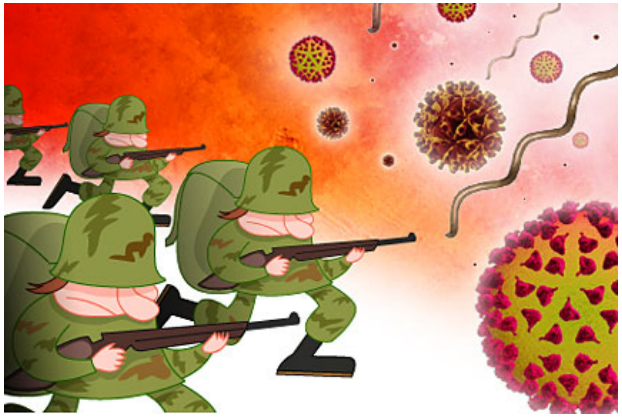
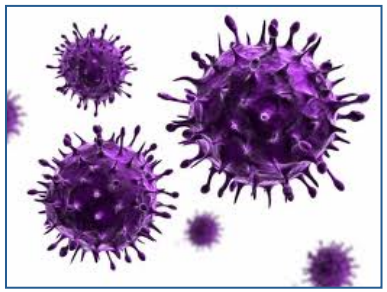
Acknowledgments: Tom Scriba, Adam Penn-Nicholson

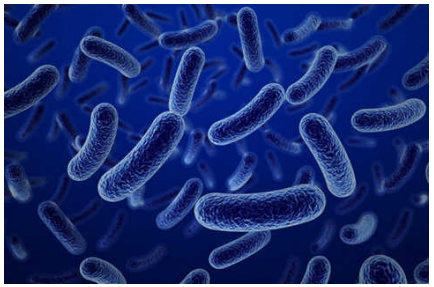


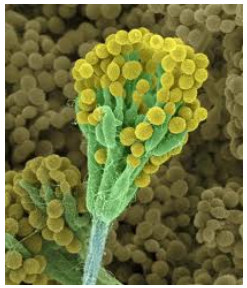
What is the immunity?

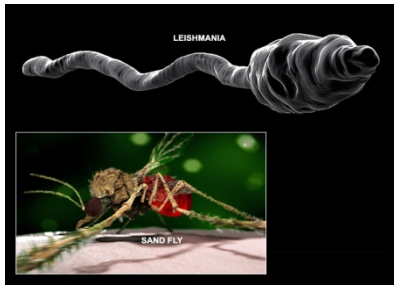
Definition: All mechanisms to protect our body against external elements

→Pathogens

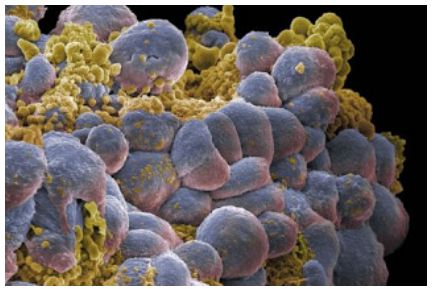






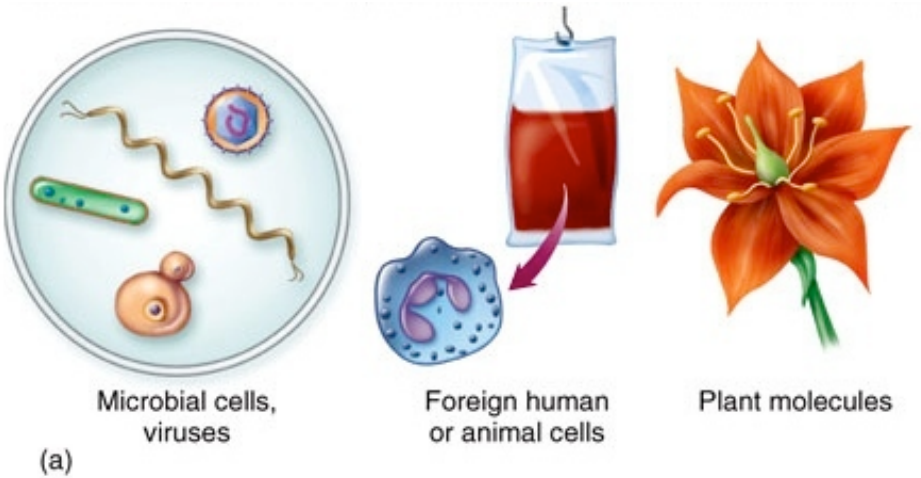


→Own altered constituants

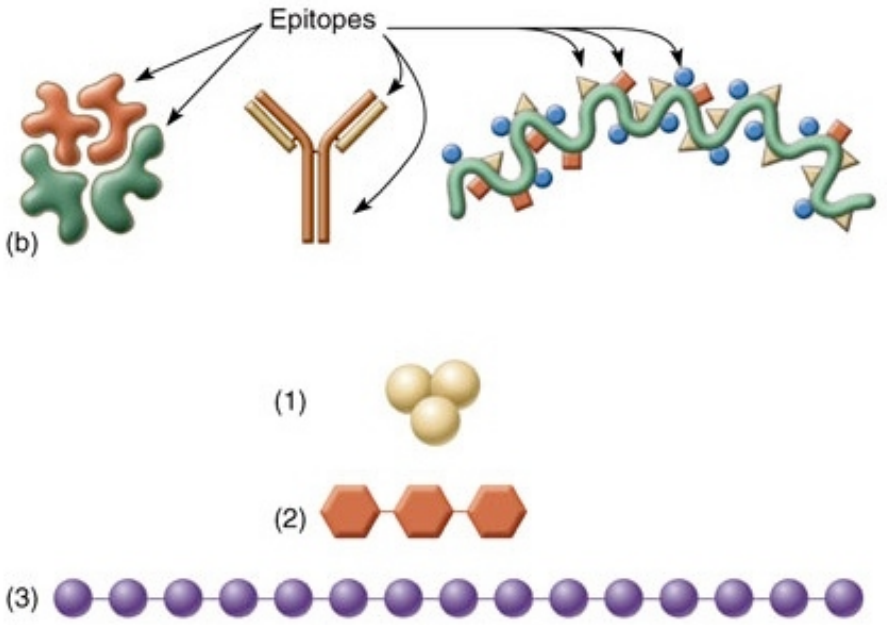


→ Pollution

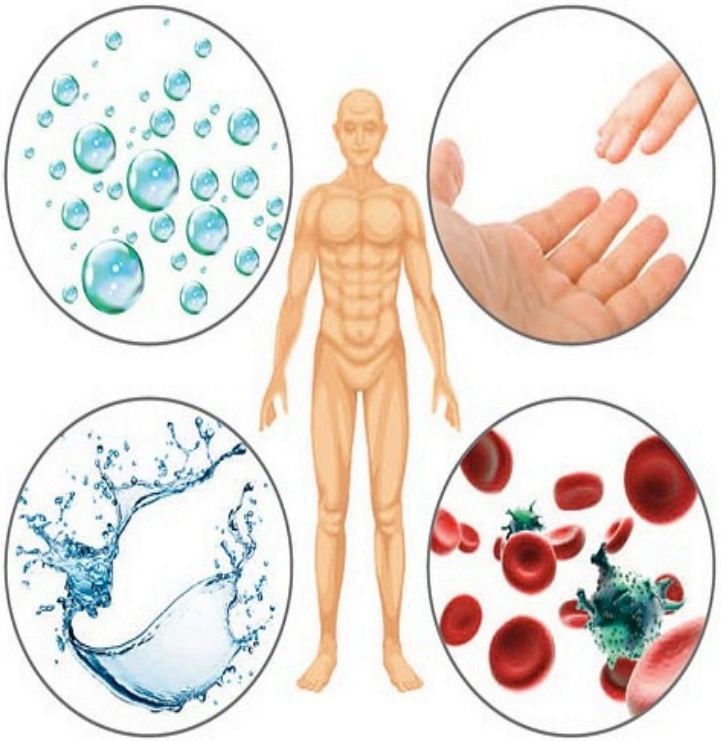
- **Antigens** are foreign to host
  - Proteins and large polysaccharides



Each antigen has many **epitopes** = portions of an antigen recognized by the immune system



The immune system



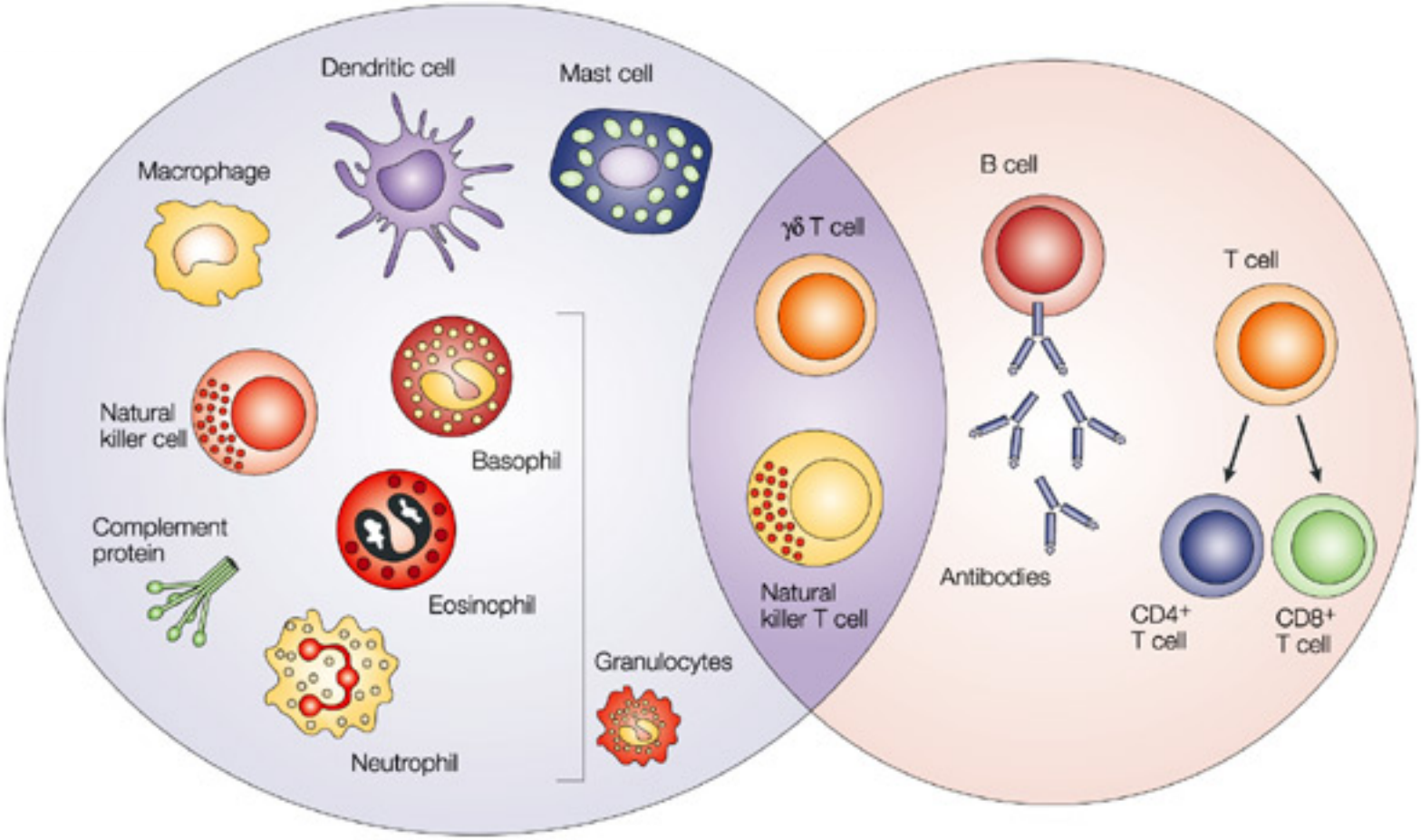
Physical protections

- The skin
- Mucosal parts

A complex system composed from:

- Organs
- Cells
- Molecules

Immune Response to Infection



Innate:

- Quick
- Does not remember!

Adaptive:

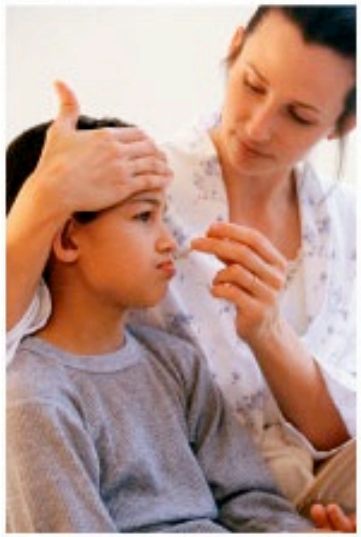
- Slower
- Remembers!

Principles of Immunity

Acquired Immunity

Natural Immunity
is acquired through the normal life experiences of a human and is not induced through medical means.

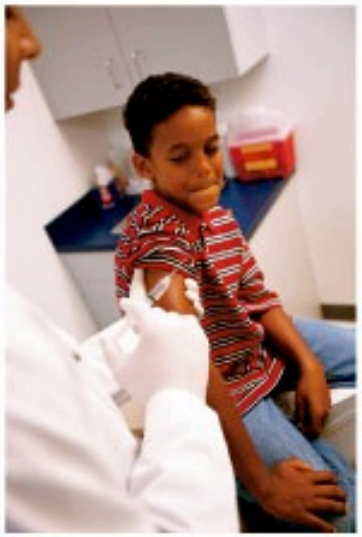
Active Immunity
is the consequence of a person developing his own immune response to a microbe.



Passive Immunity
is the consequence of one person receiving preformed immunity made by another person.

Artificial Immunity
is that produced purposefully through medical procedures (also called immunization).

Active Immunity
is the consequence of a person developing his own immune response to a microbe.

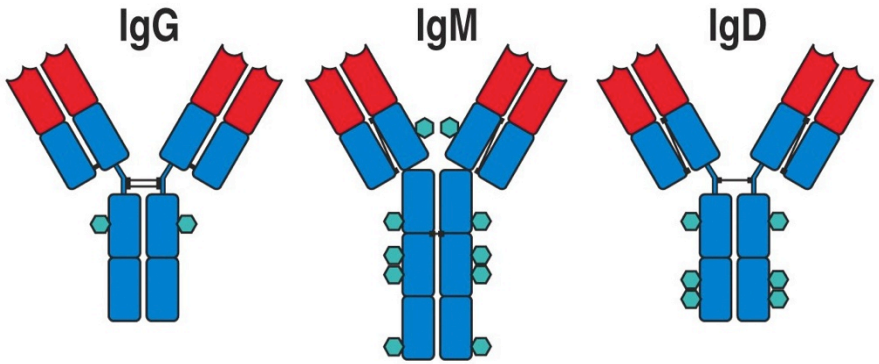


Passive Immunity
is the consequence of one person receiving preformed immunity made by another person.

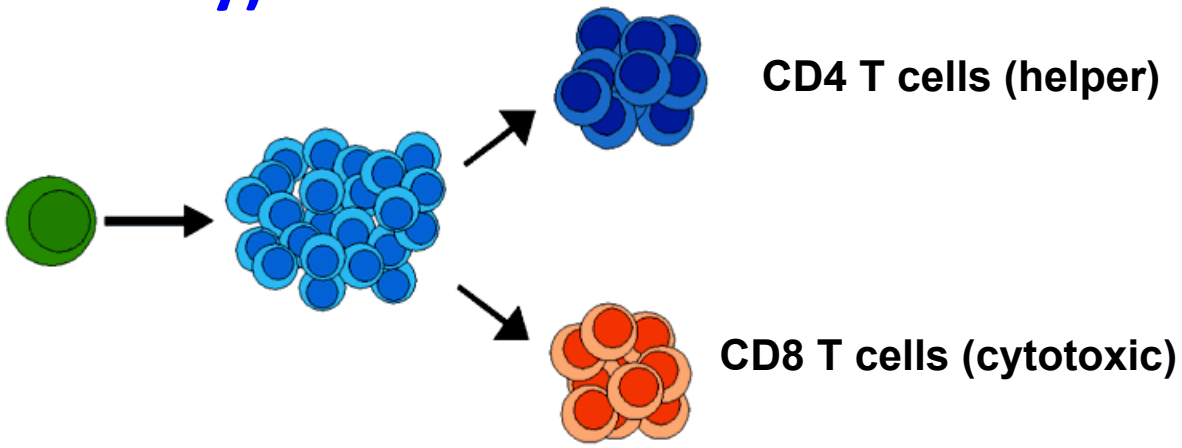
Vaccines prevent disease by stimulating our immune system

What type of immune response?

Antibodies produced by B cells (humoral immunity)

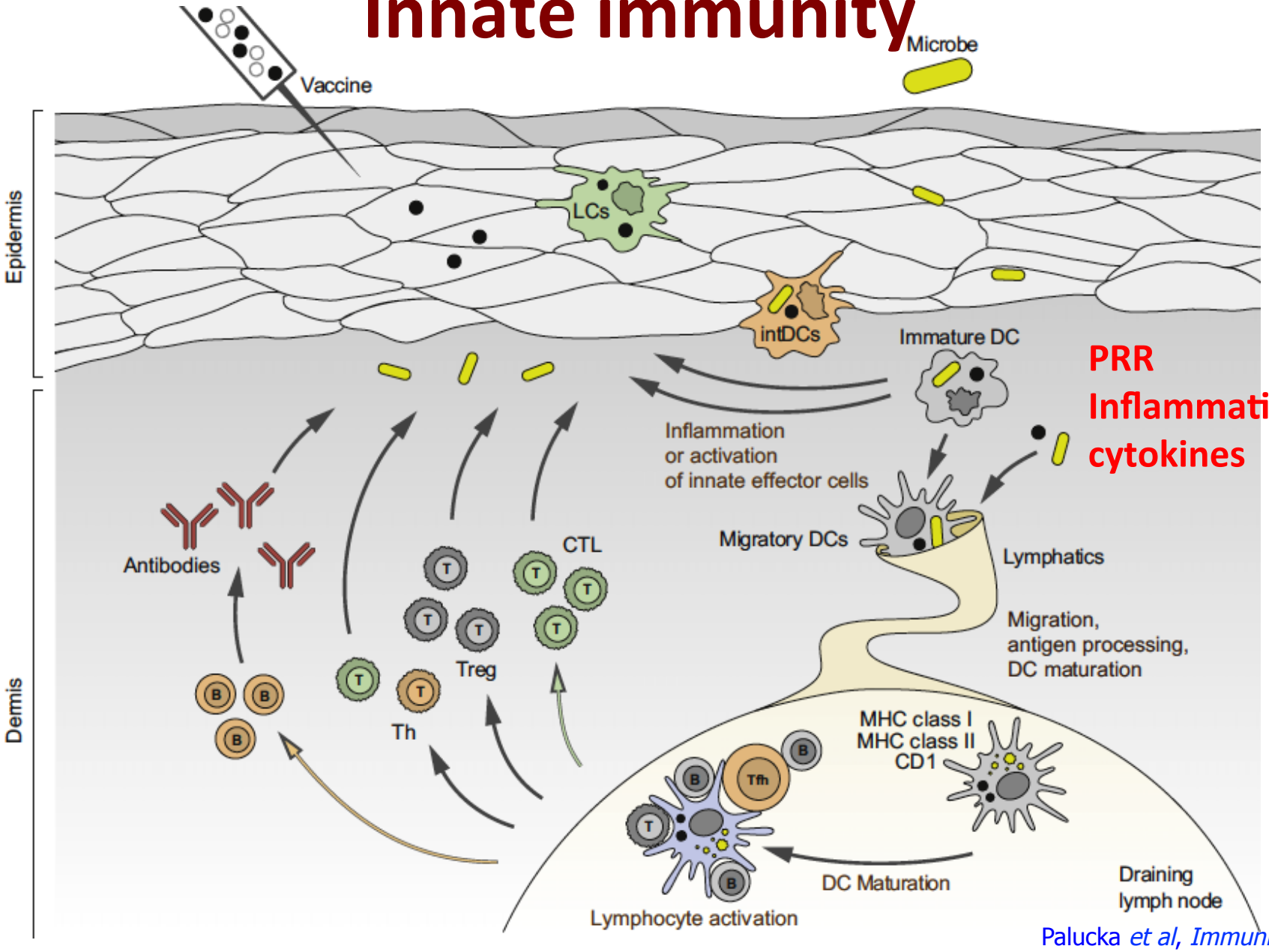


T cells (cellular immunity)



How is an immune response initiated?

Innate immunity



Palucka *et al*, *Immunity 2010*

Table 2 Innate immune activation by vaccines and adjuvants

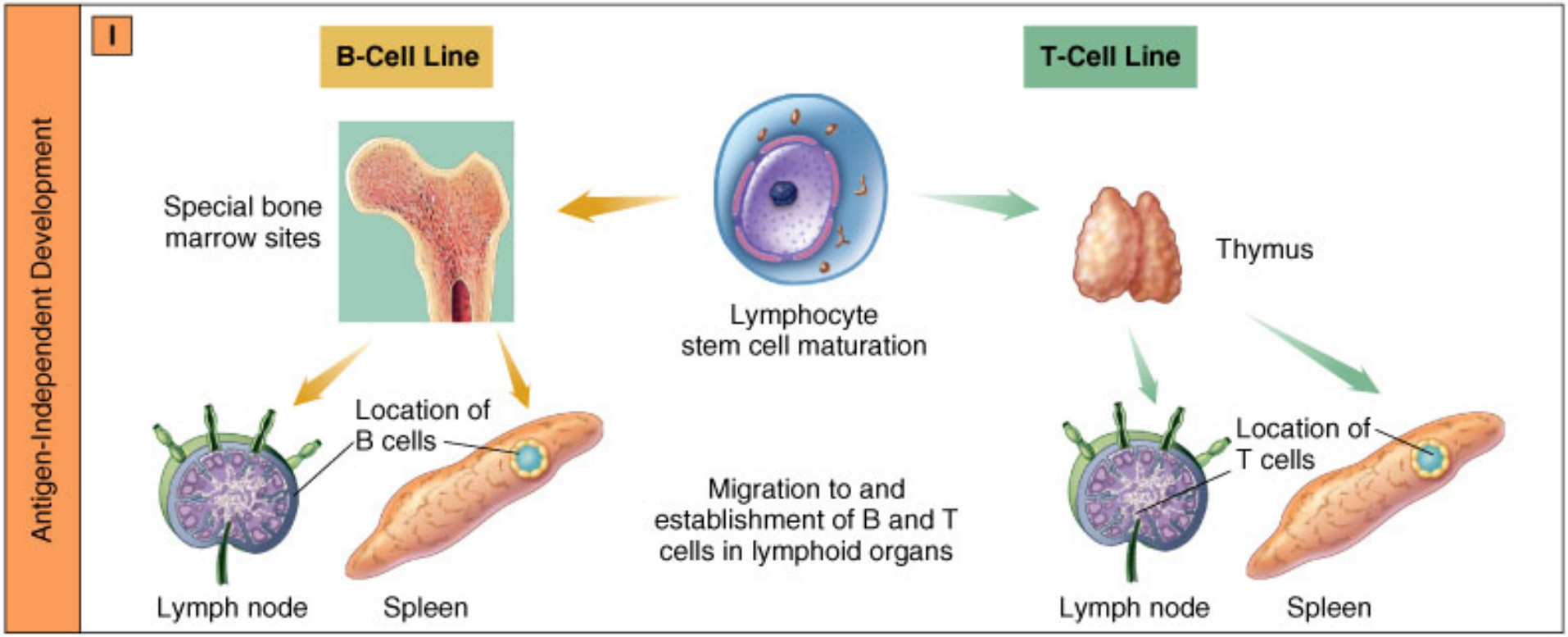
	Innate immune mechanism	Type of immune response
Licensed vaccine		
Yellow fever (YF-17D)	Activates multiple DC subsets through TLR2, TLR3, TLR7, TLR8 and TLR9; activates RIG-I and Mda5	CTLs; T_H1 and T_H2; neutralizing antibody
Smallpox (vaccinia virus)	Inhibits DC activation and causes cell death; blocks TLR4 and TLR3 signaling	CTLs; neutralizing antibody
Bacillus Calmette-Guérin	Activates TLR2, TLR4, TLR9 and DC-SIGN	T_H1 and T_H2
Licensed adjuvant-vaccine combinations		
Alum	TLR signaling not critical for induction of antibody responses; induces caspase-1 and inflammasome activation in DCs	T_H2; antibody
MF59	Mechanism unknown; enhanced uptake by antigen presenting cells probably important	T_H2; antibody
AS04	TLR4 agonist	T_H1; antibody
Emerging adjuvants		
CpG DNA	TLR9 ligand	T_H1, antibody
TLR7 and TLR8 ligands	TLR7 ligands	T_H1, antibody
Flagellin-protein fusions	Activates TLR5 and the inflammasome components IPAF and NAIP5	T_H1 and T_H2

ADJUVANTS: agents that increase the stimulation of the immune system by enhancing antigen presentation and/or by providing costimulation signals.

Adjuvants activate innate immunity in different ways, and this will shape which kind of adaptive immunity is induced by vaccination

Pulendran, Nat Immunol 2011

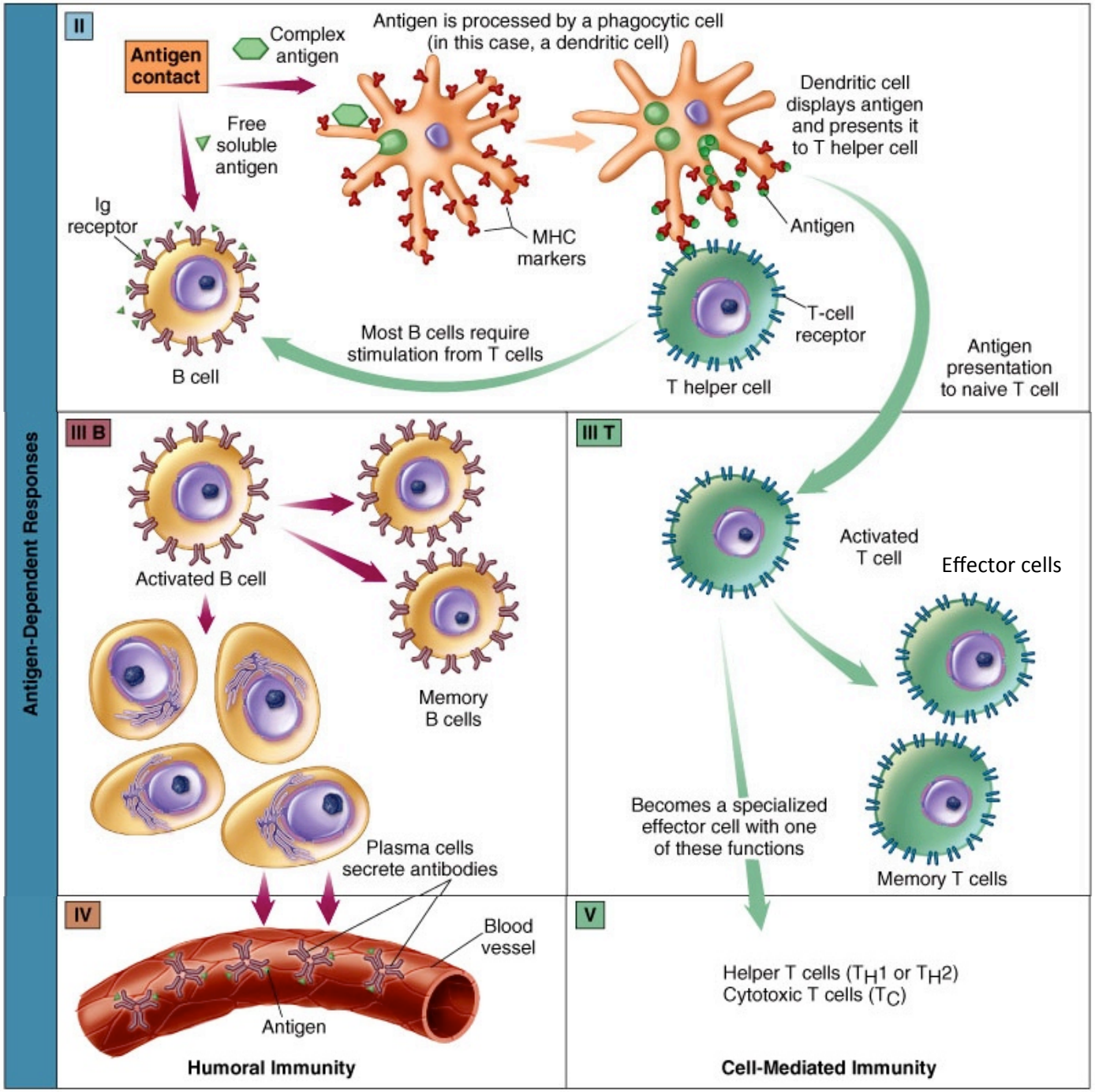
B and T Lymphocytes



B and T Cells have **receptors** that recognize (bind) antigens specific to individual pathogens

B cells directly recognize antigens as they are (**conformational epitopes**)

T cells recognize **linear epitopes** "presented" by other cells (proteins only)

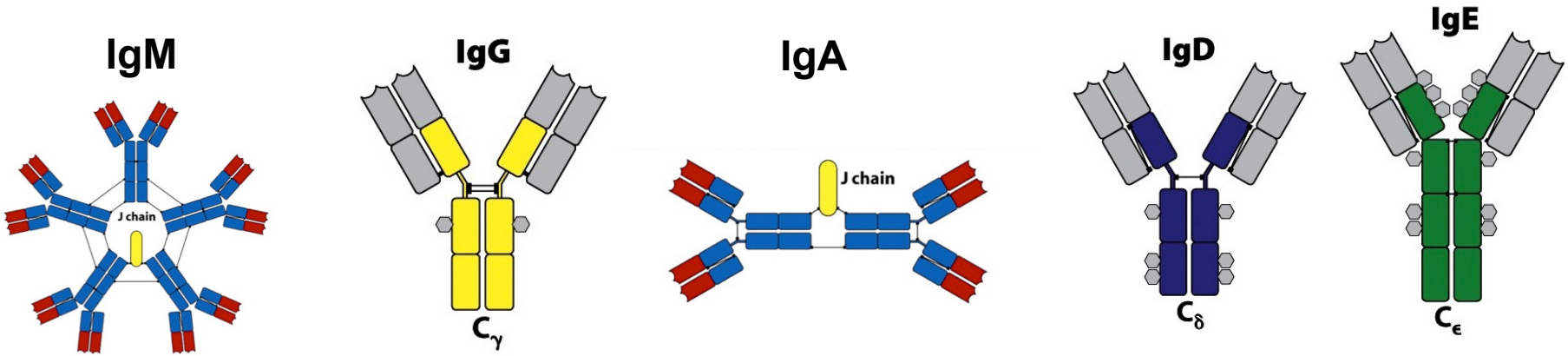


Antigen binding →

activation/
proliferation
(clonal expansion)
-->

effector cells +
memory cells
(differentiation)

B cells: 5 different Immunoglobulin classes



10%	70-75%	15-20%	<1%	<1%
Circulating Ig major role in primary immune response	Circulating Ig major role in secondary immune response	Secretory or mucosal saliva, milk, genito-urinary, respiratory & intestinal tracts	B cell surface molecule	Parasitic immunity and allergy

Humoral Effector mechanisms triggered by vaccines

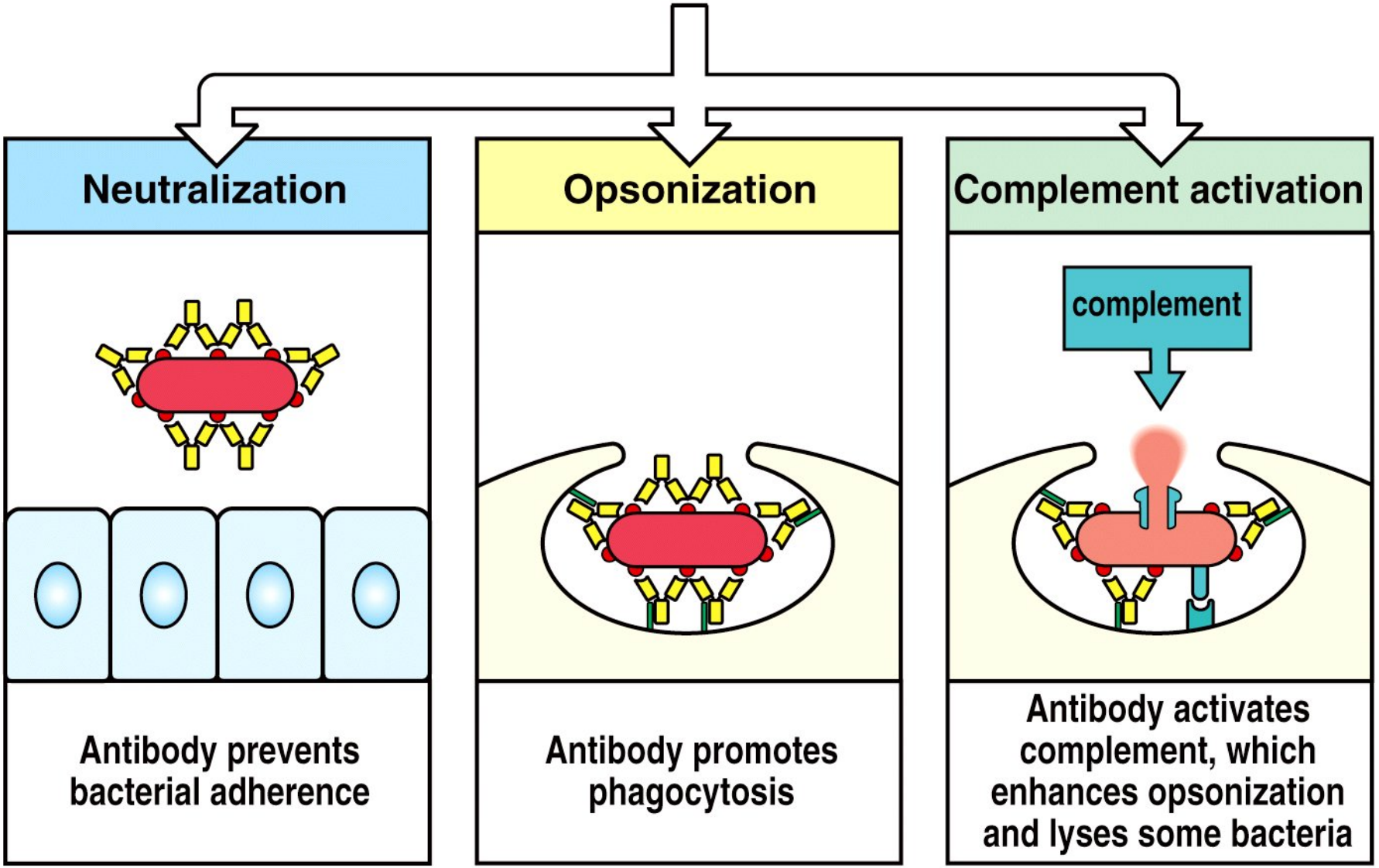


Figure 9-1 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Antibody-dependent cell-mediated cytotoxicity (ADCC)

Used to destroy large organisms that cannot be phagocytosed, or infected cells.

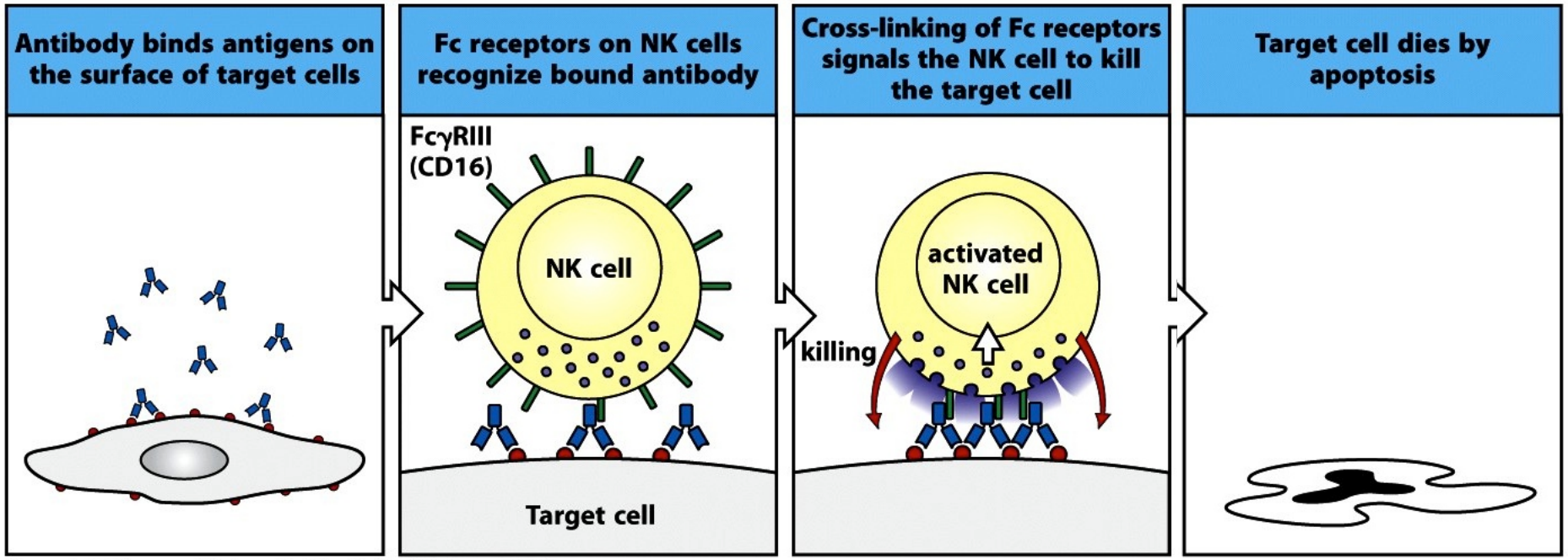
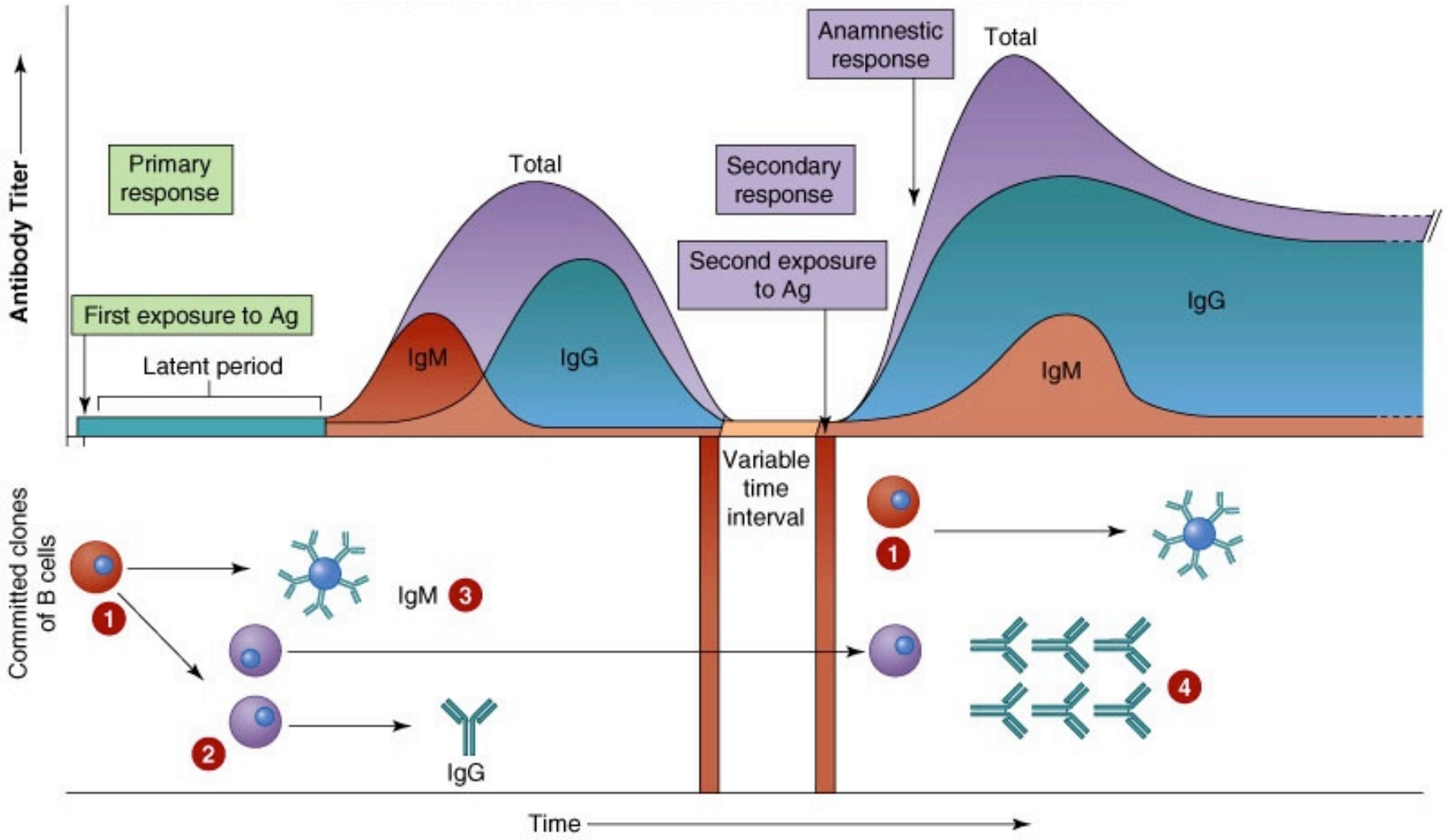


Figure 9-34 Immunobiology, 7ed. (© Garland Science 2008)

Primary and Secondary response to antigen the basis for prophylactic immunization



Types of antigen

- **T-dependent (TD) antigens**
  - activate via BCR but depend on additional signals from **helper T cells** to cause division/differentiation
    - Protein antigen

- **T-independent (TI) antigens**
  - induce division/differentiation by BCR signaling without MHC class II T help
  - bacterial polysaccharides, repeating subunits (bacterial capsules)
  - Polyclonal B cell activation, but poor memory

- Most pathogens contain both TI and TD antigens
- Only TD antigens can induce **memory** B cells

Thymus Dependent (TD) and Thymus Independent (TI) second signals for B cell activation

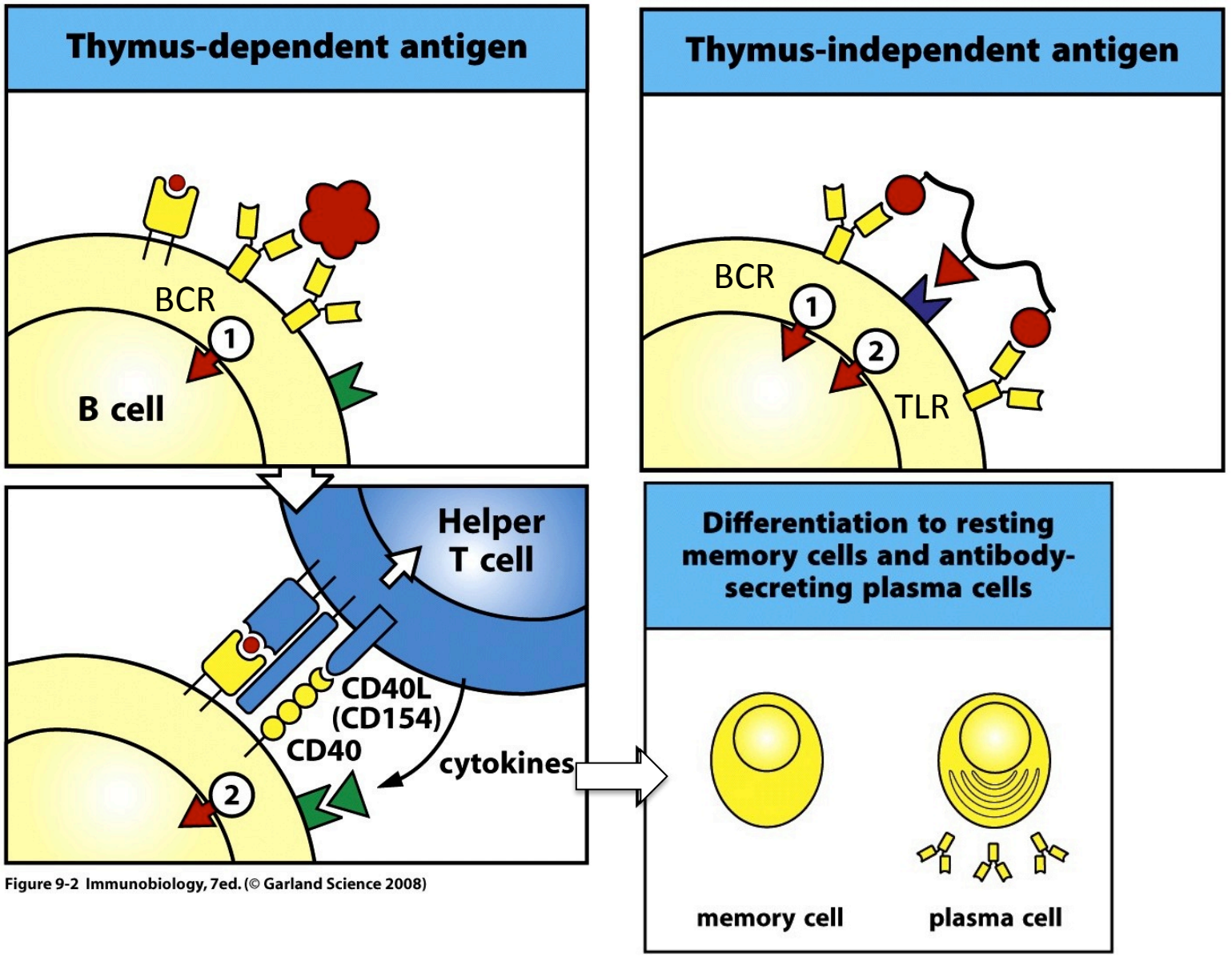
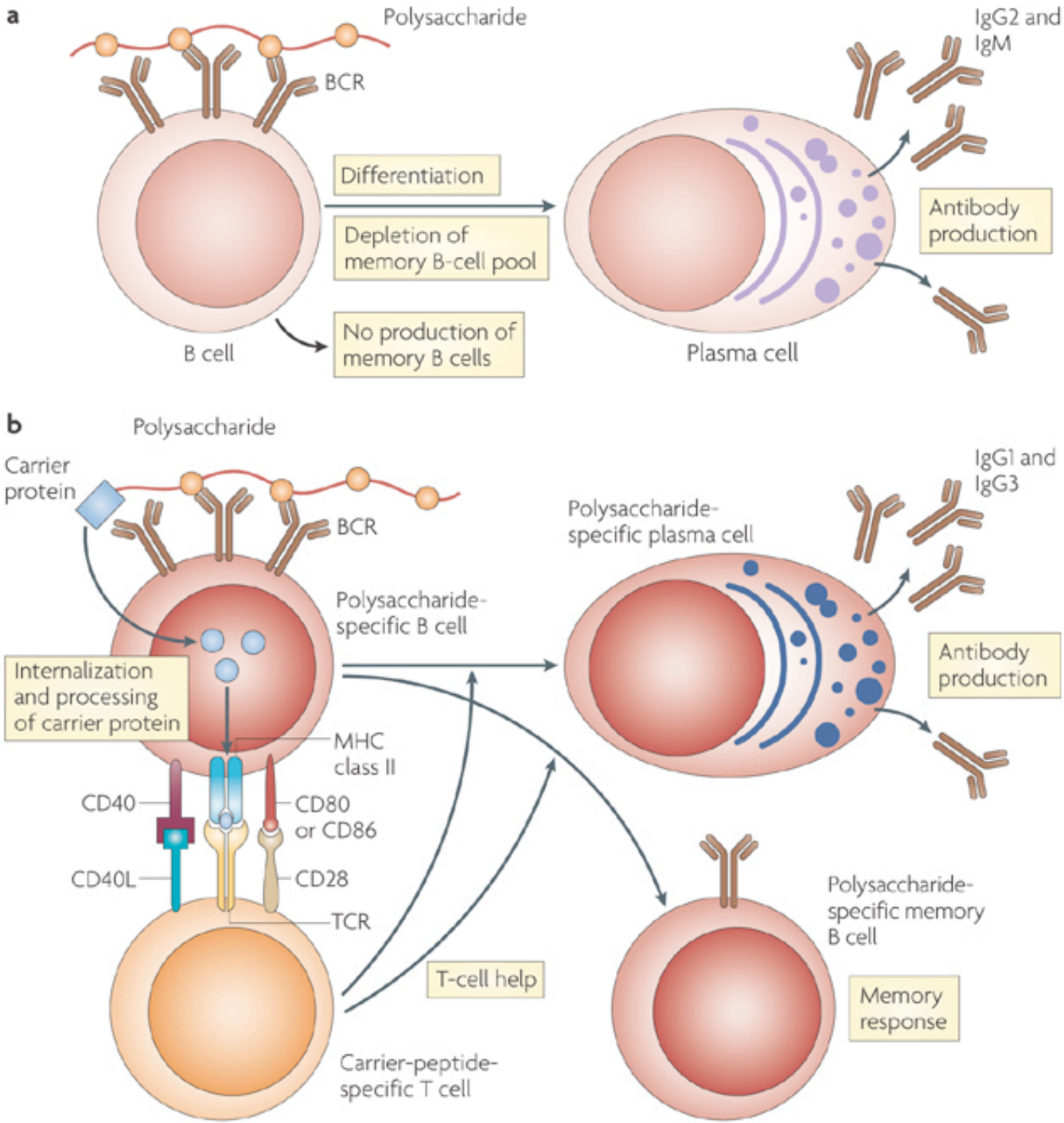


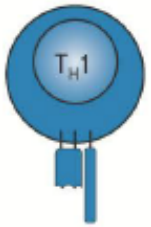
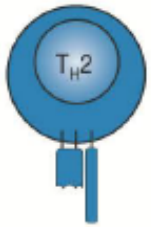
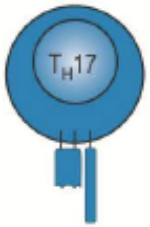
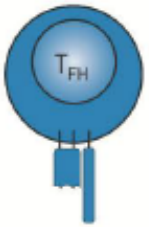
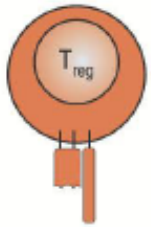
Figure 9-2 Immunobiology, 7ed. (© Garland Science 2008)

Conjugating a polysaccharide vaccine induces T cells that "help" B cells to become plasma cells and memory B cells



Pollard, Nature Reviews Immunology 2009

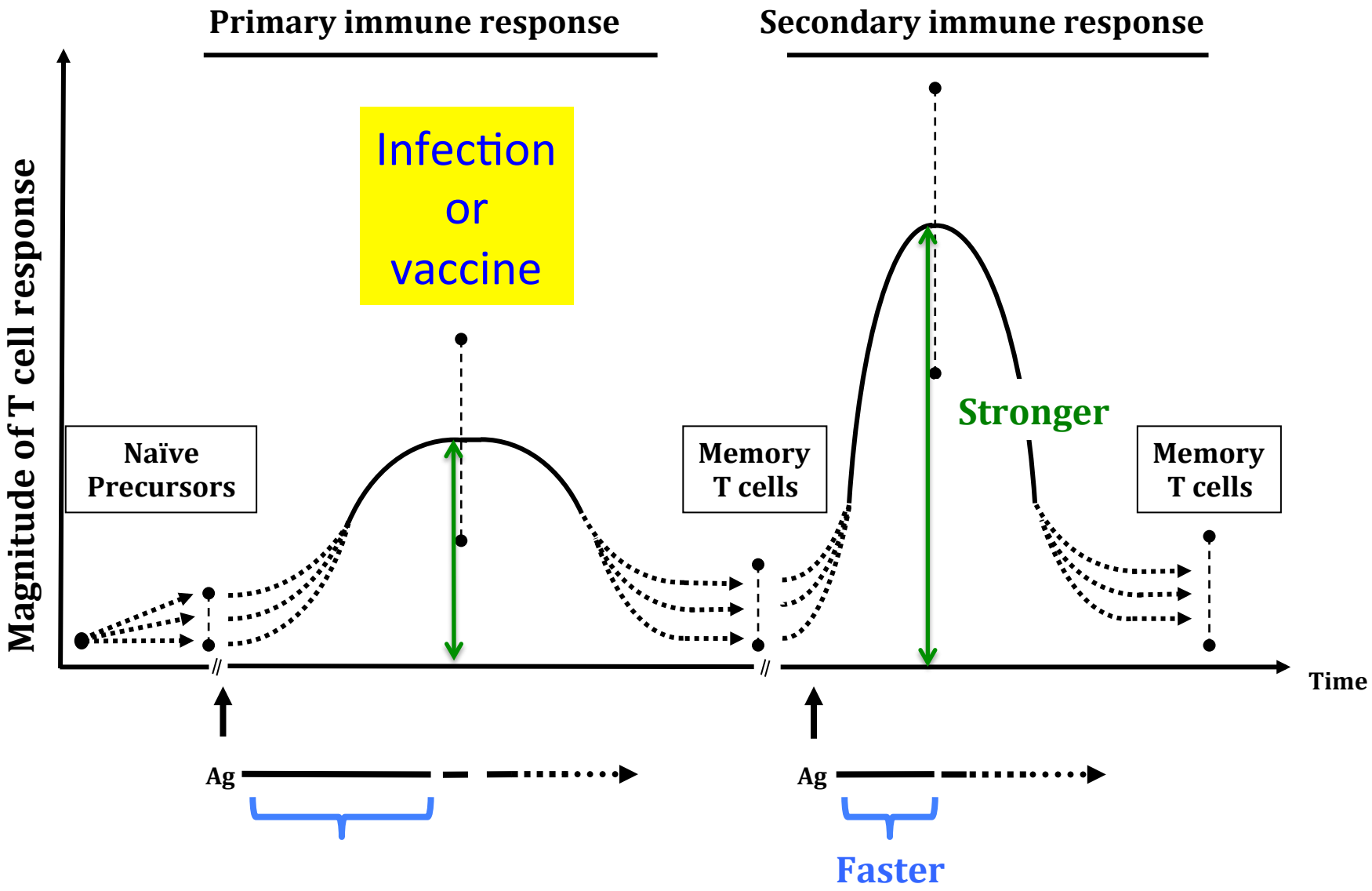
Different pathogens elicit different T cell effector functions

	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells	CD4 T_H17 cells	T_{FH} cells	CD4 regulatory T cells (various types)
Types of effector T cell						
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B cells for antibody production, especially switching to IgE	Enhance neutrophil response Promote barrier integrity (skin, intestine)	B-cell help Isotype switching Antibody production	Suppress T-cell responses
Pathogens targeted	Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria	Microbes that persist in macrophage vesicles (e.g. mycobacteria, *Listeria*, *Leishmania donovani*, *Pneumocystis carinii*) Extracellular bacteria	Helminth parasites	*Klebsiella pneumoniae* Fungi (*Candida albicans*)	All types	

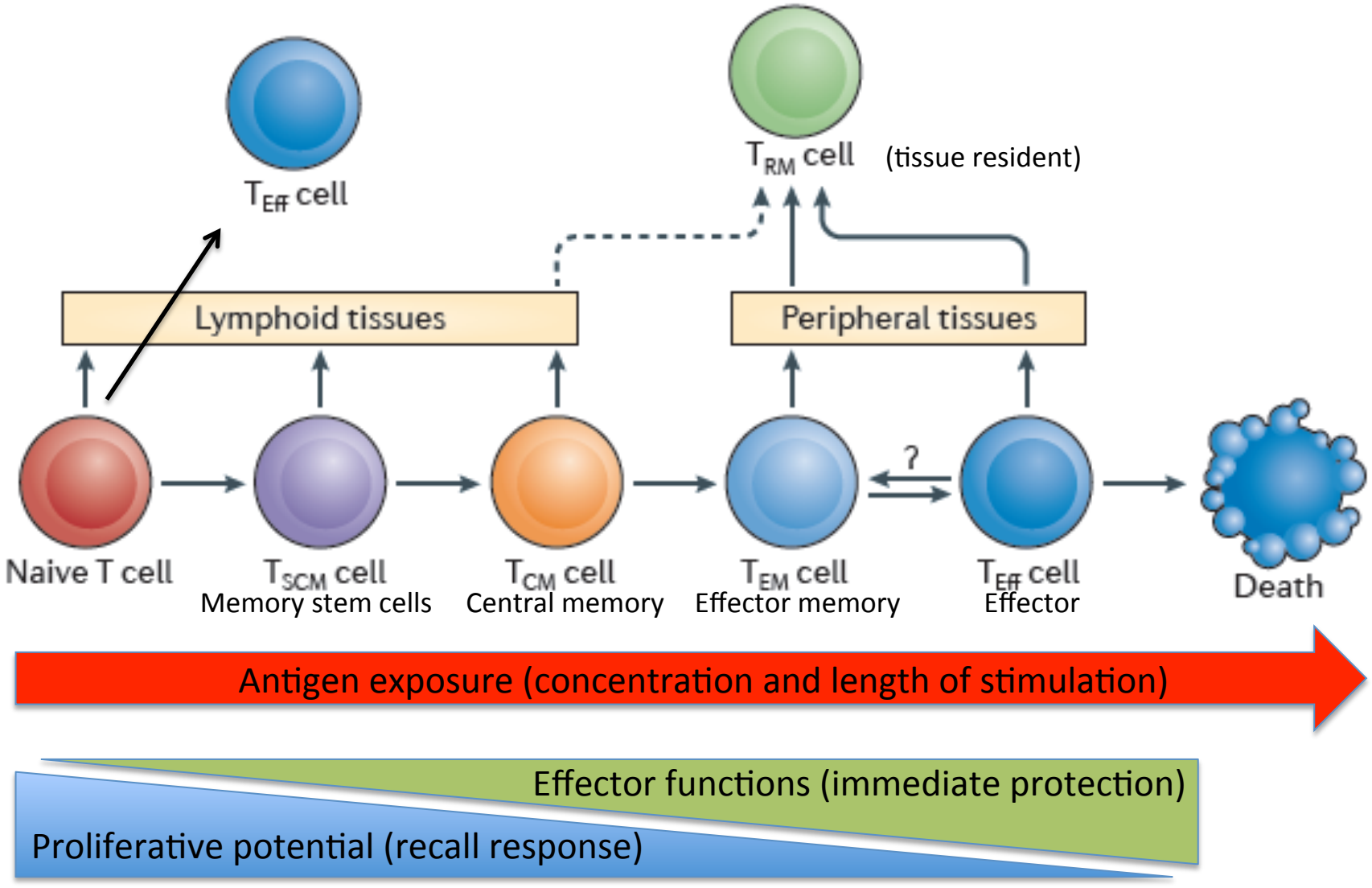
Knowledge about appropriate response to a pathogen helps us design better vaccines to induce such response

The second time T-cells encounter the infection

More Powerful Response

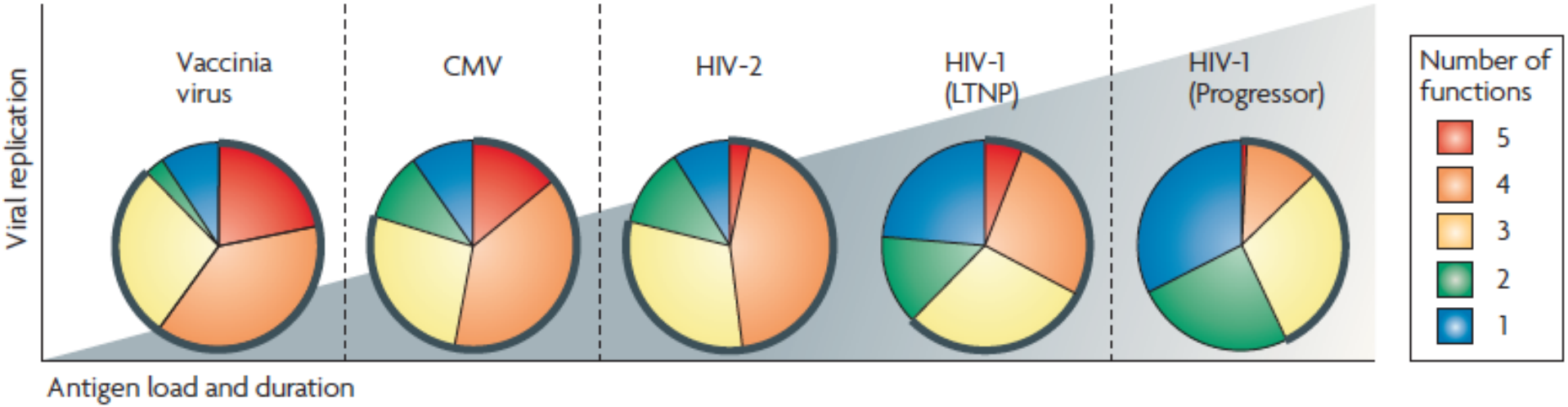


Which memory T cells should be induced by vaccination?



Farber et al; Nat Rev Immunol 2013

CORRELATION OF ANTIGEN-SPECIFIC CD8+ T-CELL QUALITY AND VIRAL LOAD



WHY POLYFUNCTIONAL T CELLS ARE "BETTER"?

- A single cell is able to respond to the antigen through multiple effector functions
- Polyfunctional T cell produce more cytokine on a per-cell basis than double or monofunctional T cells

Seder *et al*, *Nat Rev Immunol* 2008

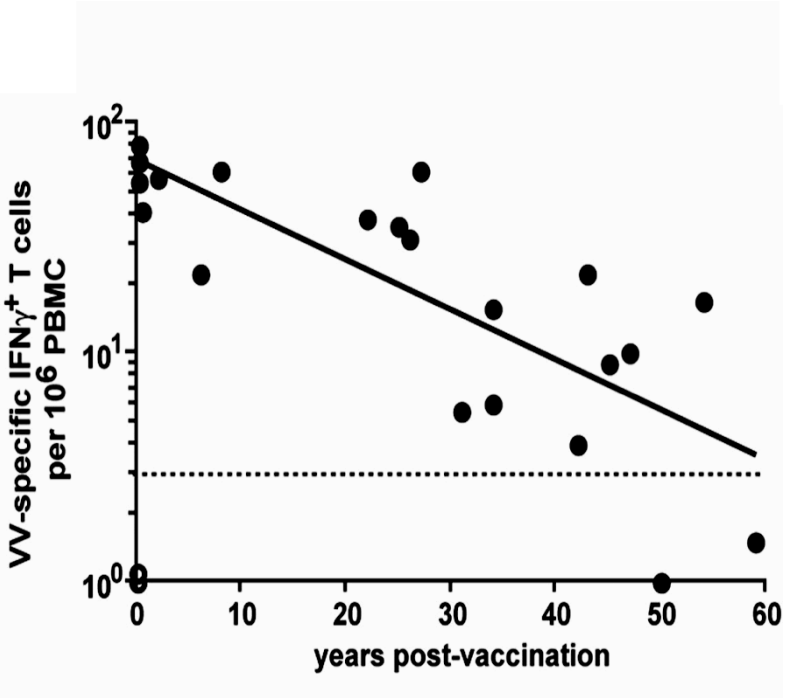
- Immunological memory is essential for **long-term protection** against disease

- The length and amount of **antigen (vaccine) exposure** influences the functional quality of the memory T cell response

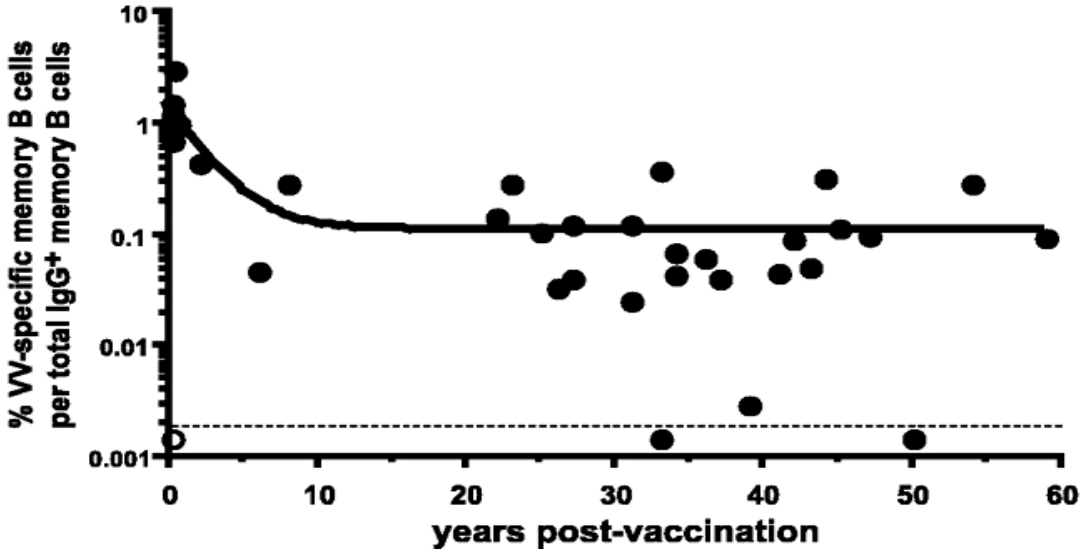
For how long does immunological memory last?

Smallpox vaccine

T cell memory

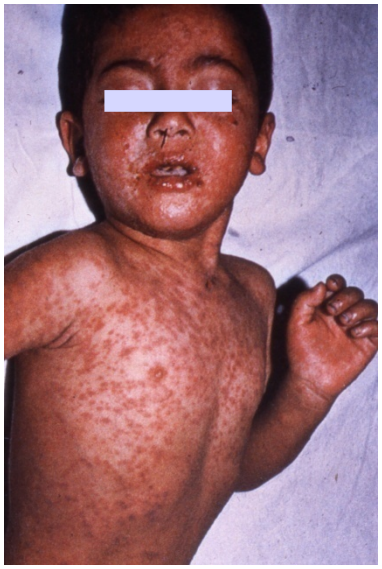


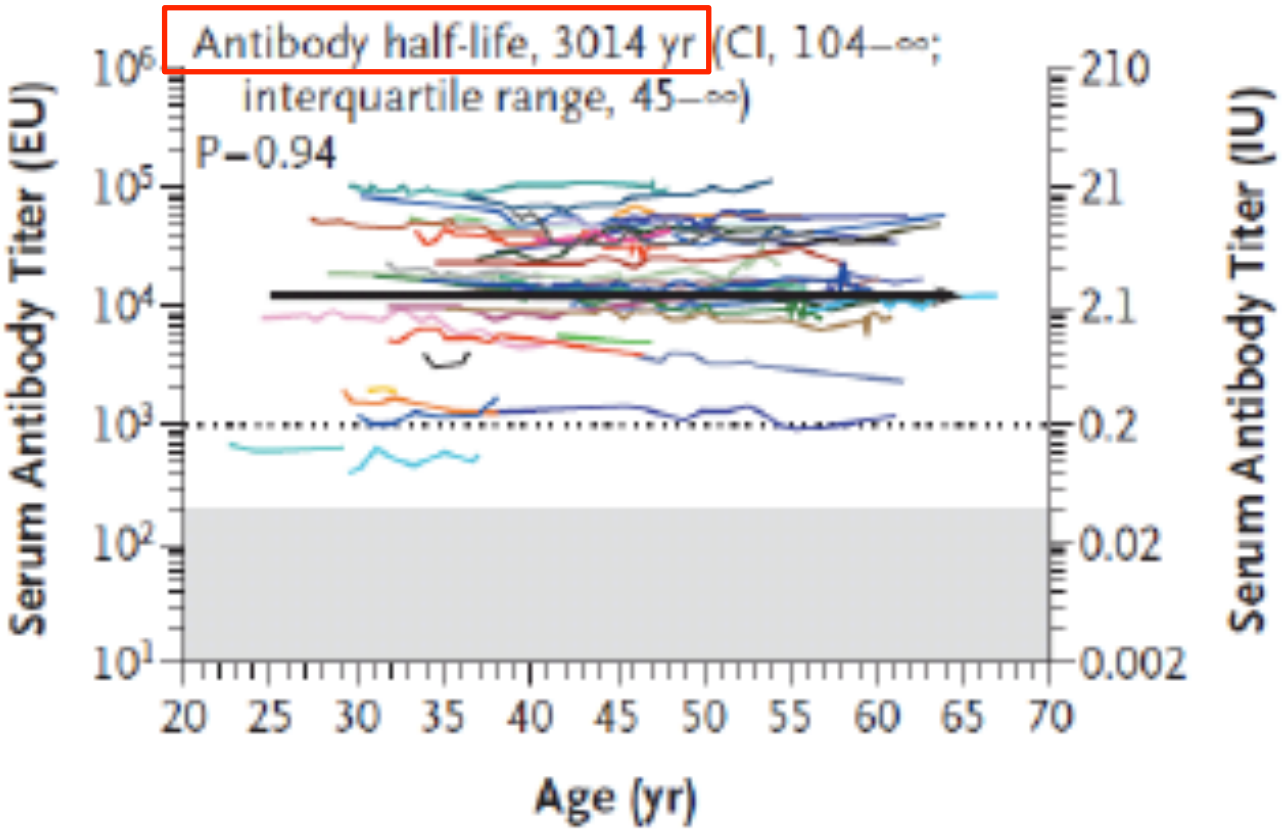
B cell memory



Crotty S, et al. J Immunol. 2003; 171:4969

Live vaccines: measles

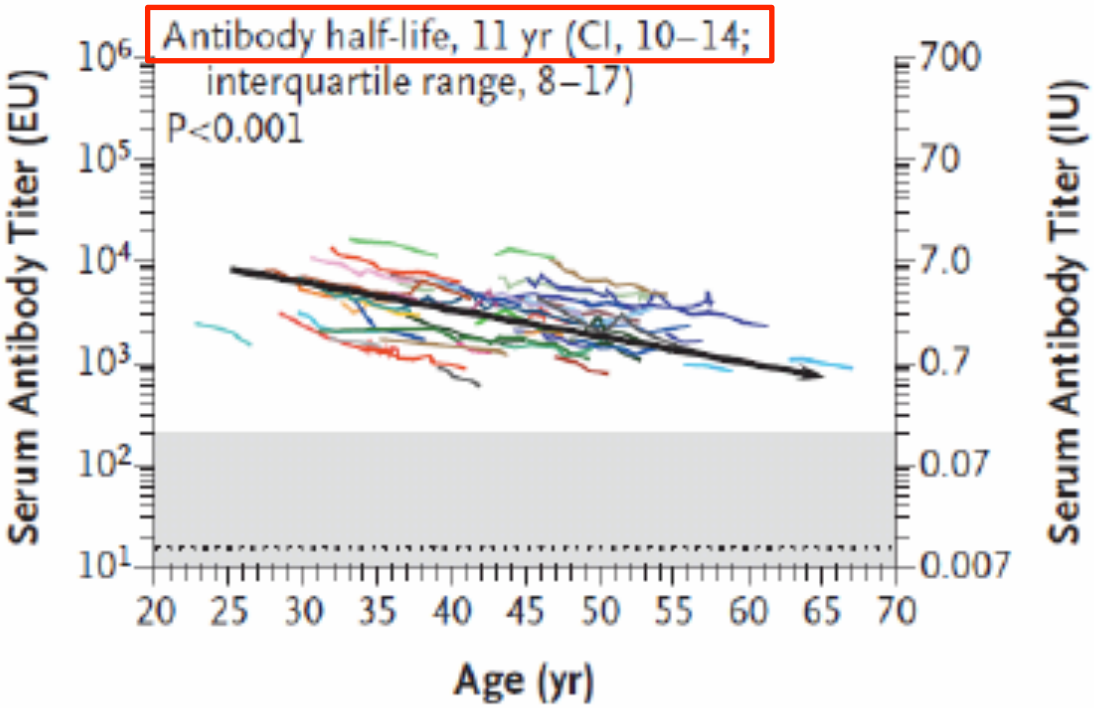




Long-lived immunological memory after one shot of vaccine

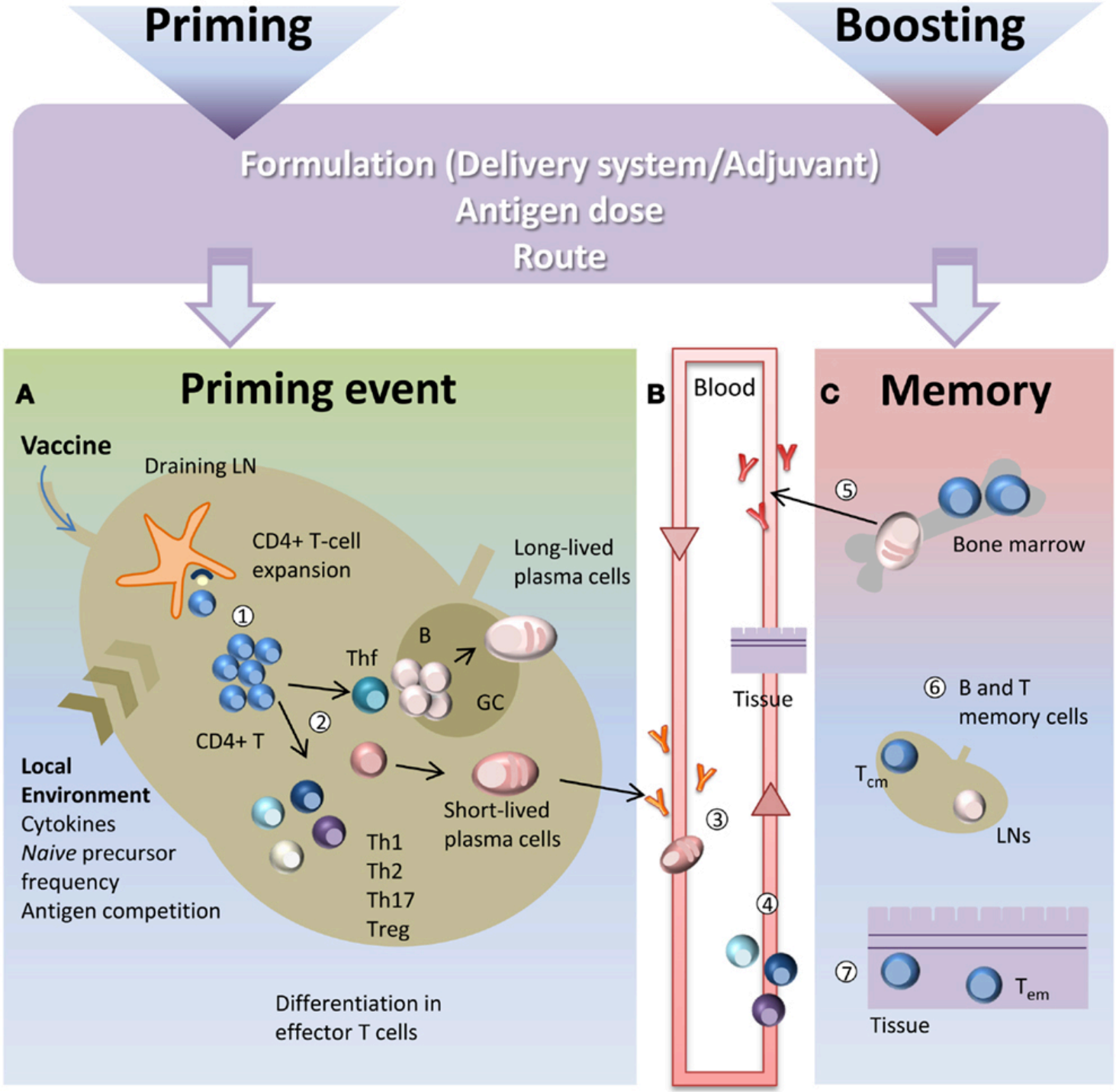
Amanna, et al. New Engl J Med 357: 1903-15 (2007).

Protein vaccines: tetanus toxoid

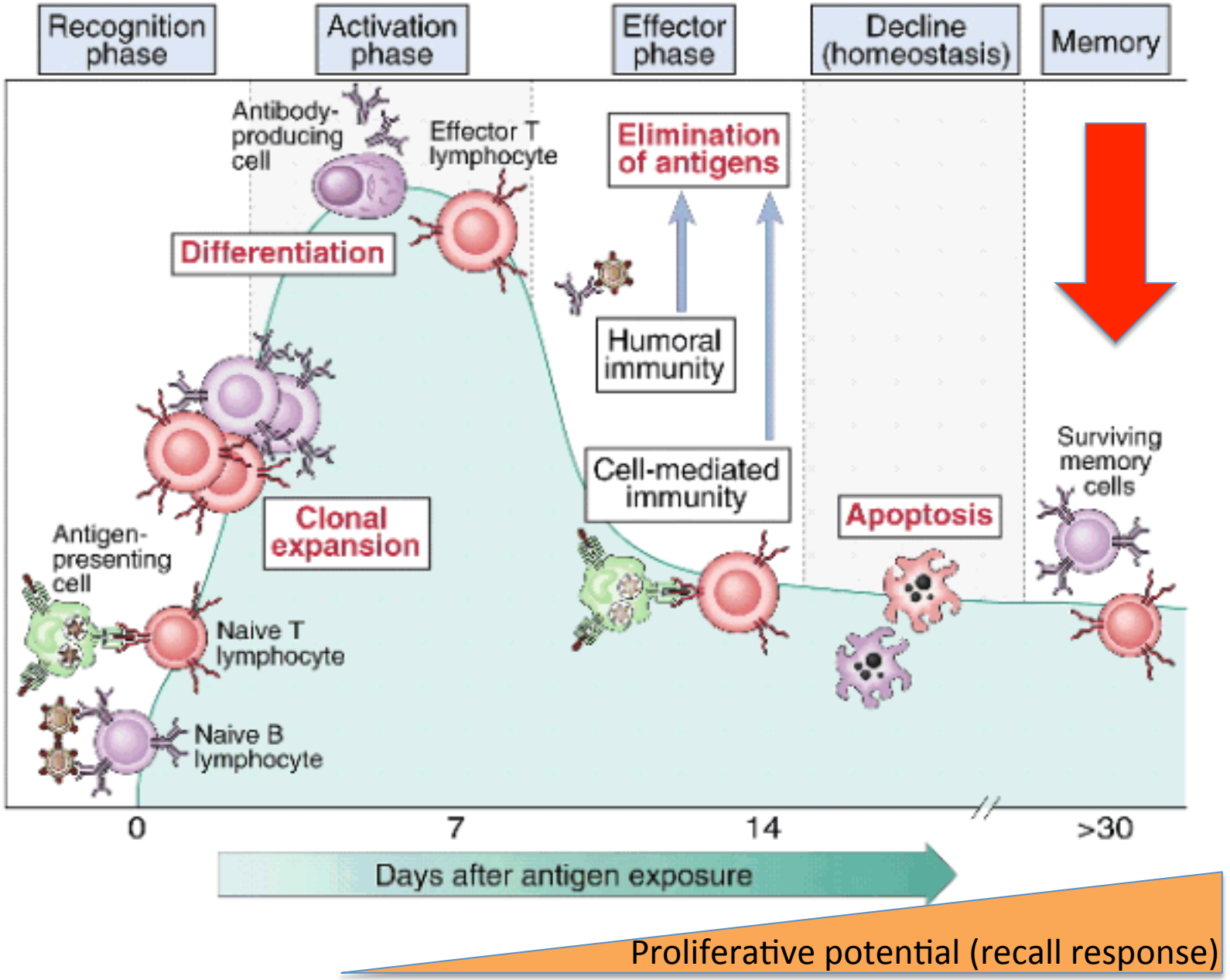


Limited immunological memory after one shot of vaccine

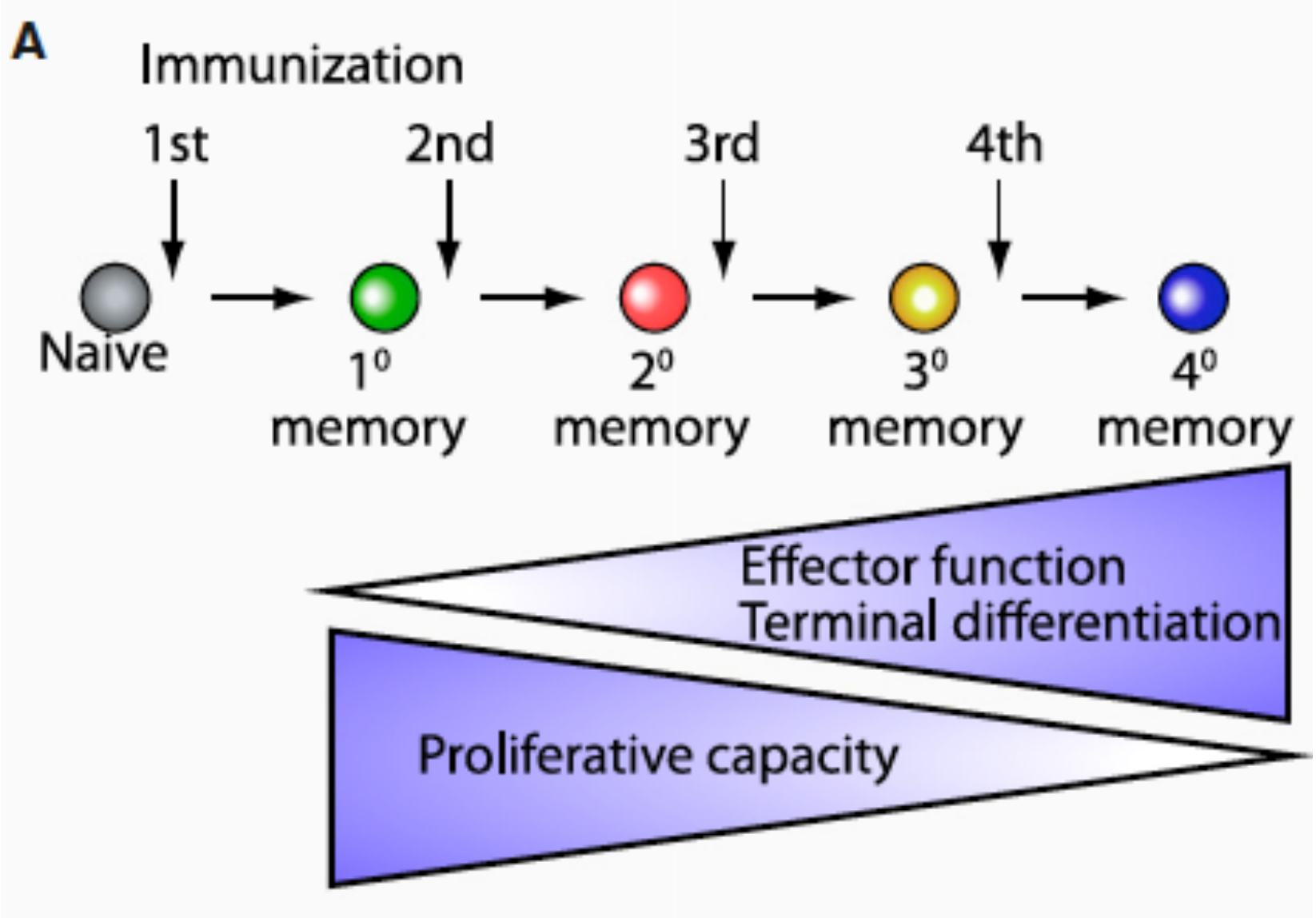
Amanna, et al. New Engl J Med 357: 1903-15 (2007).


Priming
Boosting
Formulation (Delivery system/Adjuvant)
Antigen dose
Route
A
Priming event
Vaccine
Draining LN
CD4+ T-cell expansion
Long-lived plasma cells
①
B
Thf
GC
CD4+ T
②
Local Environment
Cytokines
Naive precursor frequency
Antigen competition
Th1
Th2
Th17
Treg
Short-lived plasma cells
Differentiation in effector T cells
B
Blood
Tissue
③
④
C
Memory
⑤
Bone marrow
⑥ B and T memory cells
Tcm
LNs
⑦
Tem
Tissue

When should we boost?



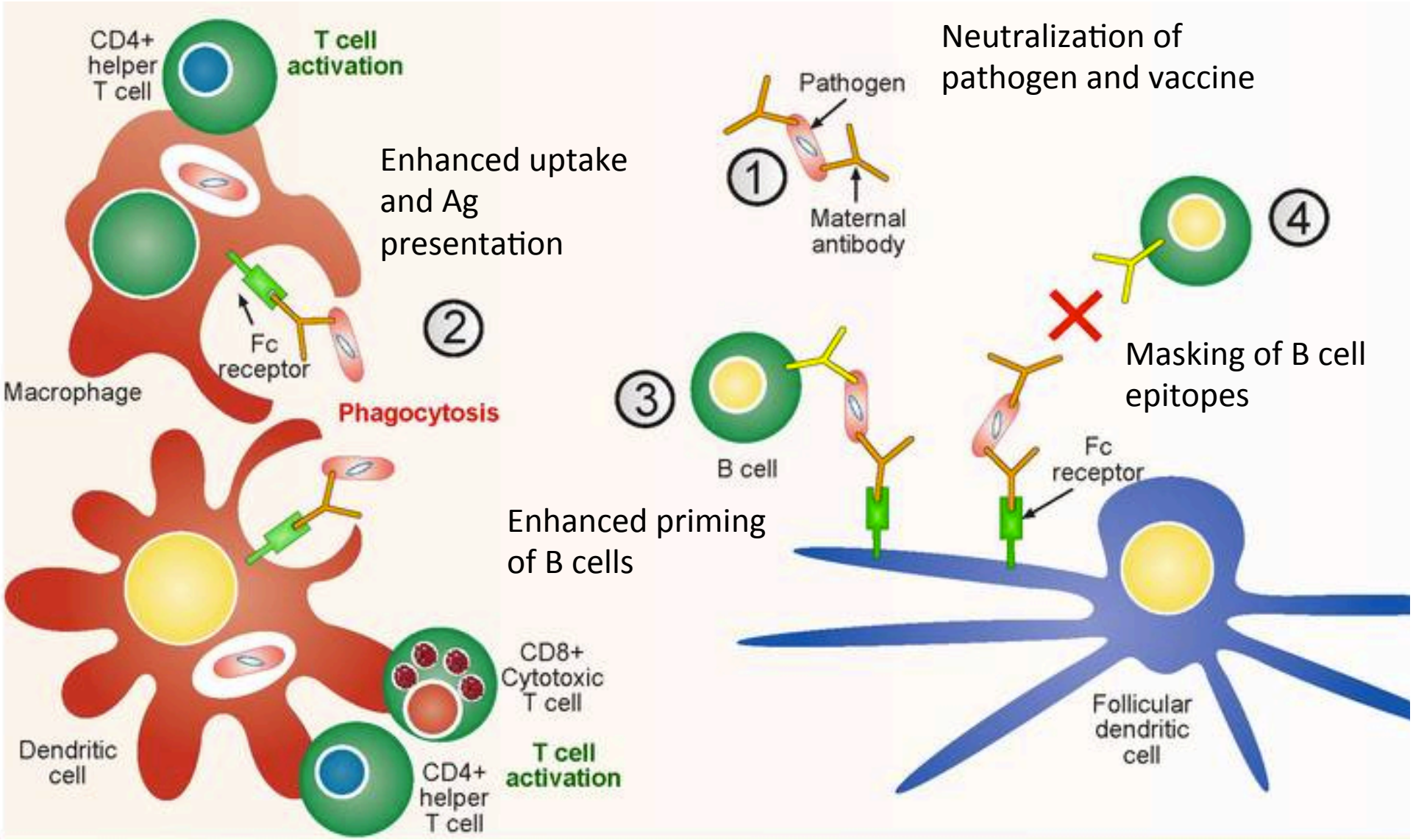
How many times should we boost?



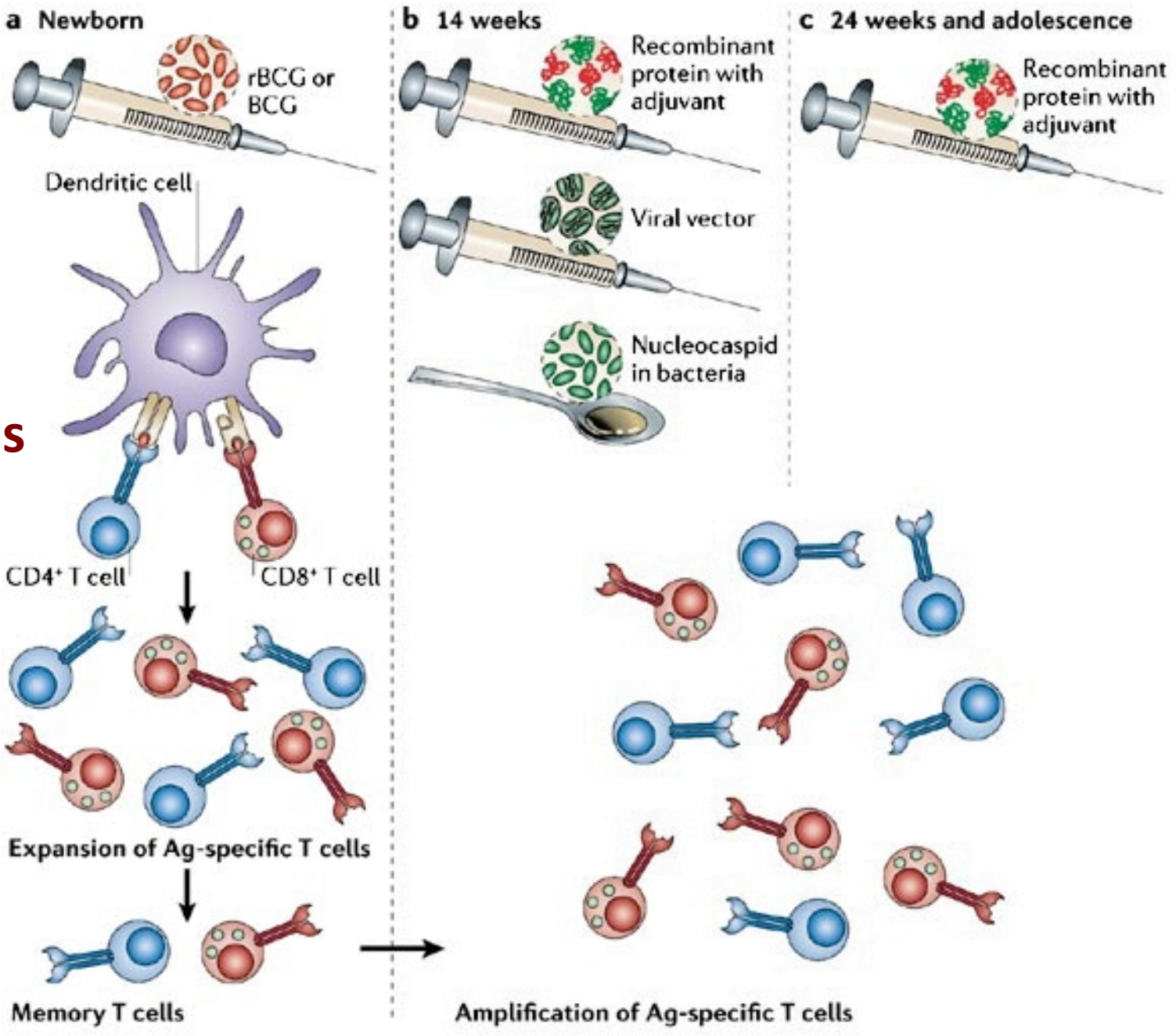
Sallusto et al., Immunity 2010

When should we start? ASAP

Maternal antibodies inhibit or enhance immunity



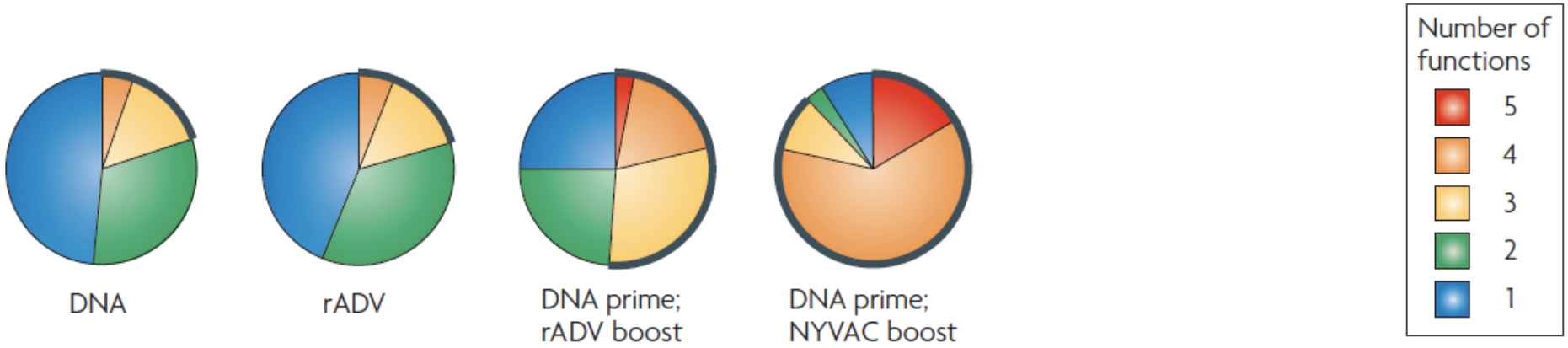
Dealing with pre-existing, suboptimal immunity: Heterologous prime-boost



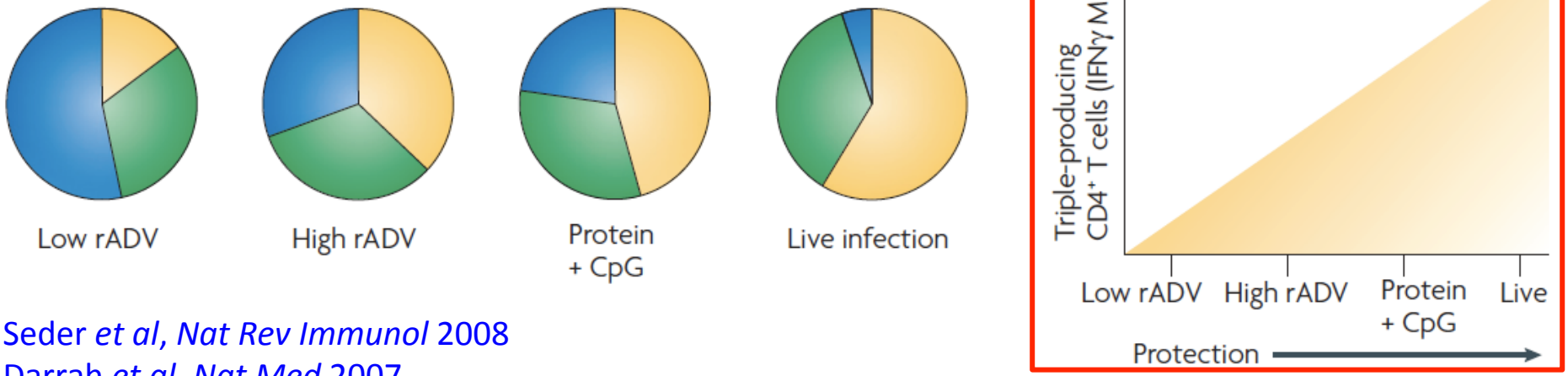
Skeiky *et al. Nature Reviews Microbiology* **4**, 469–476 (June 2(

THE IMPACT OF VACCINE FORMULATION ON T-CELL QUALITY

CD8+ T-cell quality in response to HIV envelope elicited by different vaccine formulations



CD4+ T-cell quality in response to *Leishmania major* elicited by different vaccine formulations

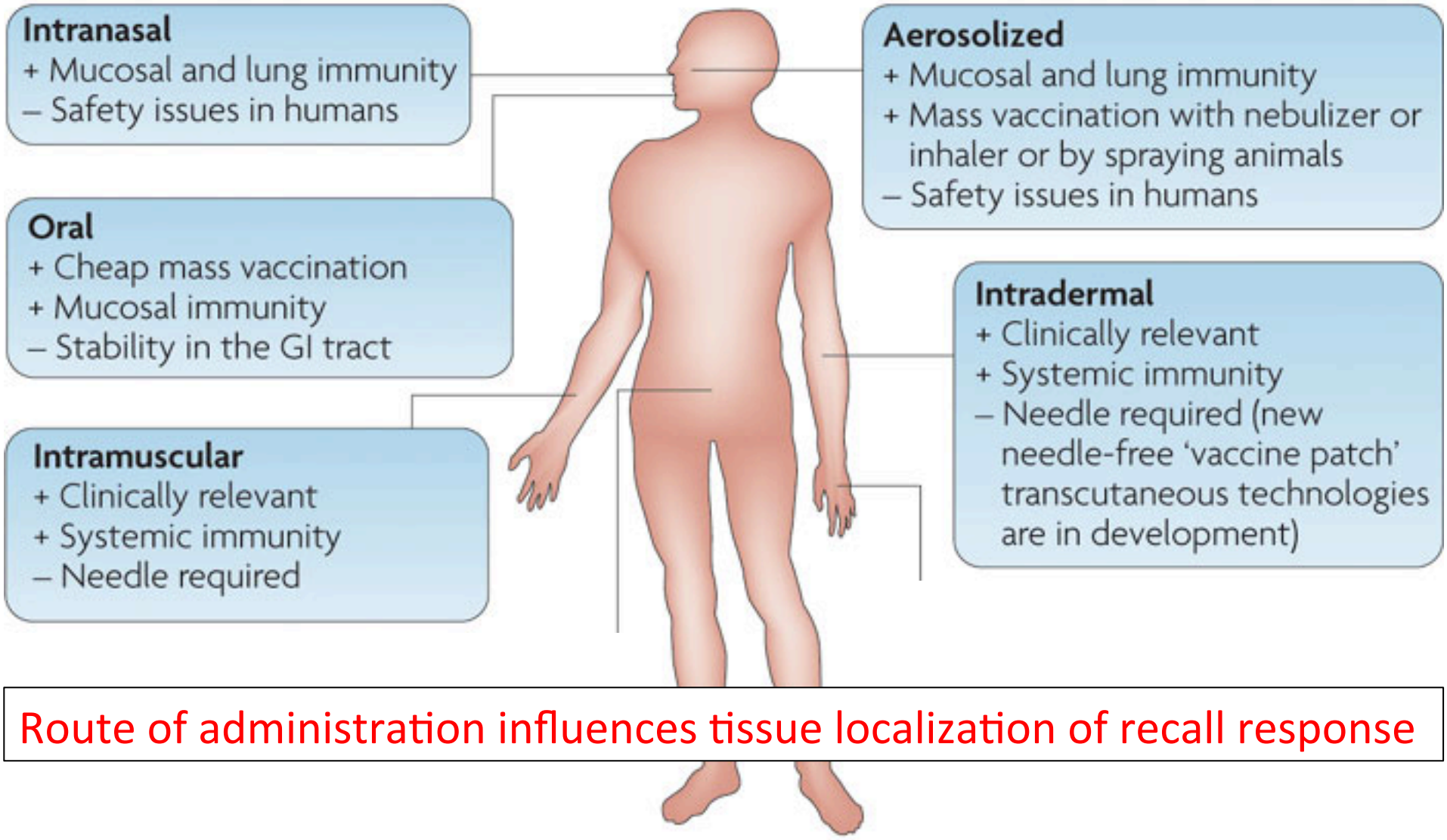


Seder *et al*, *Nat Rev Immunol* 2008
Darrah *et al*, *Nat Med* 2007

Age considerations

Early life	Elderly people
Limited magnitude of Ab responses to polysaccarides and proteins	
Shorter persistence of Ab responses to proteins	
Shorter duration of immune memory	Limited quality of Ab
Limited Th1 responses, and skew towards Th2	Limited induction of new T cell responses (decline in naïve cell reservoir)
Limited innate responses	Limited persistence of CD4+ responses

How can we direct the immune response where it's needed?



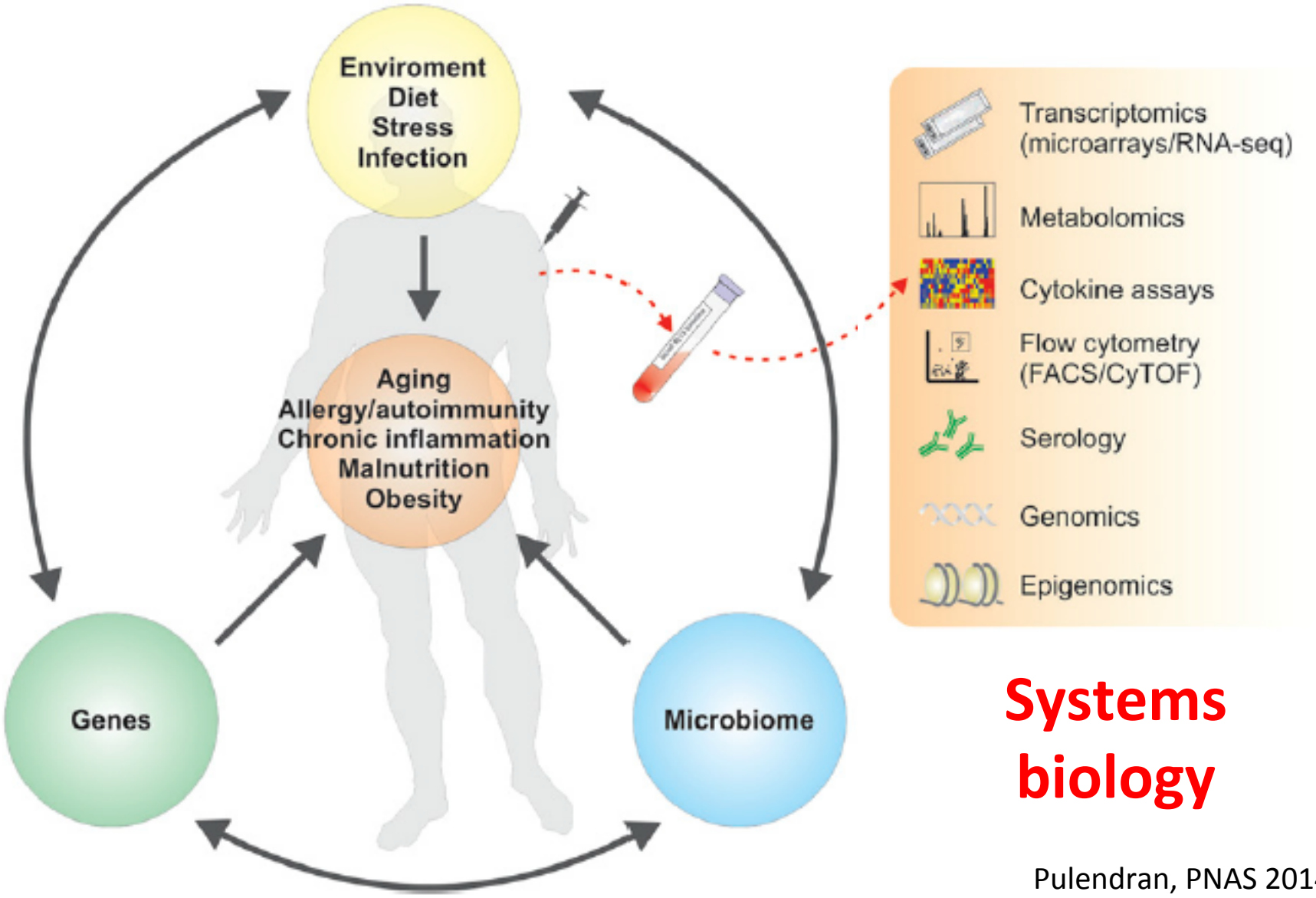
Route of administration influences tissue localization of recall response

Draper and Heeney, Nat Rev Microbiol, 2010

Vaccinology: the past

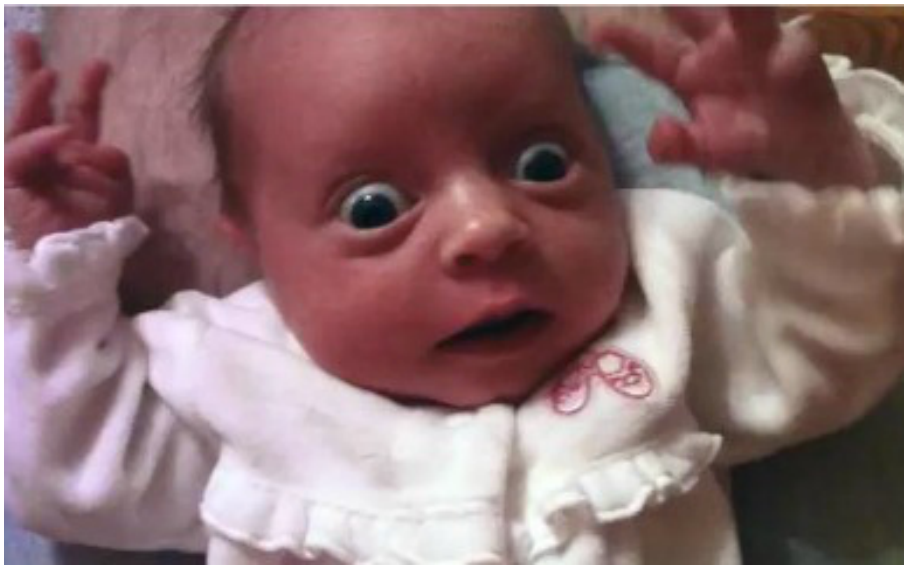
Edward Jenner

Vaccinology: the future



Systems biology

Pulendran, PNAS 2014



THANK YOU

satvi

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