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Immunologia: cosa c'è di nuovo?

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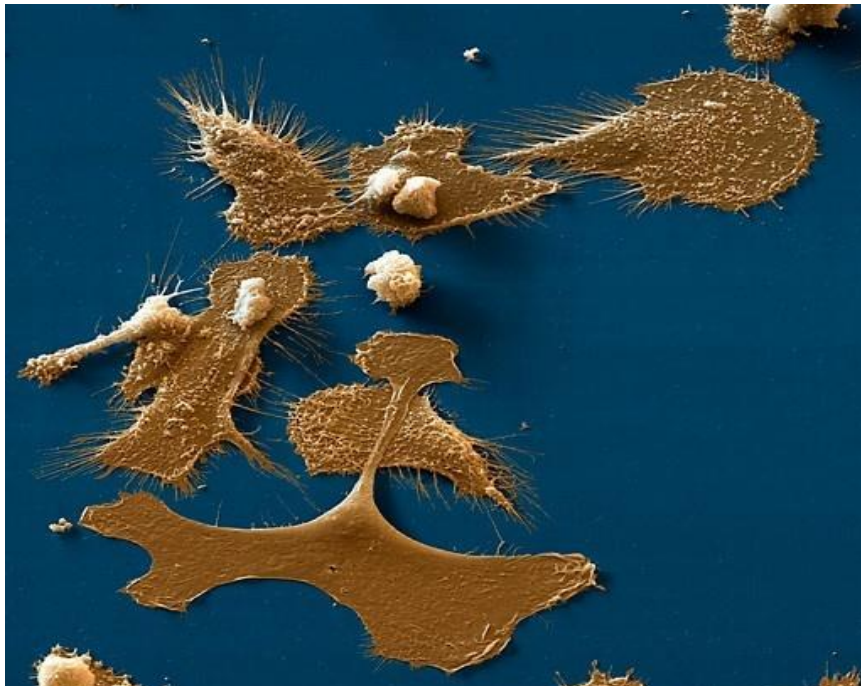
I sistemi dell’immunità innata ed adattativa sono strettamente integrati tra loro a livello cellulare e molecolare

Antigen Presenting Cells (APC)
Cellule dendritiche

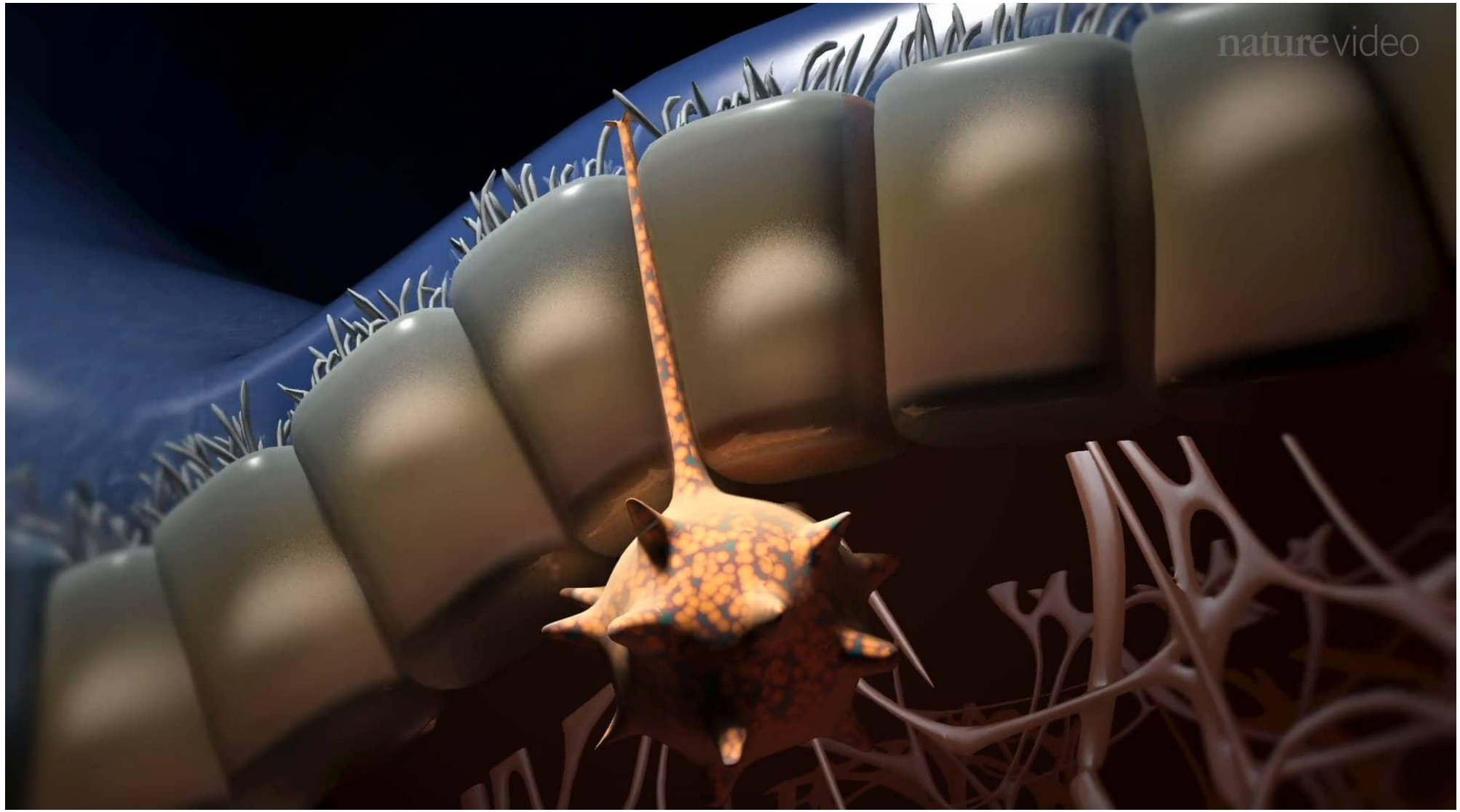


Ponte tra immunità innata e acquisita

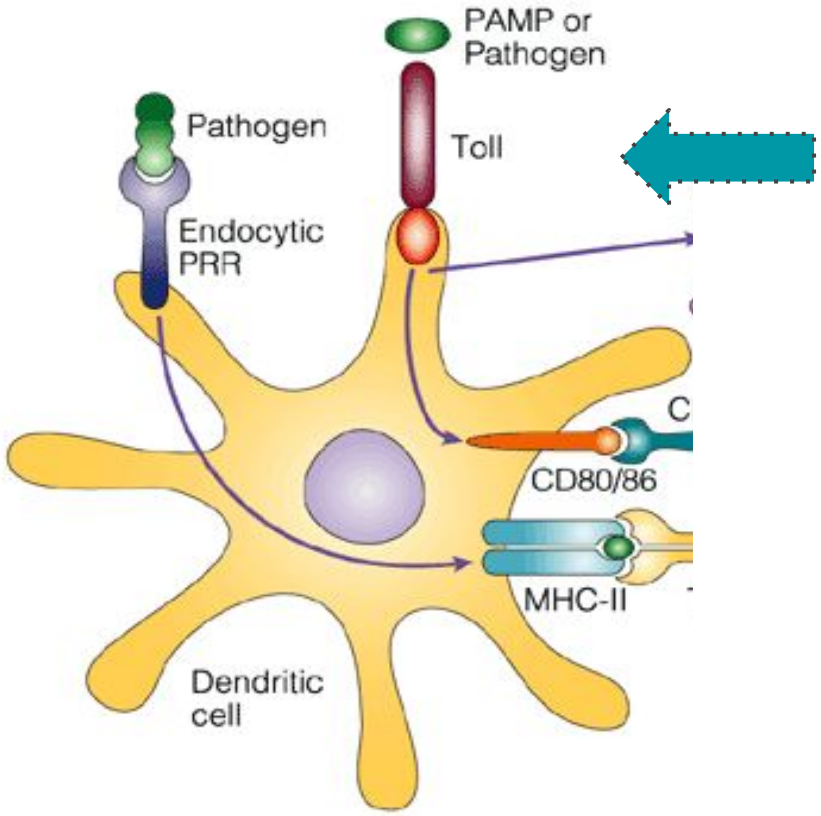
Dendritic cells (DC) are present in all the tissues that are in contact with the external environment including:

- **The skin (specialized DC population: Langherans cells)**
- **The inner lining of the nose, lungs, stomach and intestines and genital tract**

DC can also be found in an immature state in the blood



RECOGNITION OF ANTIGENS



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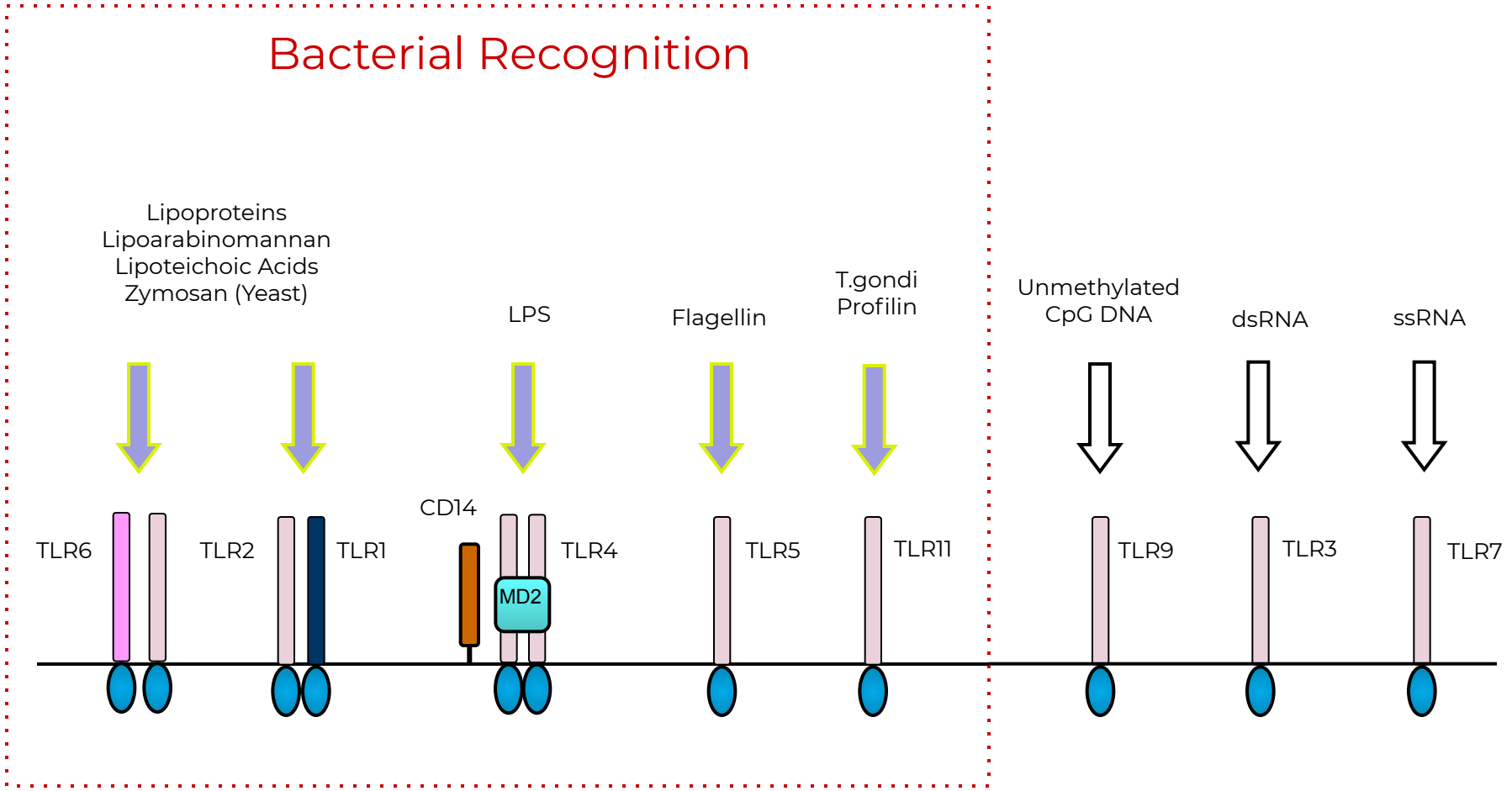
INNATE IMMUNE RECOGNITION BY TOLL-LIKE RECEPTORS



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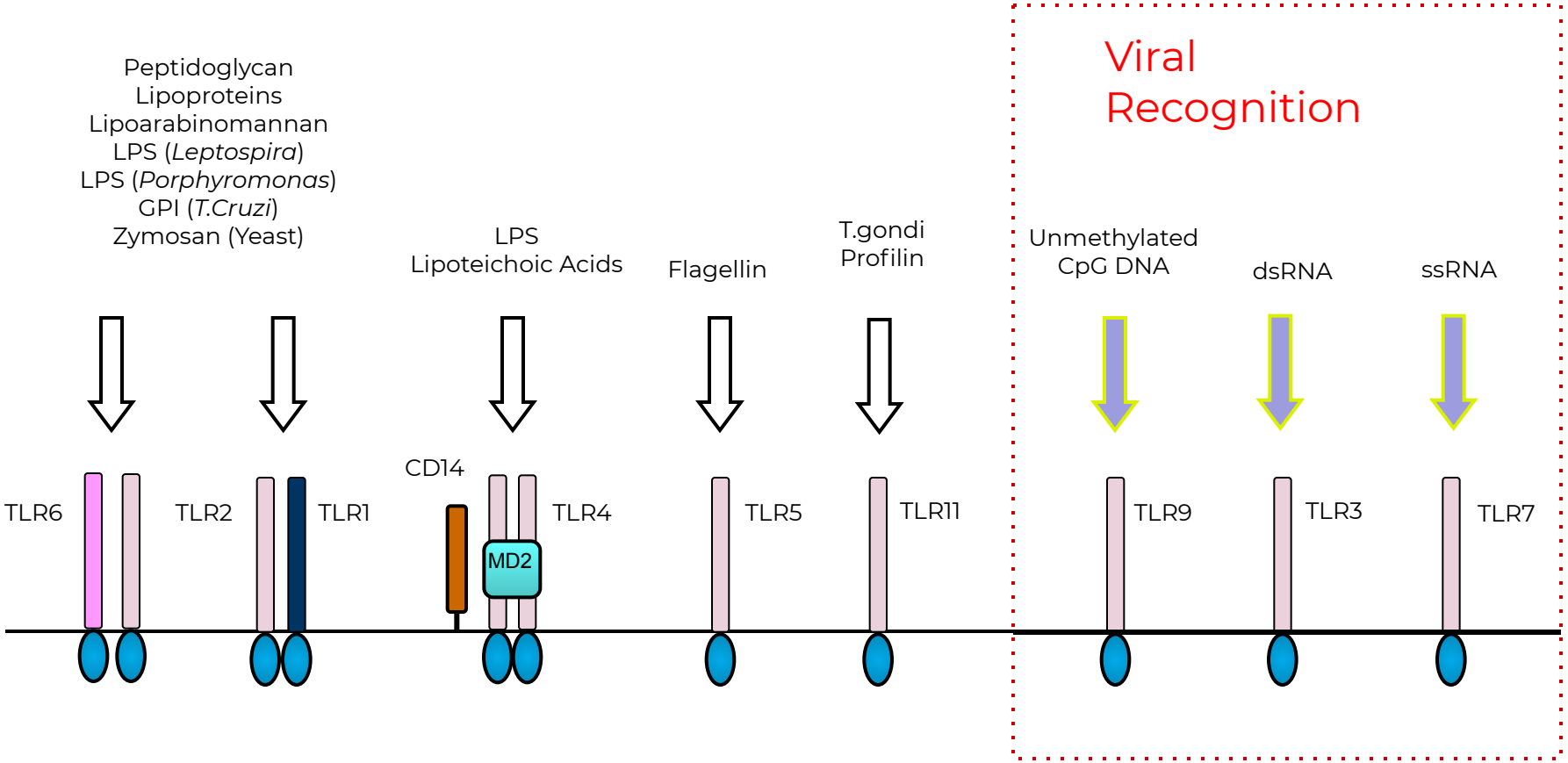
INNATE IMMUNE RECOGNITION BY TOLL-LIKE RECEPTORS



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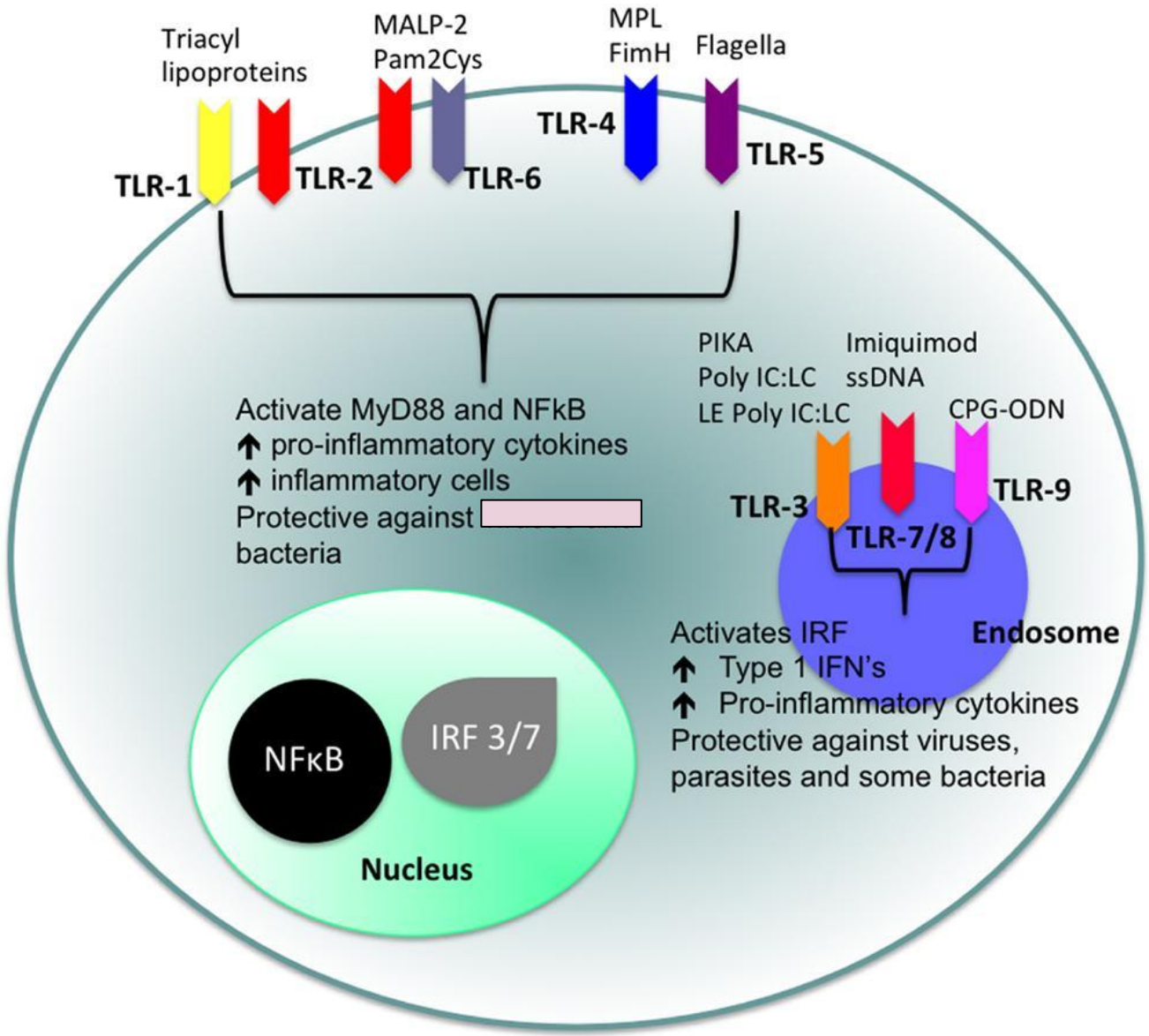
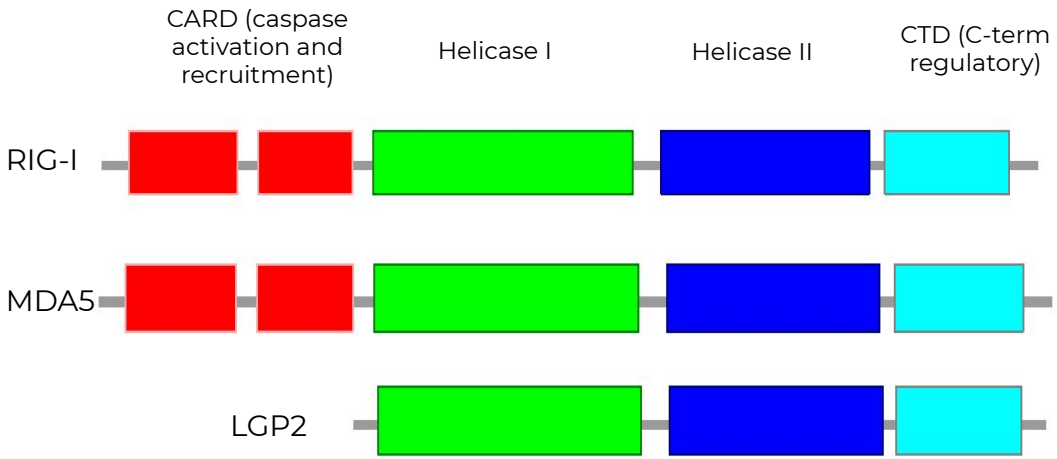


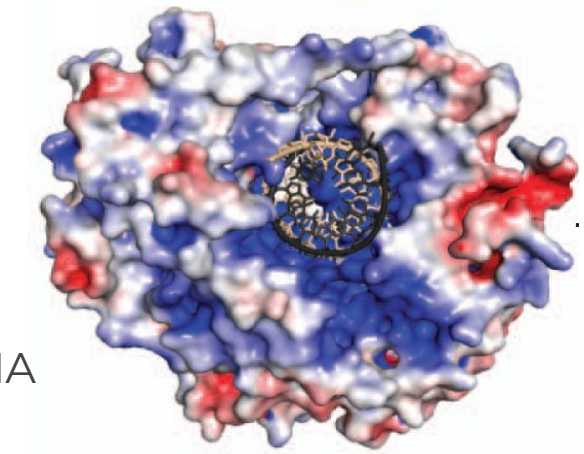
RLRs: RIG-I-like receptors



RIG-I	RNA molecules with 5' triphosphorilated (5'ppp) ends and short dsRNAs	Paramixoviruses, rhabdoviruses, influenza viruses, flaviviruses
MDA5	Long dsRNA, higher-order structure or branched RNA	Picornaviruses, vaccinia virus
LGP2	??	??

- cytoplasmic localization
- recognize viral RNA

RIG-I bound to dsRNA



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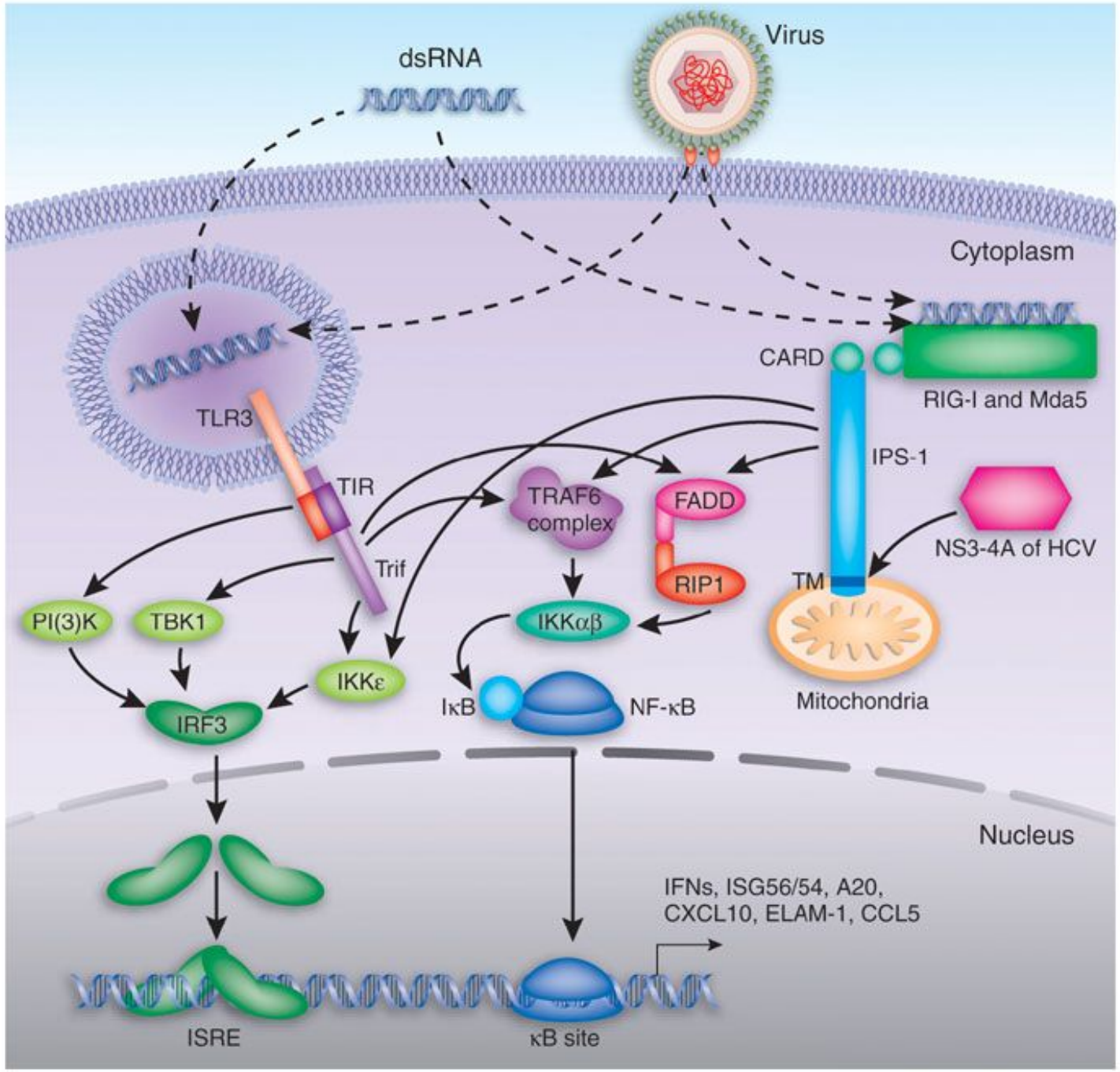


Genes regulated by NF-kB

Genes under the control of NF-κB	
Inflammatory cytokines	**Adhesion molecules**
TNF	ICAM-1
IL-1	VCAM-1
IL-6	E-selectin
IL-12	**Immune effector molecules**
Lymphotoxin α/β	FasL
GM-CSF	iNOS
IFN-β	COX-2
Chemokines	β-defensins
IL-8	**Pro-survival molecules**
MIP-1a	Bcl-XL
MCP	A1
RANTES	c-IAP1, 2
Eotaxin	

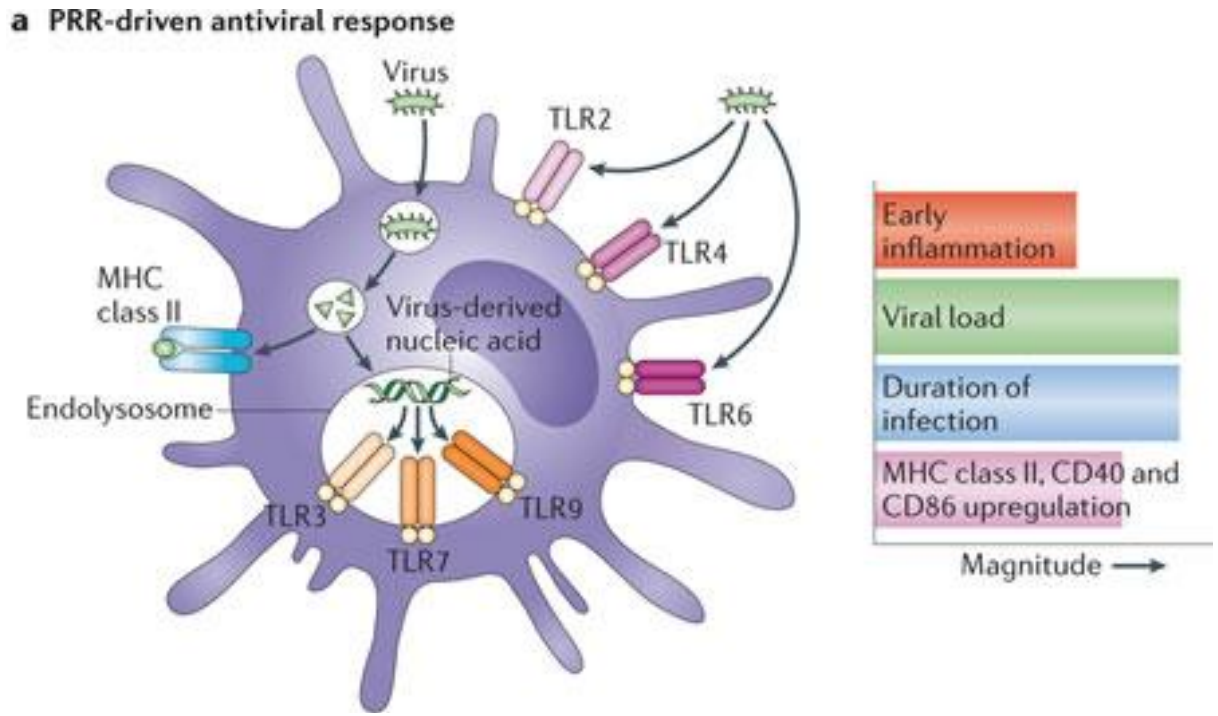
Table I

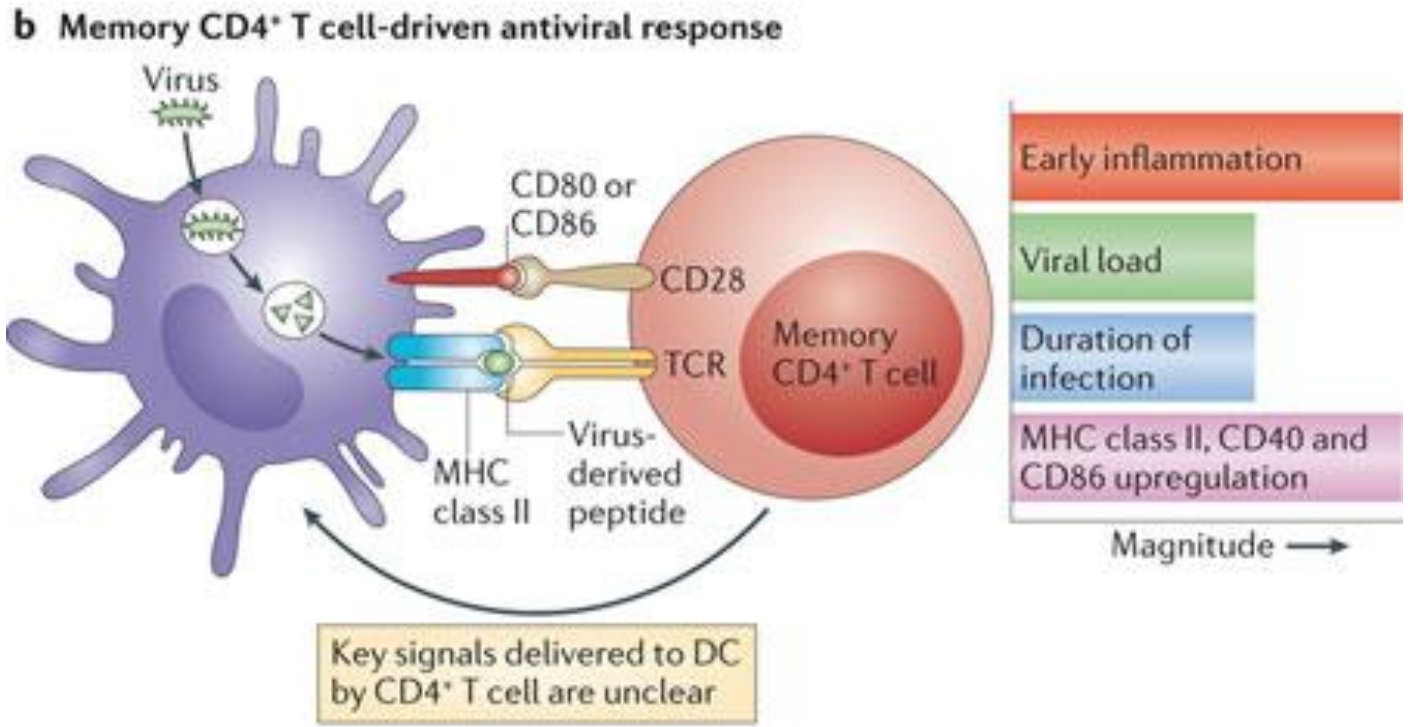
Antiviral interferon-stimulated genes

Gene Symbol	Targeted Viruses	Viral life cycle	Mechanism related to antiviral activity	Ref.
ADAR	HCV(r), HDV [enhances CHIKV, HIV-1, MV, VEEV, VSV, WNV, YFV]	replication	viral RNA editing, suppress PKR	[22,46]
APOBEC3	HIV-1, other retroviruses	replication	cytidine deamination of viral genome	[14]
BST2 (tetherin)	filovirus, FLUAV, HIV-1, LASV, VSV	egress/budding	block release of nascent virions	[47–49]
C6orf150(MB21D1)	CHIKV, VEEV, WNV, YFV	translation	unknown	[22]
CD74	HIV-1	replication	unknown	[22]
DDIT4	HCV	translation	unknown	[22]
DDX58 (RIG-I)	numerous RNA and DNA viruses	translation, replication	viral sensing, activation of IRFs	[50,51]
DDX60	HCV, PV, PV	translation (HCV)	promote RIG-I-like receptor signaling	[22,42]
EIF2AK2 (PKR)	numerous RNA and DNA viruses	translation	targets EIF2A	[52]
GBP1,GBP2	EMCV, HCV(r), VSV	replication	unknown	[53]
HPSE	CHIKV, VEEV, WNV, YFV	unknown	unknown	[22]
IFI44L	HCV	translation	unknown	[22]
IFI6 / G1P3	HCV(r), YFV	unknown	unknown, possibly antiapoptotic	[22,54]
IFIH1 (MDA5)	numerous RNA and DNA viruses	translation, replication	viral sensing, activation of IRFs	[50,51]
IFIT1/2/3/5	FLUAV, HPV, MHV*, RVFV, SINV, VSV, WNV*	translation, replication	target EIF3 subunits, target HPV helicase, bind 5'-triphosphate RNA	[25–28]
IFITM1/2/3	DENV, filovirus, FLUAV, HIV-1, SARS-CoV, VSV, WNV, YFV	entry	unknown, possibly target enodyctic pathway	[32,48,55]
IRF1	numerous RNA and DNA viruses	similar to IFN	IFN induction, direct ISG induction	[22,35,56]
IRF7	numerous RNA and DNA viruses	similar to IFN	IFN induction, direct ISG induction	[22,57,58]
ISG15	FLUAV, HIV-1, HSV-1, JEV, MHV-68, SINV, VVΔE3L	various	modulate protein function by ISGylation	[59,60]
ISG20	BVDV, DENV, EMCV, FLUAV, HCV, SINV, VSV, WNV(v), YFV	viral RNA synthesis	exonuclease activity	[19,61,62]
MAP3K14 (NIK)	HCV	translation	unknown, possiblyNF-κB activation	[22]
MOV10	HIV-1, HCV	post-entry (HIV-1)	unknown	[22,63]
MS4A4A	HCV	translation	unknown	[22]
MX1(MxA)	CVB, FLUAV, HCV(r), HPIV3, LACV, MV, SFV, THOV, VSV, others	primary transcription, nucleocapsid shuttling	formation of highly ordered oligomers	[64]
MX2 (MxB)	HIV-1, HNTV, LACV, RVFV, VSV	unknown	unknown	[22,64]
NAMPT (PBEF1)	VEEV, WNV	unknown	unknown	[22]
NT5C3	HCV	translation	unknown	[22]
OAS1/2/3	CHIKV, DENV, EMCV, HCV(r), SFV, SINV, WNV	replication	activate RNaseL to degrade viral genome	[65]

Antiviral Interferon-sti mulated genes (ISG)

Dopo avere attivato la risposta immune innata, le Cellule Dendritiche stimolano la risposta immune adattativa attraverso la presentazione del complesso binario antigene- MHC Classe II





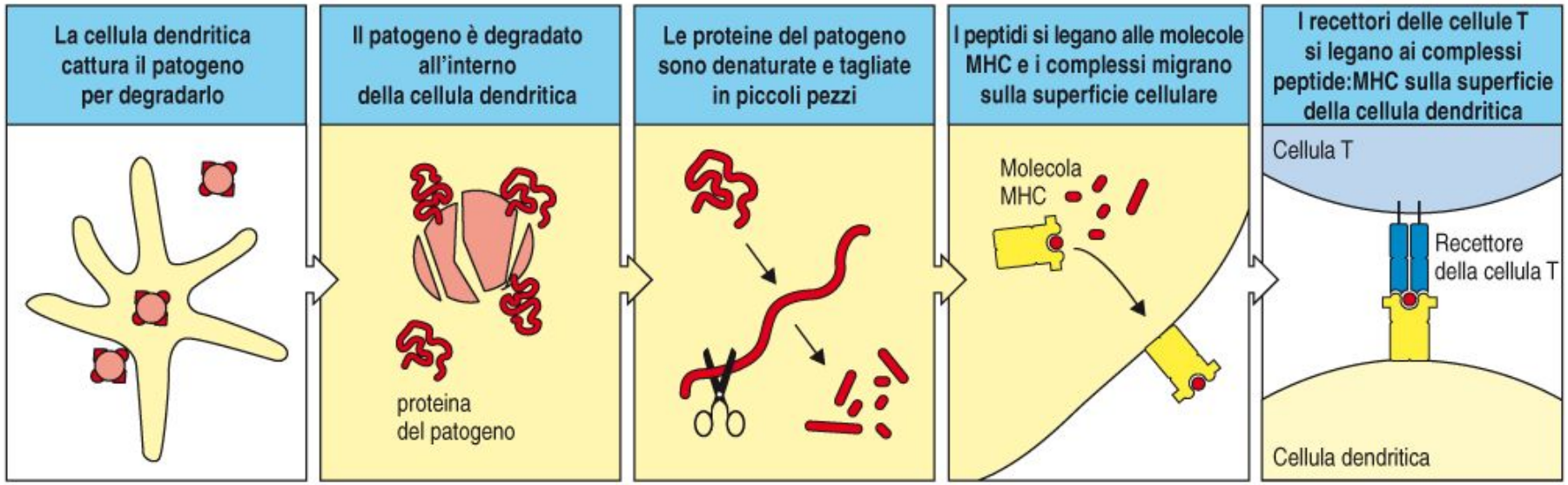
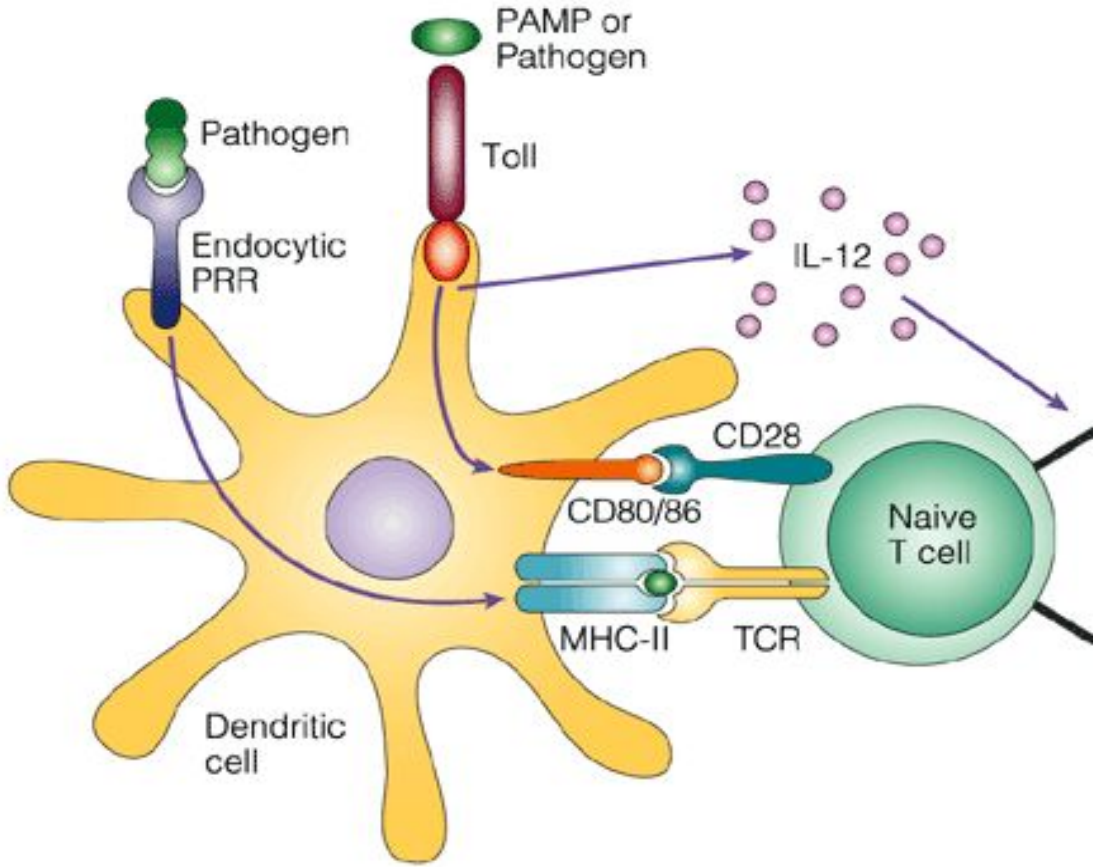


Figura 3.7 I recettori dei linfociti T riconoscono gli antigeni peptidici prodotti dalla degradazione delle proteine del patogeno. Le cellule dendritiche inglobano i patogeni e ne degradano le proteine in piccoli peptidi e aminoacidi. Alcuni di questi peptidi vengono legati all'interno della cellula ad alcune proteine dette molecole MHC, che trasportano i peptidi sulla superficie cellulare delle cellule dendritiche. Una volta in superficie, il complesso rappresentato dalla molecola MHC e dal peptide antigenico è accessibile ai recettori dei linfociti T circolanti. Se vi è corrispondenza tra l'antigene e il recettore della cellula T, i linfociti T restano legati alla cellula dendritica e sono stimolati a dividersi e a differenziarsi. Sebbene altri tipi cellulari possiedano le molecole MHC e presentino gli antigeni, la cellula dendritica è la più adatta a tal fine ed è responsabile dell'innesco della risposta immunitaria primaria – cioè della risposta immunitaria verso un patogeno che infetta un individuo e determina la malattia per la prima volta.

Peter Parham
Il Sistema Immunitario
EdiSES

RECOGNITION OF ANTIGENS



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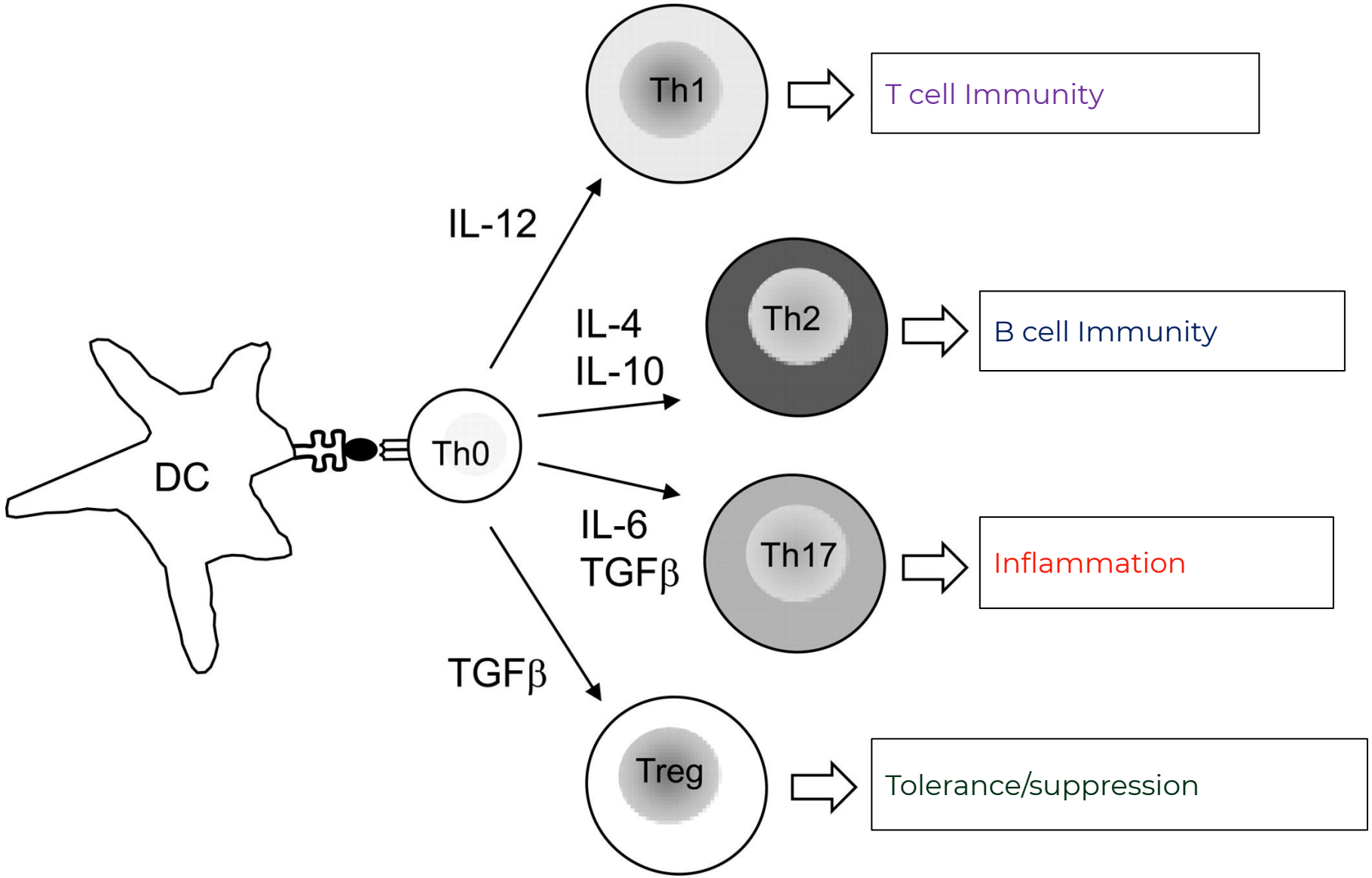
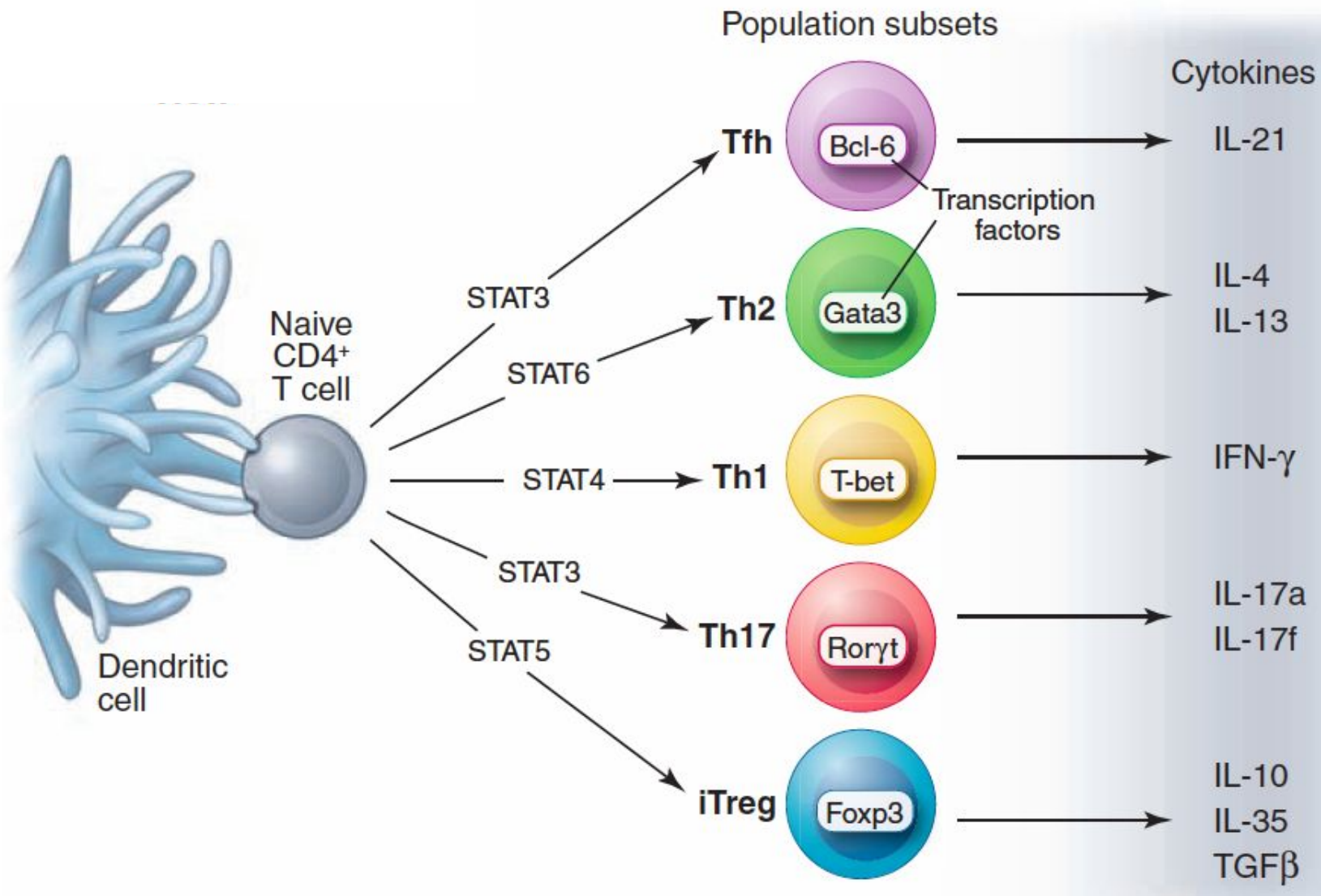
La produzione di diverse combinazioni di citochine da parte delle cellule dendritiche durante la presentazione del complesso antigene/MHC ai T linfociti guida la differenziazione dgli stessi verso diverse linee funzionali (TH1, TH2, TH9, TH17, Treg, etc)
Ciascuna di tali linee differenziative è meglio specializzata a sostenere una particolare risposta effettrice



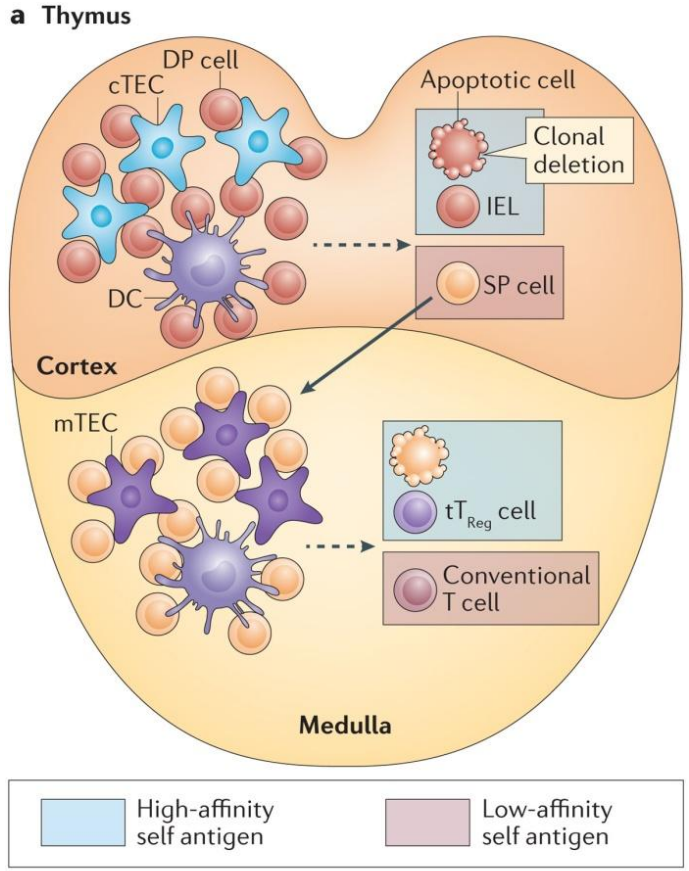


Th group	Function	Target cells
 IFN-γ IL-2 Th1	Cellular immunity Intracellular bacteria Viruses	Macrophages Dendritic cells
 IL-4 IL-13 IL-5 Th2	Humoral immunity Allergic disease Parasites	Eosinophils Basophils
 IL-17A IL-17F IL-21 IL-22 Th17	Autoimmunity Extracellular bacteria Fungi	Neutrophils
 TGF-β IL-10 Treg	Immune tolerance Regulation of immune responses	Antigen presenting cells

- The existence of **a suppressor T cell population** was postulated several years ago, *(Tada T et al., Annu Rev Immunol 1984)*.

- Suppressor T cells restrict induction or expression of effector T cells thereby prevent or terminate eccessive responses or, in the case of self-reactive T cells, autoimmune disease.

- Suppressor T cells, now renamed **"regulatory" T cells (T_{reg} cells)** have been isolated from mouse and human, and their suppressive or regulatory capacity has been demonstrated *in vivo* and *in vitro*.



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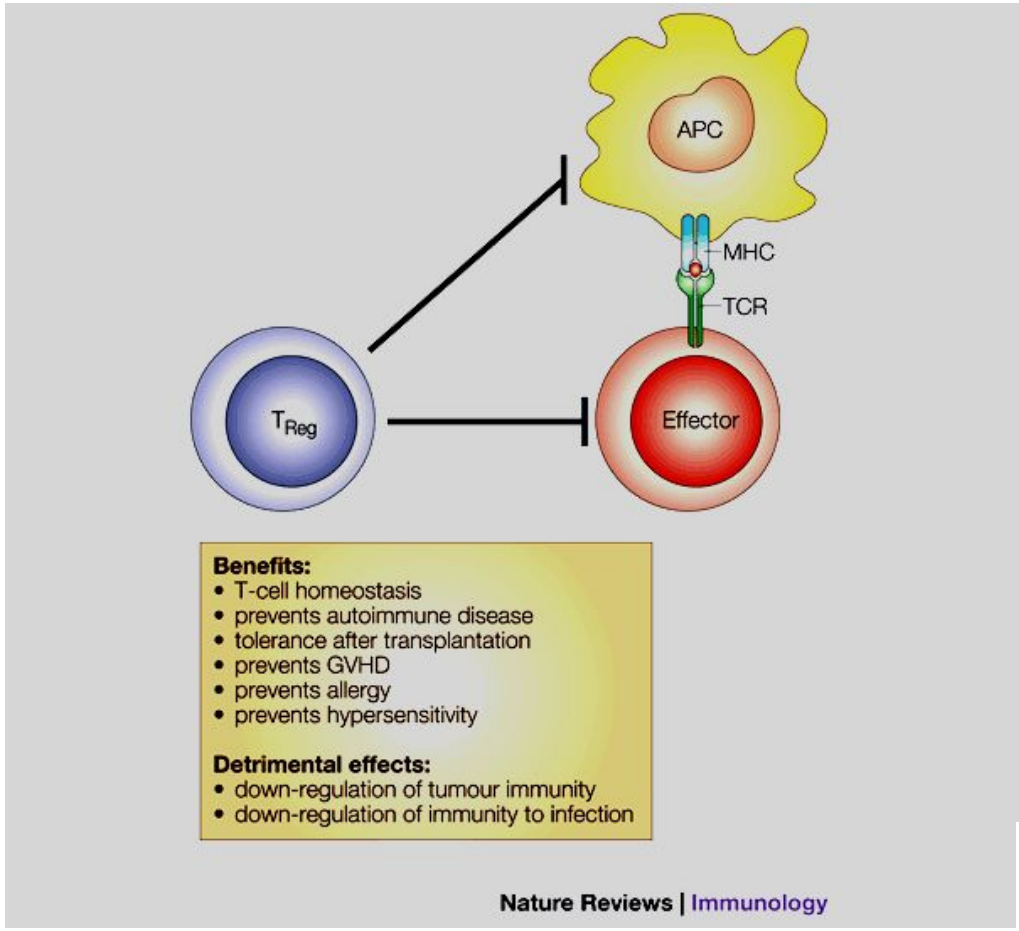
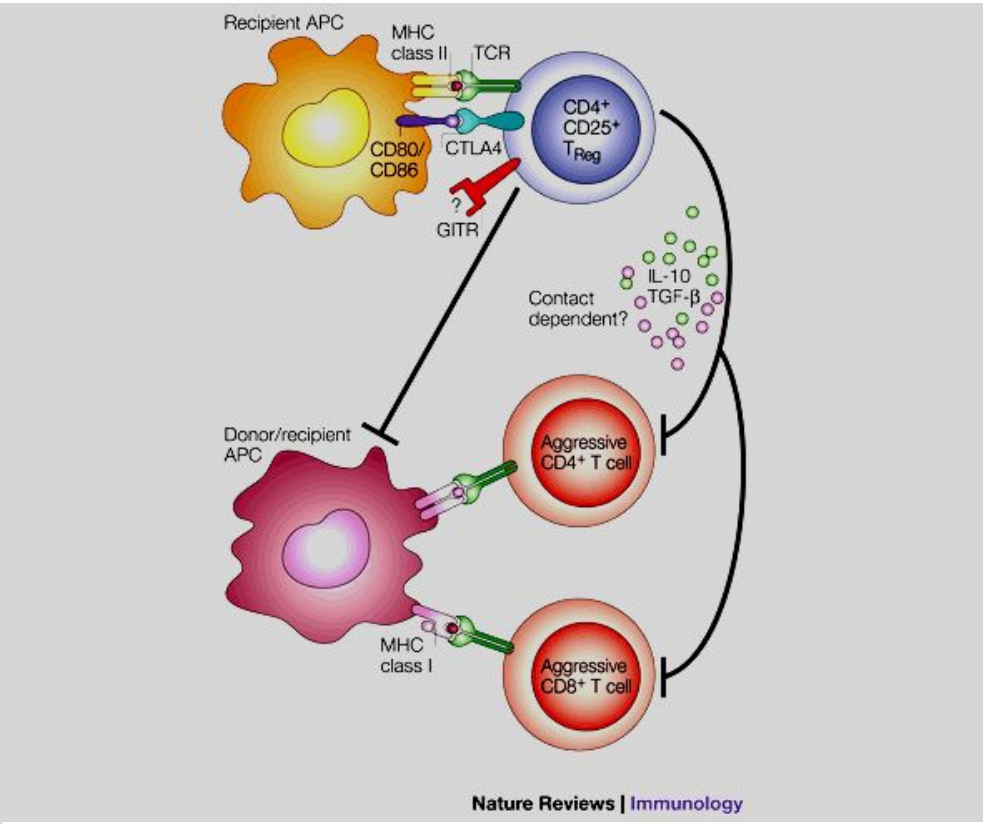
T_{reg}: benefici e svantaggi





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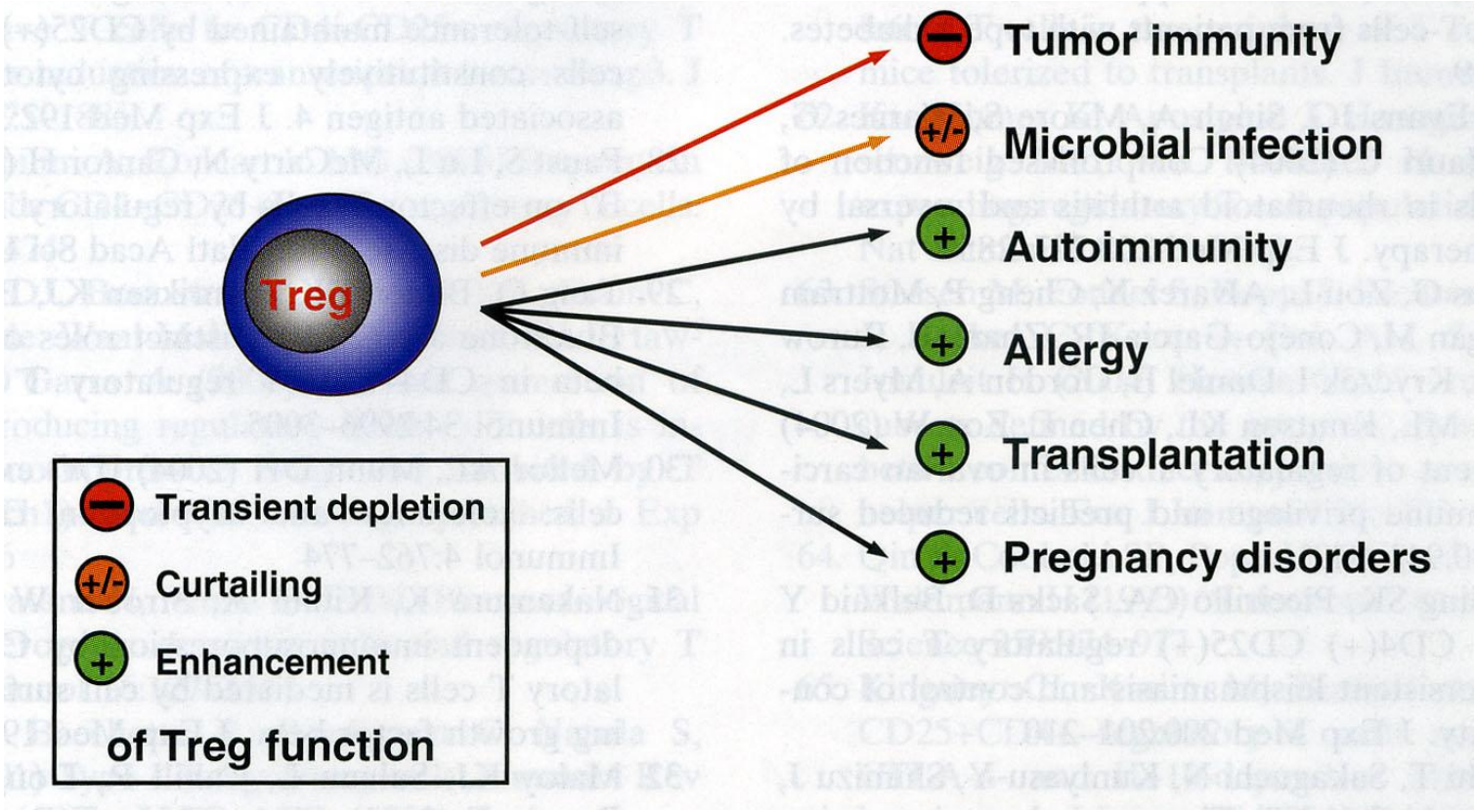
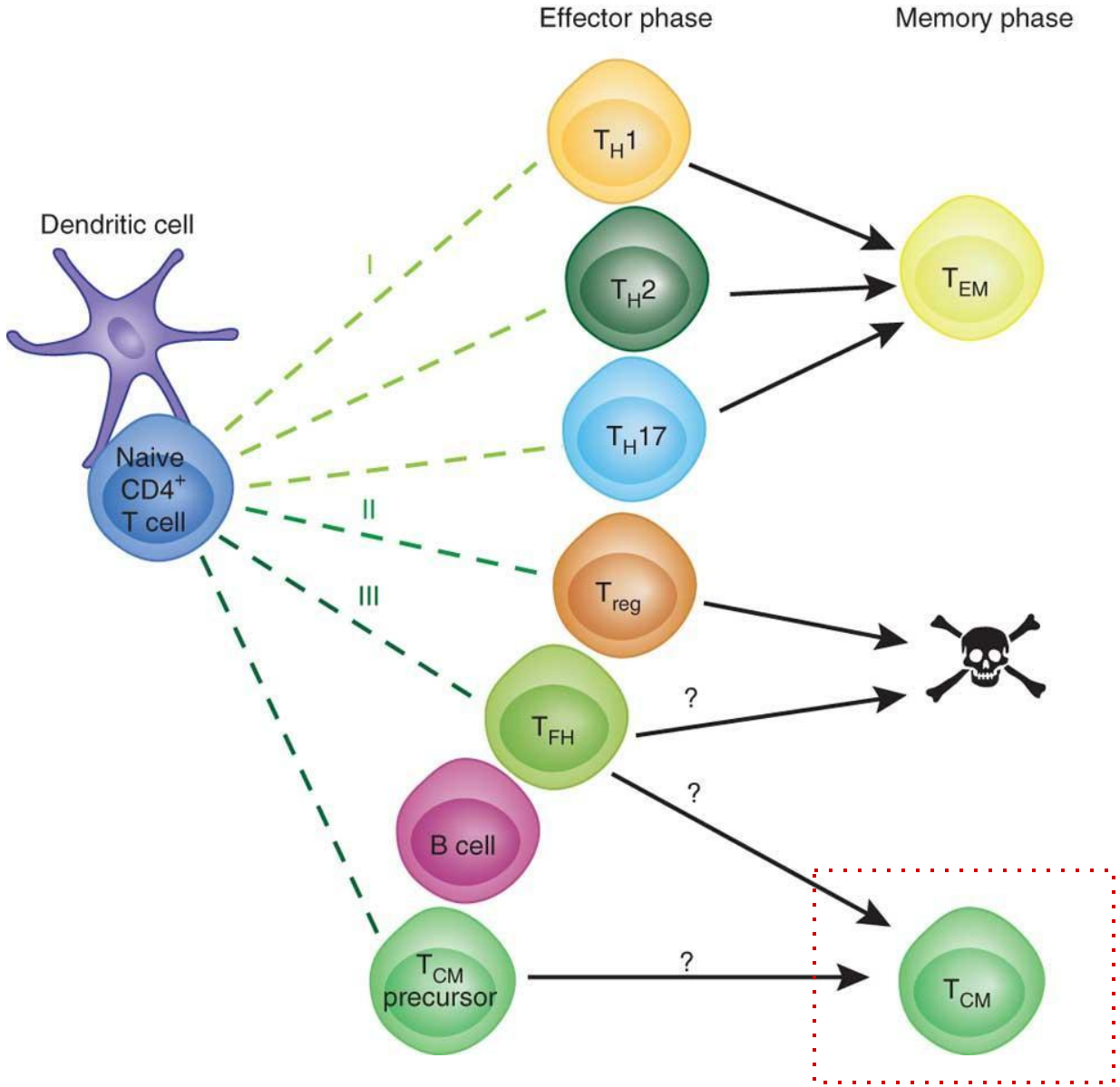
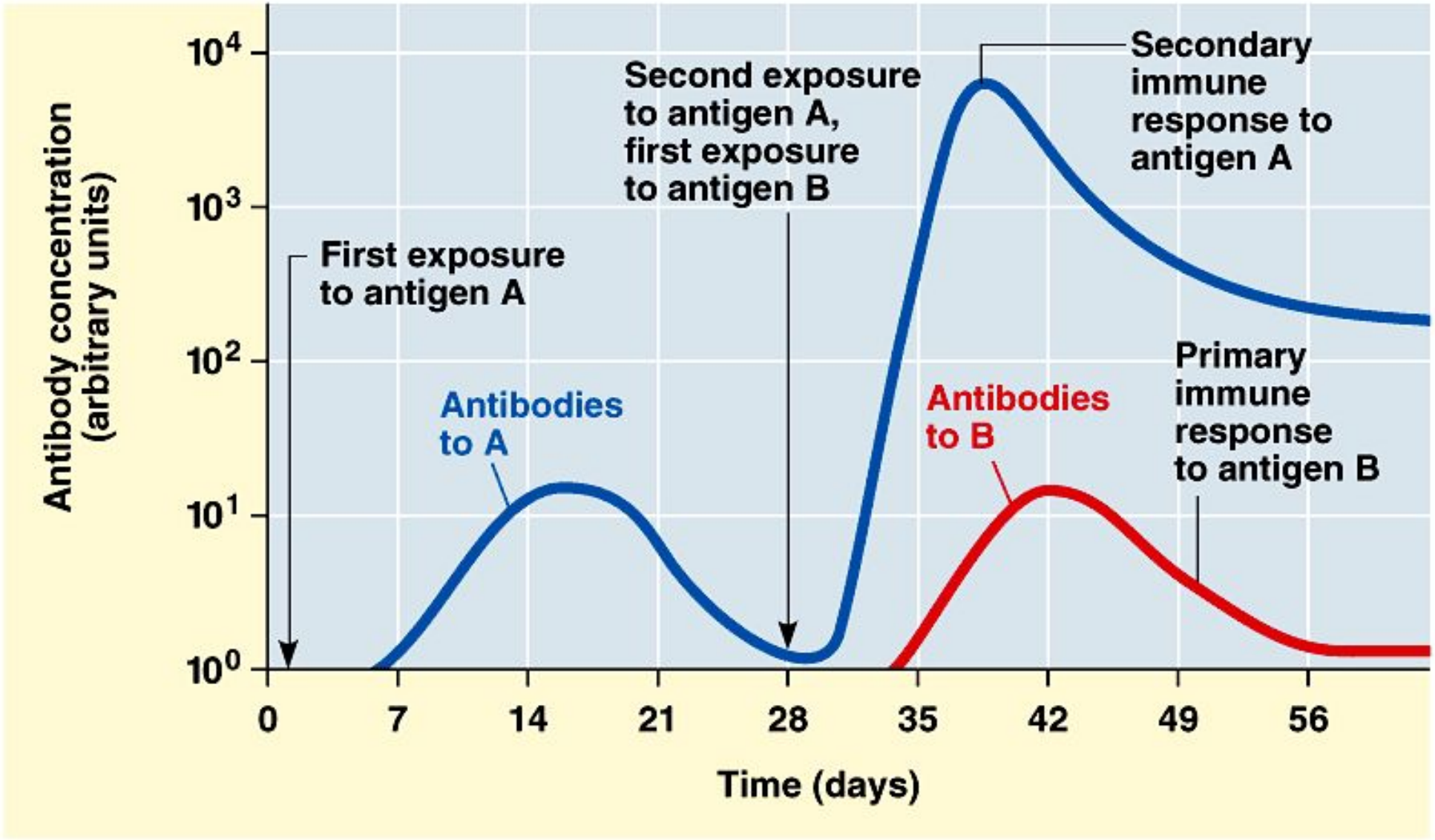
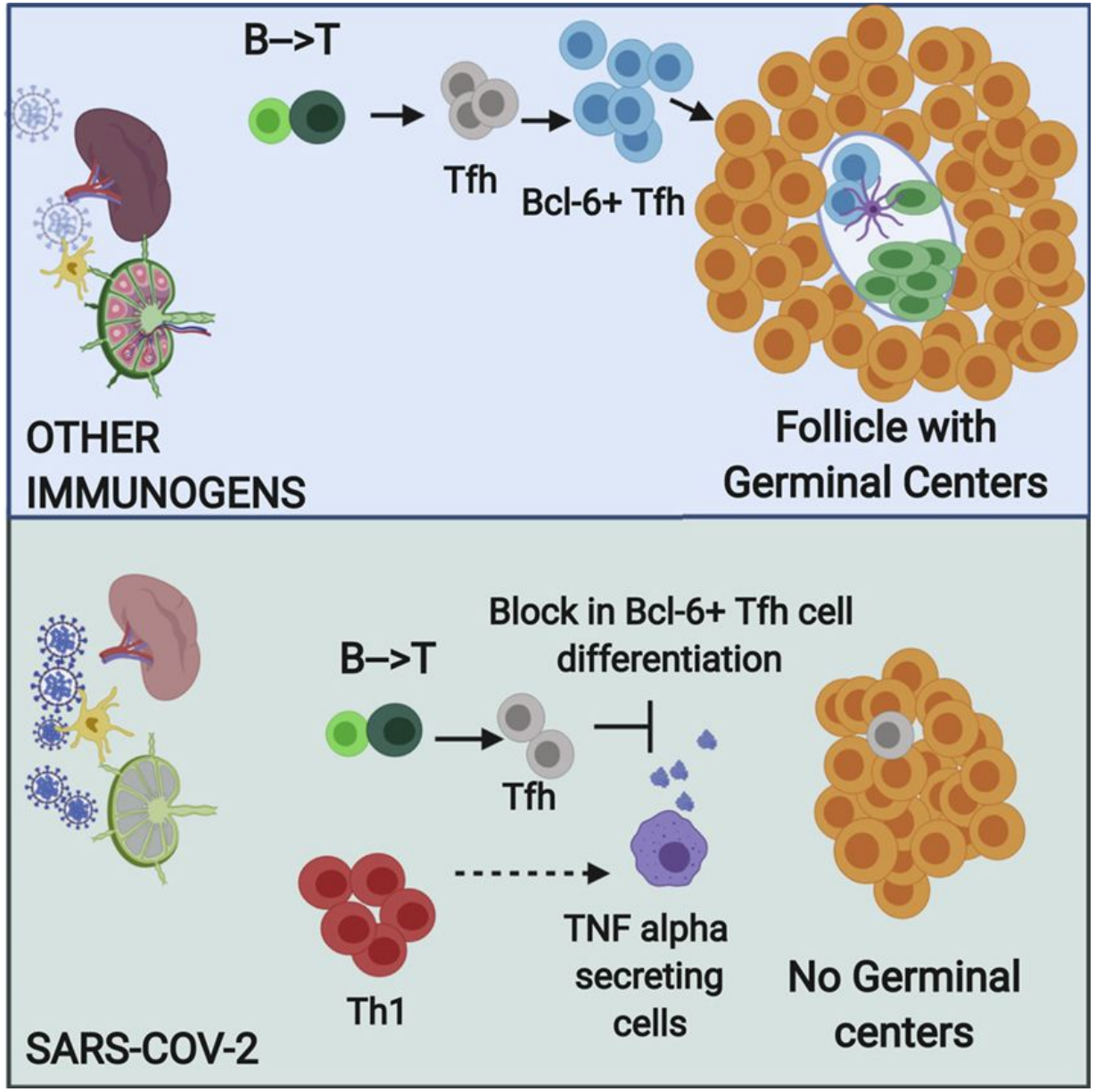
T_{reg}-based immune intervention strategies







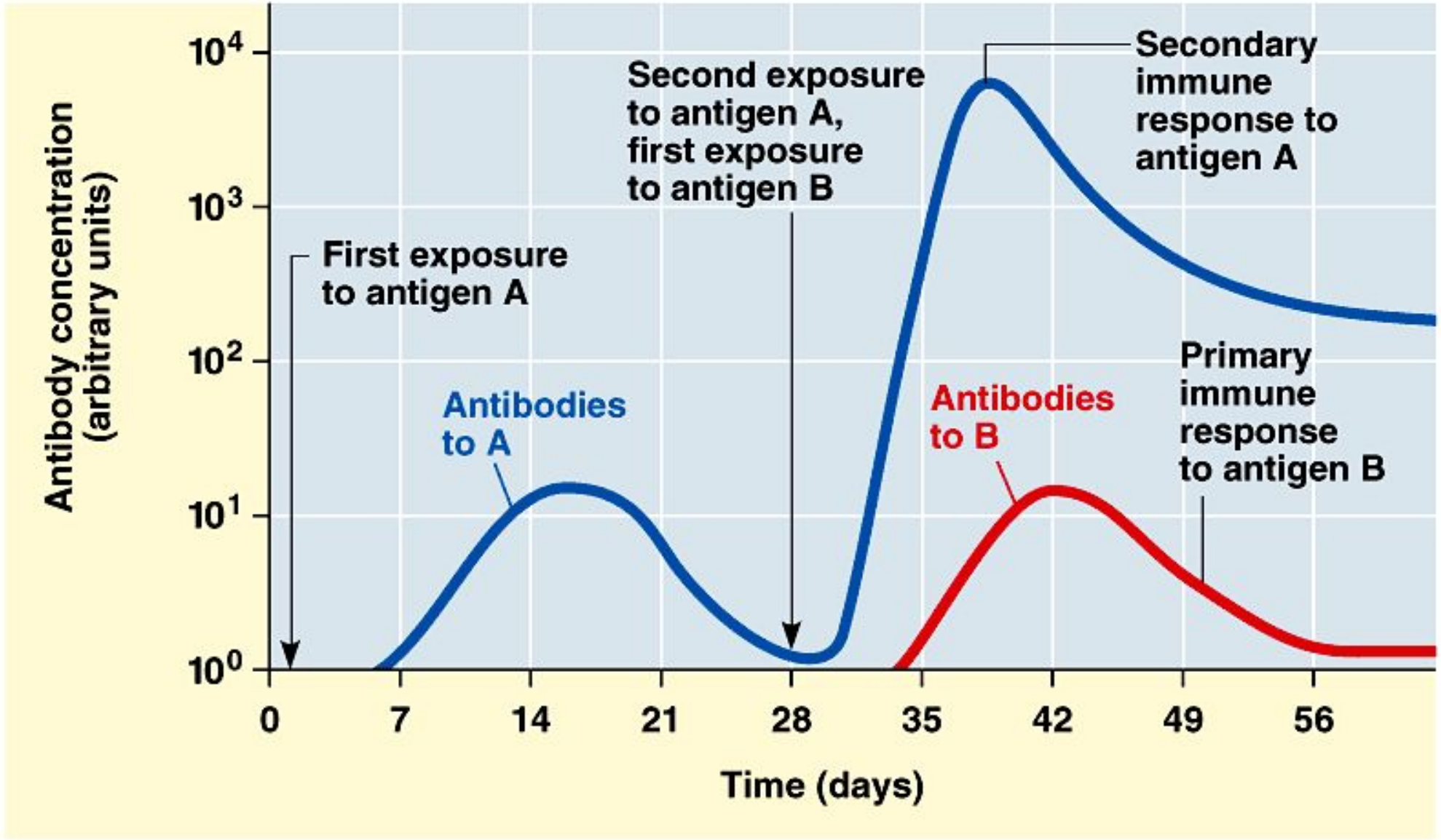


T ed i B linfociti memoria migrano nei centri germinativi nei linfonodi; ciò e la espressione di particolari proteine (p.es. Bcl6) è fondamentale per permettere la loro sopravvivenza e la produzione di anticorpi ad alta affinità.
SARS-CoV-2 altera questo meccanismo

COSA FA UN VACCINO?

Un vaccino utilizza proteine del patogeno private della componente di tossicità per indurre il priming dei linfociti vergini e trasformarli in cellule della memoria.

Un vaccino, dunque, trasforma la natura della risposta immune da primaria a secondaria



MECCANISMI IMMUNOLOGICI INDOTTI DAL VACCINO IDEALE

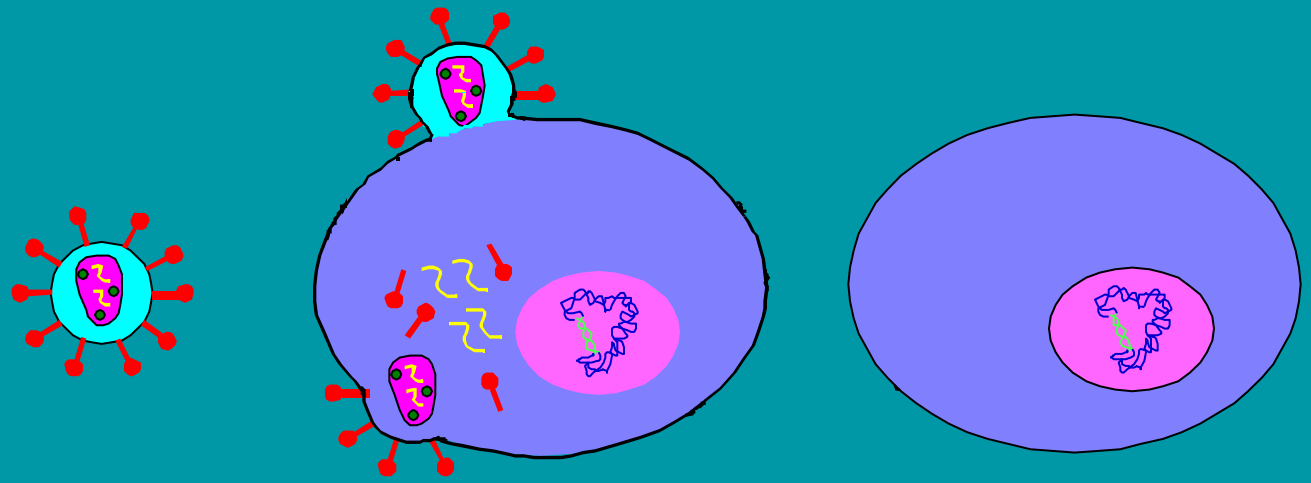
ANTICORPI

- **Legano il patogeno; ne neutralizzano la infettività e gli impediscono di infettare le cellule; contribuiscono alla eliminazione del patogeno**

T LINFOCITI CITOTOSSICI (CTL)

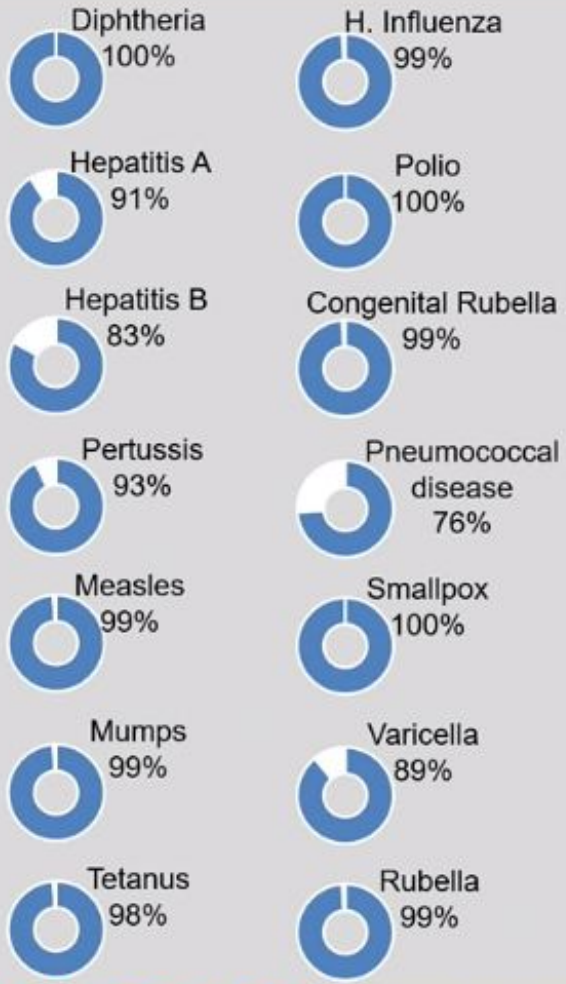
- **Riconoscono le cellule che sono state infettate e le uccidono**

Ruolo delle diverse risposte immune indotte da un vaccino



Anticorpi	+++	+/-	-
T linfociti	-	+++	-

% Decrease of viral infections in most recent reports vs pre-vaccine era of the in the US[1]



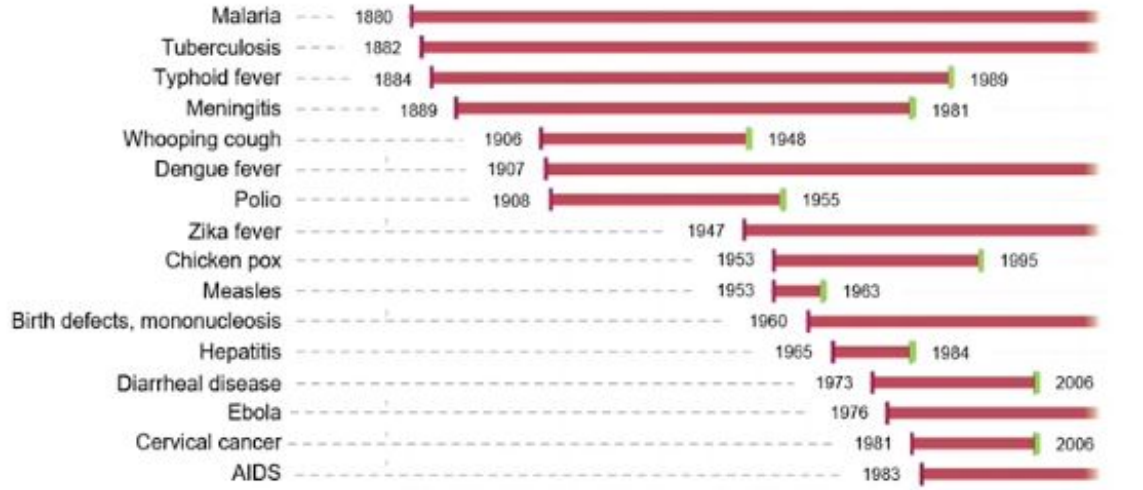
#VaccinesWork!

Vaccines greatly reduce:

- Disease • Disability • Death (prevent 6–9 million/year) • Inequity worldwide

Herd immunity can help eliminate diseases without 100% coverage

Vaccine innovation: 1880 to 2016[2]

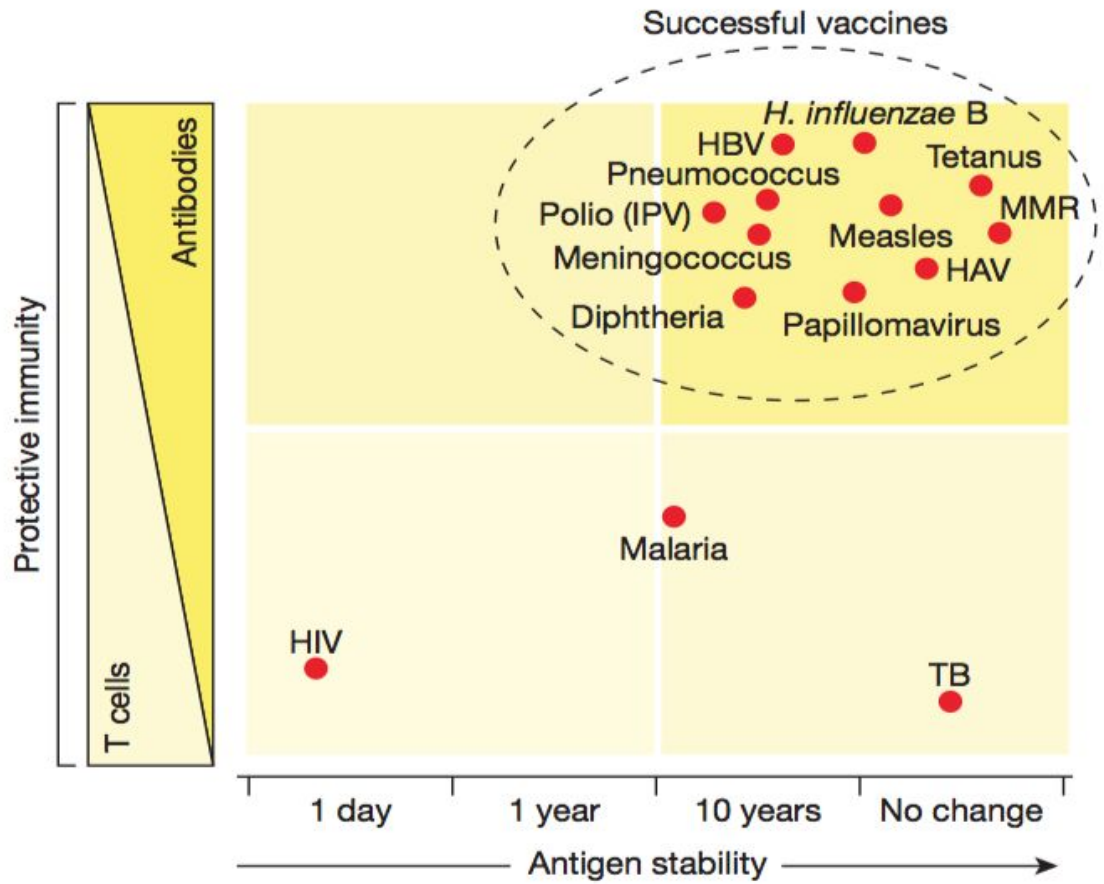


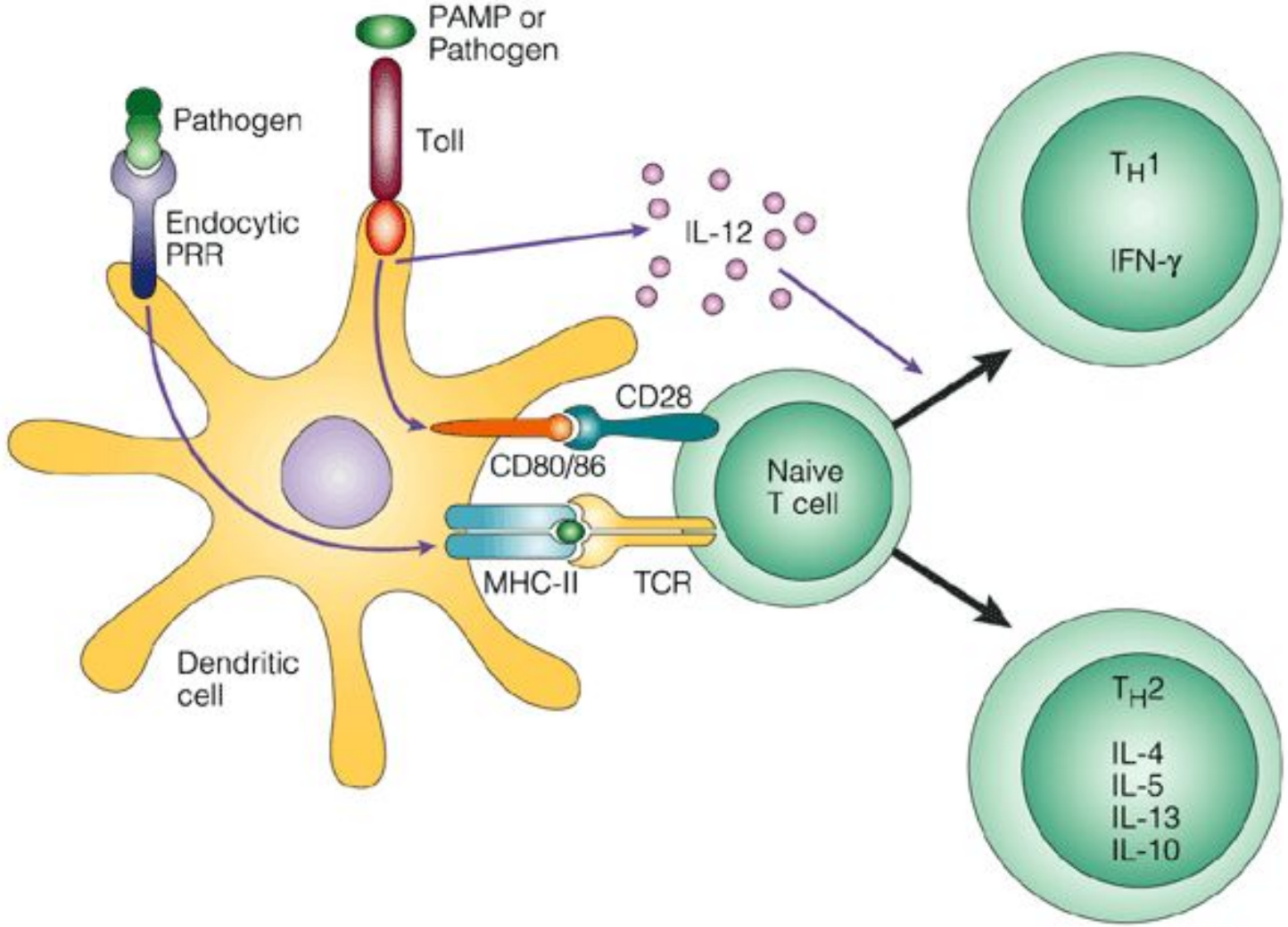
Average vaccine development: 10.7 years

1. Online. Available at: https://www.forbes.com/sites/matthewherper/2013/02/19/a-graphic-that-drives-home-how-vaccines-have-changed-our-world/#3b1e007c3302. Accessed Sept 20
2. Online. Available at: https://ourworldindata.org/vaccination#vaccine-innovation. Accessed Sept 20

Challenging infectious diseases

Historically successful vaccines have been developed mostly against those pathogens that can be treated by antibodies and have a stable antigen repertoire (Box 1 Figure). HIV, malaria and tuberculosis vaccines do not fall within the cluster of successful vaccines in the graph, because of antigenic variability and the requirement of T-cell immunity for protection. Developing vaccines against these pathogens requires novel approaches.





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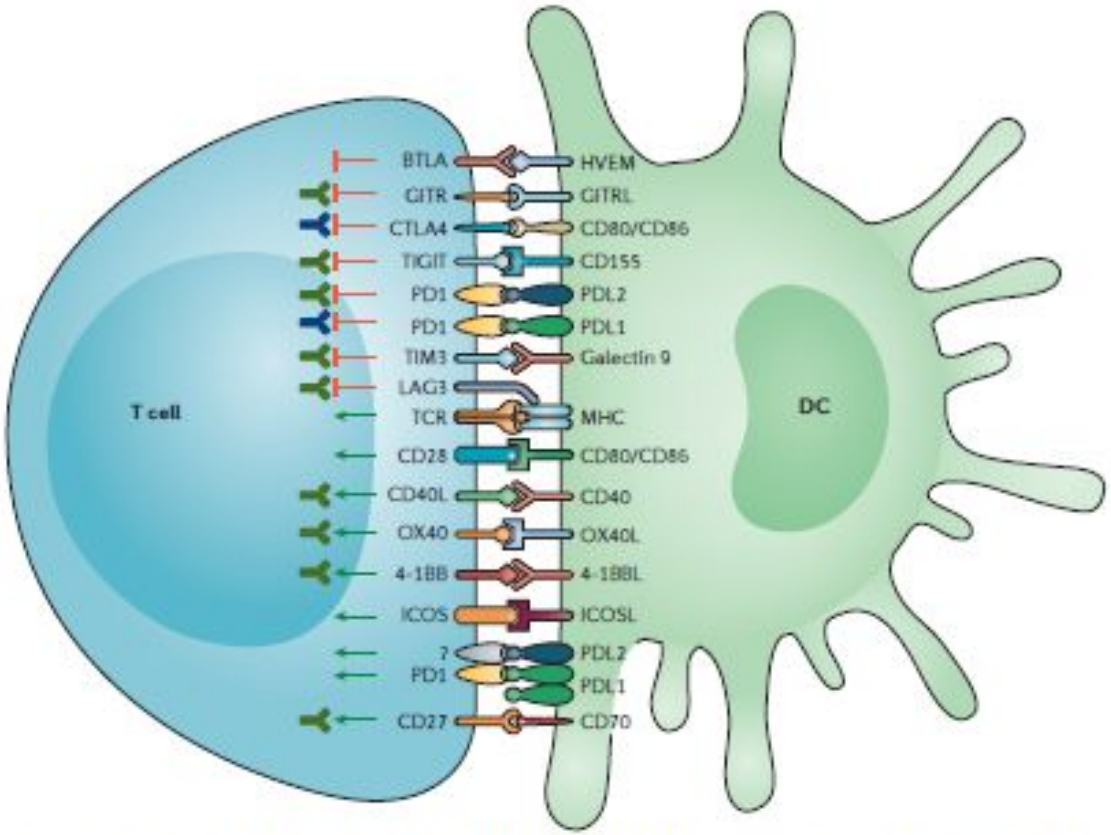
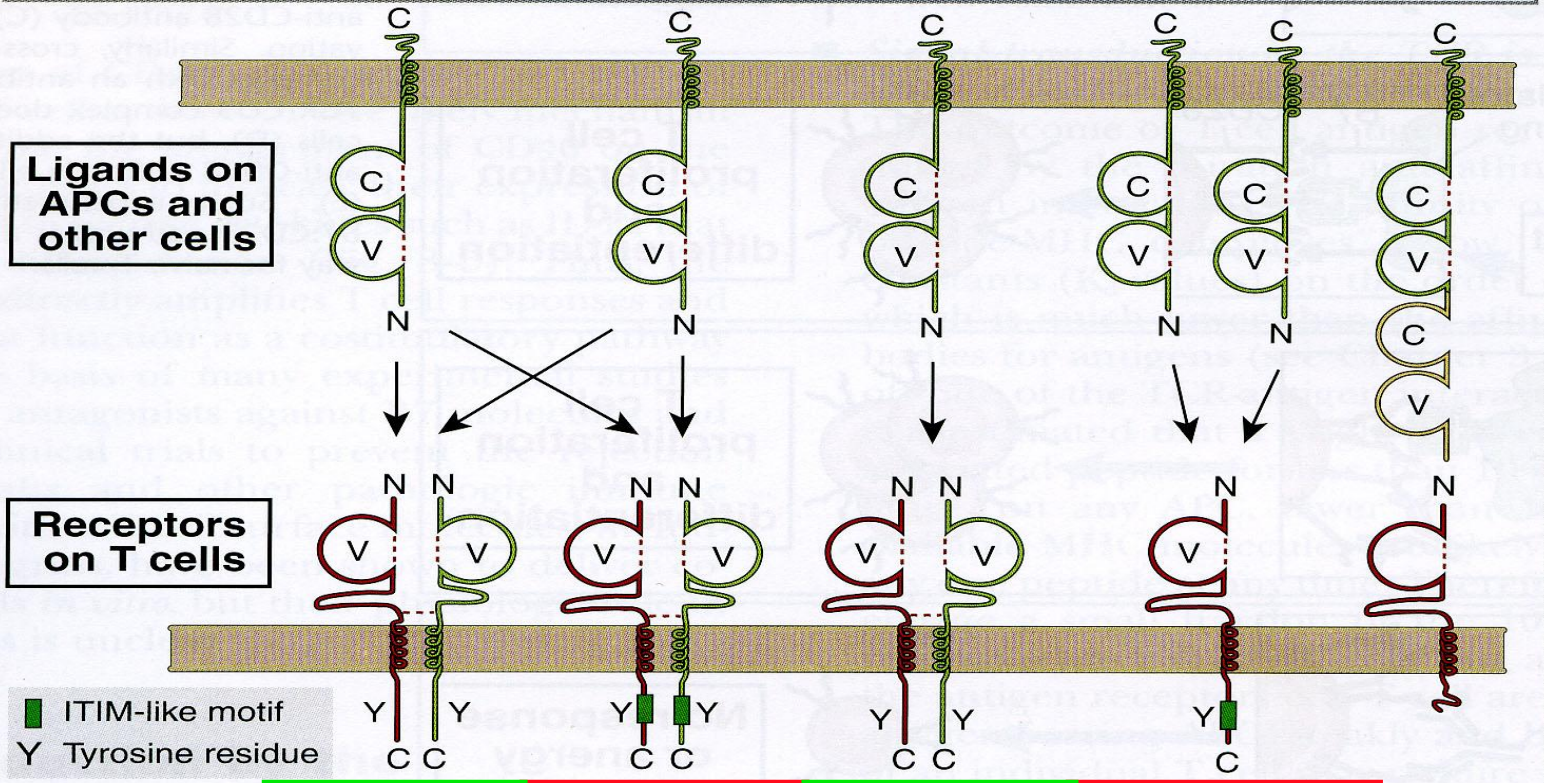


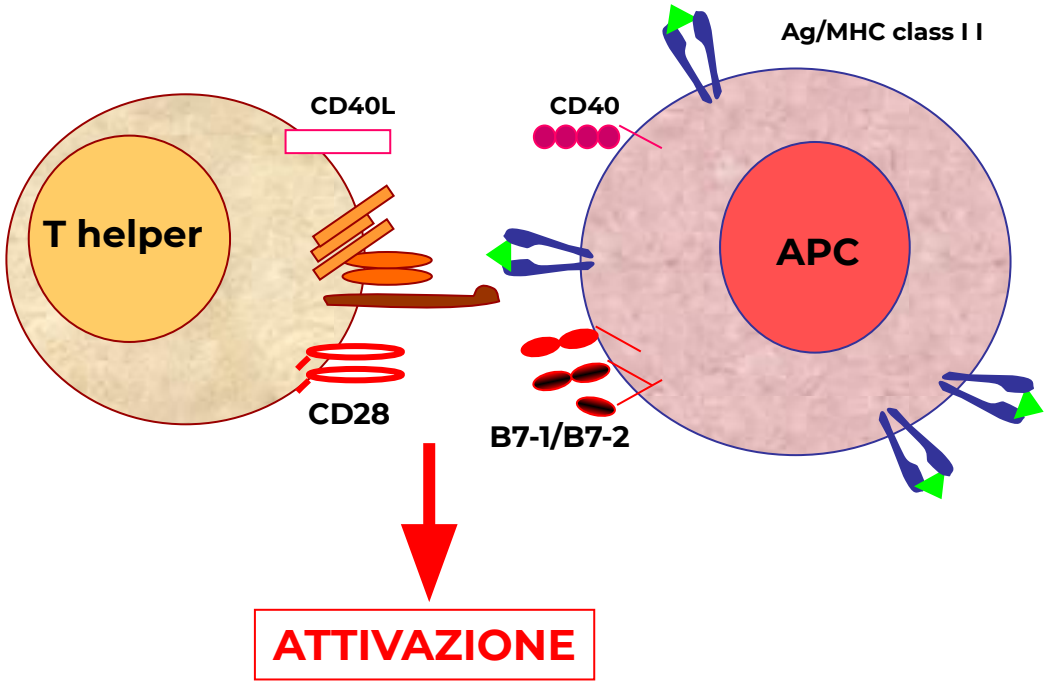
Figure 1 | **Interactions with antigen-presenting cells that regulate T cell responses.** Antigen-presenting cells (APCs), such as dendritic cells (DCs), regulate antigen-specific T cell responses to pathogens or malignant cells. The T cell receptors (TCRs) on antigen-specific T cells first recognize their cognate antigens, which are presented on MHC molecules on APCs (signal 1). This step must be followed by a signal to CD28 on T cells from CD80 on the APCs, which is described as 'signal 2'. Several different ligands on DCs then provide signals to T cells that determine the quality and duration of the effector response. Receptor–ligand interactions that amplify effector T cell responses (indicated by green arrows) include CD40–CD40 ligand (CD40L), OX40–OX40L, 4-1BB–4-1BBL (also known as CD137L), inducible T cell co-stimulator (ICOS)–ICOSL and CD27–CD70. There are also receptor–ligand interactions that suppress effector T cell responses (red square arrows) to maintain self-tolerance and limit the duration of the immune responses to minimize bystander damage to host tissue. These include lymphocyte activation gene 3 protein (LAG3)–MHC class II, T cell immunoglobulin mucin receptor 3 (TIM3)–galectin 9, programmed cell death protein 1 (PD1)–programmed cell death 1 ligand 1 (PDL1), PD1–PDL2, T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT)–CD155, cytotoxic T lymphocyte antigen 4 (CTLA4)–CD86 or CTLA4–CD80, glucocorticoid-induced TNFR-related protein (GITR)–GITR ligand (GITRL) and B and T lymphocyte attenuator (BTLA)–herpes virus entry mediator (HVEM). The '?' refers to an unknown receptor that 'activates' T cells. Antibody symbols represent pathways being tested in current clinical trials. The green antibodies indicate pathways undergoing clinical trials for cancer, and the dark blue antibodies indicate those already in clinical use.

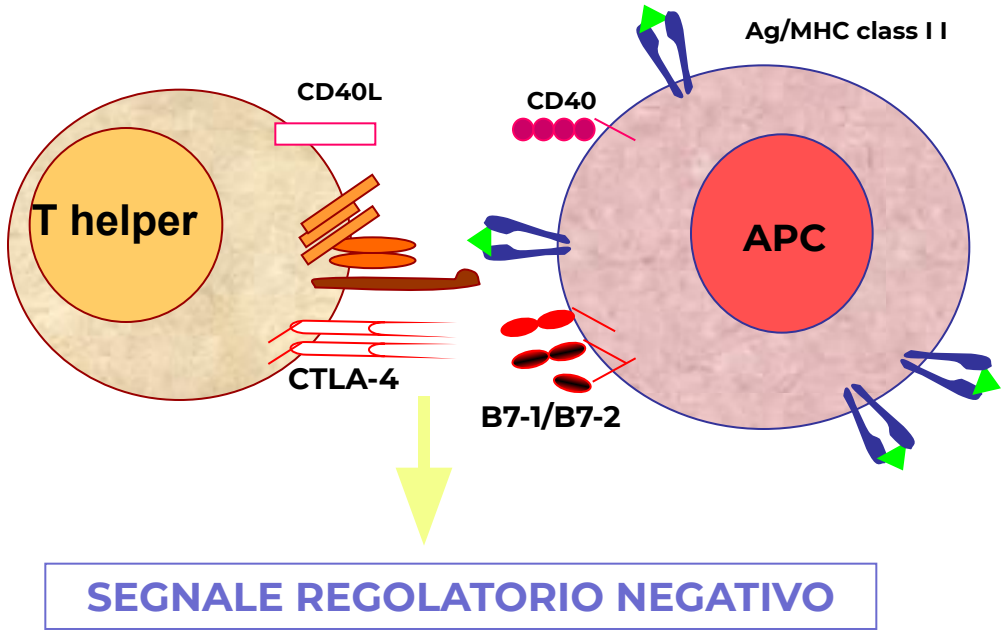
Expression	APCs; inducible	APCs; inducible	APCs, B cells, other tissues; inducible	APCs, B cells, other tissues; inducible		
Name	**B7-1 (CD80)**	**B7-2 (CD86)**	**ICOS-L**	**PD-L1**	**PD-L2**	**B7-H3**

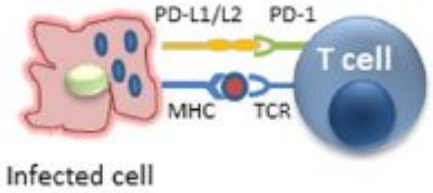
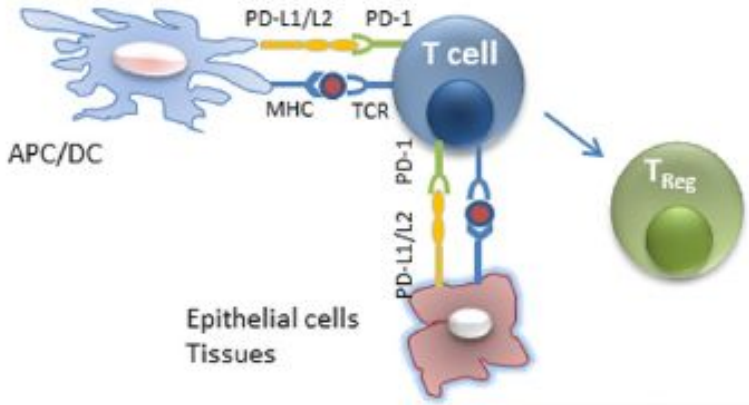
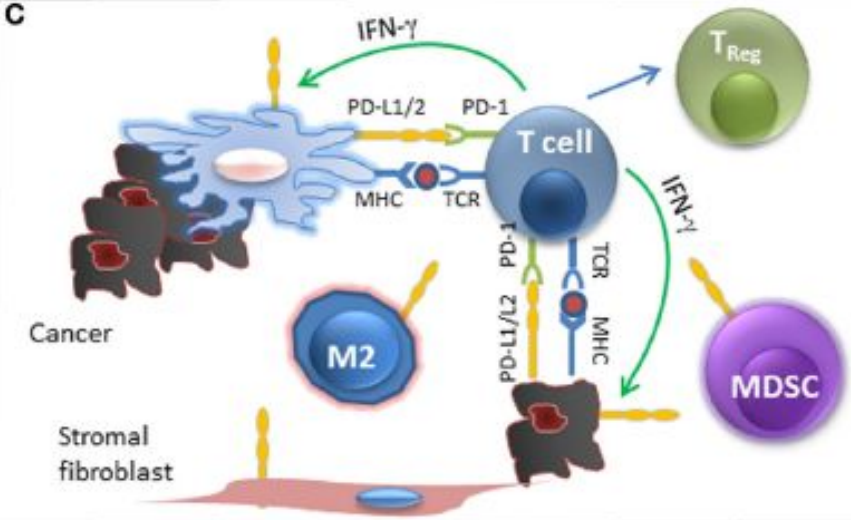


Name	CD28	CTLA-4	ICOS	PD-1	?
Expression	T cells; constitutive	T cells; inducible	T cells; inducible	T cells, B cells, myeloid cells; inducible	
Major function	Costimulation of naive T cells	Negative regulation of immune responses; self-tolerance	Costimulation of effector T cells	Negative regulation of T cells in peripheral tissues	

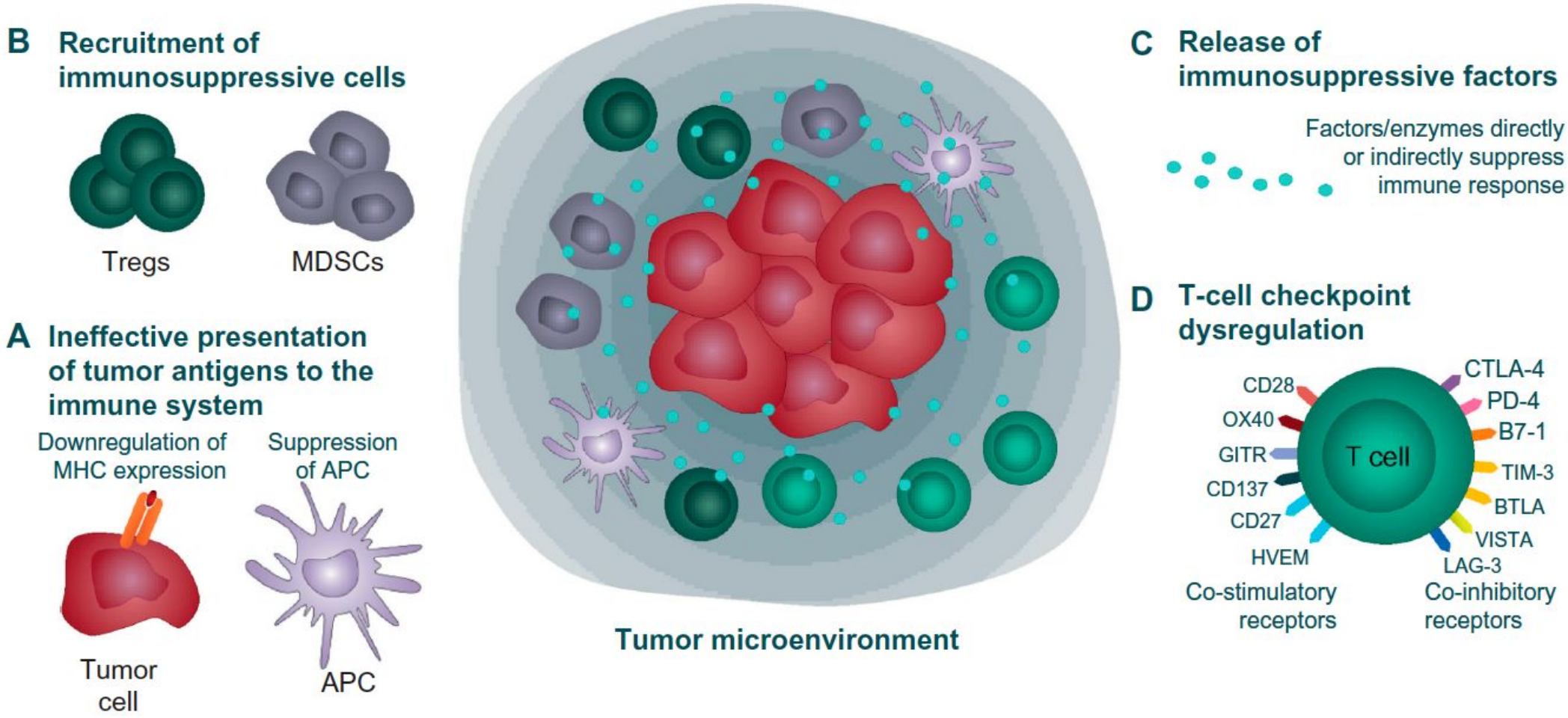
ATTIVAZIONE LINFOCITI T





	Pathway activation	Biological consequences	Therapeutic application
A 	T cell ligation of PD-1 by PD-L1 expressed on infected cells	- Prevents T effector cell generation and expansion - Inhibits immunity against viruses and other pathogens	PD-1: PD-L1 blockade to: - Activate immunity against chronic infections (e.g. HCV, HIV, malaria) - Improve outcome of vaccination
B 	T cell ligation of PD-1 by PD-L1 expressed on APC and tissues	- Prevents generation of self-reactive T effectors - Suppresses activation of escaping self-reactive T effectors - Induces T_{Reg} cells - Maintains self tolerance - Prevents autoimmunity	PD-1 activation to: - Induce self tolerance in autoimmune diseases - Induce donor-specific tolerance in allogeneic organ transplantation and hematopoietic stem cell transplantation
C 	T cell ligation of PD-1 by PD-L1 expressed on cancer cell and APC (DC, MDSC, M2, stromal fibroblasts) of the TME	-Inhibits expansion of tumor-specific T effector cells - Induces Treg cells - Induces tumor tolerance - Prevents anti-tumor immunity	PD1: PD-L1 blockade to: - Activate immunity against cancer

Mechanisms of tumor evasion



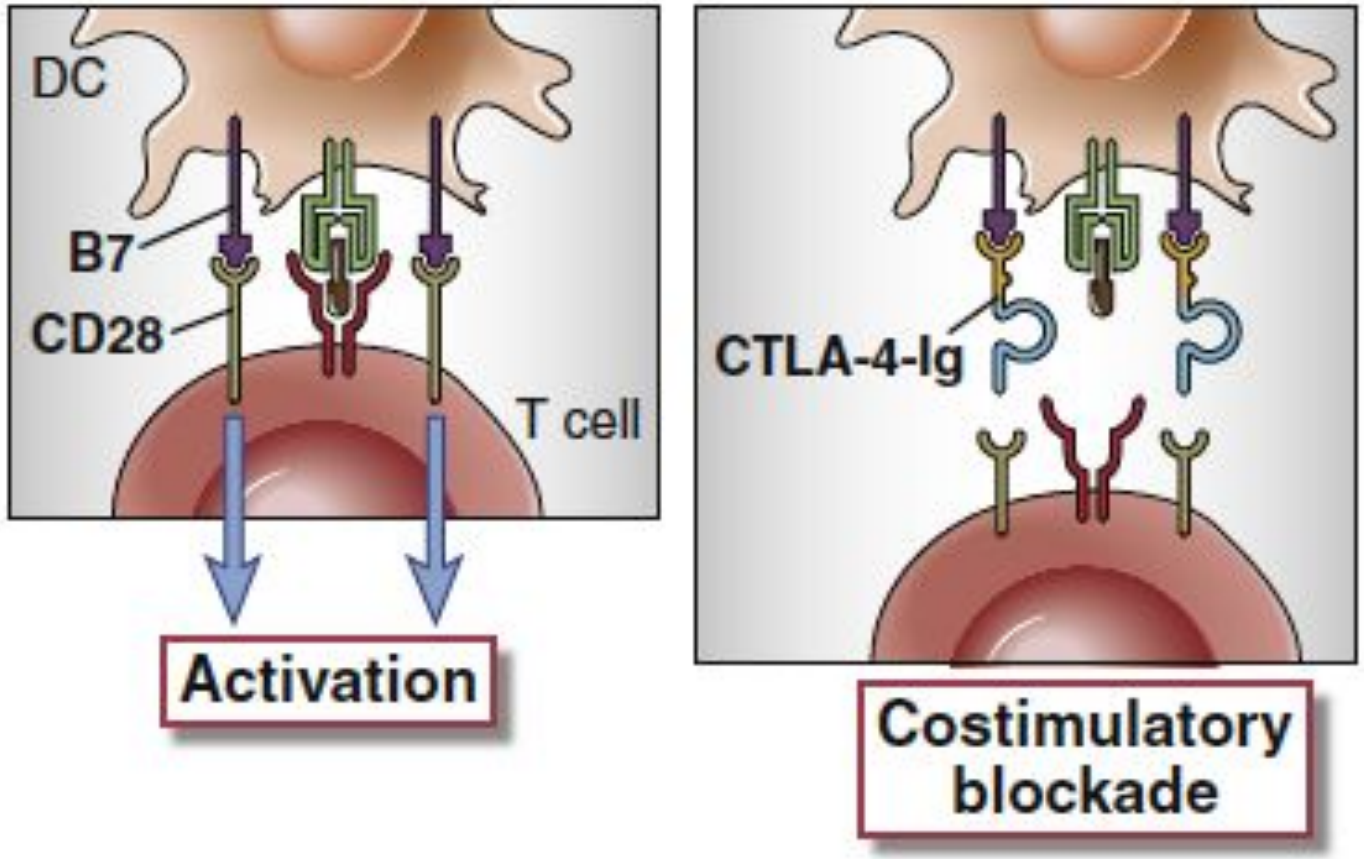
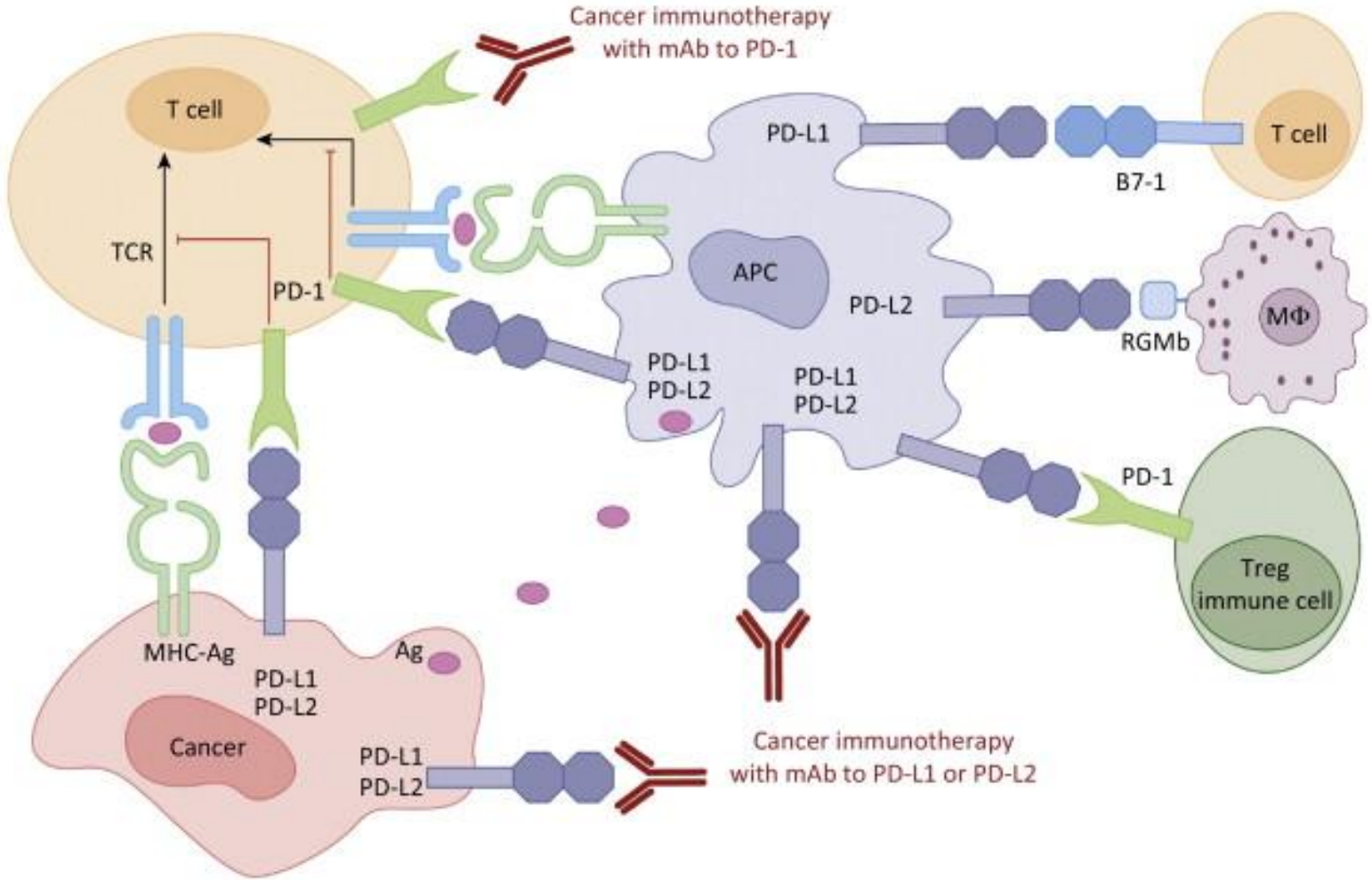


FIGURE 9-7 The mechanism of therapeutic costimulatory blockade. A fusion protein of the extracellular portion of CTLA-4 and the Fc tail of an IgG molecule is used to bind to and block B7 molecules, thus preventing their interaction with the activating receptor CD28 and inhibiting T cell activation.



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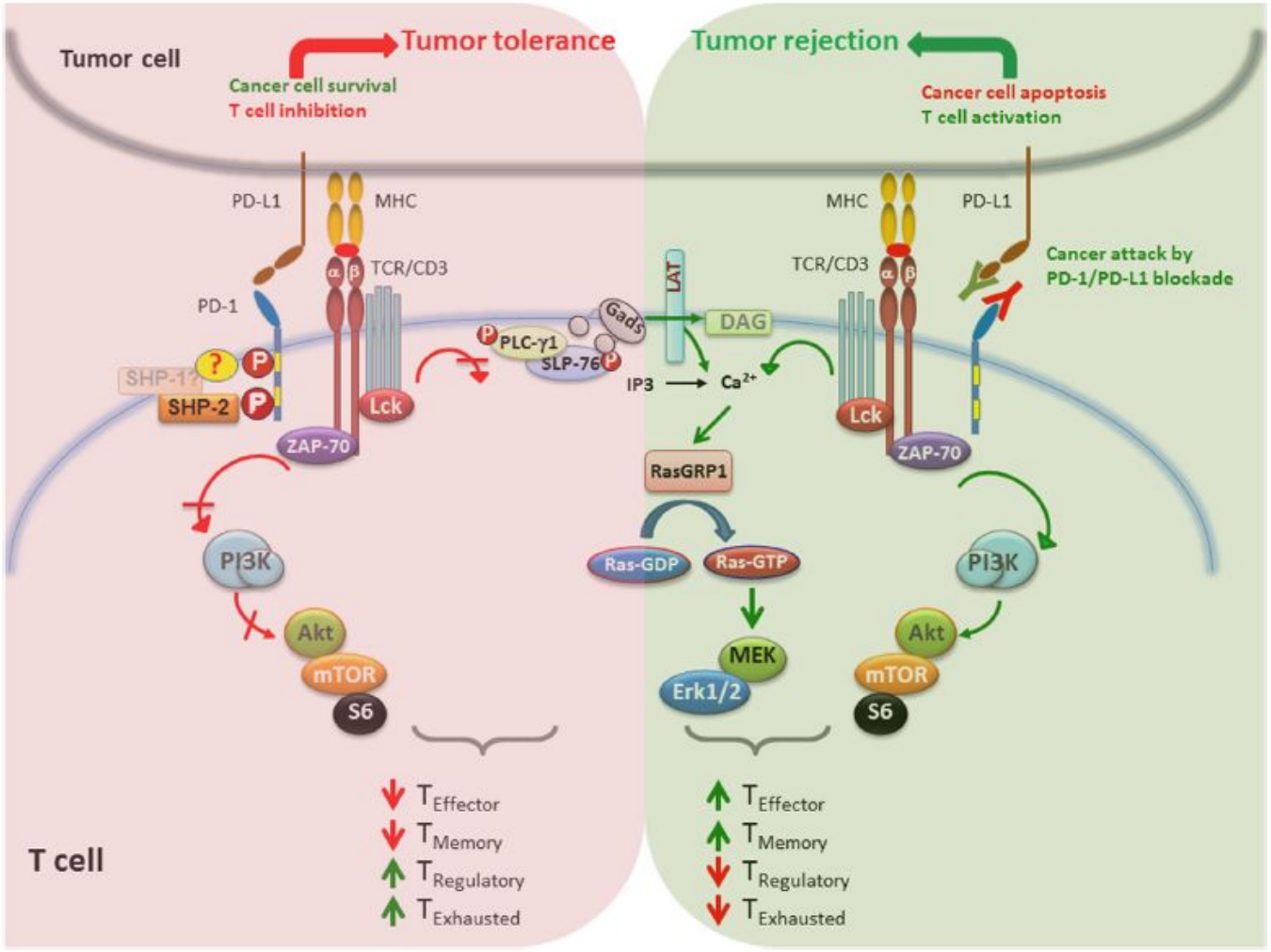
PD-1/PD-L1 blockage enhances tumor rejection by activated T cells



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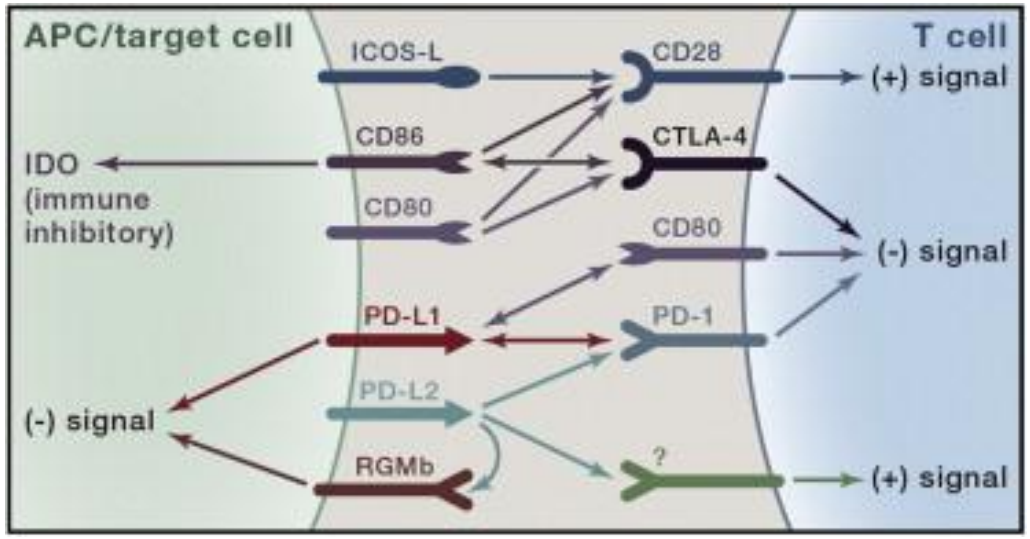
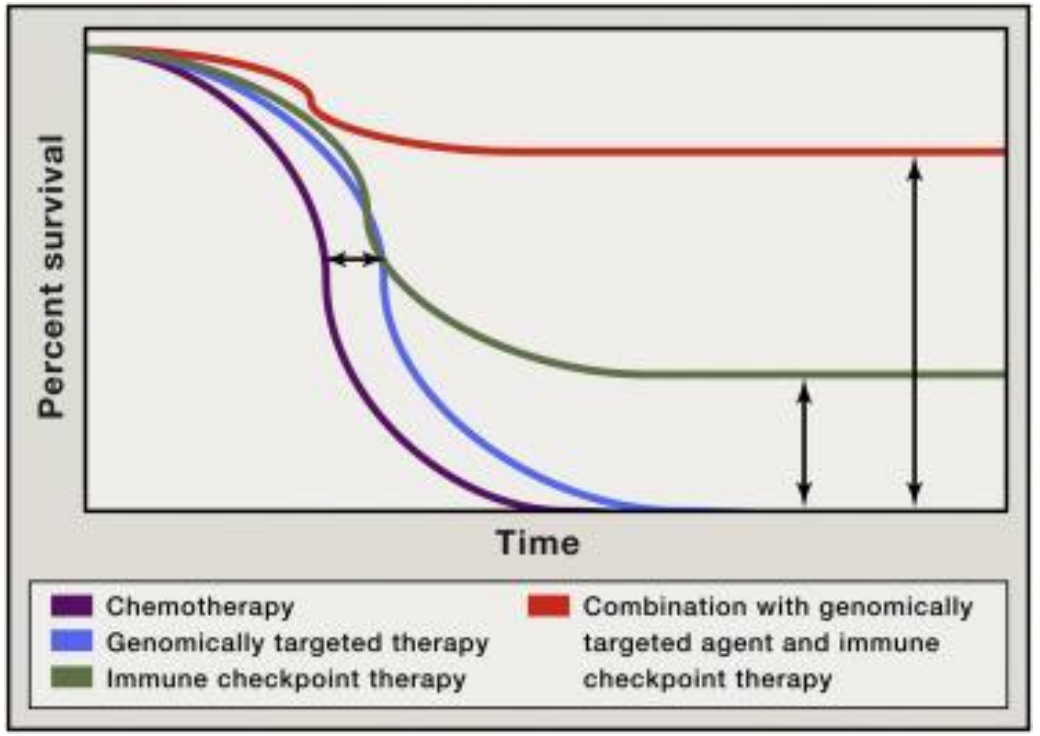
Improved Overall Survival (advanced stage melanoma) by immune checkpoint blockade therapy





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