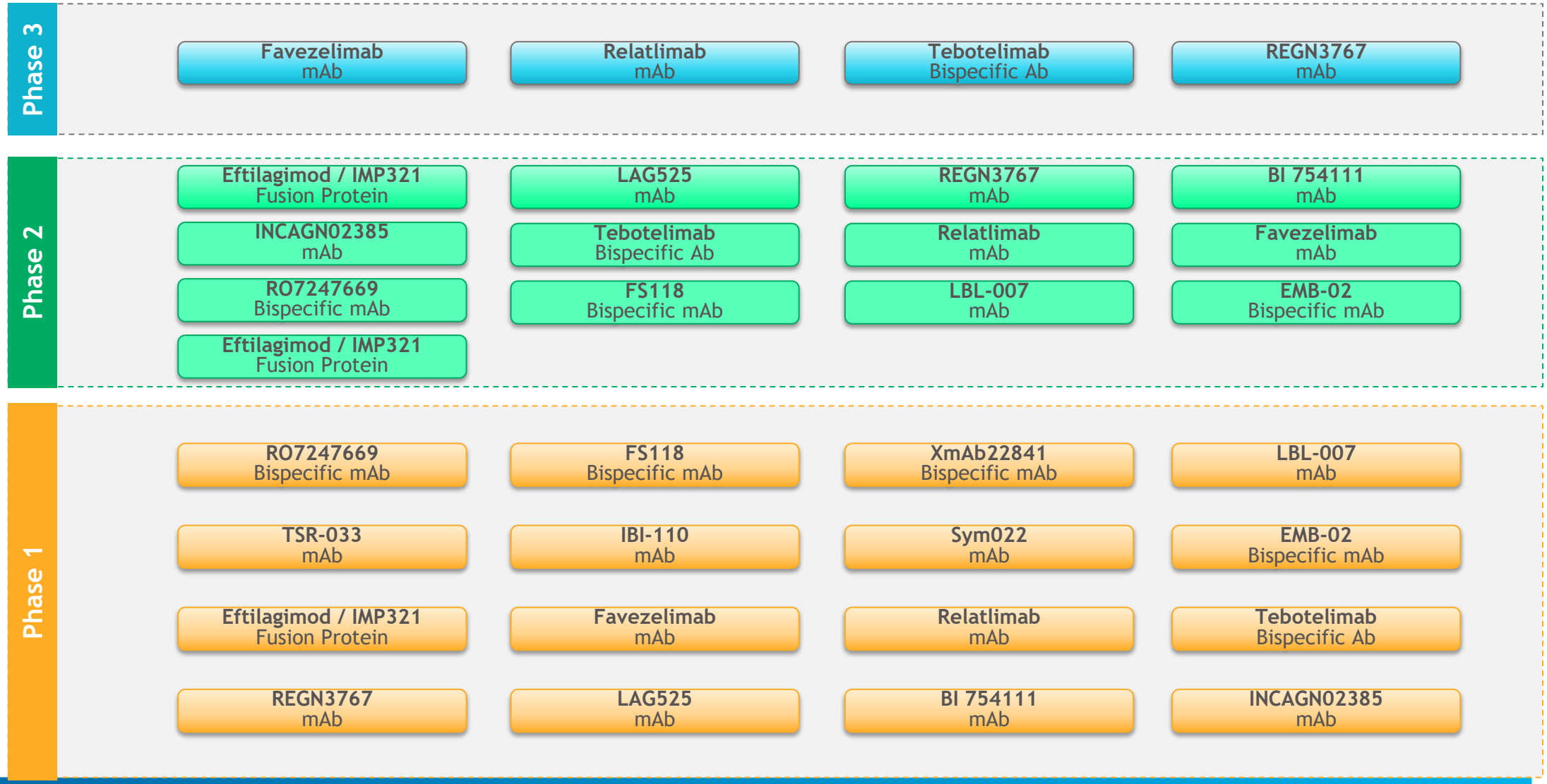
- LAG-3–blocking antibodies binds to LAG-3 on T cells, restoring effector function of exhausted T cells, and enhancing the immune response against cancer



FGL1, fibrinogen-like protein 1;

1. Long L, et al. Genes Cancer 2018;9:176–89; 2. Huang RY, et al. Oncoimmunology 2017;6:e1249561; 3. Wang J, et al. Cell 2019;176:334-47.e12; 4. Maçon-Lemaître L, Triebel F. Immunology 2005;115:170–8; 5. Ruffo E, et al. Semin Immunol 2019;42:101305; 6. Grosso JF, et al. J Clin Invest 2007;117:3383-92; 7. He Y, et al. Cancer Sci 2016;107:1193-7; 8. Nguyen LT, Ohashi PS. Nat Rev Immunol 2014;15:45-56; 9. Anderson AC, et al. Immunity 2016;44:989-1004

LAG-3 inhibitors: overview of agents in Phase I–III trials



ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home. Accessed Aug 2022.

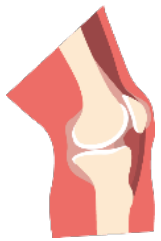
For full information of individual agents, always refer to the Summary of Product Characteristics

TNF-blocking agents

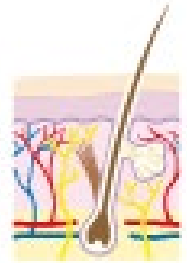
Types of immunotherapy

An overview of TNF-blocking agents

- The dysregulation of **cytokines**, such as TNFα, has been found to play a vital role in the pathogenesis of immune-mediated inflammatory diseases
- TNF-blocking agents are approved for the treatment of many non-malignant, inflammatory diseases, notably in **rheumatology**, **dermatology**, and **gastroenterology**, among others (not covered in this module)



- Infliximab
- Etanercept
- Adalimumab
- Certolizumab
- Golimumab



- Infliximab
- Etanercept
- Adalimumab

- Infliximab
- Adalimumab
- Certolizumab
- Golimumab

Images are not related to specific indications, but a broad category of disease types.
TNF, tumor necrosis factor.
1. Armuzzi et al. Int J Immunopathol Pharmacol 2014;27(1 Suppl.):11–32; 2. Zhang H, et al. Genes Dis 2020;8:38–47.
For full information of individual agents, always refer to the Summary of Product Characteristics

TNF-blocking agents and their mechanisms of action

- TNF-blocking agents can either be **whole antibodies** (such as infliximab, adalimumab, and golimumab) or pegylated **Fab fragments (**certolizumab)[1]
- TNFα has a key role in the pathogenesis of inflammatory diseases such as **rheumatoid arthritis** and **inflammatory bowel disease**[2]
- The **binding and neutralizing of sTNFα** is the key, common mechanism of action of TNF-blocking agents;[2] however, their **mechanisms of action may vary,** despite them occasionally having the same targets[2]

Etanercept[3]
Binds sTNF α, preventing its interaction with the receptor

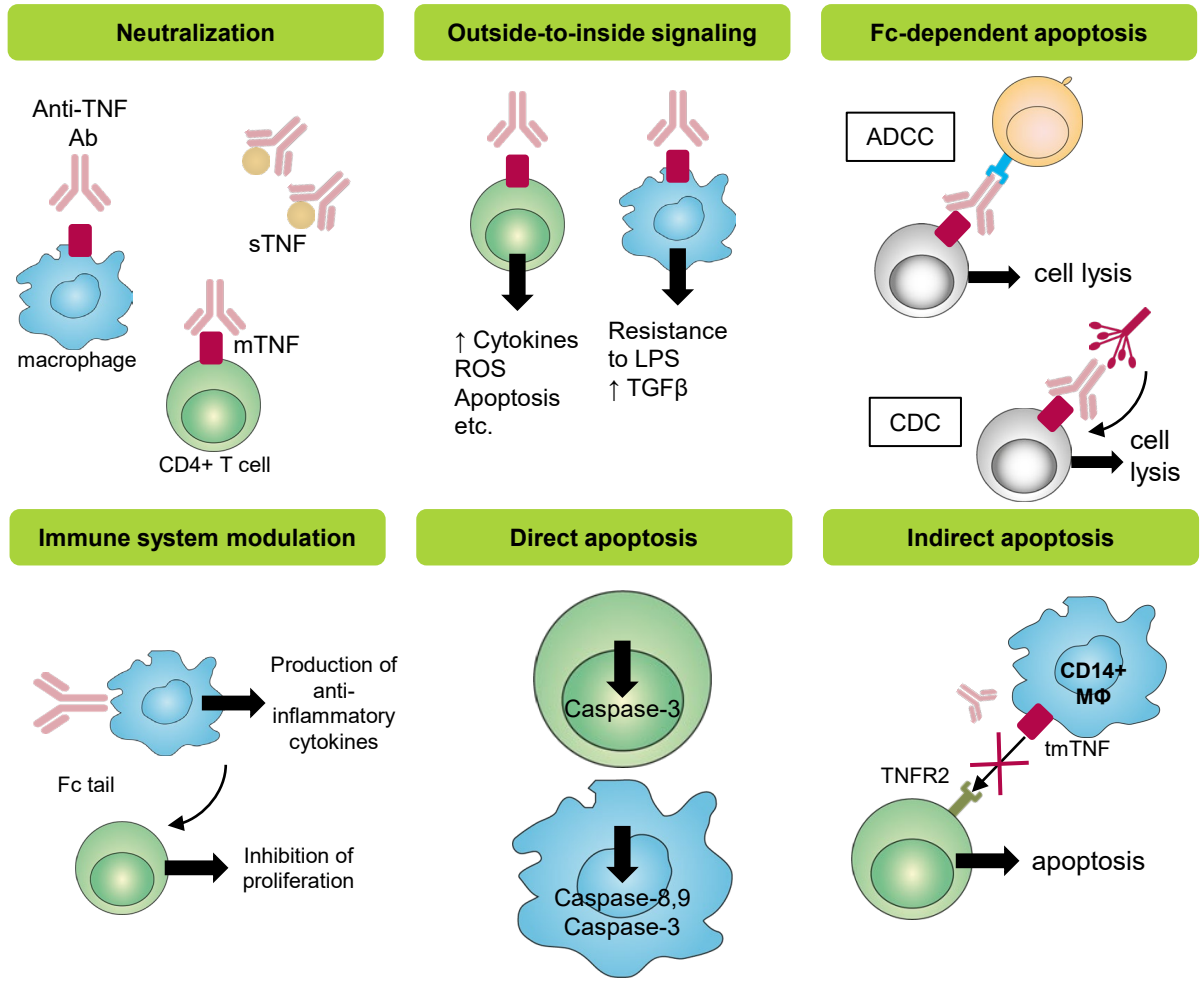
Infliximab[3]
Binds and neutralizes both sTNFα and tmTNF and can fix complement and cause cell apoptosis

Golimumab[4]
Binds sTNFα and tmTNF; neutralizes TNFα-induced E-selectin expression by endothelial cells

Certolizumab[3,5]
is unique in that it does not have the Fc portion of the antibody and has a pegylated Fab fragment. It binds and neutralizes sTNF and tmTNF

Adalimumab[3]
Binds to sTNFα and prevents its interaction with TNFR1 and TNFR2 receptors.

Mechanisms of action of anti-TNF antibodies[6]



Ab, antibody; ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; LPS, lipopolysaccharide; MΦ, macrophage; ROS, reactive oxygen species; sTNF, soluble tumor necrosis factor; TGFβ, transforming growth factor beta; tmTNF, transmembrane tumor necrosis factor; TNFR1/2, tumor necrosis factor receptor 1/2.

1. Armuzzi et al. Int J Immunopathol Pharmacol 2014;27(1 Suppl.):11–32. 2. Mitoma et al. Cytokine 2018;101:56–63. 4.3. Sehgal et al. Indian J Dermatol 2014;59:425–41. 4. Shealy et al. MAbs 2010;2:428–9. 4. Goel & Stephens. MAbs 2010;2:137–47. 6. Billmeier et al. World J Gastroenterol 2016;22:9300–13.

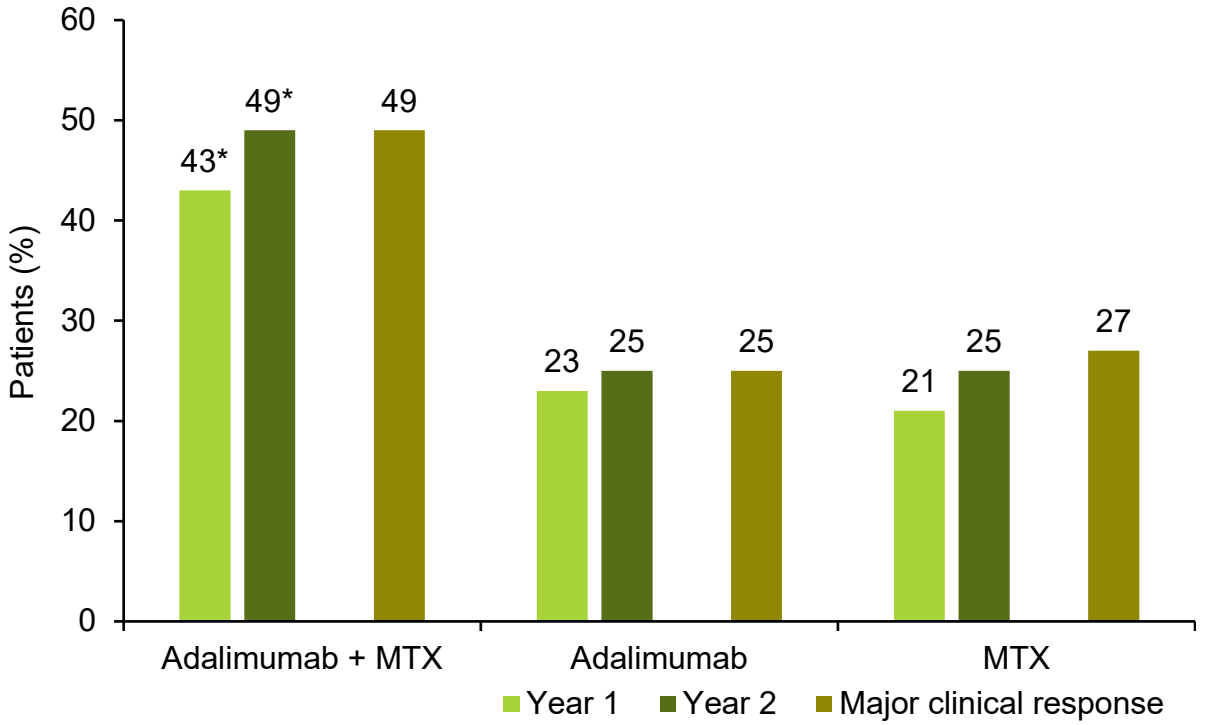
For full information of individual agents, always refer to the Summary of Product Characteristics

TNF-blocking agents: clinical overview and selected key data

- In many patients with rheumatic diseases (e.g. rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis) who are resistant to first-line therapies, TNF-blocking agents are used in combination with MTX, in view of the synergy between both categories of drugs

TNF-blocking agents: licensed indications	
Infliximab[1]	Rheumatoid arthritis, Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, psoriasis
Adalimumab[2]	Rheumatoid arthritis, psoriasis, hidradenitis suppurativa, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, pediatric plaque psoriasis, pediatric Crohn's disease, ulcerative colitis, uveitis, pediatric uveitis
Golimumab[3]	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
Certolizumab[4]	Rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, plaque psoriasis
Etanercept[5]	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, plaque psoriasis, pediatric plaque psoriasis

Clinical remission at Years 1 and 2 and major clinical response at Year 2 in adalimumab ± MTX in patients with early, aggressive rheumatoid arthritis[6]



*p < 0.001 versus adalimumab alone and versus MTX alone.

MTX, methotrexate; TNF, tumor necrosis factor.

1. Remicade SmPC 2022. 2. Humira SmPC 2022. 3. Simponi SmPC 2022 4. Cimzia SmPC 2022. 5. Enbrel SmPC 2022. All SmPCs available from: http://www.ema.europa.eu and accessed October 2022. 6. Breedveld et al. Arthritis Rheum 2006;54:26–37.

For full information of individual agents, always refer to the Summary of Product Characteristics

TNF-blocking agents: selected adverse events

AEs associated with TNF-blocking agents[1,2]

	Example
Infections	Tuberculosis, serious infections
Infusion reactions	Anaphylaxis, delayed-type hypersensitivity
Autoimmunity	Antinuclear antibodies, systemic lupus erythematosus
Malignancies	Non-melanoma skin cancer
Demyelinating disorders	Guillain-Barré syndrome, multiple sclerosis
Abnormal liver function tests	Hepatitis, cholestatic disease
Cardiac abnormalities	Heart failure
Skin eruptions	'Paradoxical' psoriasis

- **Neutralizing antibody formation**
  - Commonly reported with infliximab and adalimumab[1]
- **Tuberculosis**
  - Risk is lower with etanercept vs infliximab and adalimumab[3]
- **Life vaccines**
  - Administration of life vaccines is presently contraindicated in patients receiving TNF-blocking agents
- **Surgical site infections**
  - Increased risk in patients with RA who use or have recently used anti-TNFs at the time of orthopedic surgery[4]
- **Heart failure**
  - Administration of TNF-blocking agents is contraindicated in patients with impaired cardiac function
- **Non-melanoma skin cancer**
  - TNF-blocking agents are presently contraindicated in patients with past history of cancer

This list is not exhaustive. Specific adverse events depend on the target of individual agent used.

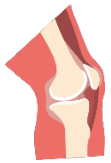
AE, adverse event; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

1. Hoentjen & van Bodegraven. World J Gastroenterol 2009;15:2067–73. 2. Connor. Rheumatol Int 2011;31:327–37. 3. Dixon et al. Ann Rheum Dis 2010;69:522. 4. Goodman et al. Rheumatology (Oxford) 2016;55:573–82. 5. Mercer et al. Ann Rheum Dis 2012;71:869–74.

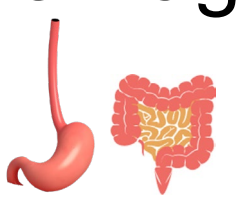
Other monoclonal antibodies

Types of immunotherapy

Monoclonal antibodies have become one of the largest classes of new agents approved in the past decade



Non-malignant diseases
- Eculizumab
- Infliximab
- Golimumab
- Certolizumab pegol
- Tocilizumab
- Etanercept
- Adalimumab
- Secukinumab



Malignancies
- Ramucirumab
- Golimumab
- Panitumumab
- Cetuximab
- Trastuzumab
- Pembrolizumab
- Nivolumab
- Bevacizumab

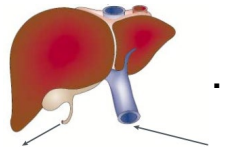
Non-malignant diseases
- Infliximab
- Ustekinumab
- Adalimumab

Malignancies
- Daratumumab
- Elotuzumab
- Obinutuzumab
- Rituximab
- Ibritumomab tiuxetan
- Pembrolizumab
- Nivolumab

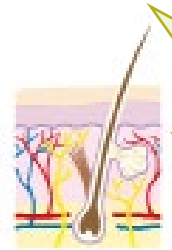
Non-malignant diseases
- Mepolizumab

Malignancies
- Bevacizumab
- Pembrolizumab
- Ramucirumab
- Nivolumab
- Cemiplimab
- Atezolizumab
- Durvalumab

Non-malignant diseases
- Reslizumab
- Mepolizumab
- Omalizumab



Malignancies
- Ramucirumab

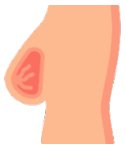


Learn more about anti-CTLA-4 Mabs

Learn more about anti-PD-1/L1 Mabs

Malignancies
- Bevacizumab
- Belimumab
- Pembrolizumab
- Nivolumab
- Avelumab
- Cemiplimab

Non-malignant diseases
- Secukinumab
- Infliximab
- Ustekinumab
- Etanercept
- Adalimumab
- Golimumab
- Certolizumab



Malignancies
- Trastuzumab
- Bevacizumab
- Trastuzumab emtansine
- Pertuzumab
- Atezolizumab

Malignancies
- Bevacizumab
- Pembrolizumab
- Nivolumab
- Avelumab

Non-malignant diseases
- Basiliximab

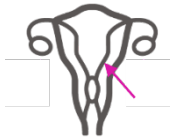
Malignancies
- Natalizumab
- Alemtuzumab

Non-malignant diseases
- Ofatumumab

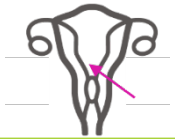
Malignancies
- Cetuximab
- Pembrolizumab
- Nivolumab

Non-malignant diseases
- Mepolizumab
- Omalizumab

Malignancies
- Pembrolizumab
- Nivolumab
- Atezolizumab
- Avelumab



Malignancies
- Pembrolizumab
- Dostarlimab
- Bevacizumab



Malignancies
- Pembrolizumab
- Bevacizumab

This list is not exhaustive. Images are not related to specific indications, but a broad category of disease types.

1. Falzone L, et al. Front Pharmacol 2018 ;9:1300. 2. Remicade SmPC 2022. 3. Humira SmPC 2022. 4. Simponi SmPC 2022. 5. Cimzia SmPC 2022. 6. Enbrel SmPC 2022.
All SmPCs available from: http://www.ema.europa.eu [accessed October 2022].

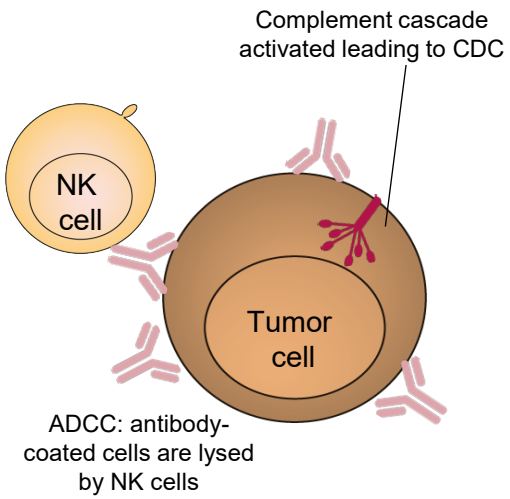
For full information of individual agents, always refer to the Summary of Product Characteristics

www.immunoscienceacademy.be

Monoclonal antibodies and their mechanism of action

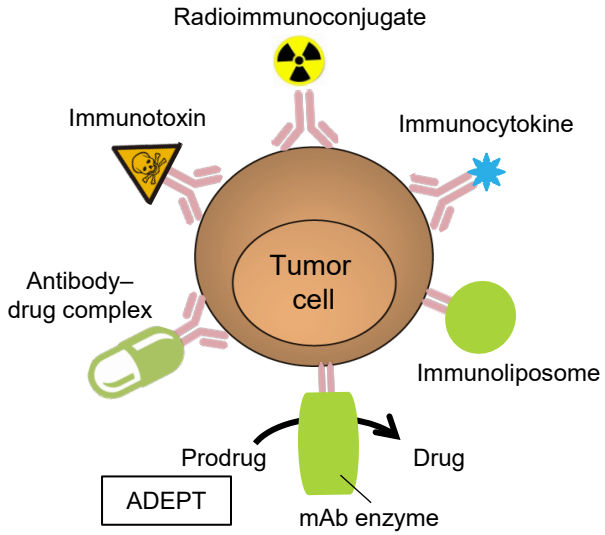
- The most commonly used class of therapeutic antibody is IgG, which is divided into subclasses based on unique properties such as ADCC and CDC[1]
- Monoclonal antibodies are used in a range of therapeutic areas and are particularly known for their multifactorial antitumor mechanisms.[1,2] Effector mechanisms of therapeutic monoclonal antibodies include:

Native IgG mechanisms[3]



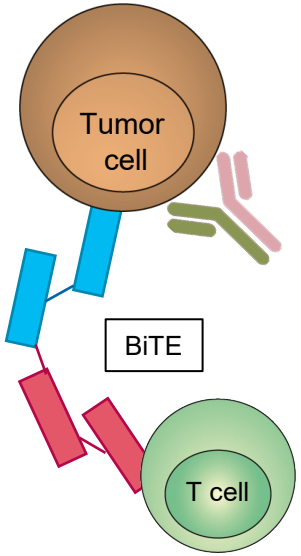
Fc region of mAb promotes cell death via ADCC and CDC[2]

Immunoconjugates[3]



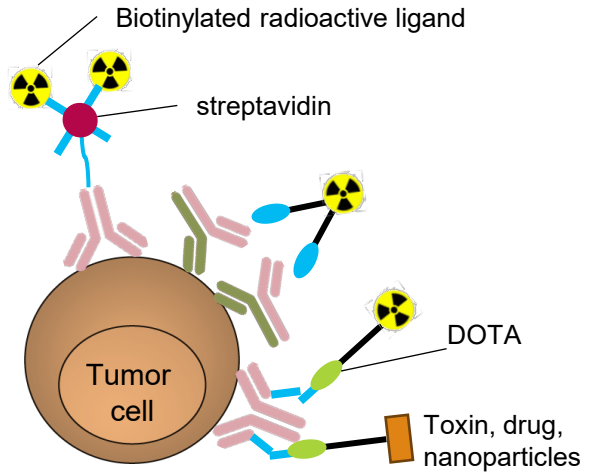
Target cell killing can be enhanced by using immunoconjugates[2]

Bispecific mAb[3]



A BiTE specifically binds two targets[1] and can enhance the antitumor effect of antibodies[2]

Multistep targeting[3]



A multistep targeted approach enhances antibody access to solid tumors to improved therapy delivery[4]

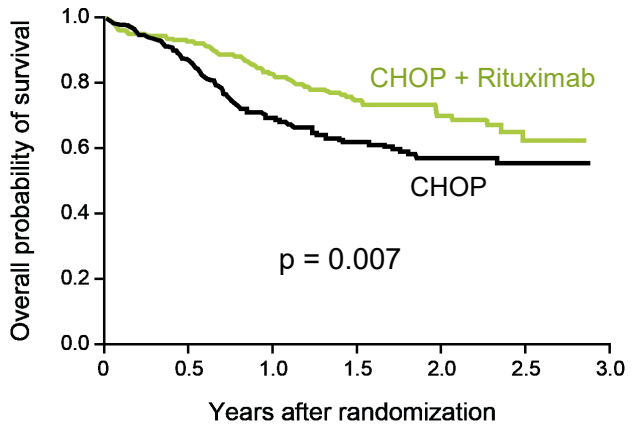
ADCC, antibody-dependent cellular cytotoxicity; ADEPT, antibody-directed enzyme prodrug therapy; BiTE, bispecific T-cell-engaging mAb; CDC, complement-dependent cytotoxicity; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; mAb, monoclonal antibody; NK, natural killer. 1. Redman et al. Mol Immunol 2015;67:28–45. 2. Cheung. Available from: https://clinicalgate.com/therapeutic-antibodies-and-immunologic-conjugates-2/ [Accessed Aug 2022]. Images adapted from 3. Carter. Nat Rev Cancer 2001;1:118–29. 4. Nguyen et al. Cancer Biol Ther 2010;10:775–9.

Monoclonal antibodies: clinical overview and selected key data

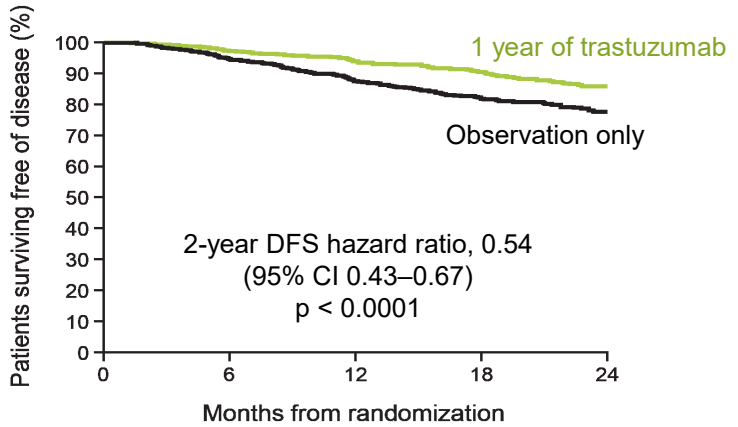
- A large number of monoclonal antibodies have been licensed or are in clinical trials, the majority of which are approved or intended for oncology indications[1]
- Two key approved monoclonal antibodies approved to treat malignancies are rituximab and trastuzumab

Selected monoclonal antibodies: licensed indications	
Rituximab[2]	• **Non-Hodgkin's lymphoma:** FL (first-line advanced; maintenance; relapsed/refractory) and DLBCL (with CHOP) • **Chronic lymphocytic leukemia:** with chemotherapy for previously untreated and relapsed/refractory • **Rheumatoid arthritis:** with MTX • **Granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis:** with glucocorticoids for induction of remission • **Pemphigus vulgaris**
Trastuzumab[3]	• **Breast cancer**: HER2+ metastatic and HER2+ early breast cancer • **Gastric cancer:** adenocarcinoma of the stomach or gastroesophageal junction in combination with chemotherapy for HER2+ metastatic disease

Significant increase in OS with rituximab + CHOP vs CHOP alone in DLBCL (n = 399)[4]



Significant increase in DFS with trastuzumab in metastatic HER2+ breast cancer (n = 1694)[5]



CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HER, human epidermal growth factor receptor; MTX, methotrexate; OS, overall survival. 1. Redman et al. Mol Immunol 2015;67:28–45. 2. MabThera SmPC 2022. Available from: http://www.ema.europa.eu [Accessed October 2022]. 3. Herceptin SmPC 2021. Available from: http://www.ema.europa.eu [Accessed October 2022]. 4. Coiffier et al. N Engl J Med 2002;346:235–42. 5. Piccart et al. N Engl J Med 2005;353:1659–67.

For full information of individual agents, always refer to the Summary of Product Characteristics

Safety profiles of monoclonal antibodies

- Monoclonal antibodies have a wide range of indications, and their typically low mass and high specificity enable their precise action as a therapy[1]
- However, their use carries some risk of immune reactions

Infusion reactions[2,3]

Usually occur within ≤ 2 h

Affect any organ system

Range from injection-site reactions to potentially life-threatening anaphylaxis

Undesired effects related to the target antigen[2,3]

AEs may be directly related to the biology of the target antigen,

e.g. risk of cardiotoxicity with trastuzumab

Other irAEs[2,3]

Dermatologic, gastrointestinal, endocrine, and other inflammatory reactions

Infections and autoimmunity

Cytokine-release syndrome

AE, adverse event; irAE, immune-related adverse event.

1. Hansel et al. Nat Rev Drug Discov 2010;9:325–82. 2.Demlova et al. Physiol Res 2016;65:S455–62. 3. Perez & Rodeheffer. J Clin Oncol 2004;22:322–9.

Monoclonal antibodies: selected adverse events

- mAbs are established therapies for many conditions, including a range of different cancers[1,2]
- mAbs may be associated with a variety of AEs depending on their type (murine, chimeric, humanized or human, target and conjugate)[1]
- Hypersensitivity reactions (including infusion-related reactions) are the most common and among the most serious AEs associated with mAbs[1,2]
- Different mAbs have different toxicity profiles; associated AEs vary widely and can range from, for example, headache, mild gastrointestinal symptoms, transient rash and itching, to severe cytopenias, cardiac toxicity and anaphylaxis[1]
- For management recommendations see[2]

Selected AEs associated with mAbs[1]

Type of AE	Selected examples
Hematologic and vascular disorders	Thrombocytopenia, neutropenia, anemia, hemolytic anemia, vasculitis, hypertension
Infusion reactions	Anaphylaxis, delayed-type hypersensitivity
Pulmonary AEs	ARDS, bronchospasm, diffuse alveolar hemorrhage, hypersensitivity pneumonitis, interstitial pneumonitis
Neurologic toxicities	Peripheral neuropathies, encephalomyelitis
Hepatic toxicities	Hepatomegaly
Cardiac abnormalities	Cardiopulmonary arrest, arrhythmias, cardiomyopathy, LVD, pericarditis
Dermatologic events	Pruritus, eczema, rash, urticaria, morbilliform eruptions, erythema, petechiae, alopecia
Others	Serum sickness-like reaction, diarrhea, fatigue, infections

This list is not exhaustive. Specific adverse events depend on the target of individual mAb used.

AE, adverse event; ARDS, acute respiratory distress syndrome; ATE, arterial thromboembolic event; CD20/30, cluster of differentiation 20/30; EGFR, epidermal growth factor receptor; LVD, left ventricular dysfunction; mAb, monoclonal antibody; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VTE, venous thromboembolic event.

1. Baldo. Oncoimmunology 2013;2:e26333. 2. Guan et al. BioMed Res Int 2015;2015:428169.

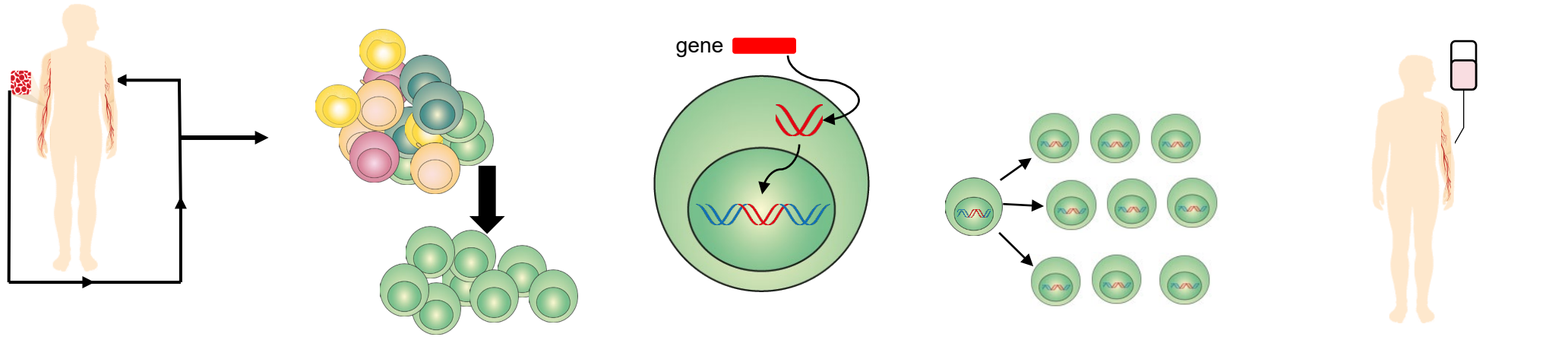
CAR T cells

Types of immunotherapy

An introduction to CAR T cells

- CAR T-cell immunotherapy is a more recently developed adoptive antitumor treatment, which involves harvesting, activating and then genetically modifying a patient's own T cells to recognize a particular TAA abundantly expressed on malignant cells[1]
- Once reinfused back into the patient, CAR T cells then recognize and kill TAA-expressing cells[1]
- CAR T-cell therapies are particularly effective in the treatment of relapsed/refractory B-cell malignancies[1,2]

An overview of the CAR T-cell immunotherapy clinical process[3]



CAR, chimeric antigen receptor; TAA, tumor-associated antigen.

1. Yu et al. J Hematol Oncol 2017;10:1–13. 2. Kerre. Belgian J Hematol 2017;8:94–101. 3. Davila et al. OncoImmunology 2012;1:1577–83. Figure based on information in Davila et al.[3]

Four generations of improved CAR T-cell construct design[1]

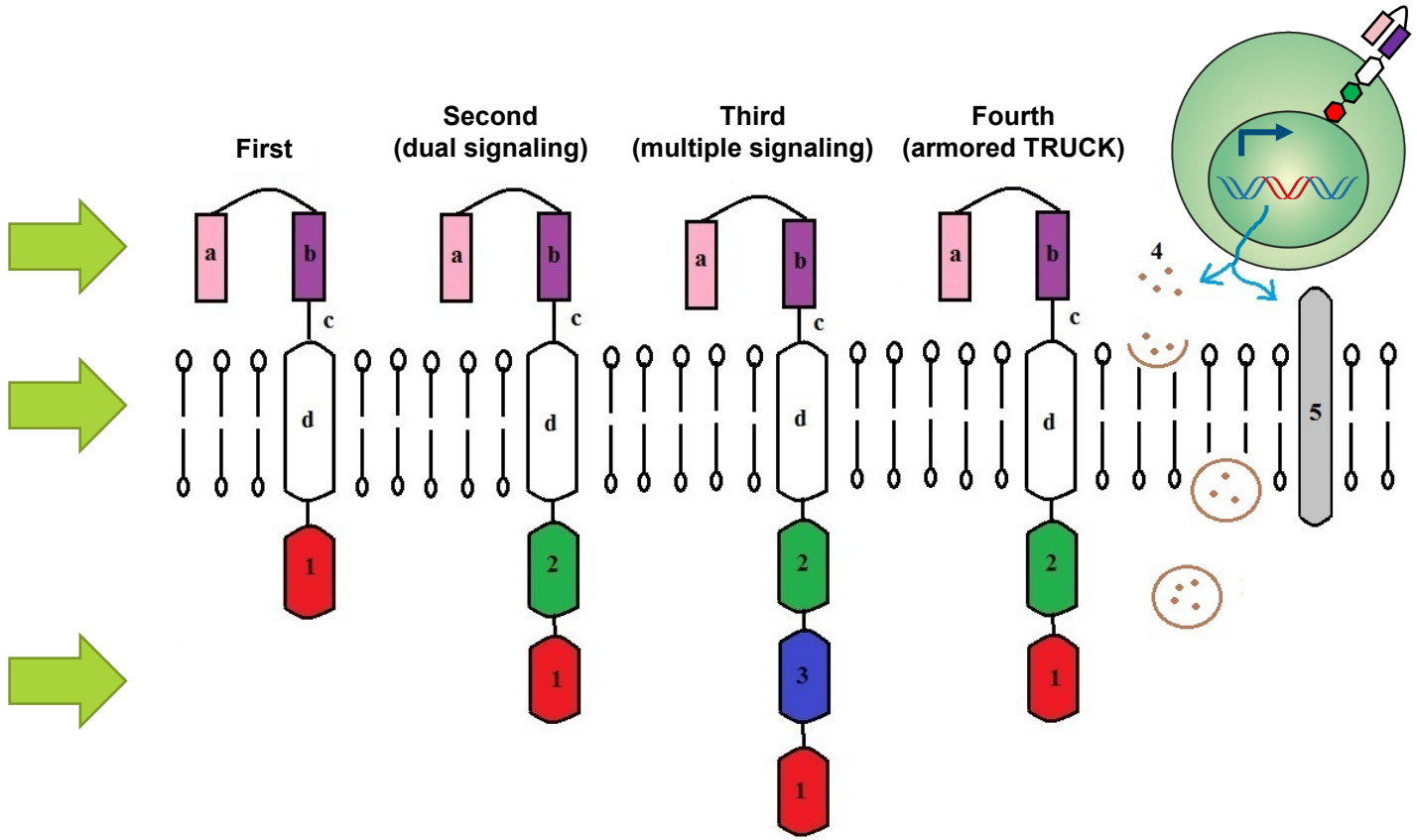
Components of the CAR construct

The extracellular, antigen-binding domain consists of an scFv [a, b]

The hinge [c] and a transmembrane domain [d] connect the extracellular and intracellular parts

The intracellular domain always contains a CD3ζ signaling domain **[1]** (first generation) and is combined with one (second generation) or two (third generation) costimulatory domains **[2, 3]**

The fourth-generation CARs contain an additional inducible cytokine cassette (inducing production of cytokines **[4]**, such as IL-12, upon recognition of the CAR ligand) **[5]**



CAR, chimeric antigen receptor; IL-12, interleukin 12; scFv, single-chain variable fragment; TRUCK, T cell redirected for universal cytokine mediated killing.

1. Kerre. Belgian J Hematol 2017;8:94–101. Figure adapted, with permission, from original artwork kindly provided by Steven Van Schandevyl.

CAR T-cell therapy antigen targets in clinical trials

CAR T cells have been engineered to target many different antigens to treat various cancers

Hematologic malignancies[1]

Antigen	Cancer
BCMA	MM
CD123	AML, leukemia, lymphoma
CD138	MM
CD16V	DLBCL, MCL, PMBCL, FL
CD19	CLL, NHL, ALL, DLBCL, PMBCL, MCL, DLBCL transf. FL, lymphoma, FL, PLL, DMBCL, leukemia, SLL, BAL, HL, MLBCL, MM
CD19/CD20	DLBCL
CD19/CD22	Leukemia, lymphoma
CD20	ALL, CLL, PLL, DLBCL, FL, MCL, leukemia, Lymphoma, SLL, MZL, NHL
CD22	FL, ALL, NHL, DLBCL, MCL, leukemia, lymphoma
CD30	NHL, HL, lymphoma, CD30+ cancer
CD33	AML
CD38[2]	B cell malignancies
CD70	CD70+ cancer
CD123[2]	B cell malignancies
Ig k	CLL, NHL, MM
IL-1RAP	CLL
Lewis Y	MM, AML, MDS
NKG2D ligand	AML, MDS, MM
ROR1	CLL, SLL, MCL, ALL

Solid malignancies[1]

Antigen	Cancer
CAIX	Renal cell carcinoma
CEA	Liver metastases, liver, adenocarcinoma, gastric, colorectal, breast
C-MET	Breast
EGFR	EGFR+ solid tumors, GBM, glioma
EGFRvIII	Glioma, GBM, glioblastoma
EpCam	Liver, stomach, breast
EphA2	Malignant glioma
ErbB2/Her2	HER2+ malignancy, sarcoma, GBM, head and neck, breast, glioblastoma,
FAP	Metastatic mesothelioma
FR-a	Ovarian
GD2	Neuroblastoma, sarcomas
GPC3	Hepatocellular carcinoma, LSCC, GPC3+ solid tumor
IL-13Ra2	Malignant glioma, brain and CNS
L1-CAM	Neuroblastoma
Mesothelin	MPM, MPDAC, malignant pleural disease, pancreatic, breast, mesothelin+ tumors
MUC1	Hepatocellular carcinoma, NSCLC, TNBC, PC, malignant glioma, CC, GC
MUC16ecto	Ovarian
PD-L1	GBM
PSCA	Pancreatic
PSMA	Prostate
ROR1	NSCLC, breast cancer (TNBC)
VEGFR-2	various

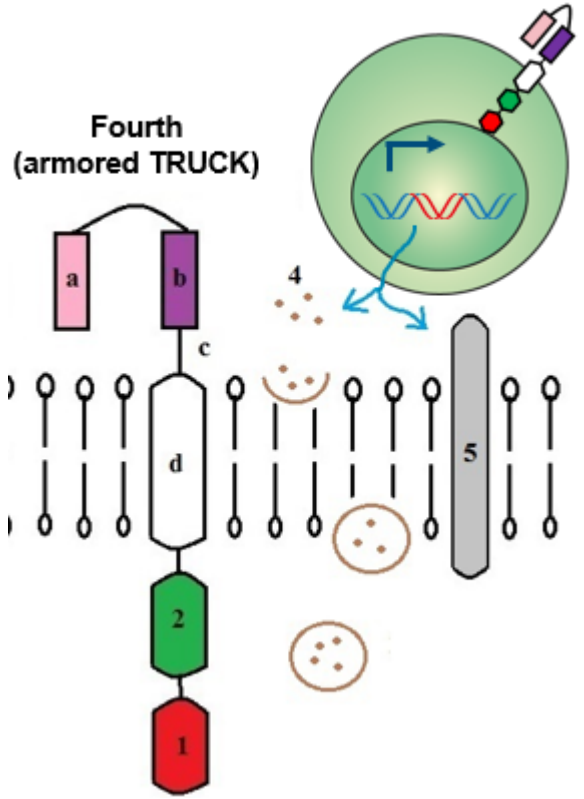
Expanded abbreviations in notes section.

1. Hartmann et al. EMBO Mol Med 2017;9:1183–97. 2. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT03125577 [Accessed Aug 2022].

Efficacy of CAR T-cell therapies[1]

- The biggest successes so far have been achieved with CAR T cells directed toward CD19+ B-cell malignancies
- However, although theoretically feasible, it is not fully clear yet whether this success can be repeated for other hematologic and solid tumors
- In solid tumors, additional challenges exist for CAR T-cell therapy:
  - The anatomical location (challenging for the T cell to traffic towards the heart of the tumor)
  - The heterogeneity of the tumor cells
  - The immune-suppressing microenvironment
- Fourth-generation CARs or 'TRUCKs' could be more effective in solid tumors, as they, by inducing cytokine production in the heart of the tumor, also stimulate the other tumor-infiltrating T cells to kill tumor cells

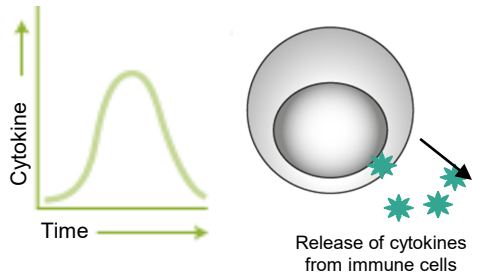
Fourth-generation CARs may be more effective against solid tumors than earlier versions



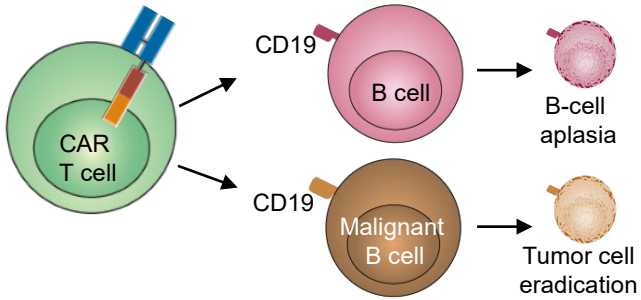
CAR, chimeric antigen receptor; TRUCK, T cell redirected for universal cytokine mediated killing.
1. Kerre. Belgian J Hematol 2017;8:94–101. Figure adapted, with permission, from original artwork kindly provided by Steven Van Schandevyl.

CAR T cells: selected adverse events

Reported/potential toxicities following the use of CAR T cells[1]



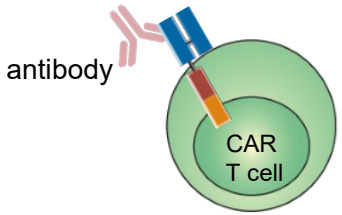
To date, the most prevalent adverse effect following infusion of CAR T cells is the onset of immune activation, known as CRS[1] (5.6–90% in clinical trials)[2]



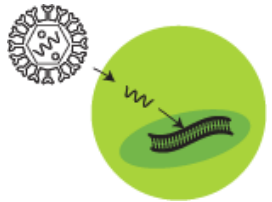
The severity of reported events for 'on-target, off-tumor' toxicity has ranged from manageable lineage depletion (B-cell aplasia) to severe toxicity (death), depending on the target[1]

The development of neurologic toxicities, including confusion, delirium, expressive aphasia, obtundation, myoclonus, and seizure, has been reported in patients who received CD19-specific CAR T cells[1] (12–48% in clinical trials)[2]

Several dermatologic complications have also been described, including secondary cutaneous malignancies[3]



Both cellular and humoral rejection of CAR T cells have been demonstrated due to the immunogenicity of foreign protein. Host reaction can manifest as anaphylaxis or allergy[1]



The risk of insertional oncogenesis following gene transfer into T cells is seemingly low; however, investigators must remain vigilant and adhere to strict monitoring[1]

CAR, chimeric antigen receptor; CD, cluster of differentiation; CRS, cytokine-release syndrome.

1. Bonifant et al. Mol Ther Oncolytics 2016;3:16011. 2. Kerre. Belgian J Hematol 2017;8:94–101. 3. Rubin et al. J Am Acad Dermatol 2016;75:1054–7. 4. Adkins S. J Adv Pract Oncol. 2019;10(Suppl 3):21–28. 5. Sievers S. Front Oncol. 2020 Jun 24;10:885.

Tumor vaccines

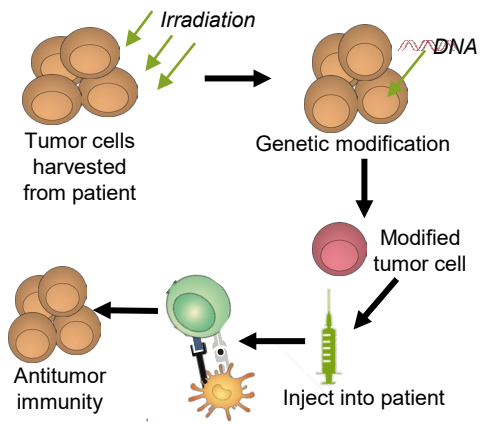
Types of immunotherapy

An overview of tumor vaccines

(see also www.ncbi.nlm.nih.gov/pmc/articles/PMC8185206/)

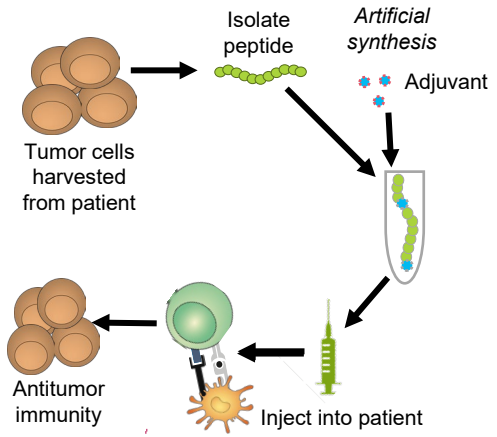
- Targeting cancer with vaccines has been investigated since the 1950s, but challenges have been encountered in the process;[1] consequently, very few are currently licensed in Europe
- They do, however, have the potential to become effective immunotherapies, and some of the key concepts underlying their activity are shown below:

Tumor cell vaccines[2]



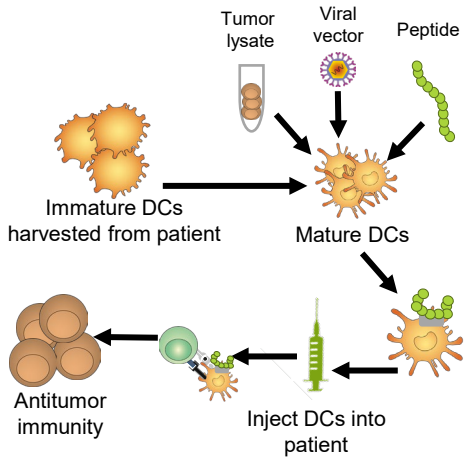
- Autologous tumor cell vaccines (colon cancer)
- Autologous renal cell tumor vaccine (RCC)
- Allogeneic irradiated pancreatic tumour cell lines (pancreatic cancer)

Antigen vaccines[3]



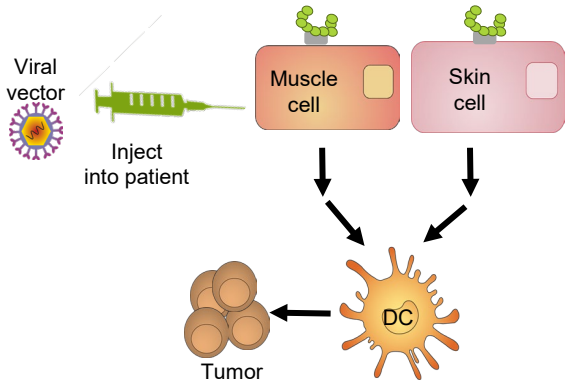
- Oncophage (renal cancer, melanoma and glioma)
- Tecemotide (lung, breast, prostate and colorectal cancers)

Dendritic cell vaccines[4]



- Sipuleucel-T (prostate cancer)

Vector-based vaccines[5]



- Ad-sig-hMUC-1/ecdCD40L (breast cancer)
- α-Fetoprotein adenoviral vector (hepatocellular cancer)

CTL, cytotoxic T lymphocyte; DC, dendritic cell; RCC, renal cell carcinoma.

1. Vergati et al. J Biomed Biotechnol 2010;2010:pii: 596432. 2. Srivastan et al. Hum Vaccin Immunother 2014;10:52–63. 3. Chiang et al. Vaccines 2015;3:344–72. 4. Tacken et al. Nat Rev Immunol 2007;7:790–802. 5. Larocca & Schlom. Cancer J 2011;17:359–71. Images adapted from Health Hearty. Available from: https://healthhearty.com/strategies-for-cancer-vaccine-development [Accessed October 2022].

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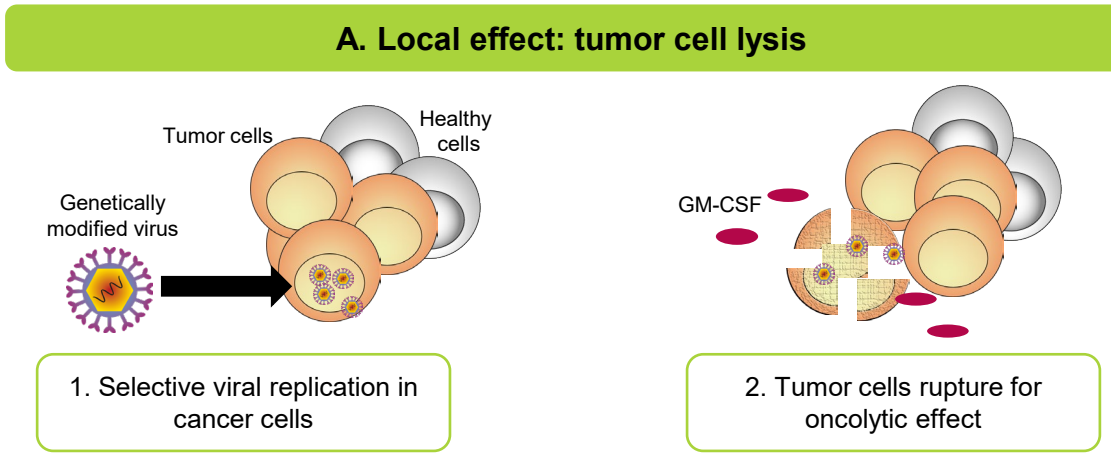
Licensed tumor vaccines in Europe[a]

- Talimogene laherparepvec is an oncolytic immunotherapy that has demonstrated therapeutic benefit against melanoma in a phase III clinical trial[1]
- Talimogene laherparepvec is designed to produce both local and systemic effects resulting in tumor lysis and death[2]
- It is currently licensed to treat adults with unresectable melanoma (regionally or distantly metastatic)[3]

- Efficacy

	T-VEC (n = 295)	GM-CSF (n = 141)	p
DRR	16.3%	2.1%	< 0.001
ORR	26.4%	5.7%	< 0.001

Mechanism of action of talimogene laherparepvec[2]



[a]Allogeneic irradiated pancreatic tumour cell lines and autologous renal cell tumor vaccine have been granted orphan designation by the EMA in Germany[4,5]

DC, dendritic cell; DRR, durable response rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; ORR, overall response rate; T-VEC, talimogene laherparepvec.

1. Andtbacka et al. J Clin Oncol 2015;33:2780–8. 2. Doepker & Zager. Am J Hematol Oncol 2016;12:17–20. 3. Imlygic SmPC 2022. Available from: http://www.ema.europa.eu [Accessed Aug 2022]. 4. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2016/02/WC500201232.pdf [Accessed Aug 2022]. 5. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500005835.pdf [Accessed Aug 2022].

Summary and key takeaways

- Immunotherapy is any treatment aimed at boosting or restoring the ability of the immune system to fight cancer, infections, and other diseases
- Several different classes of immune-modulating therapies are now in use and transforming patient outcomes
  - Checkpoint inhibitors, including agents that target CTLA-4, PD-1, and PD-L1, have been some of the most successful new therapeutic strategies in recent years
  - Checkpoint inhibitor, LAG-3 has garnered recent interest as a potential cancer treatment and there are several molecules being investigated in phase I–III trials
  - Monoclonal antibodies have become one of the largest classes of new agents approved for cancer treatment in the past decade
  - CAR T-cell immunotherapy is a more recently developed adoptive antitumor treatment, which involves collecting and then modifying a patient's own T cells, and is now available to treat B-cell malignancies
  - Tumor vaccines remain a significant area of research, with one product currently licensed in Europe for the treatment of unresectable melanoma

CAR, chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

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Partnering for Education & Optimizing Treatment in ImmunoScience

Immunotherapy adverse events and their management

Immunotherapy adverse events and their management

Click on a chapter below to start learning

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Adverse events according to organ system **(focus on checkpoint inhibitors)**	17
Principles of adverse event management **(focus on checkpoint inhibitors in oncology)**	26
Summary and key takeaways	32

Click on the ISA logo of a slide to return to the chapter homepage

A large part of this slide deck focuses on checkpoint inhibitor-related adverse events in oncology. The type, onset and severity of immunotherapy-related adverse events varies. **Healthcare providers are advised to remain vigilant for any symptoms at all times and always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies**

For full safety information of individual agents, always refer to the Summary of Product Characteristics

Introduction

Immunotherapy adverse events and their management

The type, onset and severity of immunotherapy-related adverse events varies.
Healthcare providers are advised to remain vigilant for any symptoms at all times and always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immunotherapy adverse events

The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

- ► The toxicities of immunotherapy are as diverse as the type of treatments that have been devised

○ Rare
● Common
– Not reported

Immunotherapy class[a]	Selected example	Immunotherapy-related side effects[a]						
		Flu-like symptoms[b]	Skin toxicity	GI toxicity	Hepato-toxicity	Endocrine toxicity	Infections	Other
Cytokines[1]	IFN, IL-2, etc	●	●	●	●	●	○	Congestive heart failure, anemia, pulmonary edema, hypotension
T-cell therapies[1,6-7]	TILs	●	●	○	○	●	○	Prolonged lymphopenia
	CAR	●	●	○	●	–	●	● Cytokine release Syndrome (characterized by high fevers, sinus tachycardia, hypotension, hypoxia, depressed cardiac function) , Neurotoxicity [6,7]
	TCR	●	●	●	○	–	○	Encephalopathy, myocarditis with MAGE-3 TCR
Checkpoint inhibitors[1]	CTLA-4 inhibitor	●	●	●	●	●	–	Neuropathy, nephritis
	PD-1/L1 inhibitors	●	●	○	○	●	–	Pneumonitis
TNF-blocking agents[2]	anti-TNFα antibodies	–	○	-	○	–	●	Neutralizing antibody formation, autoimmunity, malignancies, neurological disorders
Other monoclonal antibodies[3,4]	anti-IL-1, anti-CD20, etc.	●	●	●	○	●	●	CRS, infusion reactions, pulmonary adverse events, inflammatory reactions, hypersensitivity reactions, autoimmunity[3,4]
Vaccines[1,5]	Oncolytic viral vaccine	●	●	○	○	–	○	Allergic reactions (local to anaphylaxis), hypotension

[a]Individual immunotherapies may be immune-stimulating or immune-dampening and will therefore have different toxicity profiles. [b]Fever, chills, lethargy, fatigue and myalgia.

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; GI, gastrointestinal; IFN, interferon; IL-2, interleukin-2; PD-1, programmed cell death receptor 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; TNF, tumor necrosis factor.
1. Weber et al. J Clin Oncol 2015;33:2092–99. 2. Hoentjen and van Bodegraven. World J Gastroenterol 2009;15:2067–73. 3. Demlova et al. Physiol Res 2016;65:S455–S462. 4. Baldo. Oncoimmunology 2013;2:e26333. 5. Andtbacka et al. J Clin Oncol 2015;33:2780–8. 6. Yanez Let al. HemaSphere. 2019;3:e186. 7. Brudno JN.et al. Blood Rev. 2019;34:45-55.

For full safety information of individual agents, always refer to the Summary of Product Characteristics

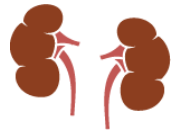
Immune-related adverse events (focus on checkpoint inhibitors)

- Increasing the activity of the immune system through immunotherapy, especially checkpoint inhibitors,[1] is associated with a unique spectrum of inflammatory side effects, so-called irAEs[1–3]
- Although any organ can be affected, irAEs most commonly involve the gastrointestinal tract, skin, endocrine glands, liver and lung[1–3]
- Less commonly, irAEs affect the nervous system and hematologic systems[1–3]
- Physicians must be ready to detect and manage this wide range of new types of adverse events[1–3]
- A collaborative, multidisciplinary approach to the management of irAEs is highly recommended[1–3]

Learn more about management of irAEs

irAEs affect many organ systems


Anemia, thrombocytopenia, neutropenia, hemophilia

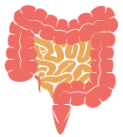

Nephritis


Rash, pruritus, psoriasis, vitiligo DRESS, Stevens-Johnson syndrome


Uveitis, conjunctivitis, scleritis, episcleritis, blepharitis, retinitis


Myocarditis, pericarditis, vasculitis


Hepatitis


Colitis, ileitis, pancreatitis, gastritis


Hyper- or hypothyroidism, hypophysitis, adrenal insufficiency, diabetes


Pneumonitis, pleuritis, sarcoid-like granulomatosis


Neuropathy, Guillain-Barré syndrome, myelopathy, meningitis, encephalitis, myasthenia


Arthritis, dermatomyositis

DRESS, drug reaction with eosinophilia and systemic symptoms; irAEs, immune-related adverse events.

1. Postow et al. N Engl J Med 2018;378:158–68. 2. Champiat et al. Ann Oncol 2016;27:559–74. 3. Haanen et al. Ann Oncol. 2017;28:iv119-iv142.

Immune-related adverse events occur due to increased activity of the Immune System

Mechanisms that result in irAEs are still being elucidated.

Potential mechanisms are:

- Cross-reactivity between T cells directed against a tumor and T cells directed against a related antigen in normal tissue
- Increasing levels of pre-existing autoantibodies (e.g. in the thyroid gland)
- Increase in the level of inflammatory cytokines (e.g. in the GI tract)
- Enhanced complement-related inflammation due to direct binding of an antibody against CTLA-4 expressed on normal tissue

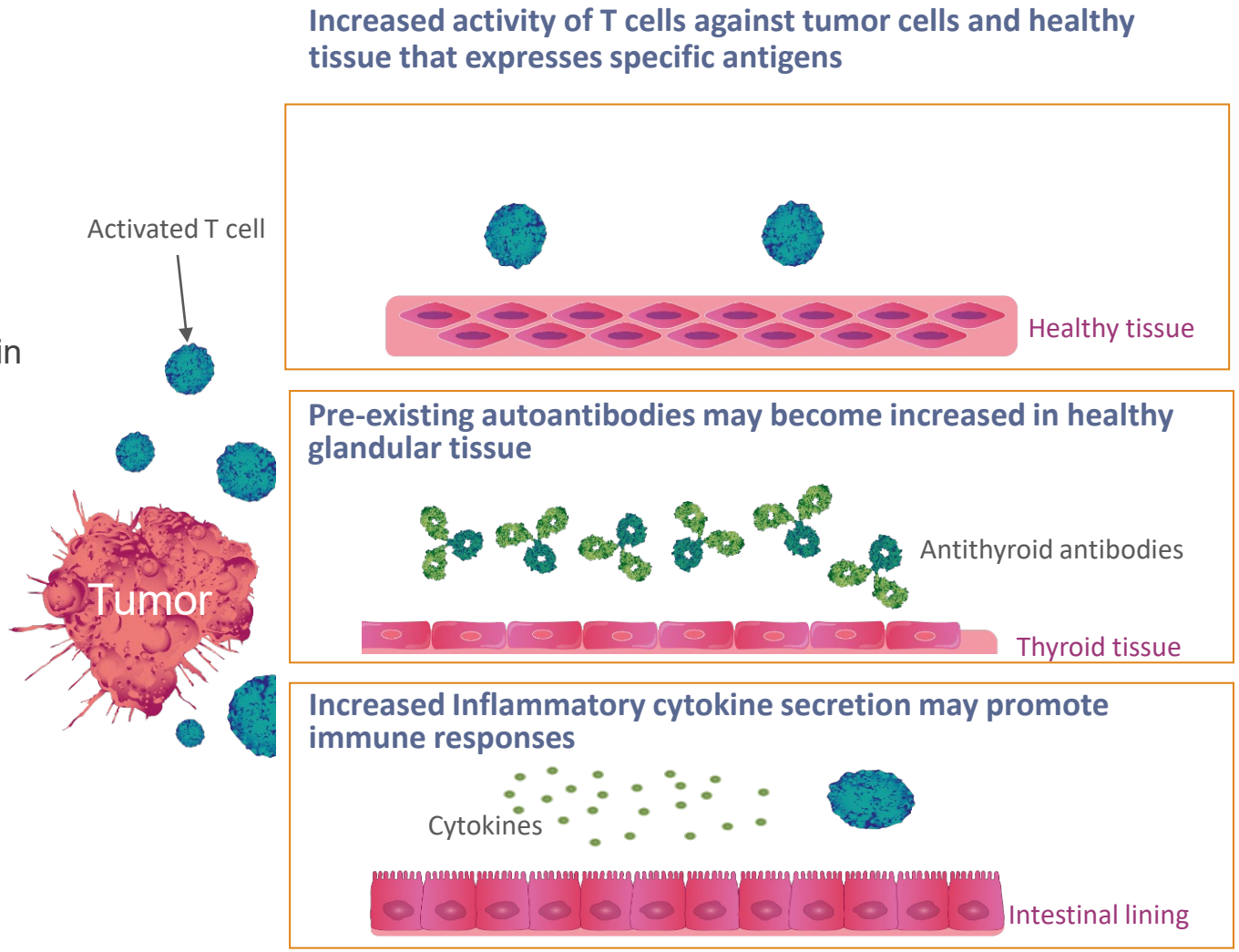


Figure adapted from Postow et al, 2018, *N Engl J Med*[1]

CTLA-4, Cytotoxic T-lymphocyte-associated antigen; GI, gastrointestinal; irAEs, immune-related adverse events.

1. Postow et al. N Engl J Med 2018;378:158–68.

Adverse events according to type of immunotherapy

Immunotherapy adverse events and their management

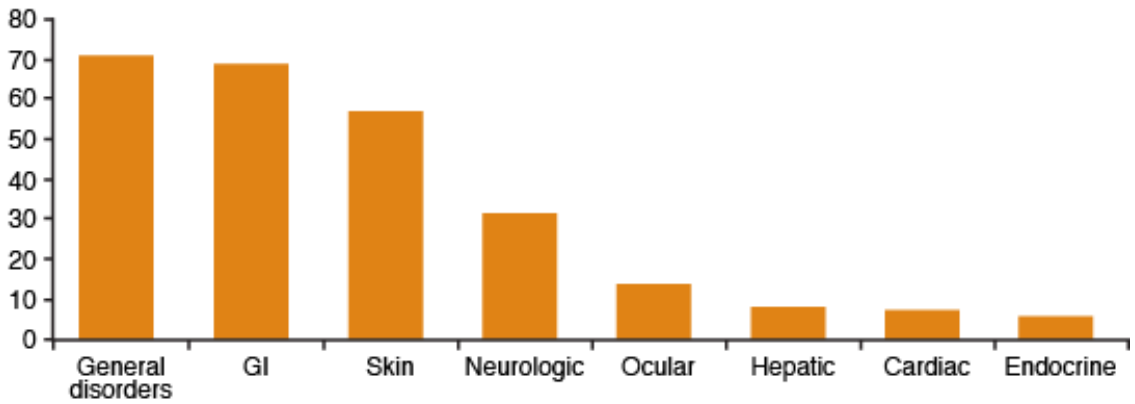
The type, onset and severity of immunotherapy-related adverse events varies.
Healthcare providers are advised to remain vigilant for any symptoms at all times and always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Back to introduction

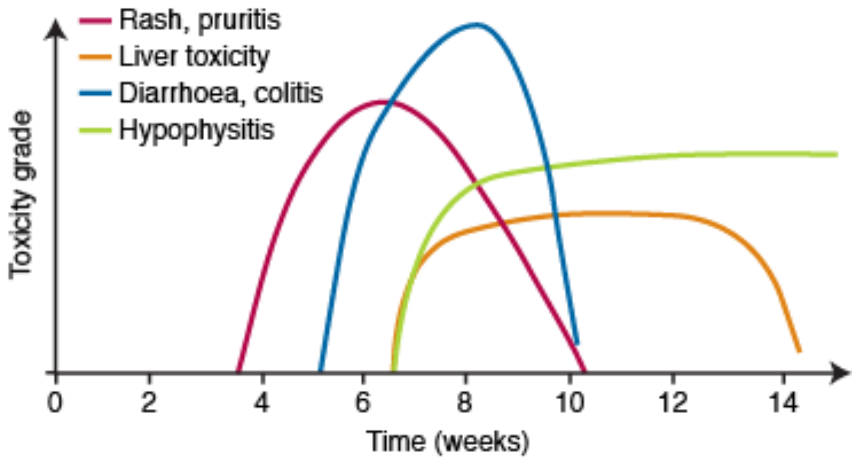
CTLA-4 checkpoint inhibitors: selected adverse events

- Owing to their immune-stimulatory action, CTLA-4 inhibitors, such as ipilimumab, are associated with a range of inflammatory and immune-related AEs[1]
- These include dermatologic, gastrointestinal, endocrine and hepatic toxicities[1,2]

Percentage of any grade AEs in 1498 patients from 14 completed clinical trials of ipilimumab (adapted from[1])[a]



Timing of occurrence of irAEs following ipilimumab treatment[3]



Published guidance on the management of checkpoint inhibitor toxicities is available[3–7]

[a]AEs were categorized by organ system. AEs were included regardless of causality. Patients may have experienced more than one event.

AE, adverse event; irAE, immune-related adverse event; CTLA-4, cytotoxic T-lymphocyte-associated antigen; GI, gastrointestinal.

1. Camacho. Cancer Med 2015;4:661–72. 2. Linardou & Gogas. Ann Transl Med 2016;4:272. 3. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv142. 4. Puzanov et al. J Immunother Cancer 2017;5:95; 5. Davies & Duffield. Immunotargets Ther 2017:6:51–71. 6. Brahmer et al. J Clin Oncol 2018; JCO2017776385 (Epub ahead of print). 7. Aspeslagh et al. BMSO ImmunoManager. Available from https://www.bsmo.be/immunomanager/. Accessed December 2022

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PD-1/PD-L1 checkpoint inhibitors: selected adverse events

- Owing to the immune-stimulatory action, PD-1/PD-L1 inhibitors are associated with a range of inflammatory and immune-related AEs[1]
- These include dermatologic, gastrointestinal, endocrine, pulmonary and hepatic toxicities[2,3]

Frequency of any grade AEs reported with PD-1/PD-L1 inhibitors[4]

		PD-1 inhibitors (%)	PD-L1 inhibitors (%)
Dermatologic[1,4]	Rash and/or pruritus	~24 (Rash) / 13-20 (Pruritus)	~7
Gastrointestinal[4]	Diarrhea, nausea or vomiting, colitis	Few data available	Few data available
Endocrine[4]	Hypophysitis	Very rare	Very rare
	Thyroid dysfunction	5–10	5–10
Hepatic[4]	Hepatitis*	5–10 (single agent) Up to 30 (in combination with CTLA-4 blockade)	5–10 (single agent) Up to 30 (in combination with CTLA-4 blockade)
Other[4]	Fatigue	16–37.	12–24
Pulmonary	Cough, dyspnoea[4]	20–40	20–40
	Pneumonitis[5]	3.6	1.3
Other reported rare (≤ 1%) toxicities include neurologic, cardiac, hematologic, ocular and renal toxicities[3]			

Published guidance on the management of checkpoint inhibitor toxicities is available[4, 6–9]

AE, adverse event; irAE, immune-related adverse event; CTLA-4, cytotoxic T-lymphocyte-associated antigen; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

1. Pillai et al. Cancer 2018;271–7. 2. Gelao et al. Toxins 2014;6:914–33. 3. Villadolid Amin A. Transl Lung Cancer Res 2015;4:560–75. 4. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv142. 5. Khunger et al. Chest 2017;152:271–81. 6. Puzanov et al. Journal for ImmunoTherapy of Cancer 2017;5:95. 7. Davies & Duffield. ImmunoTargets and Therapy 2017;6:51–71. 8. Brahmer et al. J Clin Oncol 2018;JCO2017776385 (Epub ahead of print). 9. Aspeslagh et al. BMSO ImmunoManager. Available from: https://www.bsmo.be/immunomanager/. Accessed December 2022.

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TNF-blocking agents: selected adverse events

AEs associated with TNF-blocking agents[1,2]

	Example
Infections	Tuberculosis, serious infections
Antibody formation	Anti-drug antibodies
Infusion reactions	Anaphylaxis, delayed-type hypersensitivity
Autoimmunity	Antinuclear antibodies, systemic lupus erythematosus
Malignancies	Non-melanoma skin cancer
Demyelinating disorders	Guillain-Barré syndrome, multiple sclerosis
Abnormal liver function tests	Hepatitis, cholestatic disease
Cardiac abnormalities	Heart failure
Skin eruptions	'Paradoxical' psoriasis

- **Neutralizing antibody formation**
  - Less commonly reported with use of etanercept[1]
- **Tuberculosis**
  - Risk is lower with etanercept[3]
- **Life vaccines**
  - Administration of life vaccines is presently contraindicated in patients receiving TNF-blocking agents
- **Surgical site infections**
  - Increased risk in patients with RA who use or have recently used anti-TNFs at the time of orthopaedic surgery[4]
- **Heart failure**
  - Administration of TNF-blocking agents is contraindicated in patients with impaired cardiac function
- **Non-melanoma skin cancer**
  - Risk may be increased in patients who receive TNF-blocking agents, whatever the indication[5]
  - Increased risk of lymphoma observed in gastro-enterologic indications, but absolute numbers are small.
  - TNF-blocking agents are presently contraindicated in patients with past history of cancer

AE, adverse event; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

1. Hoentjen & van Bodegraven. World J Gastroenterol 2009;15:2067–73. 2. Connor. Rheumatol Int 2011;31:327–37. 3. Dixon et al. Ann Rheum Dis 2010;69:522. 4. Goodman et al. Rheumatology (Oxford) 2016;55:573–82. 5. Mercer et al. Ann Rheum Dis 2012;71:869–74.

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Monoclonal antibodies: selected adverse events

- mAbs are established therapies for many conditions, including a range of different cancers[1,2]
- mAbs may be associated with a variety of AEs depending on their type (murine, chimeric, humanized or human, target and conjugate)[1]
- Hypersensitivity reactions[a] (including infusion-related reactions) are the most common and among the most serious AEs associated with mAbs[1,2]
- Different mAbs have different toxicity profiles; associated AEs vary widely and can range from, for example, headache, mild gastrointestinal symptoms, transient rash and itching, to severe cytopenias, cardiac toxicity and anaphylaxis[1]
- For management recommendations see reference 2

Selected AEs associated with mAbs[1]

Type of AE	Selected examples
Haematological and vascular disorders	Thrombocytopenia, neutropenia, anemia, haemolytic anemia, vasculitis, hypertension
Infusion reactions	Anaphylaxis, delayed-type hypersensitivity
Pulmonary AEs	ARDS, bronchospasm, diffuse alveolar haemorrhage, hypersensitivity pneumonitis, interstitial pneumonitis
Neurological toxicities	Peripheral neuropathies, encephalomyelitis
Hepatic toxicities	Hepatomegaly
Cardiac abnormalities	Cardiopulmonary arrest, arrhythmias, cardiomyopathy, LVD, pericarditis
Dermatological events	Pruritis, eczema, rash, urticaria, morbilliform eruptions, erythema, petechiae, alopecia
Others	Serum sickness-like reaction, diarrhea, fatigue, infections

[a]see next slide for more information

AE, adverse event; ARDS, acute respiratory distress syndrome; ATE, arterial thromboembolic event; CD20/30, cluster of differentiation 20/30; EGFR, epidermal growth factor receptor; LVD, left ventricular dysfunction; mAb, monoclonal antibody; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VTE, venous thromboembolic event.

1. Baldo. Oncoimmunology 2013;2:e26333. 2. Guan et al. BioMed Res Int 2015;2015:428169. 3. Ali et al. Drug Healthc Patient Saf 2013;5:79–99.

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Monoclonal antibodies: hypersensitivity reactions

- Adverse responses can be classified into four categories of hypersensitivity (Types I–IV)[1]
- mAbs have been known to cause adverse reactions in all four categories[1]

Type of adverse reaction	Examples	Frequency	Symptoms
Type I (Immediate) hypersensitivity	Infusion syndrome Those that impact a single organ, i.e. eyes (conjunctivitis), bronchopulmonary tissue (asthma), gastrointestinal tract (gastroenteritis) and skin (urticaria, eczema) or multiple organs (anaphylaxis) Possible immediate reactions including anaphylaxis	Typical Relatively uncommon upon administration of mAbs	Flu-like symptoms, fever, chills, nausea, headache, asthenia, rash, etc. Can range from minor itching and inflammation to death Cardiovascular collapse and bronchospasm occur frequently in the course of anaphylaxis
Type II	Immune thrombocytopenia, neutopenia, hemolytic anemia	Rare	
Type III	Vasculitis, serum sickness; some pulmonary adverse events	Very rare	Symptoms of serum sickness typically appear 6–21 days after drug administration, and include lymphadenopathy and fever
Type IV (Delayed)	Delayed mucocutaneous reactions and infusion reactions/cytokine release syndrome, tumor lysis syndrome and cardiac events Delayed-type reactions include cutaneous reactions are allergic contact dermatitis, maculopapular exanthema, psoriasis	Very rare	Various Various. Generally become apparent 7–21 days after exposure

Table adapted from 1. Baldo et al. Selected content shown. Please refer to[1] for full information. For management recommendations see[2]

1. Baldo. Oncoimmunology. 2013;2:e26333. 2. Guan et al. BioMed Res Int 2015;2015:428169.

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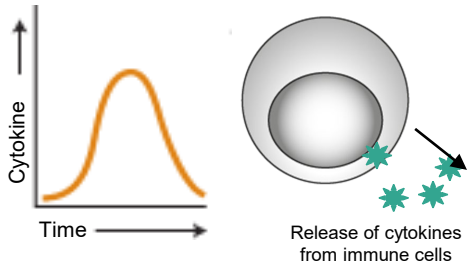
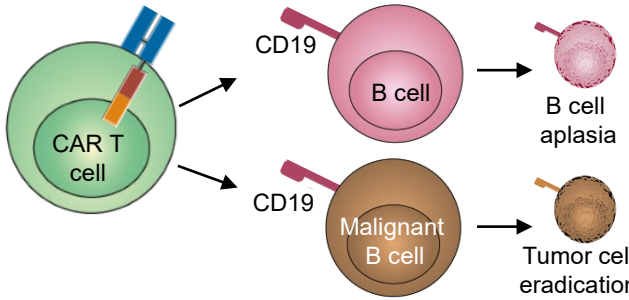
CAR T cells: selected adverse events

Reported/potential toxicities following the use of CAR T cells[1]

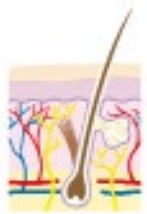


To date, the most prevalent adverse effect following infusion of CAR T cells is the onset of immune activation, known as CRS[1] (5.6% to 90% in clinical trials)[3]

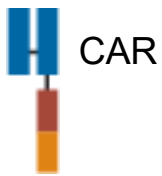


The severity of reported events for 'on-target, off-tumor' toxicity has ranged from manageable lineage depletion (B-cell aplasia) to severe toxicity (death), depending on the target[1]

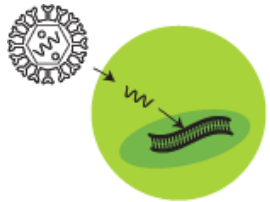
The development of neurologic toxicities, including confusion, delirium, expressive aphasia, obtundation, myoclonus and seizure has been reported in patients who received CD19-specific CAR T cells[1] (12% to 48% in clinical trials)[3]



Several dermatologic complications have also been described, including secondary cutaneous malignancies[2]



Both cellular and humoral rejection of CAR T cells have been demonstrated due to the immunogenicity of foreign protein. Host reaction can manifest as anaphylaxis or allergy[1]



The risk of insertional oncogenesis following gene transfer into T cells is seemingly low; however, investigators must remain vigilant and adhere to strict monitoring[1]

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; CD, cluster of differentiation..

1. Bonifant et al. Mol Ther Oncolytics 2016;3:16011. doi:10.1038/mto.2016.11. 2. Rubin et al. J Am Acad Dermatol 2016;75:1054–7. 3. Kerre. Belgian Journal of Hematology 2017;8:94–101. 4. Adkins S. J Adv Pract Oncol. 2019;10(Suppl 3):21–28. 5. Sievers S. Front Oncol. 2020 Jun 24;10:885.

Adverse events according to organ system

(focus on checkpoint inhibitors)

Immunotherapy adverse events and their management

This chapter is focused on checkpoint inhibitor-related adverse events. The type, onset and severity of immunotherapy-related adverse events varies.Healthcare providers are advised to remain vigilant for any symptoms at all times and always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

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Immune-related AEs: dermatologic

This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Incidence/onset [1,2]

- ~40% of patients treated with anti-PD-1
- Early onset (3-4 weeks after treatment initiation)

Manifestations [1–3]

- Maculopapular rash and/or pruritus (trunk or extremities)
- Vitiligo
- Oral lichenoid reactions
- Dry mouth

Rare manifestations [1,2,4,5]

- Lichenoid dermatitis or psoriasis
- Bullous pemphigoid
- Dermatitis herpetiformis
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

Management of dermatologic AEs [6]

Grade 2

- Symptomatic management: topical moisturizers, high-potency topical steroids, oral anti-histamines
- Reassess after 2 weeks. If worsened, manage as grade 3

Grade 3

- Symptomatic management: topical moisturizers, high–very high-potency topical steroids, oral anti-histamines, systemic corticosteroids (1 mg/kg/day)
- Withhold CPi
- Reassess after several days/weeks. If worsened, manage as grade 4. If symptoms grade ≤1, taper steroids over 1 month, resume CPi

Grade 4

- Permanently discontinue CPi; supportive measures

AE, adverse event; CPi; checkpoint inhibitor; PD-1, programmed cell death receptor 1.

1. Sibaud et al. Curr Opin Oncol 2016;28:254–63. 2. Boutros et al. Nat Rev Clin Oncol 2016;13:473–86. 3. Perret et al. Int J Dermatol 2017;56:527–33. 4. Mochel et al. J Cutan Pathol 2016;43:787–91. 5. Tetzlaff et al. Am J Dermatopathol 2017;39:121–9. 6. Sibaud. Am J Clin Dermatol 2017. doi: 10.1007/s40257-017-0336-3..

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This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immune-related AEs: endocrine

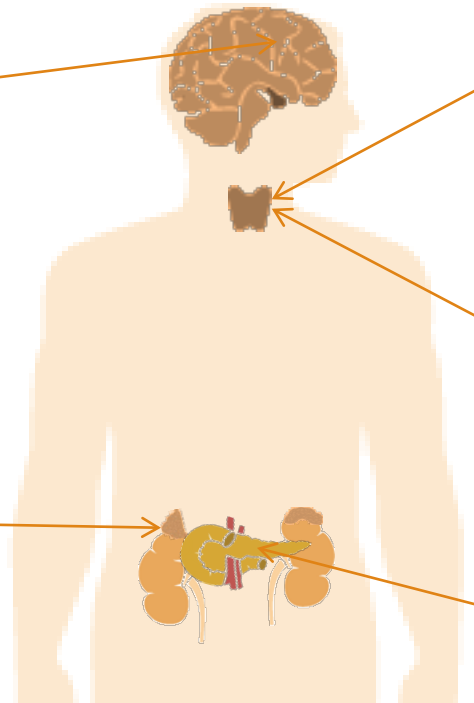
Endocrine adverse events have been reported with several immunotherapies[1,2]

Hypophysitis

- **Incidence:** 3.2–6.4%[1]
- **Management:** withhold CPi, consider administration of 1–2 mg/kg/day of oral prednisone, initiate HRT in appropriate patients[2]

Hypothyroidism

- **Incidence:** 3.8–13.2%[1]
- **Management:** consider thyroid hormone replacement in appropriate patients, consult an endocrinologist[2]



Hyperthyroidism

- **Incidence:** 1.7–8.0%[1]
- **Management:** consider beta blockers in appropriate patients, consult an endocrinologist[2]

Adrenal insufficiency

- **Incidence**: 0.7%[1]
- **Management**: hospitalization, withhold CPi, rule out sepsis, consider administration of IV corticosteroids and fluids in appropriate patients, consult an endocrinologist[2]

Type 1 diabetes mellitus

- **Incidence**: 0.2%[1]
- Monitor blood glucose regularly[3]

The management of each event is dependant upon the grade of the adverse event, and international[3,4] and national[5] guidelines should be consulted in every case

CPi, checkpoint inhibitor; IV, intravenous; HRT, hormone replacement therapy.

1. Barroso-Sousa et al. JAMA Oncol 2017. doi: 10.1001/jamaoncol.2017.3064. 2. Sznol et al. Cancer Treat Rev 2017;58:70–6. 3. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv142.
4. Brahmer et al. J Clin Oncol 2018; JCO2017776385. Epub ahead of print. 5. Aspeslagh et al. BMSO ImmunoManager. Available from: https://www.bsmo.be/immunomanager/. Accessed December 2022

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Immune-related AEs: gastrointestinal

This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Incidence[1,2]

- Adverse events involving the gastrointestinal tract are common
- Grade 3/4 diarrhea/colitis was the most commonly observed serious adverse event reported across several trials involving CPIs

Onset[1]

- 6-7 weeks

Differential diagnosis[3-5]

- *Clostridium difficile*

Management of diarrhea and colitis[3,5]

Grade 2 (4–6 liquid stools/day over baseline)

- Withhold CPi
- Symptomatic management[a]
- Prednisolone 0.5–1 mg/kg/day or oral budesonide 9 mg od if symptoms persist for >3 days or worsen

Grade 3–4 (> 6 liquid stools/day over baseline)

- Hospitalization and isolation until infection excluded
- Withhold CPi
- Prednisolone 1–2 mg/kg/day
- Sigmoido/colonoscopy
- Infliximab if no improvement after 3 days

[a]Oral fluids, loperamide, avoid high fibre/lactose diet.

Od, once daily, CPI, checkpoint inhibitor.

1. Gelao et al. Toxins 2014;6:914–33. 2. Hodi et al. N Engl J Med 2010;363:711–23. 3.Haanen et al. Ann Oncol. 2017;28(suppl_4):iv119–iv142. 4. Samaan MA et al. Nat Rev Gastroenterol Hepatol 2018;222–234. 5. Brahmer JR et al. J Immunother Cancer 2021;9:e002435.

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This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immune-related AEs: hepatic

- Hepatic adverse events (elevated liver function enzymes and/or bilirubin) have been reported with several immunotherapies including:[1]
  - Cytokines
  - Cell therapy
  - CPi
- Combination checkpoint protein inhibition is associated with more toxicity than single agents[1,2]
- Incidence of hepatitis: 5–10%[2]
- Median time of onset: 7.4 weeks[2]

Management of hepatitis[2]

Grade 2 (ALT or AST 2-5x ULN)

- Withhold CPi – do not resume until symptoms grade ≤ 1
- Prednisolone 1 mg/kg/day if symptoms do not resolve within 1–2 weeks

Grade 3–4 (G3 - ALT or AST 5-20x ULN and G4 - ALT or AST > 20x ULN)

- Permanently discontinue CPi
- Prednisolone 1–2 mg/kg/day
- Worsening despite steroids:
  - If on oral : switch to iv
  - If on iv: add MMF 500- 1000 mg BID
  - If worse on MMF , consider adding tacrolimus

ALT, alanine transaminase AST, aspartate transaminase; BID, twice daily; Cpi, checkpoint inhibitor; G3, grade 3; G4, grade 4; MMF, mycophenolate mofetil; ULN, upper limit of normal

1. Weber et al. J Clin Oncol 2015;33:2092–9. 2. Haanen et al. Ann Oncol.2017;28(suppl_4):iv119–v142.

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Immune-related AEs: pulmonary (pneumonitis)

This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Incidence[1]

- Overall: 2–4%
- Severe: 1–2%
- Observed with anti-PD-1/PD-L1 therapy, more rarely with anti-CTLA-4

Onset[1]

- Variable (very early to late)
- Median: 6–8 weeks

Assessments[1,2]

- Symptoms
- Chest X-ray
- HRCT
- Bronchoscopy with BAL
- Biopsy
- Percutaneous oximetry and PFTs

Management of suspected/documented pneumonitis[1,2]

Grade 2 (Mild to moderate new symptoms: Dyspnoea, cough, chest pain)

- Withhold immunotherapy
- Prednisolone 1 mg/kg/day or equivalent[a] (taper over ≥6 weeks)
- Follow-up at least twice weekly

Grade 3–4 (Severe new symptoms; new/worsening hypoxia; life-threatening; Difficulty in breathing, acute Respiratory Disease syndrome

- Hospitalization (consider ICU)
- Permanently discontinue immunotherapy
- Prednisolone 2–4 mg/kg/day or equivalent (taper over ≥6 weeks)
- Broad spectrum antibiotics
- Infliximab or MMF if no improvement after 2 days

[a]Exclude infection with bronchoscopy and BAL.

BAL, bronchoalveolar lavage; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; HRCT, high-resolution CT scan; ICU, intensive care unit; MMF, mycophenolate mofetil; PFTs, pulmonary function tests; PD-1, programmed cell death receptor 1; PD-L1, programmed death ligand 1.

1. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv142. 2. Professor J. Vansteenkiste, personal communication.

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This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immune-related AEs: renal (nephritis)

Incidence[1]

- Overall: <1%
- Combination of anti-PD-1/PD-L1 therapy with anti-CTLA-4: 4.9%

Onset[1]

- Variable (very early to late dependent on CPi

Assessments[1]

- Serum sodium
- Serum potassium,
- Creatinine
- Urea

Management of suspected/documented nephritis[1]

Grade 2 (Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN)

- Withhold Cpi
- Initiate steroids (oral prednisolone 0.5-1 mg/kg)

Grade 3 (Creatinine > 3 x baseline or > 3-6 x ULN)

Grade 4 (Creatinine > 6 x ULN)

- Hospitalization (for monitoring)
- Withhold CPi
- If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg (taper over 4 weeks)

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; CPi, Checkpoint inhibitor;; PD-1, programmed cell death receptor 1; PD-L1, programmed death ligand 1; ULN, upper limit of normal

1. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv142.

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This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immune-related AEs: cardiac

- Cardiac AEs are rare with immunotherapies, including CPis
- However, awareness and prompt referral to a cardiologist is important[1]

Published case reports of cardiotoxicity related to a CPi[1-3 a]:

Agent	N	AEs
Any (individual or combination)	10	Myocarditis, heart failure, cardiomyopathy, myocardial fibrosis, cardiac arrest cardiac conduction abnormalities
Ipilimumab + nivolumab	4	Myocarditis, myositis, cardiac conduction abnormalities
Ipilimumab then nivolumab	1	Myocarditis, myocardial fibrosis
Pembrolizumab	9	Myocarditis, cardiac conduction abnormalities, severe opthalmoplegia, myositis
Nivolumab	2	Complete heart block, Coronary vasospasm
Nivolumab	4	Myocarditis, cardiac conduction abnormalities
Ipilimumab	4	Cardiomyopathy with Takotsubo-like syndrome, pericardial effusion, Acute fibrinous pericarditis, Myocarditis, Heart Failure
Nivolumab	9	Myocarditis, myositis, insulin depend diabetes mellitus
Durvalumab + tremelimumab	1	Myocarditis
Atezolizumab	1	Myocarditis

Published guidance on the management of CPi induced cardiotoxicity is available [4-5]

[a]Table developed in collaboration with Prof. Dr Tessa Kerre

AE. adverse event; CPi, checkpoint inhibitor.

1. Jain et al. Curr Treat Options Cardiovasc Med 2017;19:36. 2. Agrawal N et al. Case Rep Oncol 2019;12:260–276 . 3. Zhou YW wt al. Front. Pharmacol. 10:1350. doi: 10.3389/fphar.2019.01350. 4.Brüstle & Heidecker. Oncotarget. 2017;8:106165–6. 5. Poto R. Expert Opin Drug Saf. 2021 Jun;20(6):685-694

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This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immune-related AEs: cardiac

- Cardiac AEs are rare with immunotherapies, including CPIs
- However, awareness and prompt referral to a cardiologist is important[1]

Selected cardiovascular adverse events reported for CPis from VigiBase WHO's global database of individual case safety reports (Jan 1, 2008, to Jan 2, 2018)[2]

	Anti-PD-1 or anti-PD-L1 Monotherapy (n=20643)* n (%)	Anti-CTLA-4 monotherapy (n=8266)* n (%)	Combination CPIs (n=2412)* n (%)
Myocarditis	84 (0,41%)	6 (0.07%)	32(1.33%)
Pericardial diseases	74 (0.36%)	13 (0.16%)	8 (0.33%)
Vasculitis Temporal Arteritis Polymyalgia Rheumatica	56 (0.27%) 7 (0.03%) 14 (0.07%)	18 (0.22%) 10 (0.12%) 1 (0-01%)	8 (0.33%) 1 (0.004%) 1 (0.004%)

Published guidance on the management of CPi induced cardiotoxicity is available [3-4]

* Total of individual case safety reports (ICSRs) reported in Vigibase for Anti-PD1/PD-Lq or Anti-CTLA-4 or CPIs Combination
CPis refers to any ICSR reported for treatment with nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, or tremelimumab. Anti-PD-1 or anti-PD-L1 monotherapy refers to any ICSR associated with any of the following five drugs only when used alone: nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab. Anti-CTLA-4 monotherapy refers to any ICSR associated with ipilimumab or tremelimumab alone. Combination ICIs refers to any ICSR reported with at least one anti-PD-1 or anti-PD-L1 drug combined with an anti-CTLA-4 drug. I

AE. adverse event; CPi, checkpoint inhibitor.

1. Jain et al. Curr Treat Options Cardiovasc Med 2017;19:36. 2. Salem JE Lancet Oncol 2018; 19: 1579–89 3Brüstle & Heidecker. Oncotarget. 2017;8:106165–6. 4. Poto R. Expert Opin Drug Saf. 2021 Jun;20(6):685-694

Principles of adverse event management

(focus on checkpoint inhibitors in oncology)

Immunotherapy adverse events and their management

This chapter is focused on checkpoint inhibitor-related adverse events in oncology. The type, onset and severity of immunotherapy-related adverse events varies.Healthcare providers are advised to remain vigilant for any symptoms at all times and always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Principles of irAE management: cooperation between all players

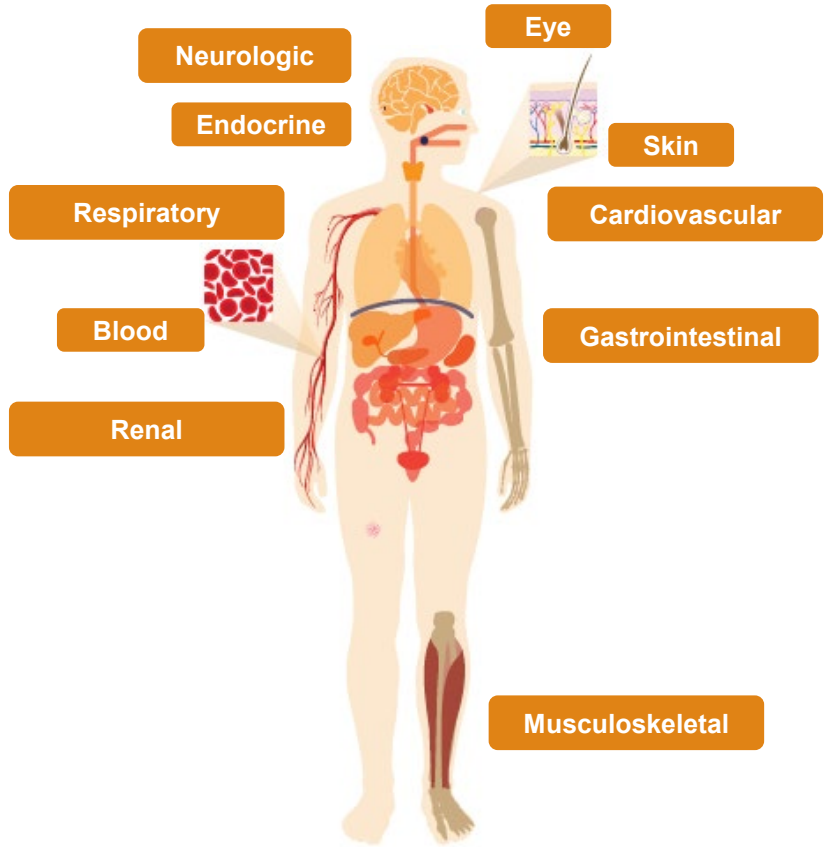
The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Communication between patients, healthcare providers and oncologists is vital to successful irAE management[1,2]

Oncologist	Patient	Healthcare provider e.g. GP
Know the immune-toxicity spectrum	Be informed about possible toxicities	Be informed about possible toxicities and their onset

All individuals, patients in particular, should be aware that the onset of toxicities is usually within 3 months of starting treatment[2]

Nearly all organ systems can be affected[1,3]



Most irAEs are mild in intensity but ~10% of patients develop grade 3–4 irAEs

GP, general practitioner; irAE, immune-related adverse event.

1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Haanen et al. Ann Oncol. 2017;28:iv119–iv142. 3. Postow et al. NEJM 2018;378:1586–8.

Principles of irAE management: vigilance

The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Identify risk factors for irAEs[1,2]

Personal and family history of autoimmune diseases[a]

History of viral infections

Physical examination[1]

Symptoms

Laboratory tests[1,2]

CBC, CRP, serum electrolytes, renal and hepatic function, glycemia, TSH, T4, urine dipstick

Morning cortisol and ACTH, LH, FSH, estradiol and testosterone (for anti-CTLA-4 therapy)

Technical tests[1,2]

Baseline ECG, chest X-ray (plus chest CT scan and PFTs, if abnormal)

Other tests depend on patient's history and symptoms

[a]Patients with a history of autoimmune disease, especially if using immunosuppressive therapy, were not evaluated in clinical trials. Therefore, the risk/benefit ratio should be discussed in-depth with the patient before starting immunotherapy.

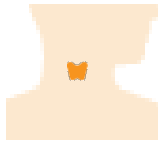
ACTH, adrenocorticotropic hormone; CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; CTLA-4, cytotoxic T lymphocyte-associated antigen; ECG, electrocardiography; FSH, follicle-stimulating hormone; irAE, immune-related adverse event; LH, luteinizing hormone; PFTs, pulmonary function tests; T4, thyroxine; TSH, thyroid-stimulating hormone.

1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Haanen et al. Ann Oncol. 2017;28:iv119-iv142.

Principles of irAE management: detection and diagnosis

The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

- IrAEs can develop at any time during treatment or even after immunotherapy discontinuation[1]

Early events Median time to onset: < 2 months			Late events Median time to onset: > 2 months		
					
Skin	Gastrointestinal	Hepatic	Pulmonary	Endocrine	Renal

- New symptoms or lab abnormalities should prompt a differential diagnosis among:[1]
  - Disease progression
  - Intercurrent event (mostly infections)
  - irAE
- Abnormalities need strict follow-up (frequency depends on the grade)
- Diagnostic assessments may include:[2]
  - Laboratory tests
  - Imaging tests
  - Biospy
  - (Referal to specialist)

irAE, immune-related adverse event.

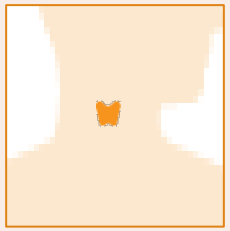
1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Haanen et al. Ann Oncol. 2017;28:iv119-iv142.

Principles of irAE management: therapy for most irAEs

The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Grade	Immunotherapy[1]	Tests[2]	Therapy[1]	Corticosteroids[1,2]
1	Continue	Close monitoring of clinical and laboratory findings	Symptomatic[a]	Topical only[c]
2	Withhold	Appropriate diagnostic tests	Antibiotics[b] Oral trimethoprim/ sulfamethoxazole if long-term corticosteroids	Prednisone 0.5–1 mg/kg[d]
3	Withhold/ discontinue	Hospitalization, specialist referral, biopsy		Prednisone 1–2 mg/kg[d]
4	Discontinue			

Treatment approach for irAE-related thyroid dysfunction depends on TSH and T4 levels[2]



Condition	Treatment
Hypothyroidism	Thyroxine 0.5–1.5 µg/kg
Hyperthyroidism	Beta blockers, carbimazole
Thyroiditis	Prednisone 0.5 mg/kg

[a]For example, appropriate steroids, loperamide for diarrhea (see Champiat et al. for further guidance). [b]If infection suspected. [c]For example, for skin toxicity. [d]Dose may be increased if no improvement after 3–5 days or add-on mycophenolate (liver toxicity), infliximab (colitis and pneumonitis) or tacrolimus.

irAE, immune-related adverse event; T4, the main thyroid hormone; TSH, thyroid-stimulating hormone.

1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Haanen et al. Ann Oncol. 2017;28:iv119-iv142.

Principles of irAE management: Follow-up

The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

- Except for grade 1 AEs, immunotherapy should be withheld to investigate and treat the AE (regardless of the cause)
- It is essential that, for cases of colitis, pneumonitis or any recurring event, the risk: benefit ratio is considered

When to resume or discontinue immunotherapy?

Careful discussion of the risk:benefit ratio is needed in the case of colitis, pneumonitis or any recurring event.

- Immunotherapy dose reduction is currently not recommended[1]
  - However, no dose/toxicity correlation for anti-PD-1, PD-L1 or CTLA4 (≤ 3 mg/kg)
- Retrospective data suggest that systemic immunosuppression for irAEs might not jeopardize the long-term efficacy of immunotherapy[2]
- Corticosteroid therapy should be tapered gradually, over a period of 4–6 weeks[1]

AE, adverse event; irAE, immune-related adverse event.

1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Professor J. Vansteenkiste, personal communication.

Summary and key takeaways

- The toxicities of immunotherapy are as diverse as the type of treatments that have been devised, affecting most organ systems of the body to some degree[1–7]
- Hypersensitivity reactions (including infusion-related reactions) are the most common and among the most serious AEs associated with mAbs[1,2]
- While several different AEs have been reported following CAR T cell infusion[3,8-9], CRS is the most prevalent[4,9]
- Treatment with immunotherapies, especially checkpoint inhibitors, is associated with irAEs that typically are transient but occasionally can be severe or fatal[5–7]
- The most common irAEs are dermatologic, gastrointestinal, hepatic and endocrinologic toxicities, while pulmonary and cardiovascular toxicities occur less frequent, but are equally important [5–7]
- Guidelines for diagnosis, treatment and follow-up of CPi-associated irAEs have been published[7]
- In general, rapid identification of irAEs and prompt initiation of local or systemic corticosteroid immunosuppression can optimize outcomes[5–7]
- Frequent and consistent communication between patients, caregivers, healthcare providers and oncologists is vital to successful irAE management[5–7]

AE, adverse event; CPi, checkpoint inhibitor; CRS, cytokine-release syndrome; irAE, immune-related adverse event.

1, Baldo. Oncoimmunology 2013;2:e26333. 2. Guan et al. BioMed Res Int 2015;2015:428169. 3. Bonifant et al. Mol Ther Oncolytics 2016;3:16011. doi:10.1038/mto.2016.11. 4. Kerre. Belgian Journal of Hematology 2017;8:94–101. 5. Postow et al. N Engl J Med 2018;378:158–68. 6. Champiat et al. Ann Oncol 2016;27:559–74. 7. Haanen et al. Ann Oncol. 2017;28:iv119-iv142. 8 Adkins S. J Adv Pract Oncol. 2019;10(Suppl 3):21–28. 9 Sievers S. Front Oncol. 2020 Jun 24;10:885.

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Immunotherapy for malignancies

Immunotherapy for malignancies

Click on a chapter below to start learning

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Introduction

Immunotherapy for malignancies

Immunotherapy for malignancies: introduction

- Immunotherapy is a therapeutic modality that harnesses the body's own immune system to fight cancer[1–3]
- Tumor cells can be recognized and killed by the immune system, mostly by the adaptive immune system[3]
- Understanding the modalities of increasing this antitumor activity has led to the development of novel therapeutic agents[4]
- Immunotherapy has changed the treatment landscape for a variety of solid tumors and hematologic malignancies and is helping to improve outcomes for patients[3-4]
- Currently, there is great interest in developing predictors of response to immunotherapy and rational combination therapies that can enhance efficacy by overcoming primary and acquired resistance in comparison with monotherapy treatment[5]

1. Murphy. Oncology 2010;4:67–80. 2. Kirkwood et al. CA Cancer J Clin 2012;62:309–35. 3. Borghaei et al. Eur J Pharmacol 2009;625:41–54. 4. Chen & Mellman. Immunity 2013;39:1–10. 5. Meric-Bernstam et al. Lancet. 2021;397:1010-1022.

Principles of immuno-oncology

Immunotherapy for malignancies

The **dual role** of the immune system in cancer[1,2]

- The immune response to tumors can vary between continuous activation and suppression, with tumor progression favored when the immune response is suppressed[1,2]

- 'Cancer immunoediting' is a three-stage model that helps us to understand the host-protective and tumor-sculpting actions of immunity during cancer[1,2]

Elimination (or immunosurveillance)
Transformed cells are destroyed by a capable immune system (innate and adaptive)[1]

Equilibrium
The immune system retains the tumor in a state of functional dormancy[2]

Escape
The immune system is no longer able to restrict tumor growth; the disease becomes clinically apparent[1,2]

1. Dunn et al. Annu Rev Immunol 2004;22:329–60. 2. Mittal et al. Curr Opin Immunol 2014;27:16–25.

Key scientific concepts of current immunotherapy for cancer

- The main effector cells against tumor cells are **cytolytic T lymphocytes**
  Patients can mount spontaneous antitumor T-cell responses; mounting such a response is a multistep process
- Cytolytic T lymphocytes can recognize **tumor-specific antigens** on the surface of tumor cells
- The **activity of T lymphocytes** can be increased by stimulatory or inhibitory **surface coreceptors**
- In addition to cytolytic T lymphocytes, the immune system can kill tumor cells through **other modalities**
- Tumors have several **mechanisms of resistance** to host antitumor immunity responses

Professor P. Coulie, personal communication.

Key scientific concepts that underpin current immunotherapy for cancer

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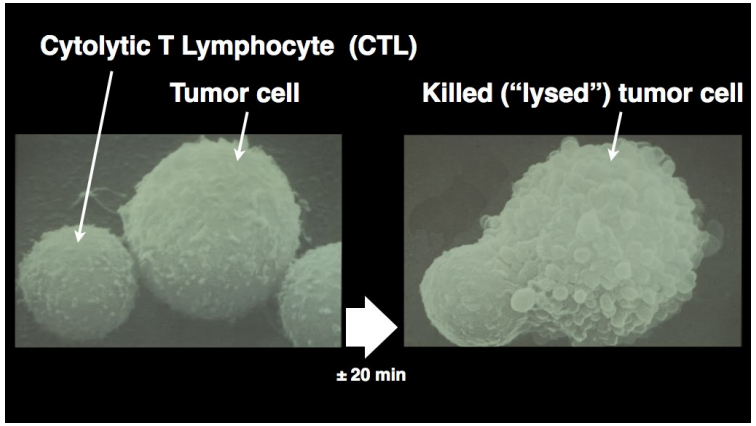
Professor P. Coulie, personal communication.

Tumor-specific cytolytic T lymphocytes

- Immunological memory is the immune system's ability to **respond more rapidly** to a previously encountered pathogen[1]
- This occurs owing to the pre-existence of clonally expanded antigen-specific lymphocytes[1]
- After an immune attack, cytotoxic T cells will either die or differentiate into memory T cells[2]
- Memory T cells remain in the body and recognize the antigen again to support a further immune response[3]
- Cytotoxic and memory T cells recognize their unique activating antigen (presented via APCs) and migrate to the relevant tissue in the event of antigen recurrence[3]
- In cancer, TAAs are one of the main triggers of the T-cell immune response against tumorigenesis[4]



Killing capacities[5]

Absolute tumor **specificity**

Memory

Unique therapeutic modality

Long-lasting, tumor-specific activity

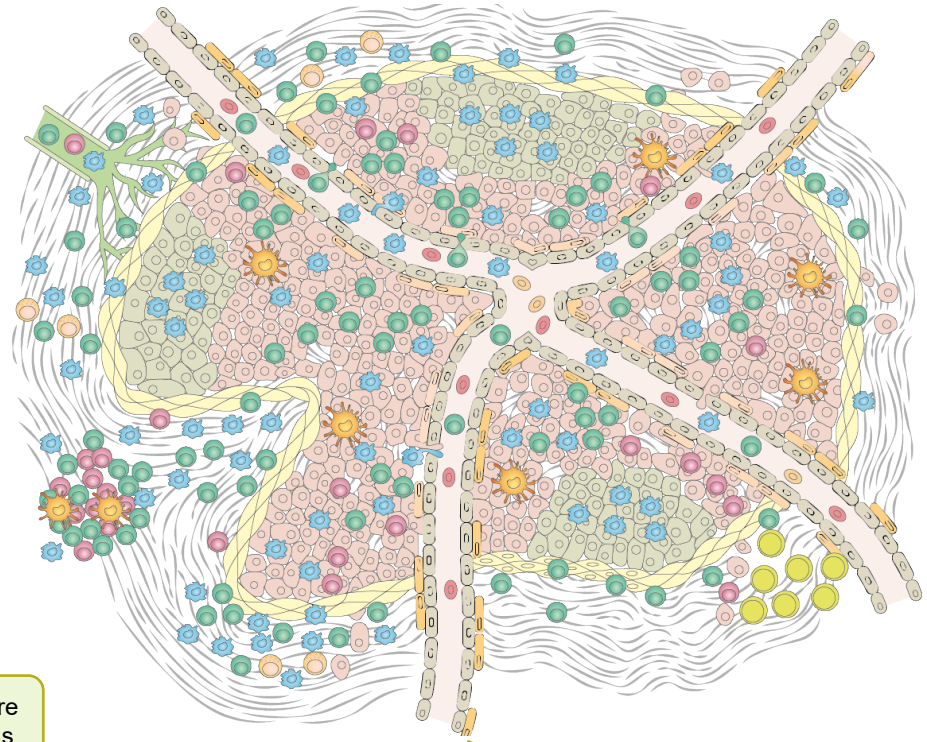
APC, antigen presenting cell; TAAs, tumor-associated antigens.

1. Immunobiology: The Immune System in Health and Disease. 5th edition. Available from: https://www.ncbi.nlm.nih.gov/books/NBK27158/ Accessed Jul 22 2022. 2. Masopust & Schenkel. Nat Revs Immunol 2013:13;309–20. 3. Woodland & Kohlmeier. Nat Rev Immunol 2009;9:153–61. 4. Spurrell & Lockley. Ecancer medical science. 2014;8:441. 5. Professor P. Coulie, personal communication. Image provided by Professor P. Coulie, personal communication.

Spontaneous antitumor T-cell responses

- Tumors contain a complex network of structures (such as blood vessels and connective tissue), cells and chemical signals[1]
- The genetic alterations characteristic of tumors can result in the expression of numerous tumor antigens, allowing the immune system to **differentiate tumor cells from normal cells**[1]
- **Evidence for spontaneous antitumor T-cell responses**
  - Antitumor CTLs are present in cancer patients prior to any treatment, including in blood and within tumors[1]
  - There is a higher incidence of tumors reported in immunosuppressed patients[2]
  - There is downregulation of surface HLA molecules in some types of tumors (most likely as a result of immunoselection)[3]
  - The prognostic or predictive value of TILs is related to the enrichment of tumor-specific T cells[3]
- These responses are insufficient (Darwinian selection of resistant tumors)[3]

The tumor microenvironment[4]



Learn more about TILs

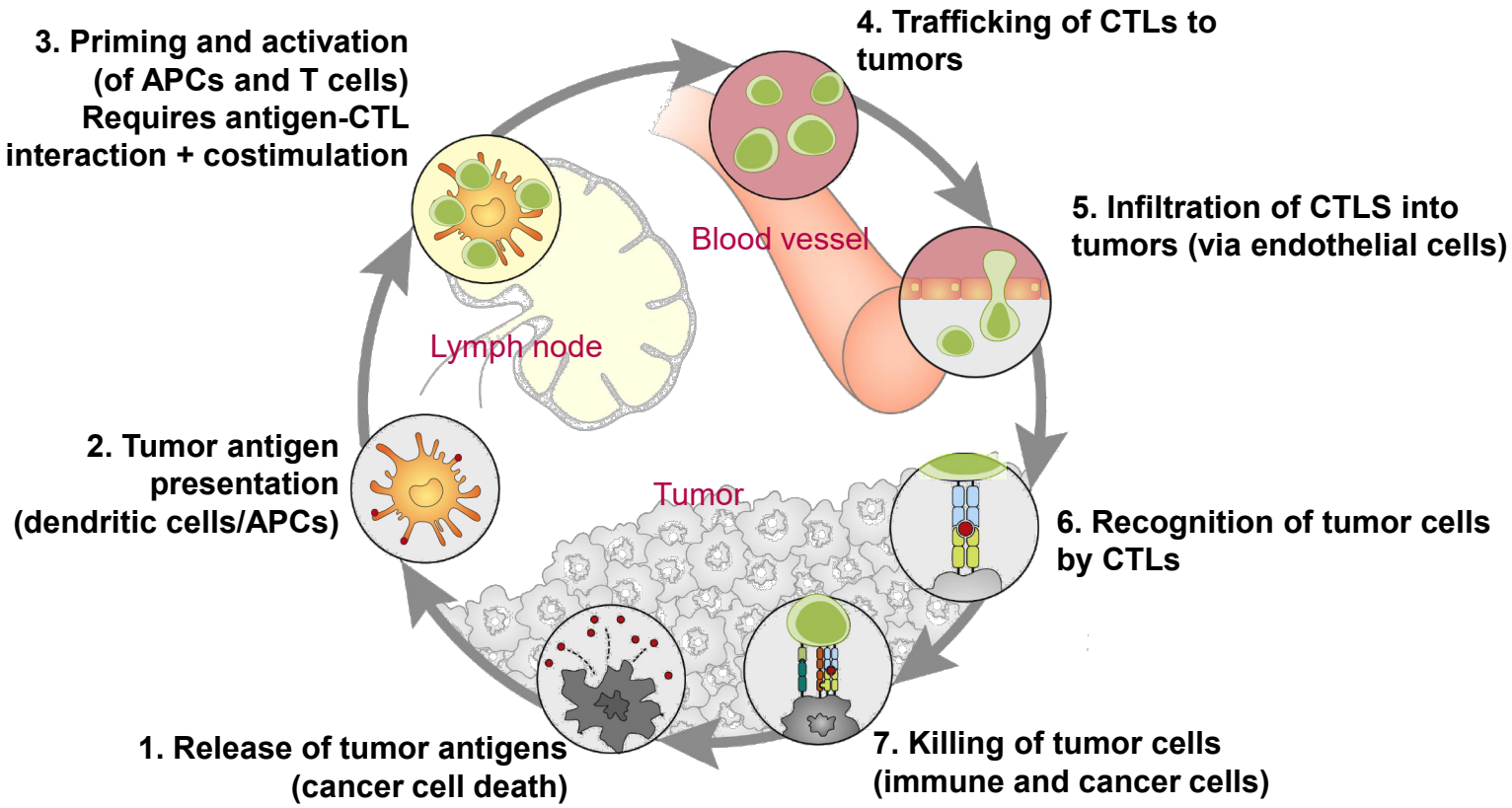
Learn more about the TME

CTL, cytolytic T lymphocyte; HLA, human leukocyte antigen; TIL, tumor-infiltrating lymphocyte; TME, tumor microenvironment.

1. Spurrell & Lockley. Ecancermedicalscience 2014;8:441. 2. Schulz. Int J Cancer 2009;125:1755–63. 3. Professor P. Coulie, personal communication. 4. Balkwill et al. J Cell Sci 2012;125:5591–6.

Mounting antitumor T-cell responses

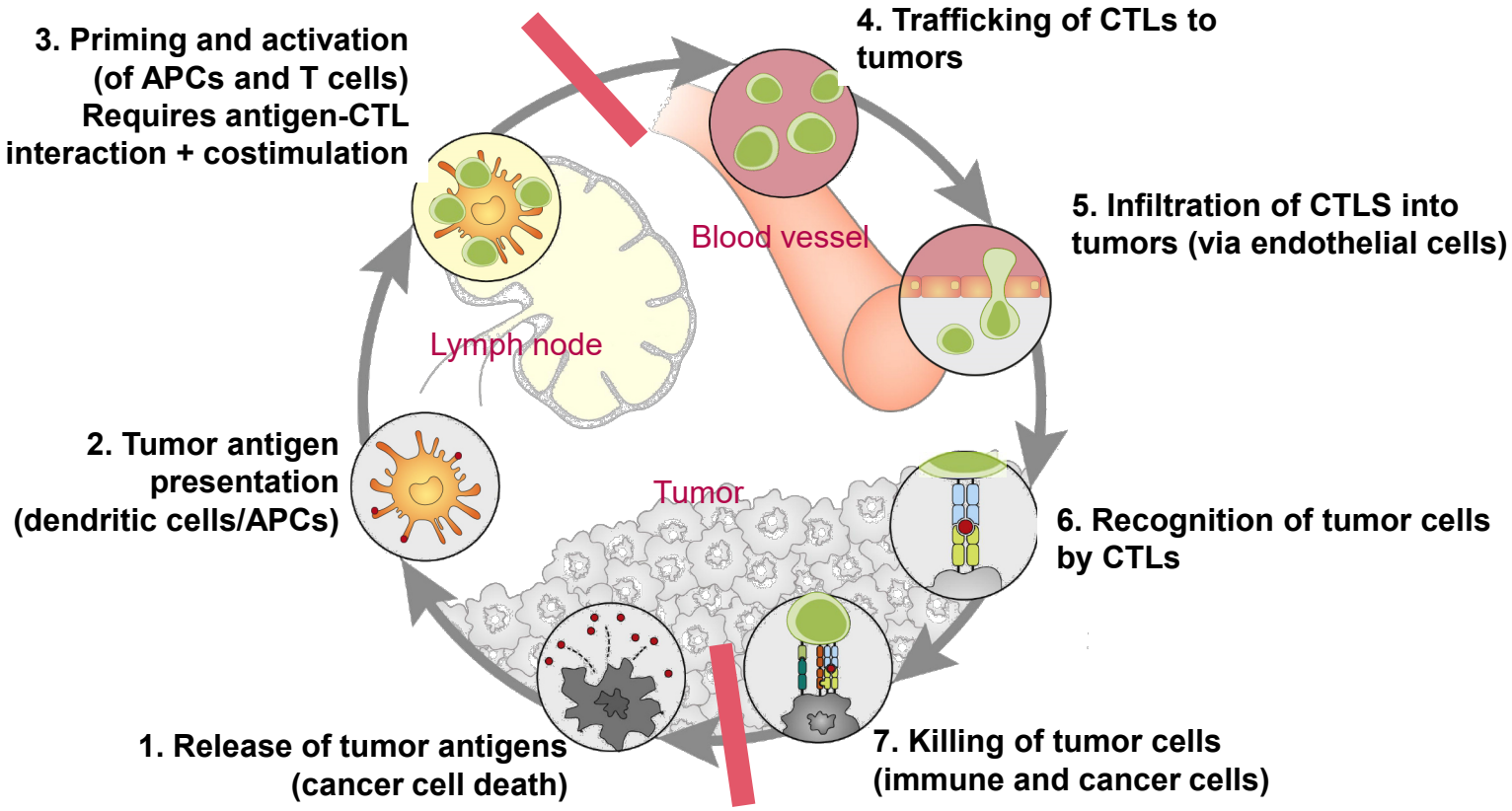
- **Immune surveillance**: identification and elimination of cancer cells by the immune system can be seen as a cyclic series of stepwise events[1]



APC, antigen presenting cell; CTL, cytotoxic T lymphocyte.
Figure adapted from 1. Chen & Mellman. Immunity 2013;39:1–10.

Mounting antitumor T-cell responses

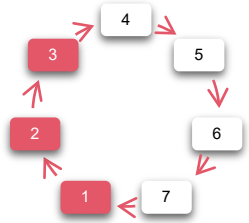
- Each step in the cycle is necessary but not sufficient to eliminate the tumor[1]
- Targeting more than one element of a defective cycle is likely to enhance the immune activity in patients compared with a single point of intervention alone, and is the premise of combination immunotherapy[1]



APC, antigen presenting cell; CTL, cytotoxic T lymphocyte.

1. Professor P. Coulie, personal communication. Figure adapted from 2. Chen & Mellman. Immunity 2013;39:1–10.

Key scientific concepts that underpin current immunotherapy for cancer



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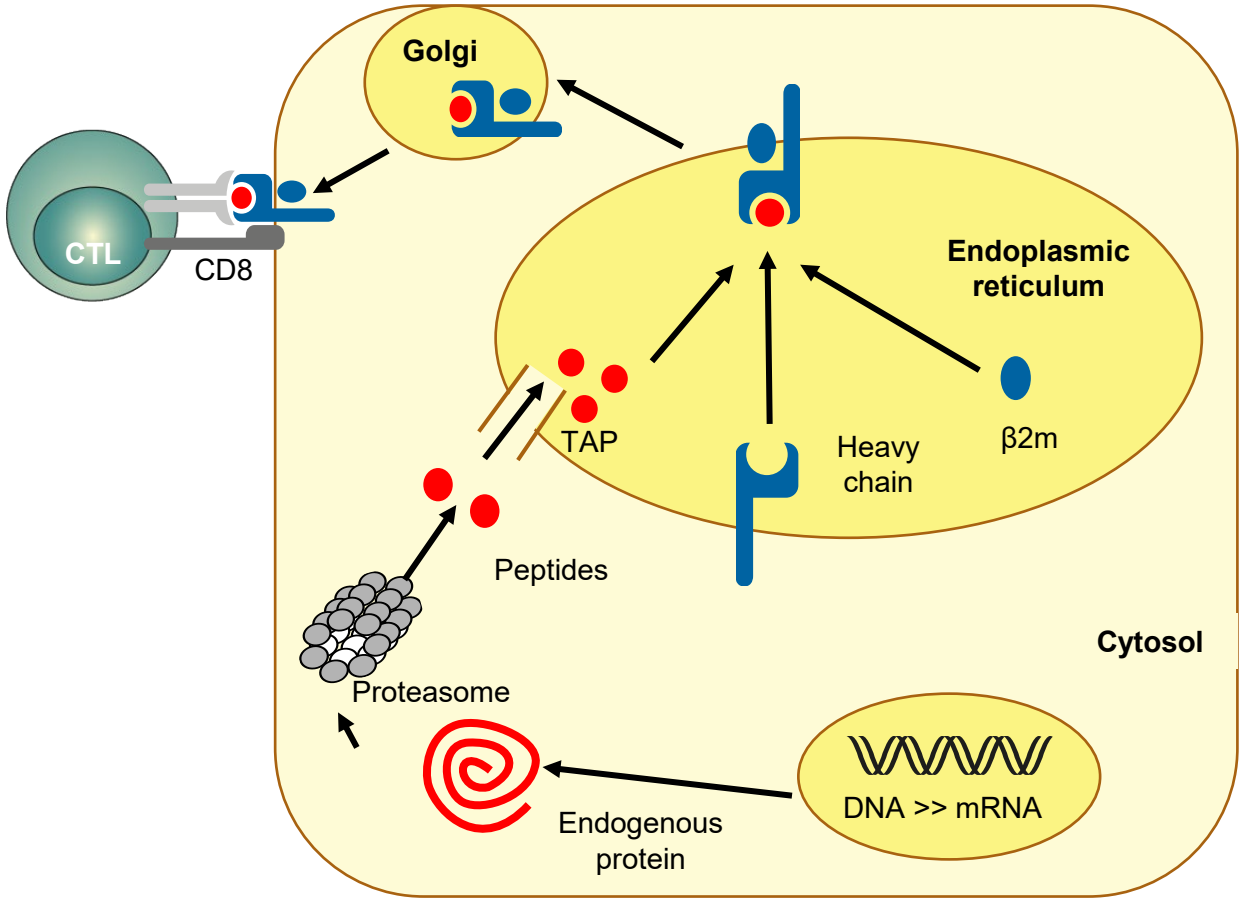
Professor P. Coulie, personal communication

Cytolytic T lymphocytes can recognize tumor-specific antigens on the surface of tumor cells

- Tumor antigens resulting from tumor cell mutations that arise during oncogenesis are released and captured by APCs such as dendritic cells for processing[1]
- Proteins are processed and antigen presentation occurs via HLA class I molecules[2]
  - Proteins are degraded by the proteasome
  - Next, the resultant peptides are translocated by TAP into the ER lumen and loaded onto HLA class I molecules
  - The peptide–HLA class I complexes are then released from the ER and transported via the Golgi to the plasma membrane
- The antigenic tumor peptide is presented to CTLs ($CD8^+$ T cells)[1]

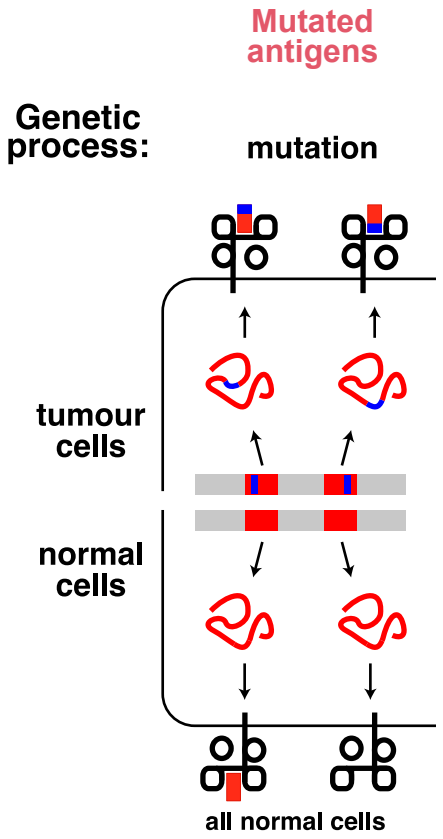


APC, antigen presenting cells; ß2m, beta2 microglobulin; CD, cluster of differentiation; CTL, cytolytic T lymphocyte; ER, endoplasmic reticulum; HLA, human leukocyte antigen; TAP, transporter associated with antigen presentation.

1. Chen & Mellman. Immunity 2013;39:1–10. 2. Neefjes et al. Nat Rev Immunol 2011;11:823–36.

Tumor antigen recognition by T lymphocytes

Five distinct genetic mechanisms lead to the expression of tumor-specific (for the first three mechanisms) or tumor-associated (for the last two) antigens recognized by T cells



DNA mutations and mutated antigens

- Mostly nonsynonymous single-nucleotide variations leading to an amino acid change in a protein
- Mostly occur at random: passenger mutations
- Sometimes occur in oncogenes (KRAS)
- Chromosomal translocations that result in chimeric proteins that are foreign to the host immune system
- A peptide that contains a mutated amino acid can be presented by HLA molecules and recognized by CTLs
- Mutated antigens are also known as 'neoepitopes' or 'neoantigens'

ALL, acute lymphocytic leukemia; CML, chronic myeloid leukemia; CTL, cytolytic T lymphocyte; EML4-ALK, echinoderm microtubule associated protein like 4; HLA, human leukocyte antigen; NSCLC, non-small-cell lung carcinoma.

Coulie et al. Nat Rev Cancer 2014;14:135–46.

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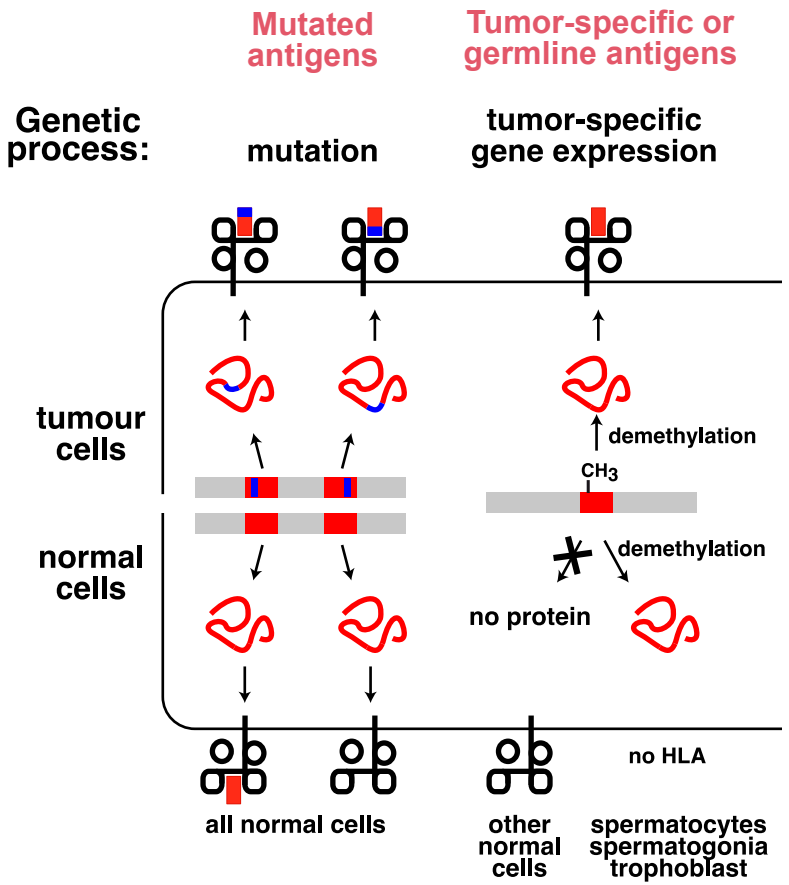

Tumor-specific or germline antigens

- Cancer-germline genes are expressed in tumors
- Most of them are silent in normal adult tissues, except for male germline cells (HLA-negative)
- The reason for this pattern of expression is DNA methylation

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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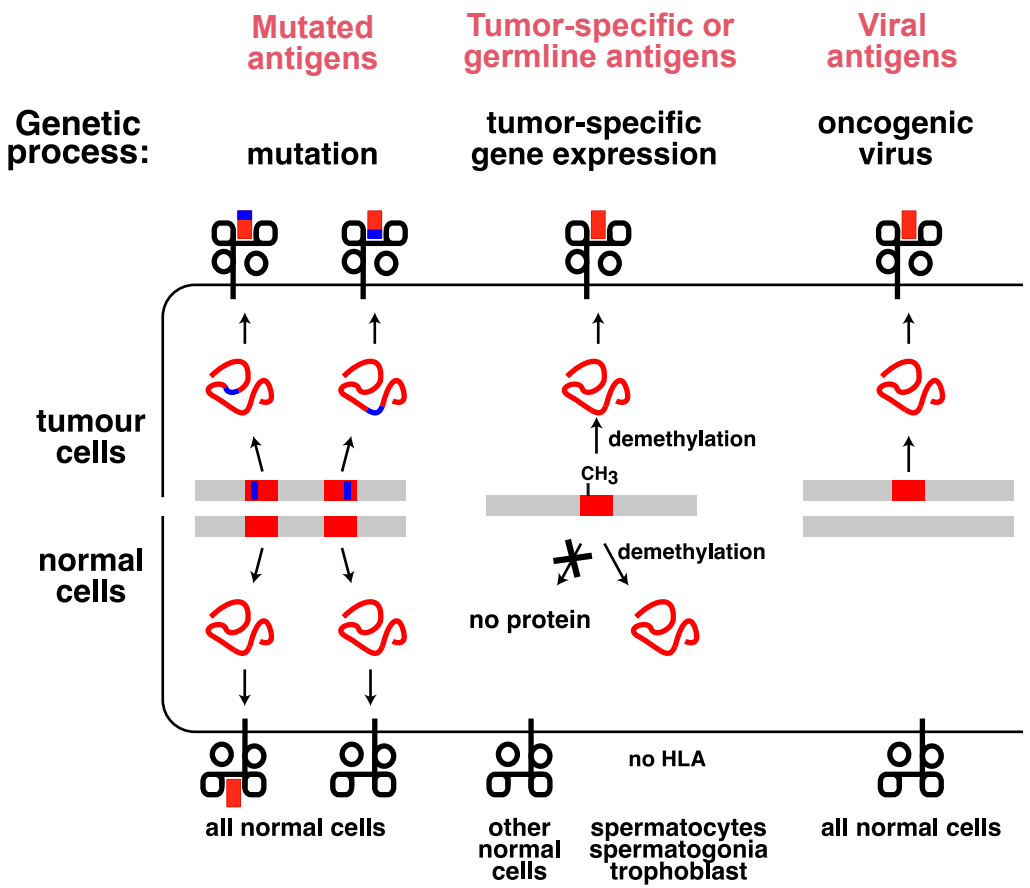

Viral antigens

- A **viral** protein is an antigen specified by the **viral** genome that can be detected by a specific immunological response
- A **viral** antigen is a protein encoded by the **viral** genome
- **Viral** antigens arise in cancer cells from oncogenic viral proteins

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

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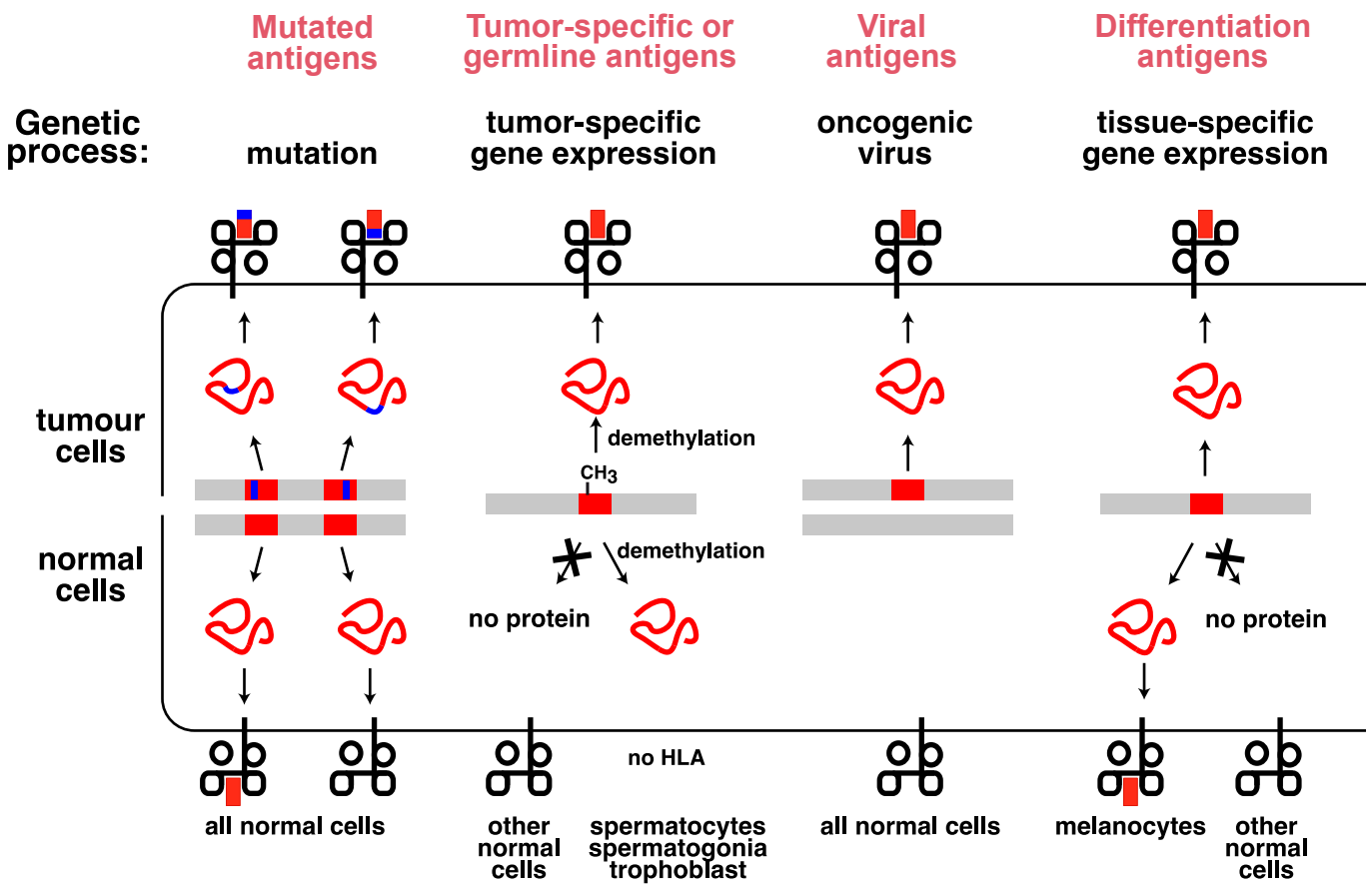


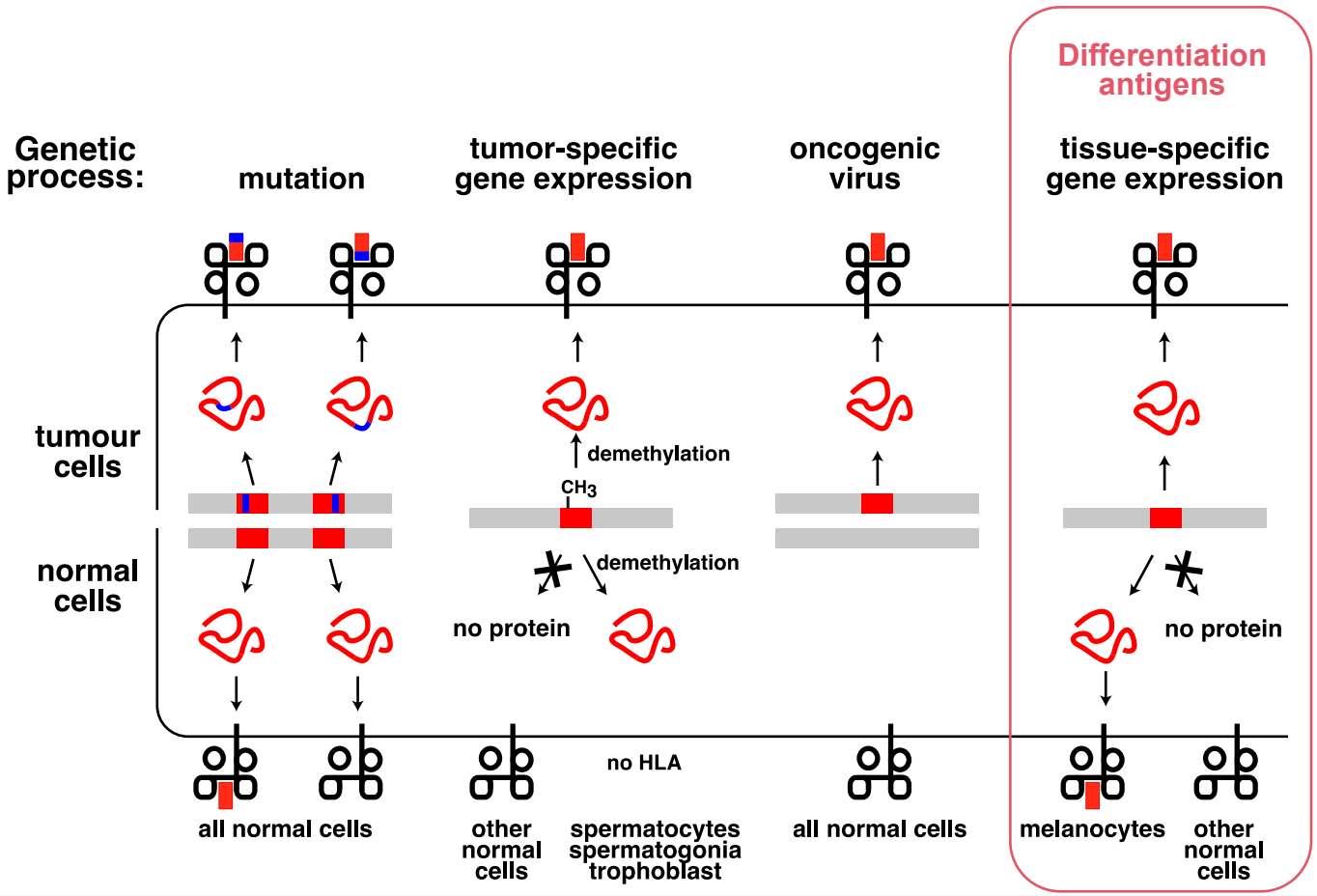
Differentiation antigens

- Differentiation antigens are expressed by both the tumor and the normal tissue from which the tumor arose

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.

Clinical relevance

Tumor antigen recognition by T lymphocytes



Selected examples of approved immunotherapies that target differentiation tumor antigens

- Sipuleucel-T (anti-PAP vaccine for prostate cancer)
- Blinatumomab (CD19–CD3 bispecific antibody for ALL)
- Rituximab (CD20 for CLL)
- Ofatumumab (CD20 for CLL)
- Obinutuzumab (CD20 for CLL and FL)
- Daratumumab (CD38 for MM)
- Elotuzumab (SLAMF7 for MM)

ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; CD, cluster of differentiation; FL, follicular lymphoma; HLA, human leukocyte antigen; MAGE, melanoma antigen gene; MM, multiple myeloma; PAP, prostatic acid phosphatase; SLAMF7, signaling lymphocytic activation molecule F7.

Coulie et al. Nat Rev Cancer 2014;14:135–46.

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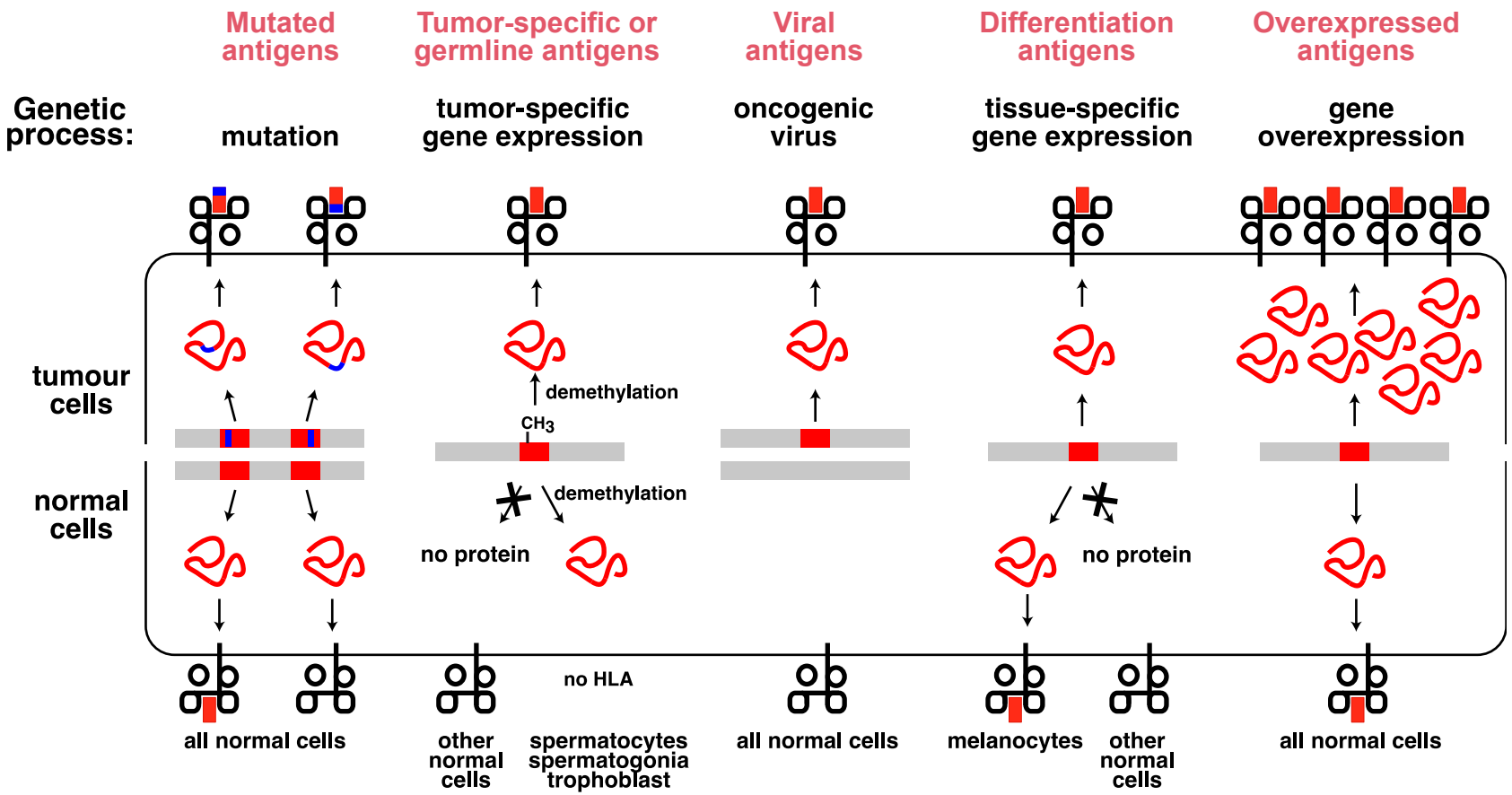

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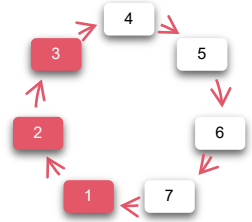
Adaptive immunity and controlling tumor growth



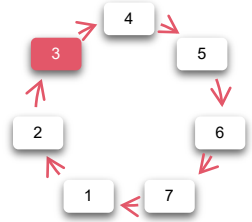
- **TAAs** are important triggers of the immune response, and are recognized by T-cells[1]

TAA	Mechanism of immune activation	Examples[1]
Mutated antigens[1] (also known as neoantigens)[2]	Arise as a result of genetic mutations or splicing aberrations, which leads to the generation of a protein that is foreign to the host immune system[1] In certain tumors, chromosomal location can result in the fusion of distant genes, and the expression of an abnormal **fusion protein** that is foreign to the host immune system[2]	• Individual **KRAS** mutations in colon, pancreatic and other cancers • **BCR-ABL** in CML and some ALL • **EML4-ALK** in NSCLC
Tumor-specific antigens[1]	Mutations in the tumor genome can cause tumors to express mutant proteins. They are not expressed on normal cells	• **MAGE** (melanoma-associated antigen) • **BAGE** (B melanoma antigen) **GAGE** (G antigen) • **LAGE1** = NY-ESO-1
Viral antigens[2]	Arise in cancer cells from oncogenic viral proteins[2]	• **HPV oncoproteins E6** and **E7** in HPV-associated cancers of the cervix, anus and oropharynx
Differentiation antigens[1]	Expressed by the tumor and the normal tissue from which the tumor arose[1]	• **CEA** – expressed in embryonic tissues and overexpressed in colorectal cancer • **PSA** – expressed in normal prostate and overexpressed in prostate cancer; • **gp100** – expressed in melanocytes and melanoma
Overexpressed antigens[1]	Expression levels in normal tissues is below the required threshold for T-cell activation. Overexpression by malignant cells therefore overrides the tolerance and triggers T-cell activation[1]	• **HER2** – overexpressed in breast cancer • **AFP** – overexpressed in HCC and some germ cell tumors

AFP, alphafetoprotein antigen; ALL, acute lymphoblastic leukaemia; CEA, carcinoembryonic antigen; CML, chronic myeloid leukaemia; EML4-ALK, echinoderm microtubule associated protein like 4 – anaplastic lymphoma kinase, gp100, glycoprotein 100; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; NSCLC, non-small-cell lung carcinoma; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen; TAA, tumor-associated antigens.

1. Spurrell & Lockley Ecancermedicalscience. 2014;8:441. 2. Yarchoan et al. Nat Rev Cancer 2017;17:209–22.

Key scientific concepts that underpin current immunotherapy for cancer



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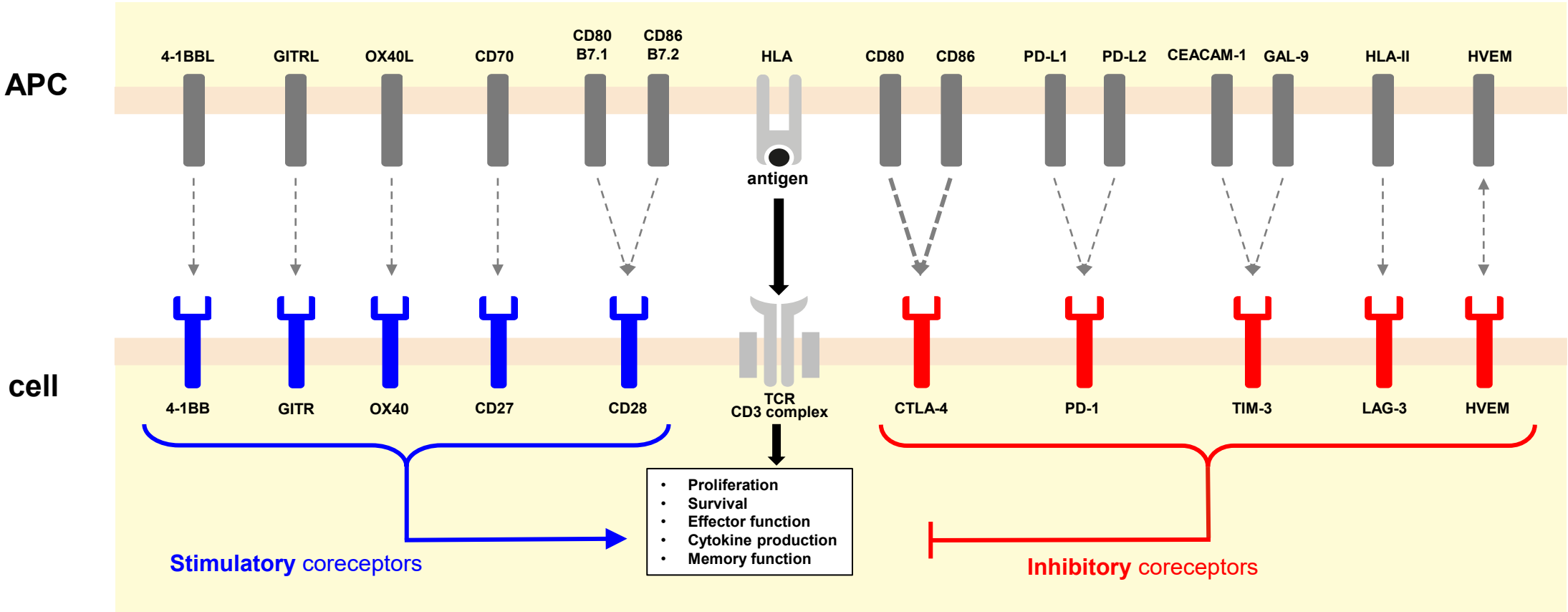
Professor P. Coulie, personal communication.

The activity of T lymphocytes can be increased by stimulatory or inhibitory surface coreceptors

Stimulatory and inhibitory T-cell coreceptors

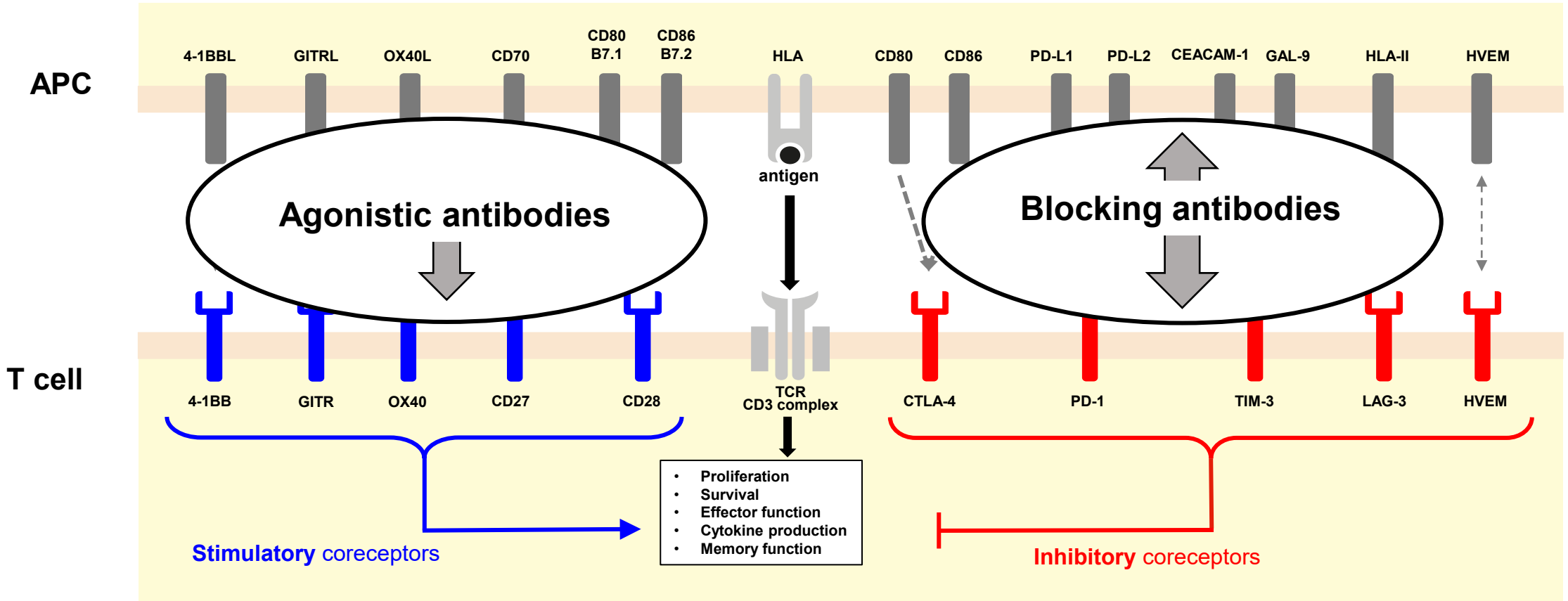


APC, antigen-presenting cell; CD, cluster of differentiation; CEACAM-1, carcinoembryonic antigen-related cell adhesion molecule 1; CTLA-4, cytotoxic T-lymphocyte associate protein 4; GAL-9, galectin 9; GITRL, glucocorticoid-induced TNF receptor ligand; HLA, human leukocyte antigen; HVEM, herpesvirus 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.

Adapted from Kershaw et al. Nat Rev Cancer 2013;13:525–41.

Manipulation of T-cell regulatory pathways by the use of antibodies can increase T-cell activity

- **Blocking** the effects of inhibitory coreceptors or **activating** stimulatory coreceptors promotes T-cell activation; this has been shown to have **clinical antitumor effects** in cancer patients



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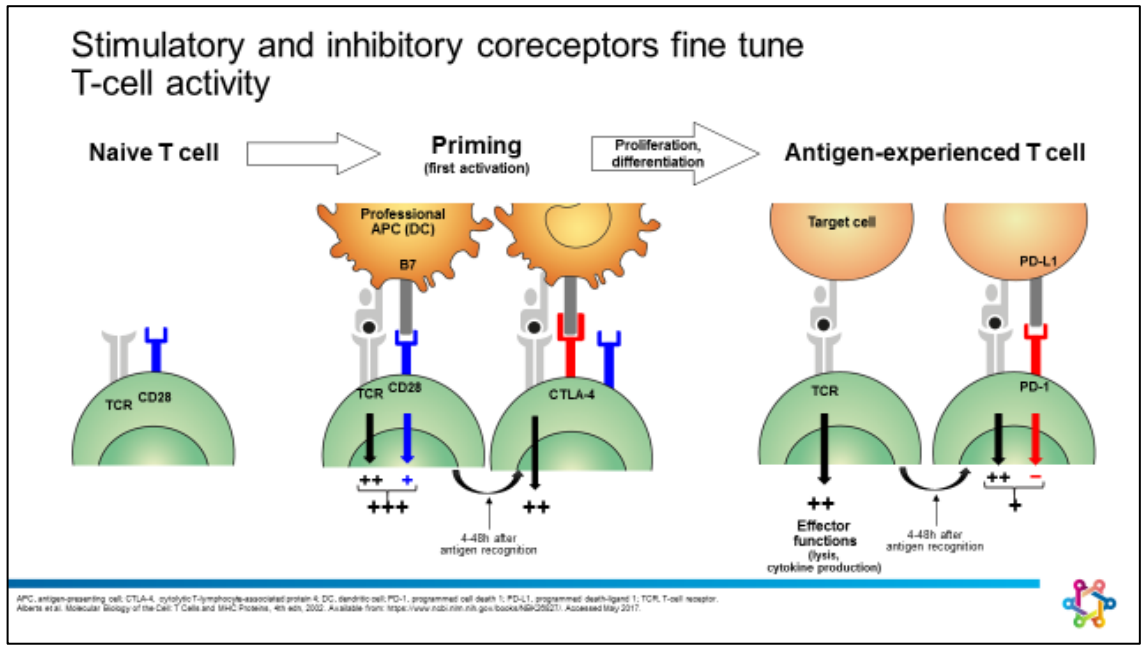
Clinical relevance
Modulation of T-cell activity



➢ Checkpoint inhibitors

Monoclonal antibodies that block T-cell inhibitory coreceptors to increase T-cell activity and are used in oncology

- **Anti-CTLA-4 antibodies**

  Ipilimumab, indicated for melanoma, RCC, NSCLC, mesothelioma, CRC and OSCC

- **Anti-PD-1 antibodies**

  Nivolumab, indicated for melanoma, NSCLC, RCC, cHL, SCCHN, urothelial carcinoma, mesothelioma, CRC, oesophageal/GEJ cancer and Gastric/Oesophageal/GEJ adenocarcinoma

  Pembrolizumab, indicated for melanoma, NSCLC, cHL, urothelial carcinoma, SCCHN, RCC, OS, triple-negative breast cancer, endometrial carcinoma, cervical cancer and MSI-H cancers (CRC, endometrial carcinoma and gastric cancer)

- **PD-L1 antibodies**

  Atezolizumab, indicated for urothelial carcinoma, NSCLC, breast cancer and hepatocellular carcinoma

  Avelumab, indicated for Merkel cell carcinoma, urothelial carcinoma and RCC

  Durvalumab, indicated for NSCLC and ES-SCLC

  Cemiplimab, indicated for NSCLC, BCC and CSCC

- **Anti-PD-1 antibody + Anti-Lag-3[a1]**

  Nivolumab + **Relatlimab**, indicated for melanoma

[a]Positive CHMP opinión on July 2022

BCC, basal cell carcinoma; cHL, classical Hodgkin lymphoma; CRC, colorectal cancer; CSCC, cutaneous squamous cell carcinoma; CTLA-4, cytolytic T-lymphocyte-associated protein 4; ES-SCLC, extensive-stage small cell lung cancer; GEJ, gastro-esophageal junction; NSCLC, non-small-cell lung cancer; OS, oesophageal squamous; OSCC, oesophageal squamous cell carcinoma; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; PI, prescribing information. RCC, renal cell carcinoma; SCCHN, squamous cell cancer of the head and neck. 1. EMA, CHMP, Summary of opinion, July 2022: 2https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-opdualag_en.pdf Always refer to the SmPC. All SmPCs are available from http://www.ema.europa.eu/ema/. Accessed August 1, 2022

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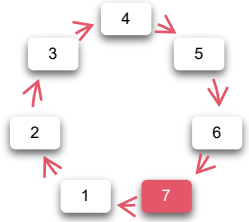
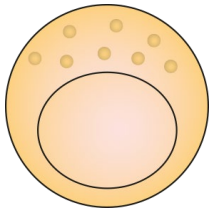
Professor P. Coulie, personal communication.

Other modalities of tumor cell killing by the immune system



Innate immune system

NK cells



- With antibodies (antibody-dependent cellular cytotoxicity)
- Without antibodies

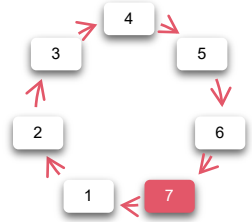
Adaptive immune system

Antibodies

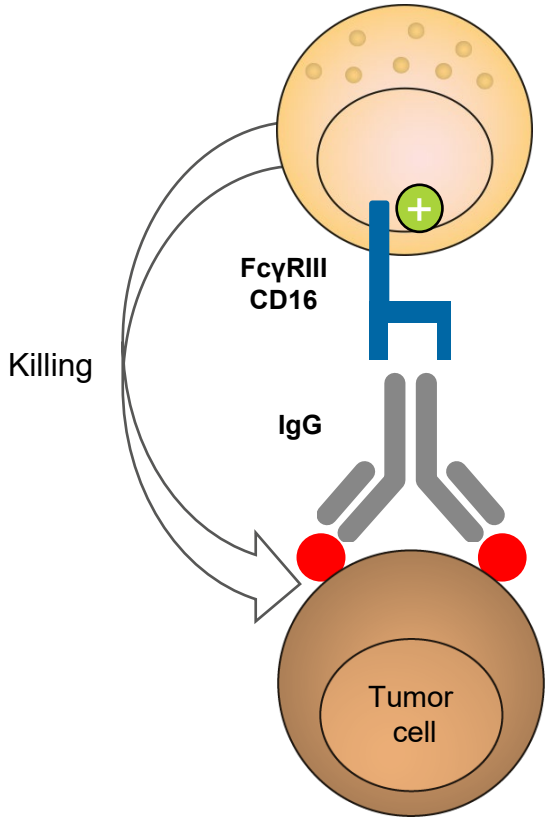
- Through NK cells (antibody-dependent cellular cytotoxicity)
- Through complement-mediated cytotoxicity

NK, natural killer.
Professor P Coulie, personal communication.

Tumor cell killing by NK cells with antibodies



Antibody-dependent cellular cytotoxicity



NK cells target cells recognized by IgG antibodies for destruction

Part of the anticancer activity of the following monoclonal antibodies is mediated by NK cells:

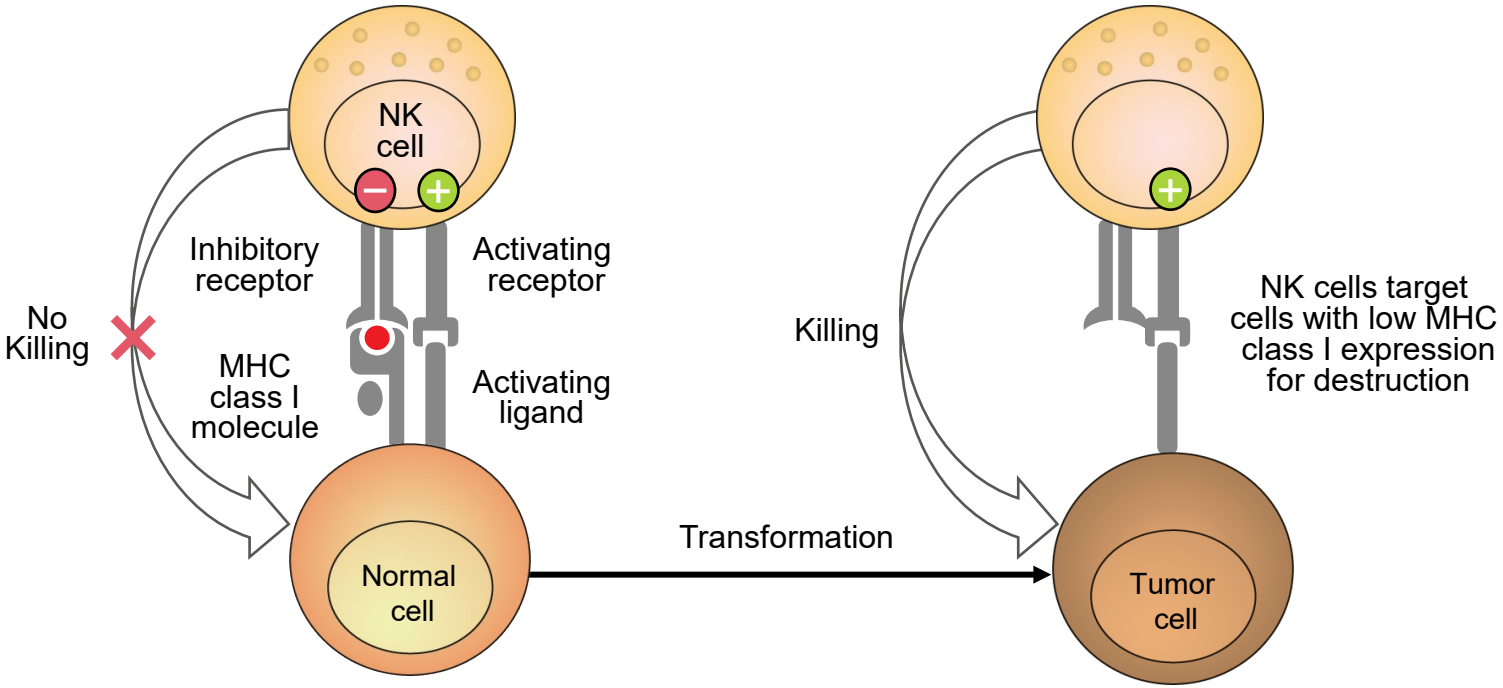
- Rituximab
- Trastuzumab

The Fc part of IgG antibodies can be engineered to allow or abrogate binding to FcγRIII and NK cell activation

CD, cluster of differentiation; Ig, immunoglobulin; NK, natural killer.
Boyerinas et al. Cancer Immunol Res 2015;3:1148–57.

Tumor cell killing by NK cells without antibodies

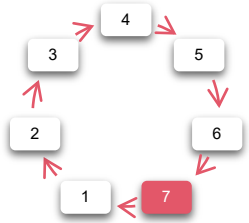
- NK cell activation is controlled by a balance between signals mediated via activating and inhibitory receptors[1]
- During tumor progression, tumor variants that upregulate ligands for inhibitory receptors and/or lose ligands for activating receptors may evolve, potentially allowing tumors to escape NK-cell-mediated recognition[1]



MHC, major histocompatibility complex; NK, natural killer.

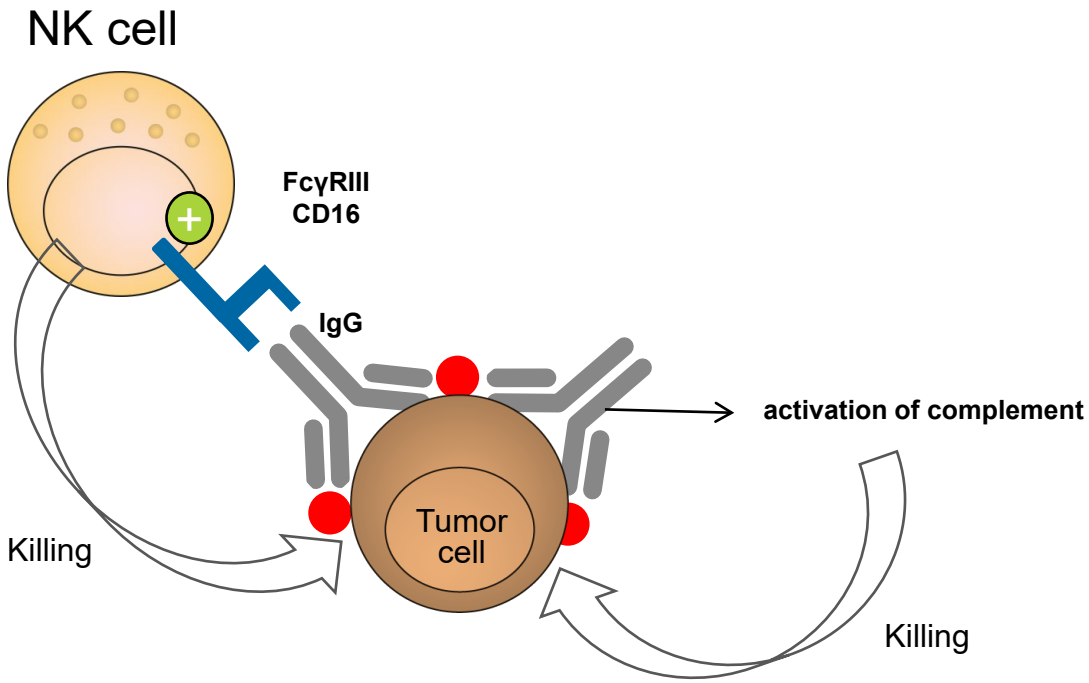
1. Ljunggren & Malmberg. Nat Rev Immunol 2007;7:329–39. 2. Pandya et al. J Immunol Res 2016;2016:4273943.

Tumor cell killing by the adaptive immune system

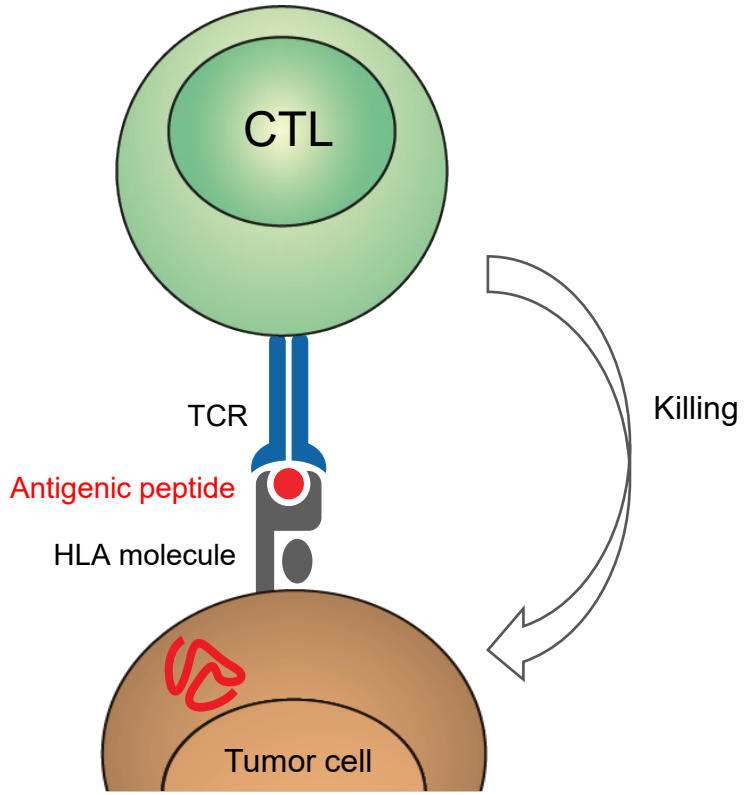


Direct recognition of **extracellular** tumor antigens by antibodies

(**CAR-T** cells are another modality of direct recognition of extracellular tumor antigens)

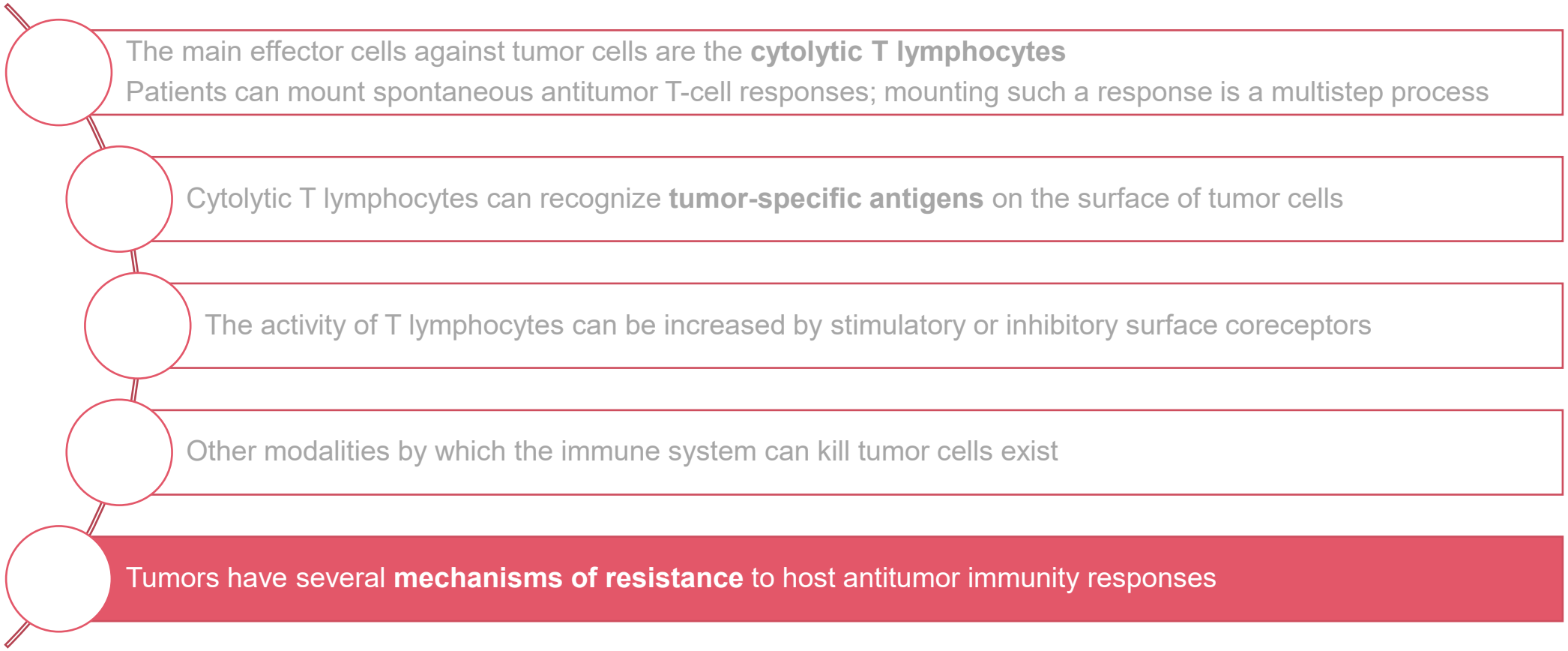


Recognition of **intracellular** tumor antigens by CTLs



CTL, cytolytic T lymphocyte; CD, cluster of differentiation; HLA, human leukocyte antigen; Ig, immunoglobulin; NK, natural killer; TCR, T-cell receptor.
Professor P Coulie, personal communication.

Key scientific concepts that underpin current immunotherapy for cancer



Professor P. Coulie, personal communication

Tumor resistance to immune attack

- The genetic instability of tumors and the selection by the immune system that destroys tumor cells create a 'darwinian machine', i.e. rounds of variation, selection and inheritance
- For all treatments that eliminate tumor cells, the residual cells resist the treatment
- If one admits that all incipent tumors are recognized by the host's immune system, clinically apparent tumors must have developed, prior to immunotherapy, mechanisms to avoid immune elimination[2]
- There are three main mechanisms of tumor resistance[2]

Loss/decrease of antigenicity[2]

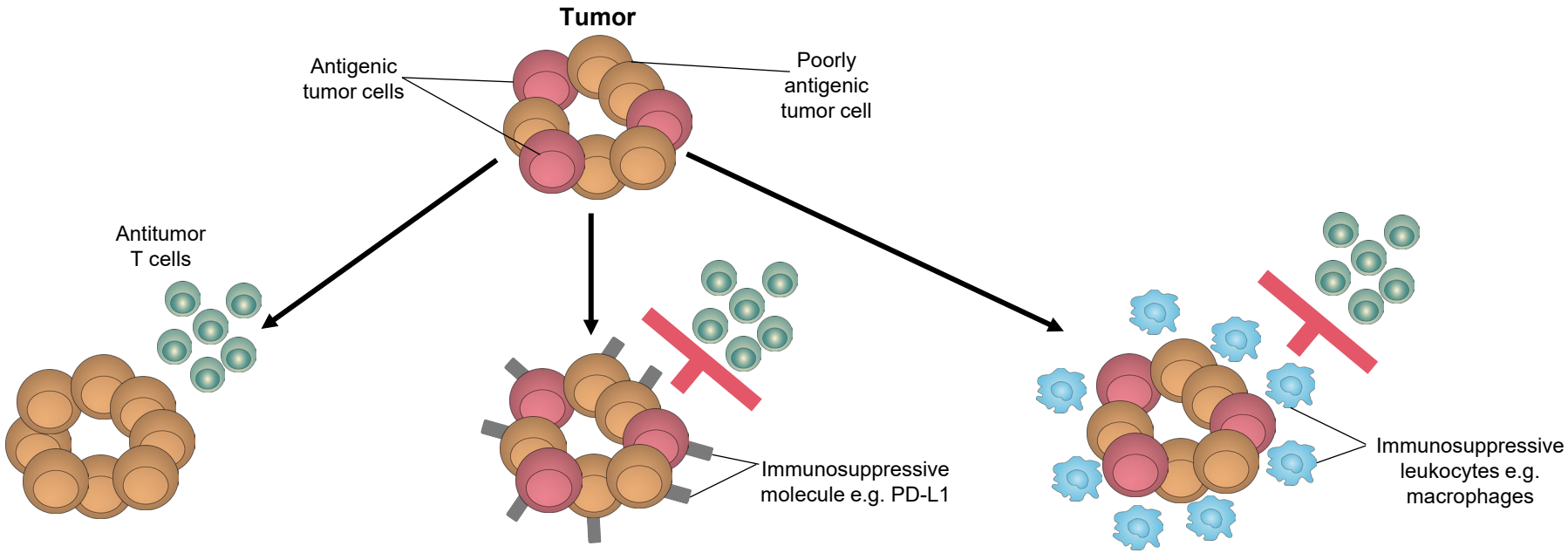
Loss/decrease of immunogenicity[2]

Tumor-driven immunosuppression[2]

TME, tumor microenvironment

1. Mittal et al. Curr Opin Immunol 2014;27:16–25. 2. Beatty & Gladney. Clin Cancer Res 2015;21:687–92. 3. Professor P. Coulie, personal communication.

Mechanisms of tumor resistance to immune attack



Loss/decrease of antigenicity[1,2]

- Can be achieved by downregulation or loss of expression of the antigenic peptide or antigen processing machinery (e.g. loss of HLA, ß2m, TAP)
- Can be irreversible (e.g. mutations, gene deletions) or reversible (mostly through IFNγ)[2]

Loss/decrease of immunogenicity[1]

- Tumors with adequate antigenicity for immune recognition can decrease their immunogenicity through modulation of checkpoint molecules
- e.g. IFN-γ produced by TILs can induce upregulation of PD-L1 on tumor cells (an example of adaptive resistance)

Immunosuppressive environment[1]

- Alterations in oncogenes and tumor suppressor genes can result in an immune reaction that suppresses or inhibits antitumor immunity within the TME

Learn more about the TME and immunosuppression

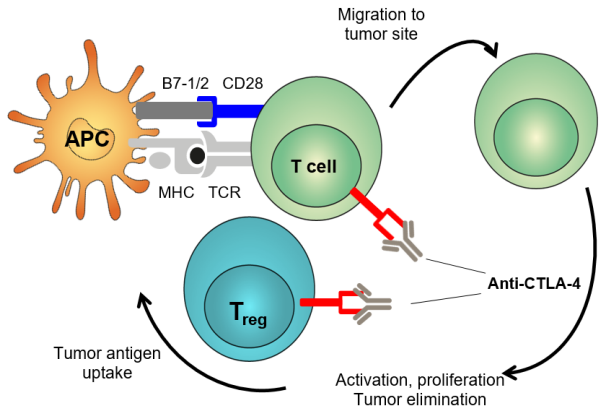
ß2m, beta$_2$ macroglobulin; HLA, human leukocyte antigen; IFN, interferon; PD-L1, programmed-death ligand 1; TAP, transporter associated with antigen presentation; TIL, tumor-infiltrating lymphocyte; TME, tumor microenvironment.

Adapted from Beatty & Gladney. Clin Cancer Res 2015;21:687–92. 2. Professor P. Coulie, personal communication.

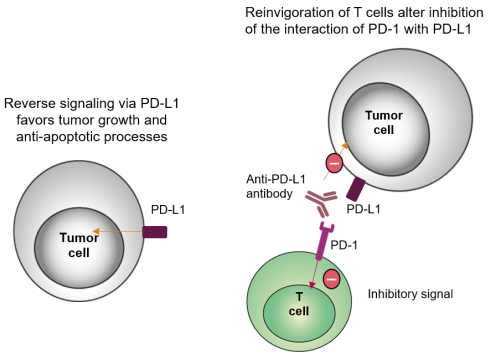
Clinical relevance

Immunoregulatory, or 'immune checkpoint' molecules in cancer treatment

CTLA-4 'checkpoint' inhibitors: targeting CTLA-4



PD-1/L1 'checkpoint' inhibitors: targeting PD-1 and PD-L1



- Immune checkpoints such as **CTLA-4** and **PD-1** serve vital roles in regulating T-cell responses[1]
- In cancer, T-cells undergo chronic exposure to continuous antigen stimulation, which can lead to deteriorated T-cell function and constitutive action of immune checkpoints, termed '**exhaustion**'[1]
- This state is commonly associated with poor tumor control[1]
- Immune checkpoints have been assessed as **potential targets in the treatment of cancer**, and have been found to be effective in reinvigorating exhausted T cells by restoring immunity to eliminate cancer[2]

Newly defined immune checkpoints:
LAG-3 , TIM-3 and TIGIT[3]

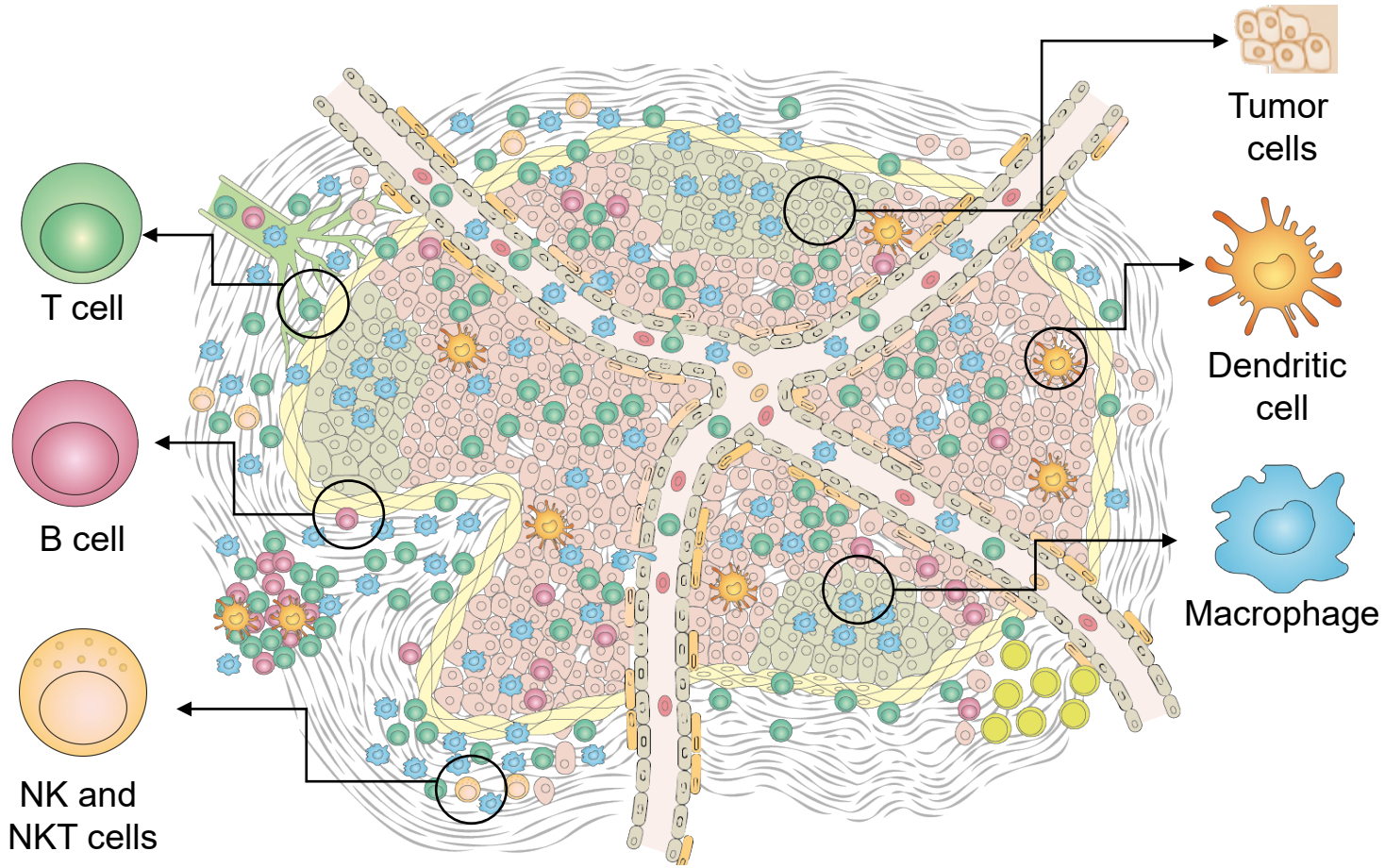
APC, antigen-presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte associated protein 4; LAG3, lymphocyte activation gene 3; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor; TIGIT, T-cell immunoreceptor; TIM-3, T cell immunoglobulin and mucin domain 3; T_{reg}, regulatory T-cell.

1. Beatty & Gladney. Clin Cancer Res 2015;21:687–92. 2. Buchbinder & Desai. Am J Clin Oncol 2016;39:98–106. 3. Tsai & Hsu. J Biomed Sci 2017;24:35–43.

Back to antitumor responses
Back to tumor resistance

The tumor microenvironment

- Interactions between tumor and normal cells, particularly immune cells, create the TME
- The TME plays a pivotal role in tumor growth and metastasis[1,2]
- There are numerous tumor-driven immunosuppressive mechanisms at work within in the TME, including:[3]
  - A shortage of nutrients e.g. tryptophan (downgraded by IDO-1), arginine, oxygen
  - Immunosuppressive soluble factors e.g. TGF-ß, IL-10, galectins, PGE2, extracellular adenosine
  - Immunosuppressive cells e.g. T_{regs}, myeloid-derived suppressor cells
  - Inhibitory cofactors e.g. constitutive expression of PD-L1 on tumor cells

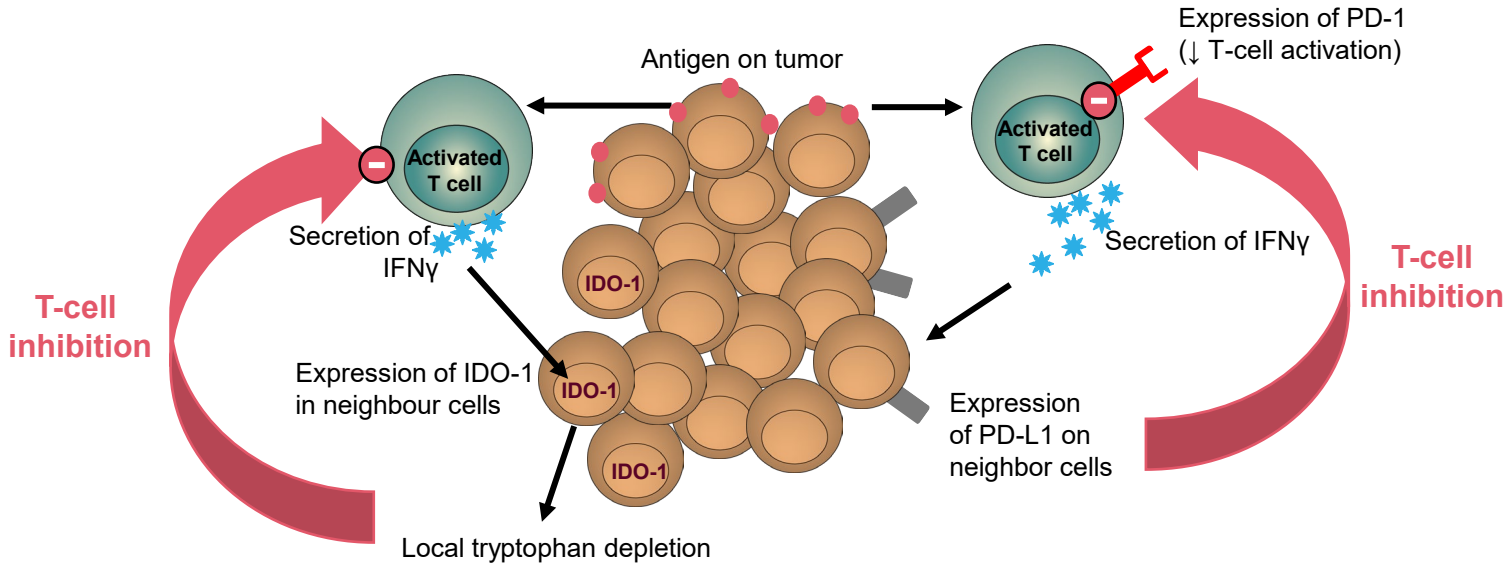


IDO-1, Indoleamine-pyrrole 2,3-dioxygenase-1; IL, interleukin; NK, natural killer; NKT, natural killer T; PD-L1, programmed death-ligand 1; PGE-2. prostaglandin E2; TGF-ß, transforming growth factor beta; TME, tumor microenvironment; T_{reg}, regulatory T cell.

1. Balkwill et al. J Cell Sci 2012;125:5591–6. 2. Chen et al. BMC Medicine 2015;13:45. 3. Professor P. Coulie, personal communication.

TILs: the numbers game

- Insufficient recruitment of immune cells into the tumor can also promote tumor resistance to the immune response[1]
- Antitumor T cells are inhibited though inhibitory coreceptors such as PD-1[1]
- Adaptive resistance describes the induction of immune suppressive pathways in the tumor (such as PD-1) following active immune attack on the tumor[2]
- It is a scalable process where the magnitude of immune suppression matches the magnitude of the immune attack; the net balance between suppression and attack determines the durability of the anti-tumor response and tumor outcome[2]
- Adaptive resistance is mediated via physiologic negative feedback systems[1]



- PD-1 and PD-L1 inhibit the function of TILs, causing tumor cells to evade immune response[3]

IDO, Indoleamine-pyrrole 2,3-dioxygenase-1; IFNγ, interferon gamma; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; TIL, tumor-infiltrating lymphocyte; T_{reg}, regulatory T.

1. Professor P. Coulie, personal communication. 2. McGray & Bramson. Adv Exp Med Biol 2017;1036:213–27. 3. Beatty & Gladney. Clin Cancer Res 2015;21:687–92. Figure adapted from 1.

Mounting antitumor T-cell responses: the prognostic value of TILs

There is a demonstrable correlation between the level of immune cell infiltration and prognosis in a number of cancers

Tumor type	Immune cell infiltrate	Clinical outcome
Melanoma	CD4 T cell	Improved survival and spontaneous tumor regression
Breast cancer	Intratumoral T cells, including CD8 T cells and Th1 CD4 T cells	Improved survival and earlier stage disease
Ovarian cancer	T cells, including CD8 T cells	Improved survival and reduction in VEGF
NSCLC	CD4 and CD8 T cells	Improved prognosis in early stage and advanced stage disease
Breast cancer	High T_{reg} cells	Poor prognosis disease (high-tumor grade, ER-negative negative lymph node positive); reduced disease-free and overall survival
Melanoma	High T_{reg} cells	Increased recurrence rate
Ovarian cancer	High T_{reg} cells	Poor prognosis
NSCLC	High T_{reg} cells	Increased risk of recurrence in resected early stage disease

High CD4 and CD8 T cell infiltration usually indicates a clinically relevant antitumor immune response, and is associated with a positive prognosis

T_{reg} cells are immunosuppressive; tumors with high T_{reg} infiltration are associated with a poorer prognosis

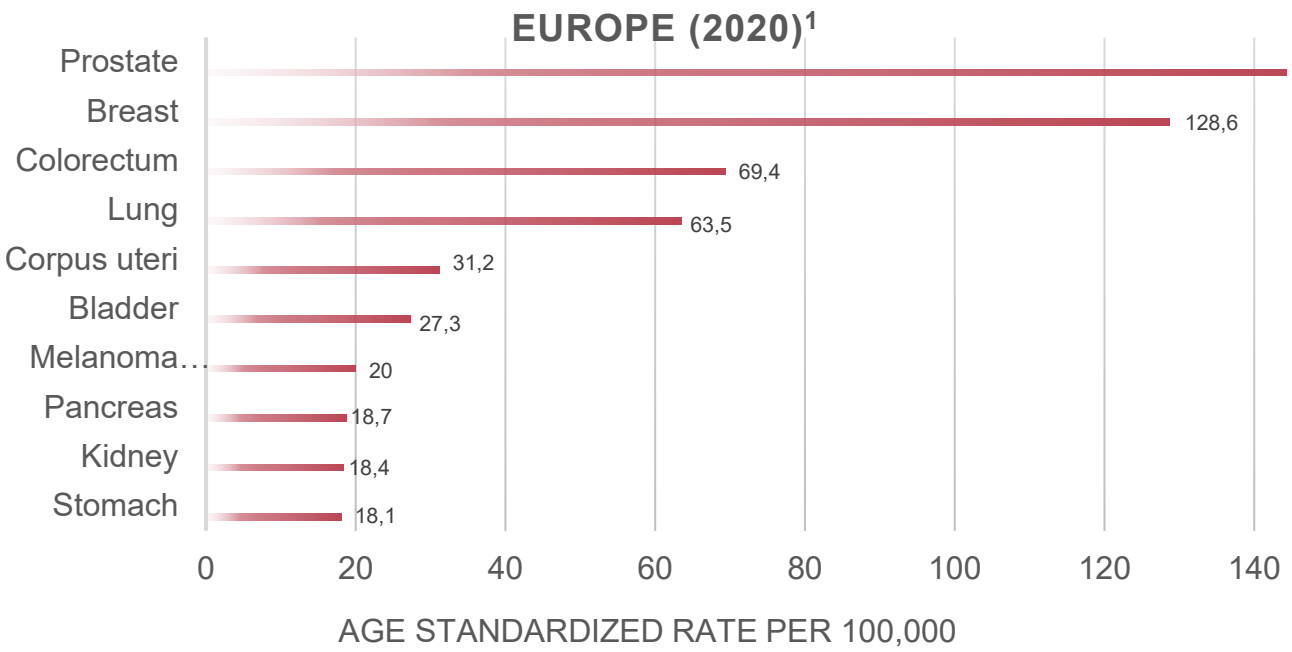
CD, cluster of differentiation; ER, estrogen receptor; NSCLC, non-small-cell lung carcinoma; Th, helper T; T_{reg}, regulatory T; TIL, tumor infiltrating lymphocyte; VEGF, vascular endothelial growth factor.
Spurrell and Lockley. Ecancermedicalscience 2014;8:441.

Immunotherapy for solid tumors

Immunotherapy for malignancies

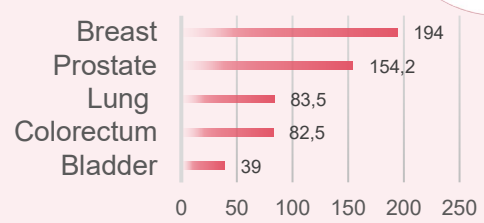
Most frequent solid tumor cancers in Europe

ESTIMATED INCIDENCE FOR BOTH SEXES

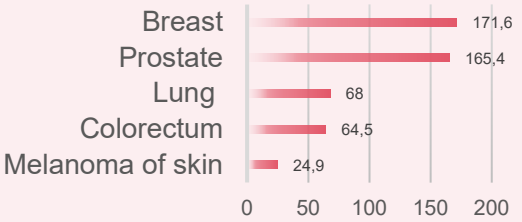


COUNTRY-SPECIFIC (2020)

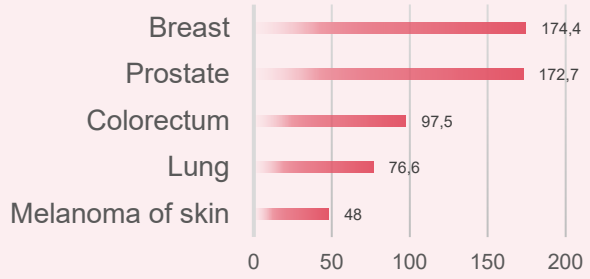
- Belgium[2]



- Luxembourg[3]



- The Netherlands[4]



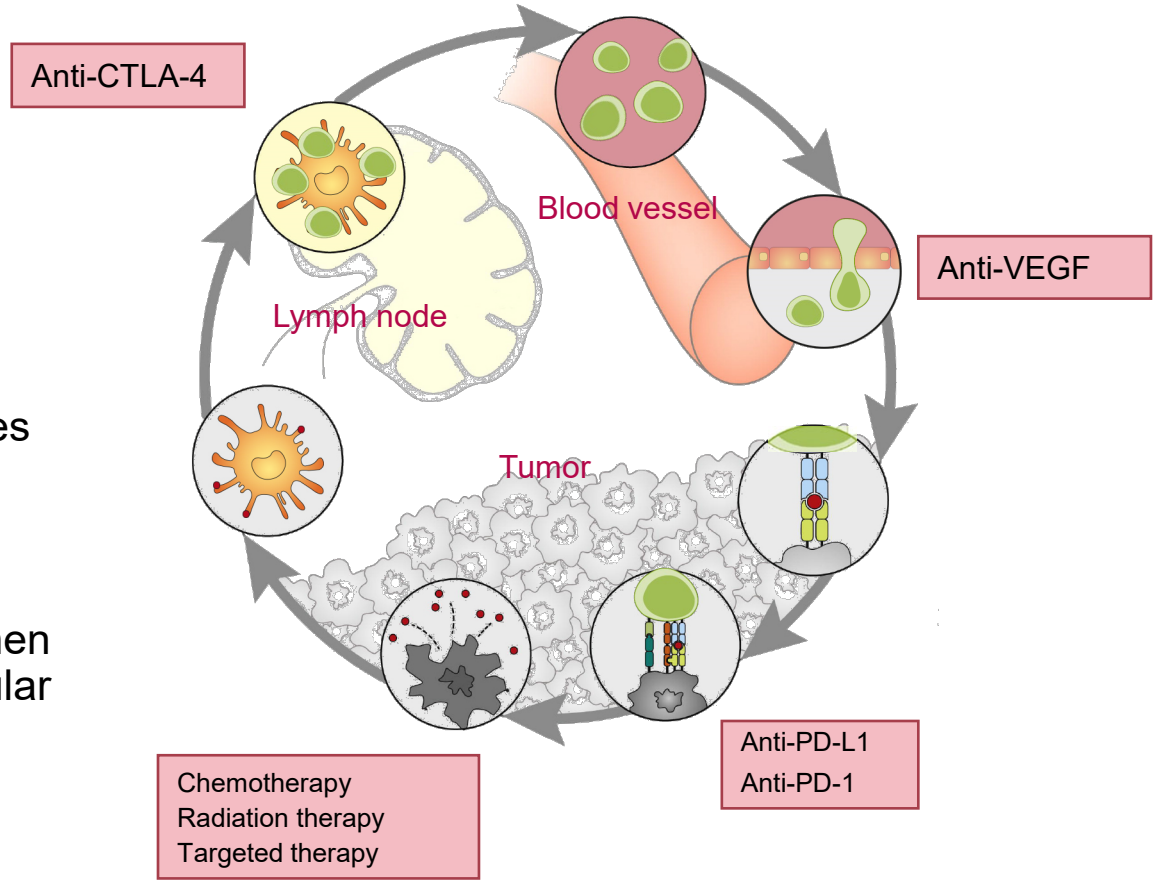
1. EUCAN. Available from http://eco.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=968. 2. EUCAN. Belgium. Available from http://eco.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=56.. 3. EUCAN. Luxembourg. Available from http://eco.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=442. 4. EUCAN. Netherlands. Available from http://eco.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=528. All URLs accessed July 26, 2022.

Immunotherapeutic agents that target the TME

- The TME is an integral part of cancer and, therefore, offers many effective treatment targets[1]

For example:

- Bevacizumab is a monoclonal antibody that blocks **angiogenesis** by inhibiting VEGF-A
- Pembrolizumab and nivolumab are monoclonal antibodies that target the **PD-1 receptor** of lymphocytes
- Ipilimumab is a **CTLA-4 blocker** that increases activation of $CD4^+$ and $CD8^+$ effector cells
- **CAR T-cell immunotherapy** involves collecting and then modifying a patient's own T cells to recognize a particular TAA, selectively expressed on malignant cells[2]



CAR, chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TAA, tumor-associated antigen; TME, tumor microenvironment; VEGF-A, vascular endothelial growth factor A.

1. Chen et al. BMC Medicine 2015;13:1–13. 2. Yu et al. Journal of Hematology & Oncology 2017;10:1–13.

Selected examples[a] of immunotherapies for solid tumor malignancies

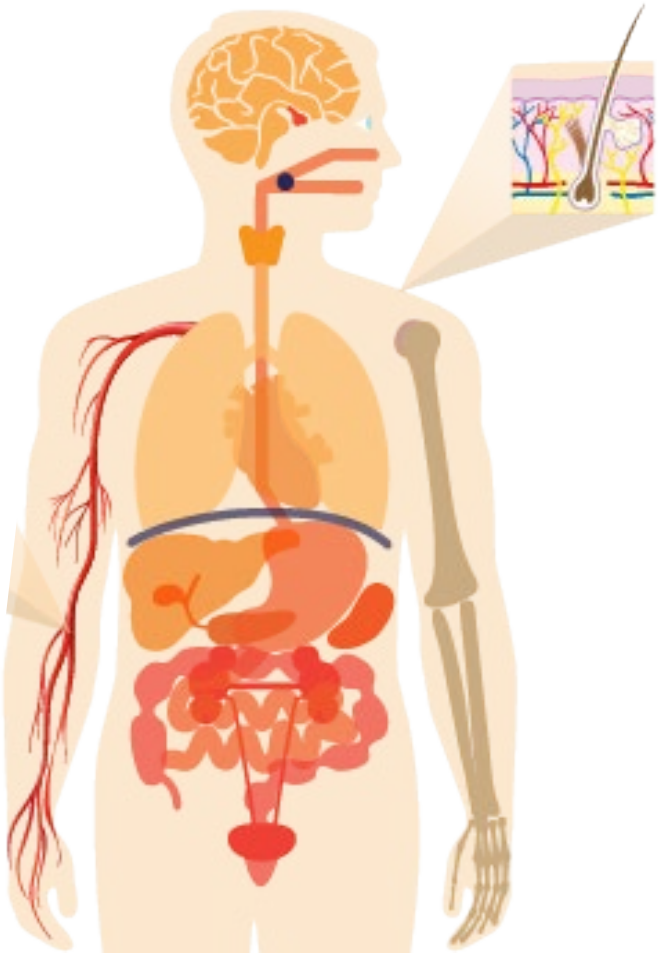
Gastric cancer
- Trastuzumab[4]
- Nivolumab[1]
- Pembrolizumab[2]

HNSCC
- Nivolumab[1]
- Pembrolizumab[2]

RCC
- Nivolumab[1]
- Pembrolizumab[2]
- Ipilimumab[6]
- Avelumab[7]

Mesothelioma
- Nivolumab[1]
- Ipilimumab[6]

NSCLC
- Nivolumab[1]
- Pembrolizumab[2]
- Atezolizumab[3]
- Ipilimumab[6]
- Durvalumab[8]
- Cemiplimab[9]



CRC
- Pembrolizumab[2]
  Nivolumab[1]
- Ipilimumab[6]

Breast cancer
- Trastuzumab[4]
- Pertuzumab[5]
- Atezolizumab[3]

Melanoma
- Nivolumab[1]
- Pembrolizumab[2]
- Ipilimumab[6]
- Avelumab[7]
- Cemiplimab[9]

Urothelial carcinoma
- Nivolumab[1]
- Pembrolizumab[2]
- Atezolizumab[3]

Esophageal cancer
- Nivolumab[1]
- Pembrolizumab[2]
- Durvalumab[8]

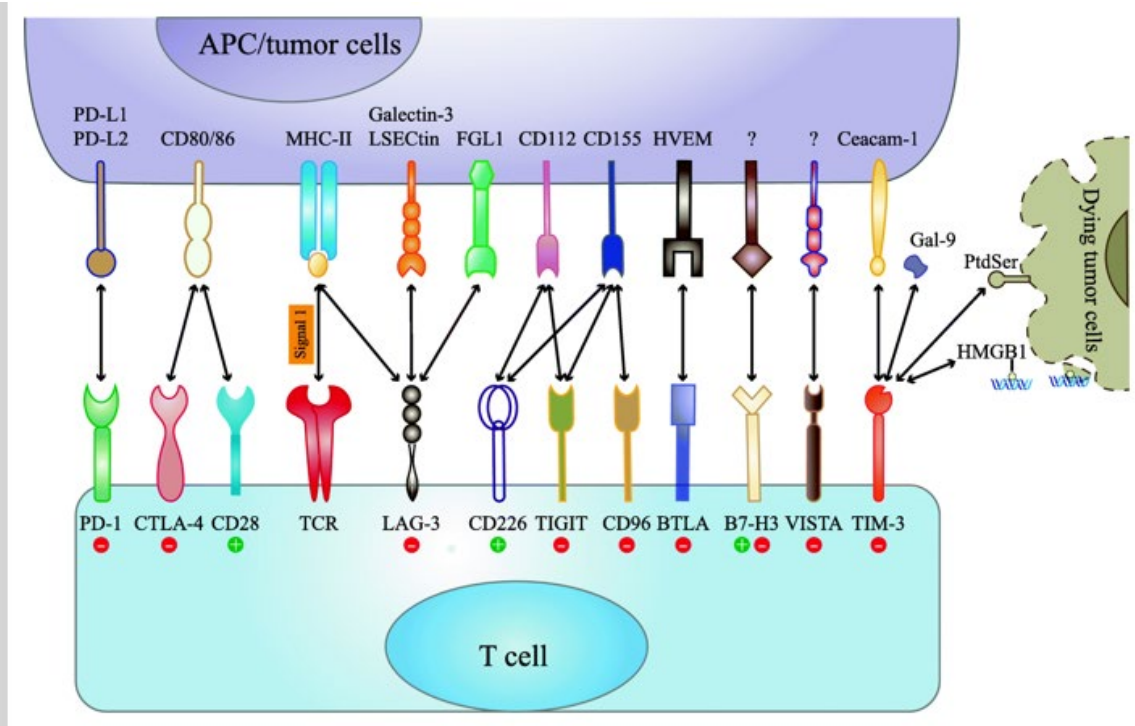
[a]These lists contain only selected examples of EMA licensed immunotherapies and are not exhaustive. For details of other monoclonal antibodies licensed to treat solid tumors, see Module 2: Types of immunotherapy.

EMA, European Medicines Agency; HCC, hepatocellular carcinoma; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung carcinoma; RCC, renal cell carcinoma;
1. Opdivo SmPC. 2. Keytruda SmPC. 3. Tecentriq SmPC. 4. Herceptin SmPC. 5. Perjeta SmPC. 6. Yervoy SmpC. 7. Avelumab SmPC. 8. Durvalumab SmPC. 9. Cemiplimab SmPC. All SmPCs available from: http://www.ema.europa.eu/. All URLs accessed July 27, 2022.

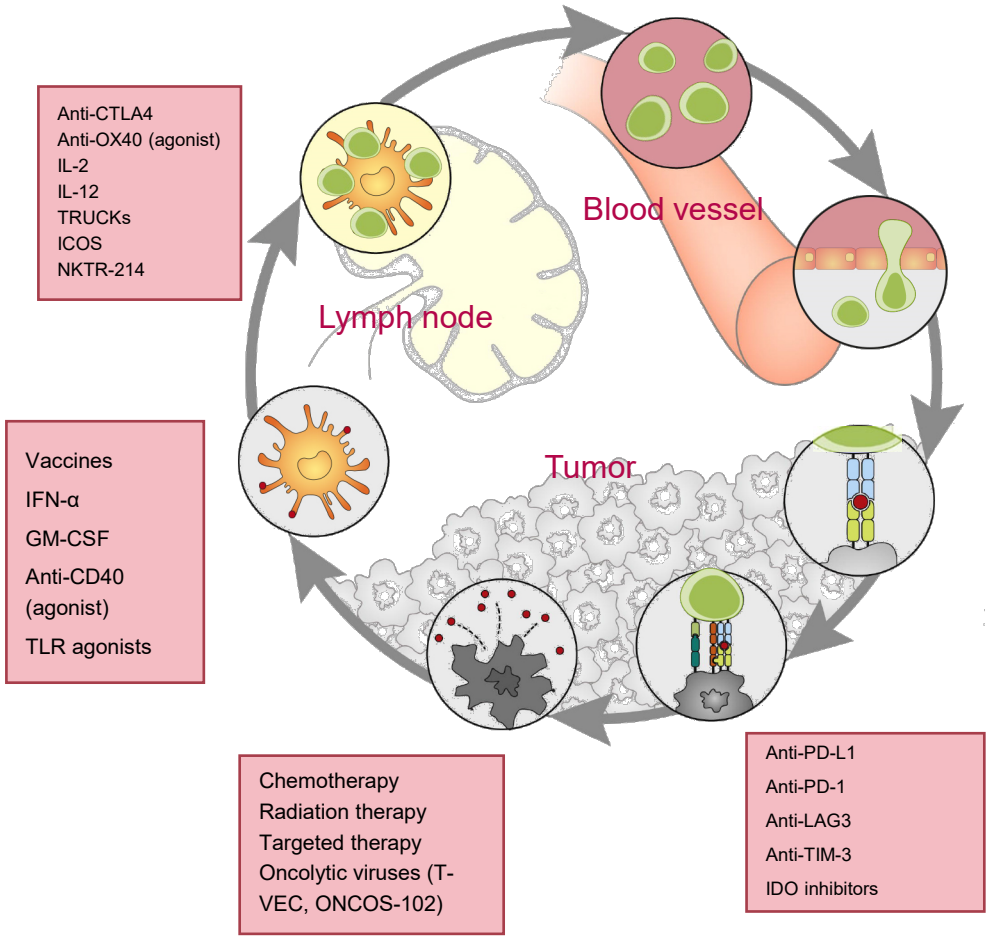
For full information of individual agents, always refer to the Summary of Product Characteristics

Future prospects for immunotherapy in solid tumors

Current and emerging immune checkpoint receptors and their respective ligands[1]



Immunotherapeutic targets investigated in cancer[2-4]



Ab, antibody; BTLA, B- and T-cell lymphocyte attenuator; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte associated protein 4; GITR, glucocorticoid-induced tumor necrosis factor-like receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; HVEM, herpes virus entry mediator; ICOS, inducible T-cell costimulatory; IDO, indoleamine 2,3-dioxygenase; IFN-α, interferon alpha; IL, interleukin; LAG-3, lymphocyte activation gene 3; PD-1, programmed cell death protein 1; TIM-3, T-cell immunoglobulin and mucin-domain 3; TLR, toll-like receptor; TRUCK, T cell redirected for universal cytokine mediated killing; T-VEC, talimogene laherparepvec; VISTA, V-domain Ig suppressor of T-cell activation.

1. Quin et al. Molecular Cancer 2019;18:155. 2. Chen & Mellman. Immunity 2013;39:1–10. 3. Kerre. Belgian J Hematol 2017;8:94–101; 4. Murciano-Goroff et al. Cell Research 2020;30:507–519

Immunotherapy in hematology

Immunotherapy for malignancies

An overview of selected hematologic malignancies relevant to immunotherapy

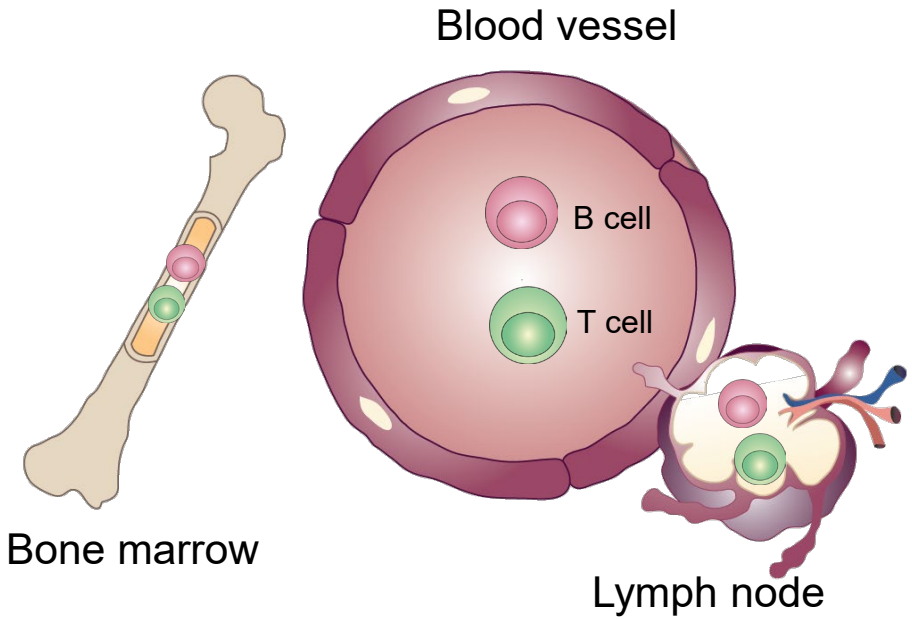
- Various types of hematologic malignancies affect the bone marrow, lymph nodes and blood – all of which are immune organs

Myeloproliferative disorders

Bone marrow disorders that lead to an excess of one or more types of myeloid cell
e.g. **CML**

Myelodysplastic syndromes

Bone marrow disorders that result in clonal production of dysplastic myeloid cells. Owing to failing to sufficiently mature, blast cells arise
e.g. **AML** (develops in ~1/3 patients)



Leukemia

A number of diseases that result in a clonal proliferation of white blood cells
e.g. **ALL, CLL, Hairy cell leukemia**

Lymphoma

Involve the clonal proliferation of lymphoid cells
e.g. **classical HL, nHL**

Myeloma

Involve the clonal proliferation of plasma cells
e.g. **Light chain/Bence Jones and non-secretory myeloma**

ALL, acute lymphoblastic leukemia; AML, acute myeloid (myelogenous) leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid (myelogenous) leukemia; HL, Hodgkin's lymphoma; nHL, non-Hodgkin lymphoma.

1. Sant et al. Blood 2010;116:3724–34. Image adapted from Di Rosa & Pabst. Trends Immunol 2005;26:360–6.

Licensed immunotherapies for hematologic malignancies

- Hematologic malignancies have unique features compared with solid tumors, such as a number of targetable surface antigens, which make them strong targets for immunotherapy[1,2]

Monoclonal antibodies	Antibody-drug conjugates	BiTE monoclonal antibodies	Immune checkpoint blockade	CAR T cell therapy
Rituximab (CLL, NHL) **Obinutuzumab** (CLL, FL) **Alemtuzumab**[a] (CLL) **Daratumumab** (MM) **Elotuzumab** (MM) **Isatuximab** (MM) **Mogamulizumab**[a] (NHL) **Tafasitamab** (DLBCL)	**Brentuximab** (HL, systemic anaplastic large cell lymphoma) **Ibritumomab tiuxetan** (NHL) **Inotuzumab ozogamicin** (ALL) **Polatuzumab vedotin** (NHL) **Gemtuzumab ozogamicin** (AML) **Tragaxofusp** (BPDCN) **Belantamab mafodotin** (MM)	**Blinatumomab** (ALL)	**Nivolumab** (cHL) **Pembroluzimab** (cHL)	**Axicabtagene ciloleucel** (NHL) **Tisagenlecleucel** (ALL, DLBCL) **Brexucabtagene autoleucel** (MCL) **Idecabtagene vicleucel** (MM) **Lisocabtagene maraleucel (**DLBCL, PMBCL, FL3B) **Ciltacabtagene autoleucel** (MM)

[a]Alemtuzumab and Mogamulizumab, approved by FDA but not EMA to date.

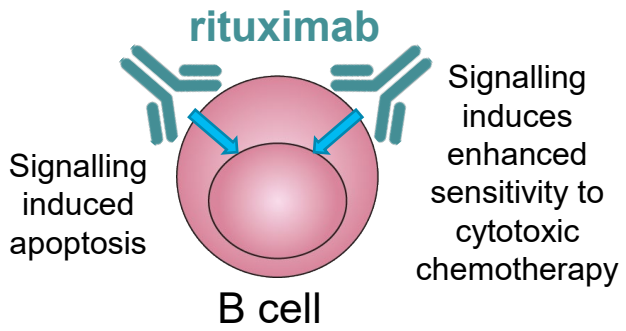
ALL, acute lymphoblastic leukemia; BPDCN: blastic plasmacytoid dendritic cell neoplasm; CAR, chimeric antigen receptor; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; FL3B, follicular lymphoma grade 3B; HCL, hair cell leukemia; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PMBCL, primary mediastinal large B-cell lymphoma. 1. Im & Pavletic. J Hematol Oncol 2017;10:94. 2. i-Yoon Noh et al. Int. J. Mol. Sci. 2020, 21, 8000;. Prescribing information available from: http://www.ema.europa.eu/ema/, https://www.fda.gov/ and https://www.cancerresearch.org/immunotherapy/cancer-types/leukemia . All URLs accessed Aug 22, 2022.

For full information of individual agents, always refer to the Summary of Product Characteristics

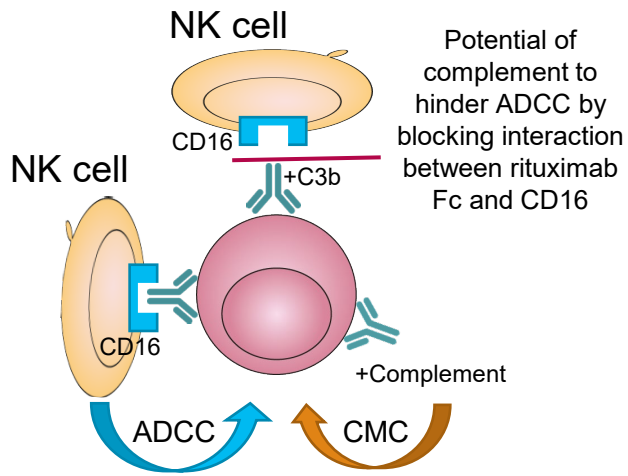
Monoclonal antibodies for hematologic malignancies: a key example

- Rituximab – an anti-CD20 antibody – was the first monoclonal antibody to be approved for a hematological malignancy by the EMA in 1998[1]
- Rituximab-mediated signaling, CMC and ADCC are mechanisms by which rituximab likely exerts its anti-tumor action[2]

Rituximab mechanisms of action[2]



Direct rituximab/CD20-induced signalling



Rituximab-induced CMC and ADCC

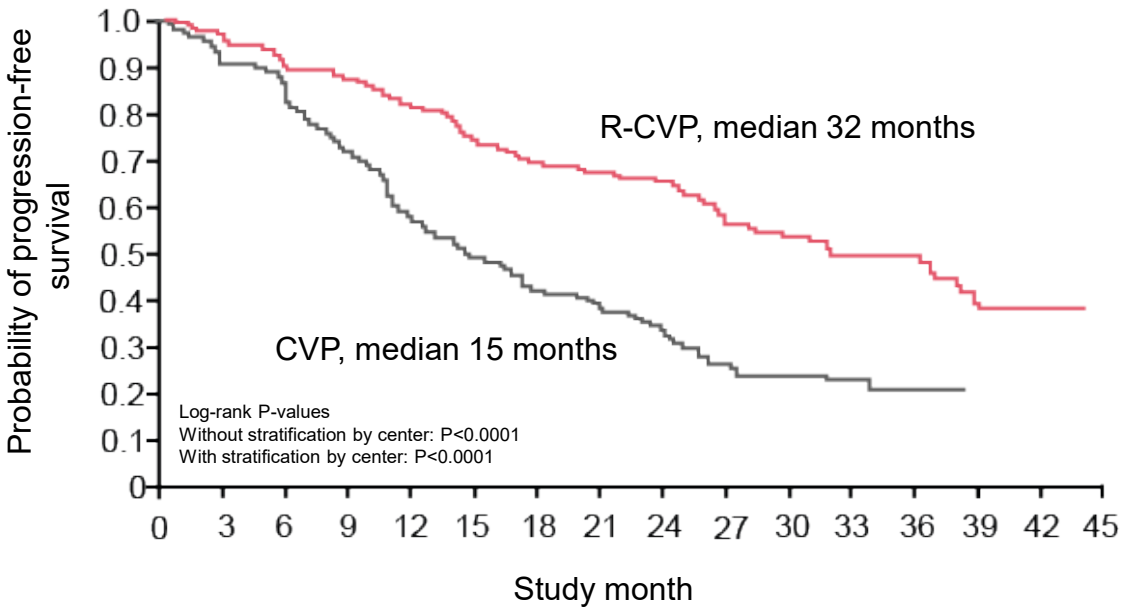
Selected monoclonal antibodies: licensed indications

Rituximab[3]	• Non-Hodgkin lymphoma: FL (first-line advanced; maintenance; relapsed/refractory) DLBCL (with CHOP); BL; BAL or BLL. • Chronic lymphocytic leukemia: previously untreated and relapsed/refractory • Rheumatoid arthritis: with MTX • Granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis: with glucocorticoids • Pemphigus vulgaris: moderate to severe

ADCC: antibody-dependent cellular cytotoxicity; BAL, Burkitt leukaemia (mature B-cell acute leukaemia); BL, Burkitt lymphoma; BLL, Burkitt-like lymphoma. CD, cluster of differentiation; CDC: complement mediated cytotoxicity; CHOP, cyclosphamide, hydroxydaunorubicin, oncovin and prednisone; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FL, follicular lymphoma; MTX, methotrexate; NK, natural killer; SmPC, Summary of Product Characteristics. 1. ACTIP. Available from: http://www.actip.org/products/monoclonal-antibodies-approved-by-the-ema-and-fda-for-therapeutic-use/. Accessed: Aug 22, 2022. 2. Weiner. Semin Hematol 2010;47:115–23. 3. Rituximab. SmPC available from: http://www.ema.europa.eu. Accessed Jul 26, 2022.

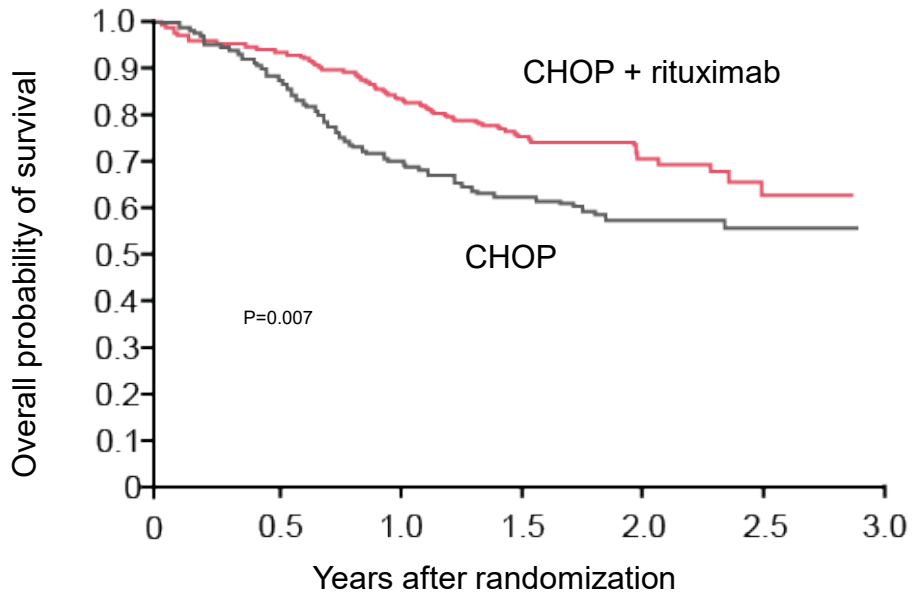
Monoclonal antibodies for hematologic malignancies: clinical overview and selected key data

Rituximab + CVP significantly prolonged time to progression vs CVP[1]



Time to disease progression, relapse or death[1]. R-CVP vs CVP as first-line treatment for advanced follicular lymphoma (n = 321). At a median follow-up of 30 months, patients treated with R-CVP had a significantly prolonged time to progression (median 32 months versus 15 months for CVP; p < 0.0001). Adapted from Marcus et al.[1]

Rituximab + CHOP significantly improved OS vs CHOP[2]



Overall survival in previously untreated patients with previously untreated diffuse large B-cell lymphoma (n = 399). Survival was significantly longer for patients treated with CHOP plus rituximab vs those treated with CHOP alone (p = 0.007): at 2 years, 70% patients treated with CHOP + rituximab were alive vs 57% of those treated with CHOP alone. Adapted from Coiffier et al.[2]

CHOP, cyclosphamide, hydroxydaunorubicin, oncovin and prednisone; CVP, cyclophosphamide, vincristine and prednisione; OS, overall survival; R, rituximab.

1. Marcus et al. Blood 2005;105:417–23. 2. Coiffier et al. N Engl J Med 2002;346:235–42.

Monoclonal antibodies for hematologic malignancies[a]

AML	CLL	B-cell precursor ALL	HL	NHL		Multiple myeloma
Gemtuzumab ozogamicin + daunorubicin and cytarabine	**Rituximab** + chemotherapy (previously untreated; relapsed/refractory)	**Inotuzumab ozogamicin** (relapsed/refractory)	**Brentuximab** (relapsed/refractory CD30+ HL)	**Rituximab** + chemotherapy (previously untreated stage III-IV FL); **Rituximab** maintenance (FL responding to induction therapy) **Rituximab** monotherapy (relapsed/refractory stage III-IV FL) **Rituximab** + CHOP (CD20 positive DLBCL)	**Brentuximab** + CHP (previously untreated sALCL)	**Elotuzumab** + lenalidomide + dexamethasone (≥ 1 prior therapy)
	Obinutuzumab + chlorambucil (previously untreated)	**Blinatumomab** (Philadelphia chromosome negative relapse/refractory)	**Pembrolizumab** (relapsed/refractory cHL) **Nivolumab** (relapsed/refractory cHL)		**Ibritumomab tiuxetan + rituximab** (relapsed or refractory CD20+ FB-NHL)	**Daratumumab** monotherapy (relapsed/refractory multiple myeloma) **Daratumumab +** lenalidomide + dexamethasone, or bortezomib + dexamethasone (≥ 1 prior therapy)
					Polatuzumab vedotin + bendamustine and rituximab (relapsed/refractory DLBCL)	**Isatuximab +** pomalidomide + dexamethasone (≥ 2 prior therapy), or carfilzomib + dexamethasone (≥ 1 prior therapy)
					Tafasitamab + lenalidomide (DLBCL)	
					Obinutuzumab + chemotherapy (previously untreated advanced FL) **Obinutuzumab** + bendamustine (relapsed/refractory FL)	**Belantamab mafodotin** (≥ 4 prior therapy)

[a]This is not an exhaustive list. Please refer to individual SmPCs for a full list of licensed indications

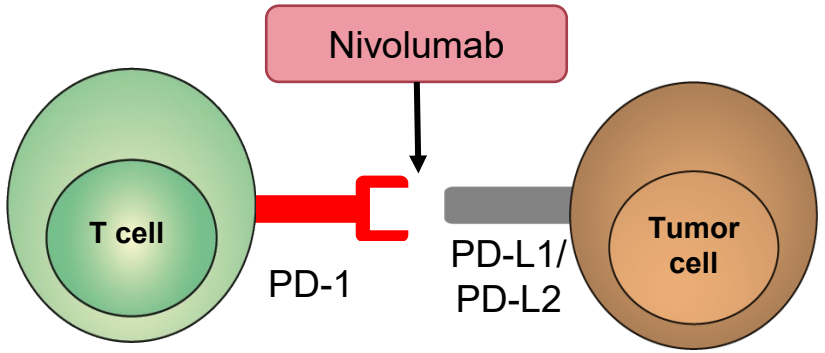
ALL, acute lymphoblastic leukemia; CD, cluster of differentiation; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; CHOP, cyclosphamide, hydroxydaunorubicin, oncovin and prednisone; DLBCL, diffuse large B-cell lymphoma; FB-NHL, follicular B-cell non-Hodgkin's lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; SmPC, Summary of Product Characteristics; sALCL, systemic anaplastic large cell lymphoma; Cut-off date: Aug 2022, SmPC available from: http://www.ema.europa.eu/ema/. Accessed Jul 26, 2022. 2. i-Yoon Noh et al.Int. J. Mol. Sci. 2020, 21, 8000

For full information of individual agents, always refer to the Summary of Product Characteristics

Checkpoint inhibitors for hematologic malignancies: key examples

- PD-1 ligands are overexpressed on Reed-Sternberg cells in cHL[1]
- Two PD-1 inhibitors are currently licensed for classical HL, nivolumab and pembrolizumab[2,3]

Nivolumab mechanism of action



Nivolumab prevents the binding of PD-1 to its ligands (PD-L1 and PD-L2), which releases T cell responses against tumor cells

	Indication
Nivolumab[2]	Adult patients with relapsed or refractory cHL after ASCT and treatment with BV
Pembrolizumab[3]	Adult patients with relapsed or refractory cHL who have failed ASCT and BV, or who are transplant-ineligible and have failed BV

ASCT, autologous stem cell transplant; BV, brentuximab vedotin; HL, Hodgkin lymphoma; PD-1, programmed cell death protein 1; PD-L1/2, programmed death-ligand 1/2.

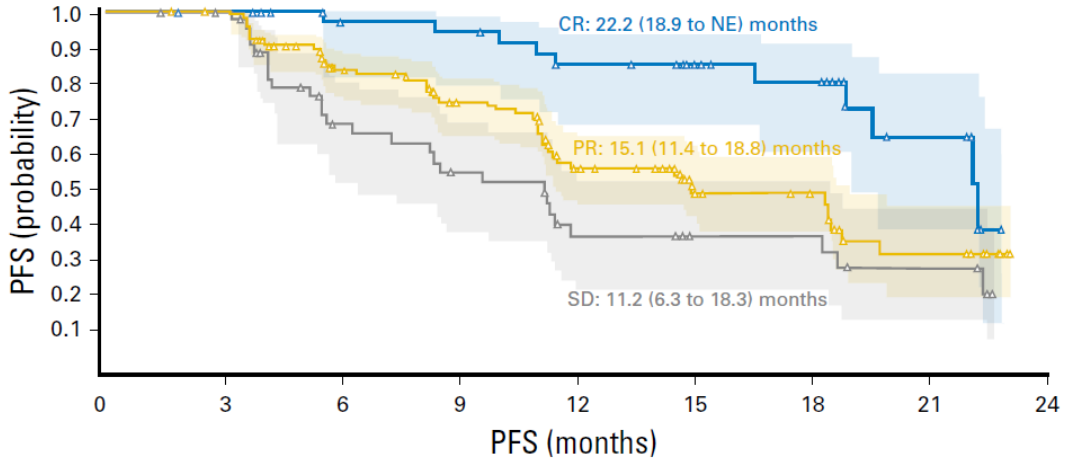
1. Younes et al. Lancet Oncol 2016;17:1283–94. 2. Nivolumab. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf. 3. Pembrolizumab. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf. Accessed Jul 27, 2022.

For full information of individual agents, always refer to the Summary of Product Characteristics

Checkpoint inhibitors for hematologic malignancies: clinical overview and selected key data

- Checkpoint inhibitors for the treatment of hematologic malignancies is a rapidly evolving field, and selected results from some key studies are shown below

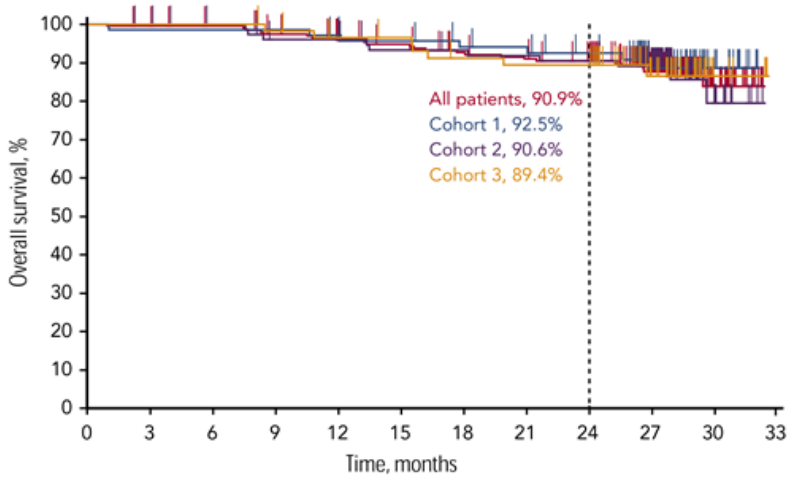
PFS in adult patients with cHL treated with nivolumab



No. at risk:									
CR	40	40	33	32	27	20	16	7	0
PR	128	126	89	71	46	25	21	8	0
SD	47	44	25	19	11	8	8	5	0

Armand et al. [1]

OS in patients with relapsed or refractory cHL treated with pembrolizumab



No. at risk												
	210	207	205	198	190	186	178	175	170	115	26	0
	69	68	68	68	64	64	61	60	56	40	11	0
	81	79	77	72	71	68	67	66	65	47	10	0
	60	60	60	58	55	54	50	49	49	28	5	0

Chen et al.[2]

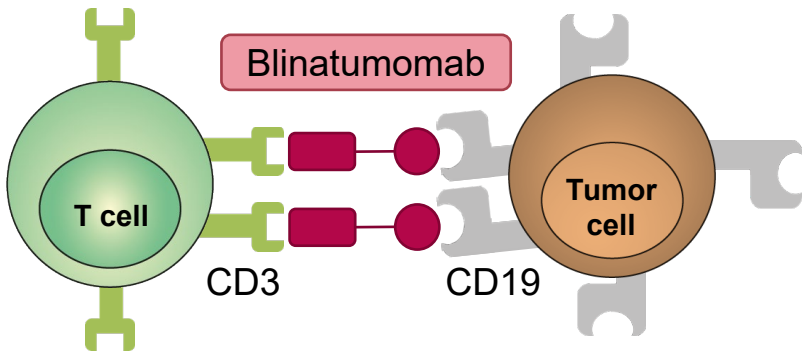
cHL, classical Hodgkin lymphoma; CI, confidence interval; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival.

1. Armand et al. J Clin Oncol 2018 36:1428-1439.. 2. Chen et al. Blood 2019 Oct 3;134(14):1144-1153.

Bispecific T-cell engagers for hematologic diseases

- BiTEs are a class of antibody that has multiple binding sites and specificities[1]
- Blinatumomab is the only BiTE currently approved to treat Philadelphia chromosome negative relapsed or refractory B-precursor ALL[2]
- It binds to CD19 on B cells and to CD3 on T cells
- B cells and T cells are brought together by blinatumomab molecules and T cells are activated by CD3 cross-linking
- Blinatumomab facilitates the formation of a cytolytic synapse between T cells and tumor cells, which kills proliferating and resting target cells by releasing proteolytic enzymes[3]

Blinatumomab mechanisms of action[4]



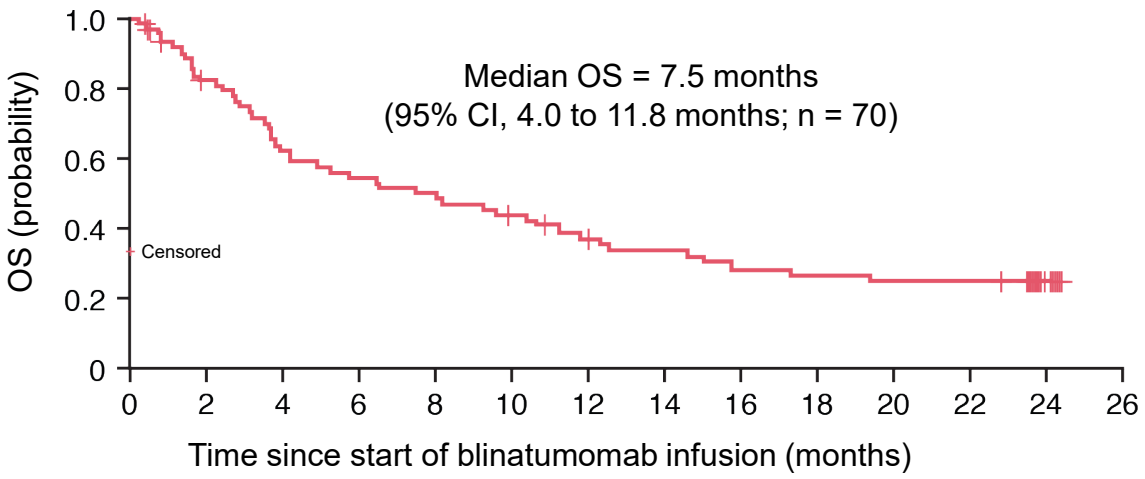
One arm of blinatumomab binds to CD19, and the other binds to CD3, thereby activating T cells, which destroy the CD19+ cells

ALL, acute lymphoblastic leukemia; BiTE, bispecific T-cell engager; CD, cluster of differentiation.

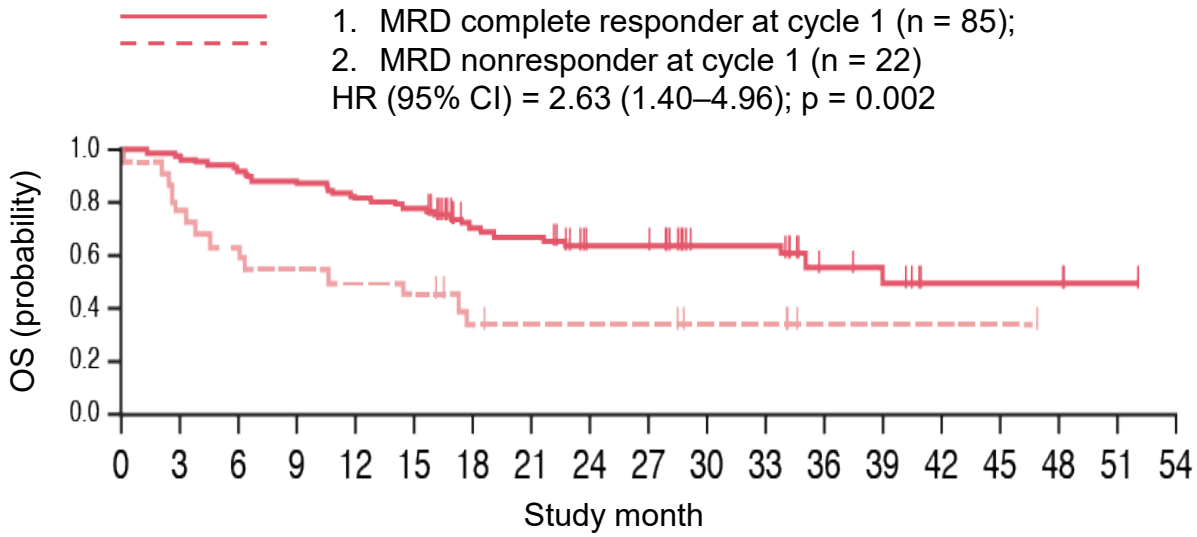
1. Huehls et al. Immunol Cell Biol 2015;93:290–6. 2. Blinatumomab SmPC. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003731/WC500198228.pdf. Accessed Jul 27, 2022. 3. Von Stackelberg et al. J Clin Oncol 34:4381–9. 4. Wu et al. Journal of Hematology & Oncology 2015;8:104.

BiTEs for hematologic malignancies: clinical overview and selected key data

Overall survival in all patients who received the recommended dosage of blinatumomab[1]



Median overall survival was 38.9 vs 12.5 months (p = 0.002) in patients with and without a complete MRD response (cycle 1)[2a]



[a]Overall survival by MRD response during cycle 1, without censoring at allogeneic SCT and post-blinatumomab chemotherapy

BiTE, bispecific T-cell engager; CI, confidence interval; HR, hazard ratio; MRD, minimal residual disease; OS, overall survival; SCT, stem cell transplantation.

1. Von Stackelberg et al. J Clin Oncol 2016;34:4381–9. 2. Gökbuget et al. Blood 2018;131:1522–31.

Summary and key takeaways

- Immunotherapy is a therapeutic modality that harnesses the body's own immune system to fight cancer[1–3]
- The immune response to tumors can vary between continuous activation and suppression, with tumor progression favored when the immune response is suppressed[4,5]
- The TME plays a pivotal role in tumor growth and metastasis by suppressing infiltrating immune cells[6,7]
- Tumors may target activating and inhibitory mechanisms of immune pathways, resulting in tumor evasion of the immune system and tumor survival/growth[8,9]
- A number of therapeutic approaches have been developed or are being studied to harness the immune system and control malignancy[4]. These approaches include:
  - Cytokines
  - Checkpoint inhibitors
  - Agonism of costimulatory receptors
  - Manipulation of T cells
  - Oncolytic viruses
  - Therapies directed at non immune cell types in the TME
  - Vaccines

BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte antigen protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TME, tumor microenvironment.

1. Murphy. Oncology 2010;4:67–80. 2. Kirkwood et al. CA Cancer J Clin 2012;62:309–35. 3. Borghaei et al. Eur J Pharmacol 2009;625:41–54. 4. Chen & Mellman. Immunity 2013;39:1–10. 4. Dunn et al. Annu Rev Immunol 2004;22:329–60. 5. Mittal et al. Curr Opin Immunol 2014;27:16–25. 6. Balkwill et al. J Cell Sci 2012;125:5591–6. 7. Chen et al. BMC Medicine 2015;13:45. 8. Mittal et al. Curr Opin Immunol 2014;27:16–25. 9. Beatty & Gladney. Clin Cancer Res 2015;21:687–92.

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