B and T cell vaccine responses :

what a vaccinologist should know…

Claire-Anne Siegrist

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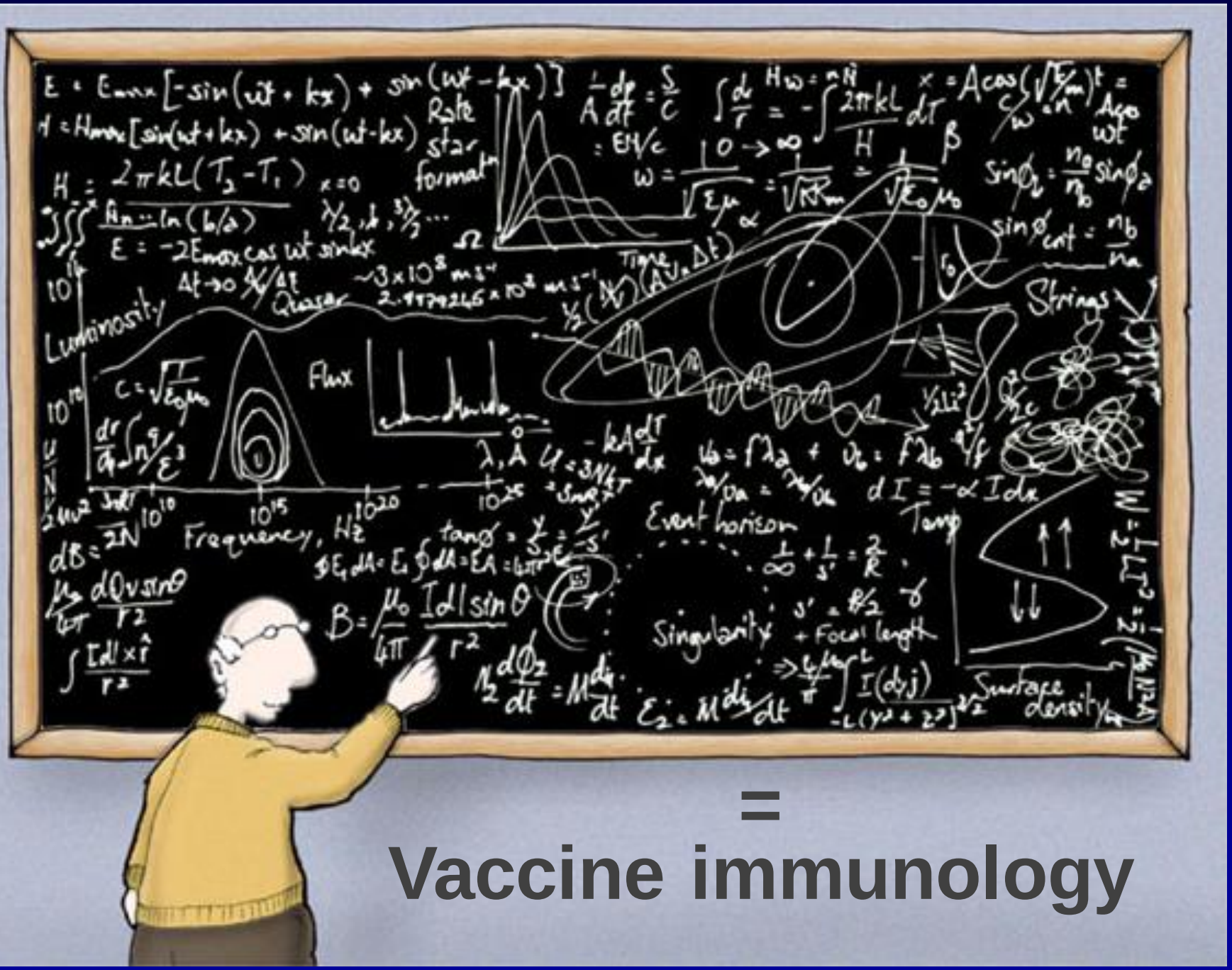
University of Geneva
Switzerland



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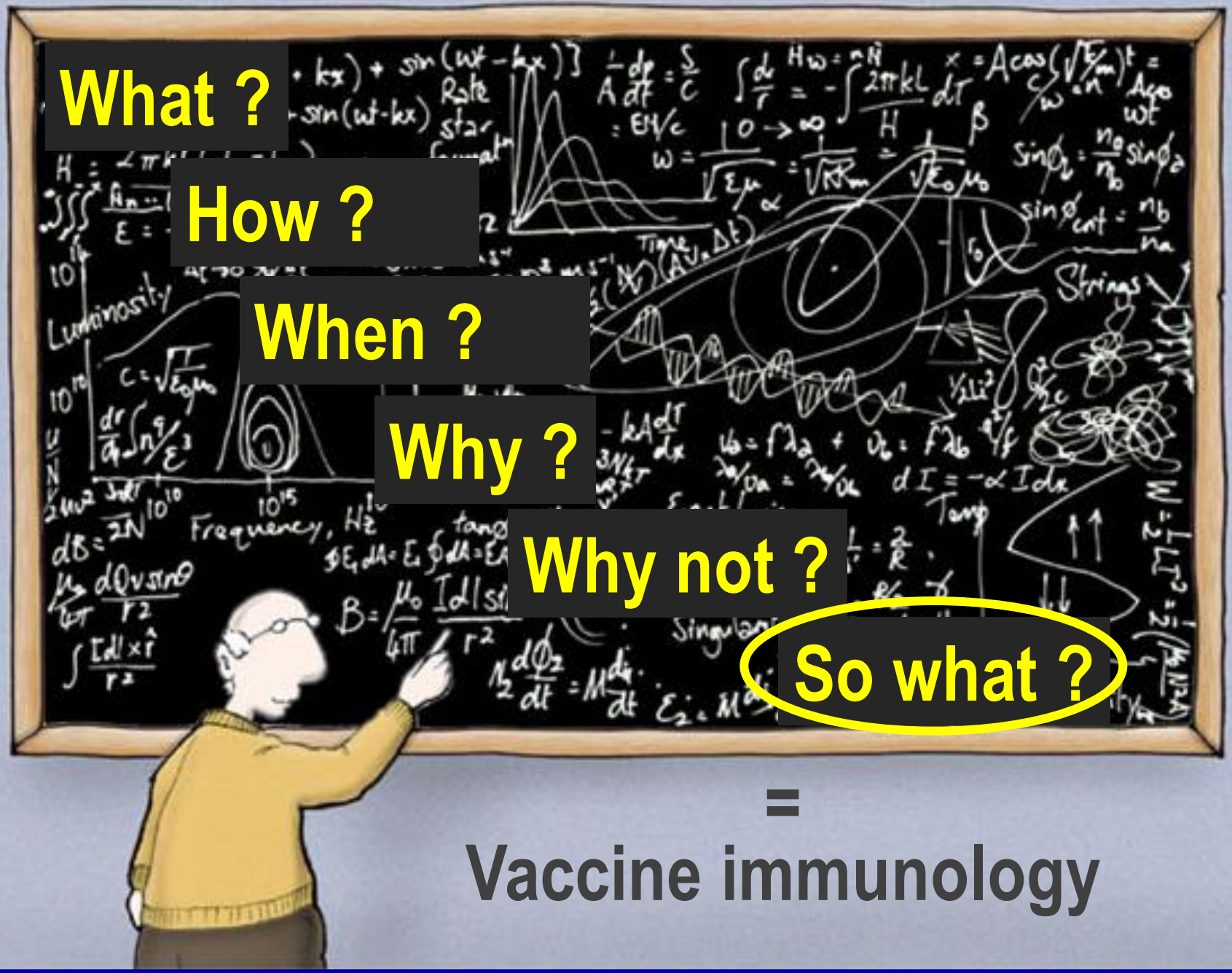
Vaccine immunology



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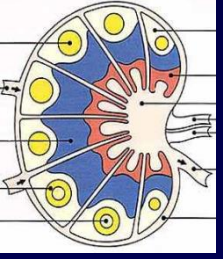
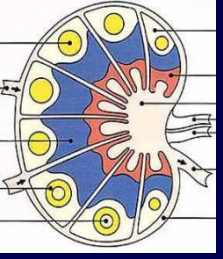


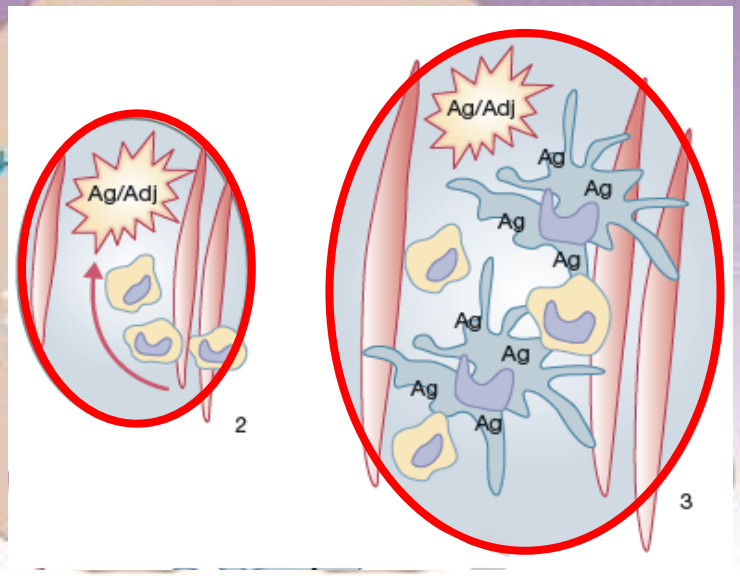
What happens first after immunization ?



What happens first after immunization ?

PAIN !

1. Innate responses



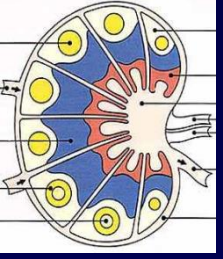
Detection of danger signals

Injection-site innate activation

=

Cell recruitment and activation

= inflammatory focus



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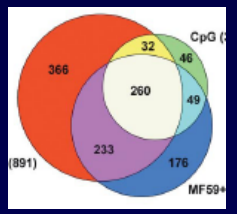

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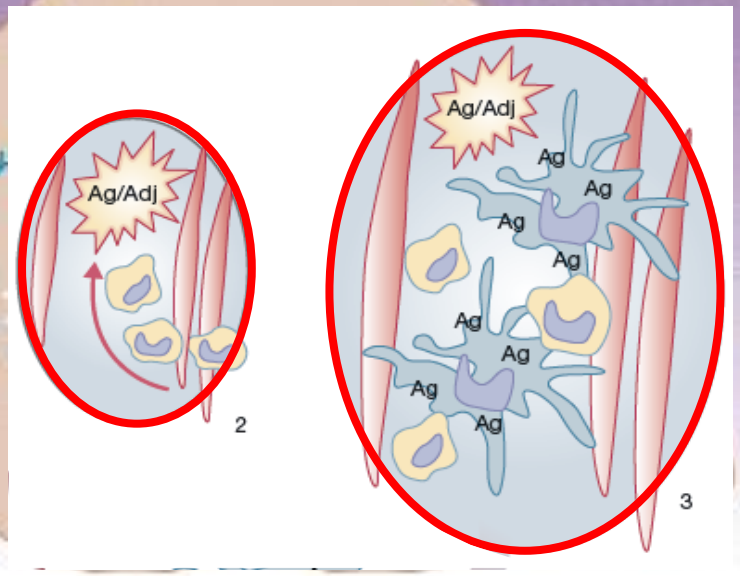


Detection of danger signals

Injection-site innate activation

=

Cell recruitment and activation

= inflammatory focus

Cell migration to the draining LN

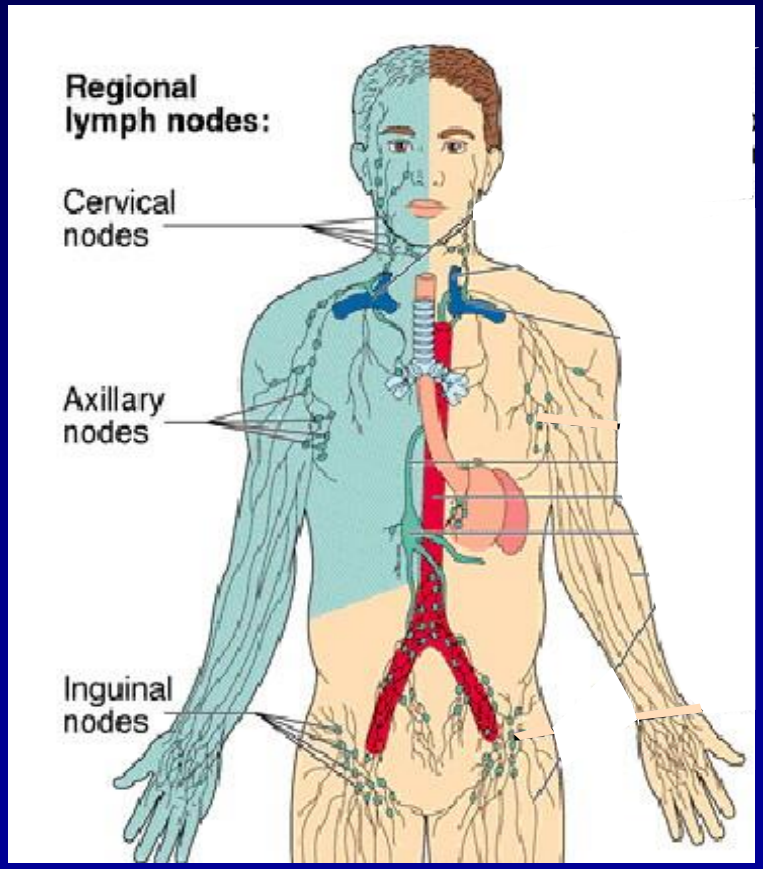
Migration of Ag towards the draining lymph nodes

1. Non live vaccines

Ag uptake and transport by Antigen-presenting cells and/or free-fluid diffusion of soluble Ag :

- Deltoid ⟹ axillary
- Thigh ⟹ inguinal

Mostly local and unilateral lymph node activation !



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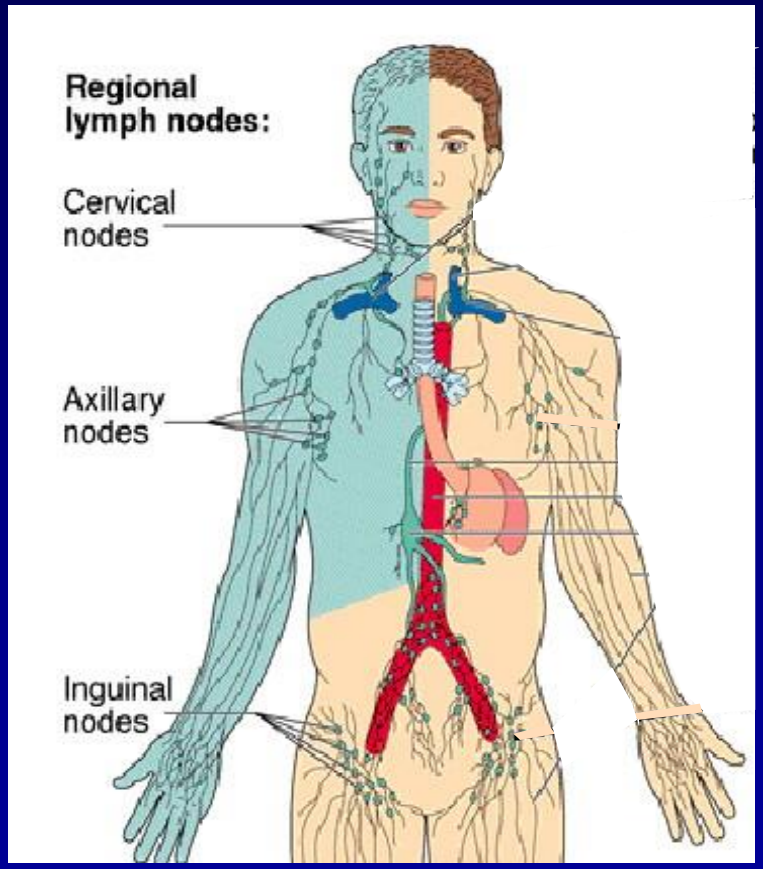

Which are the administration rules for multiple vaccines to be given during the same visit?

Migration of Ag towards the draining lymph nodes

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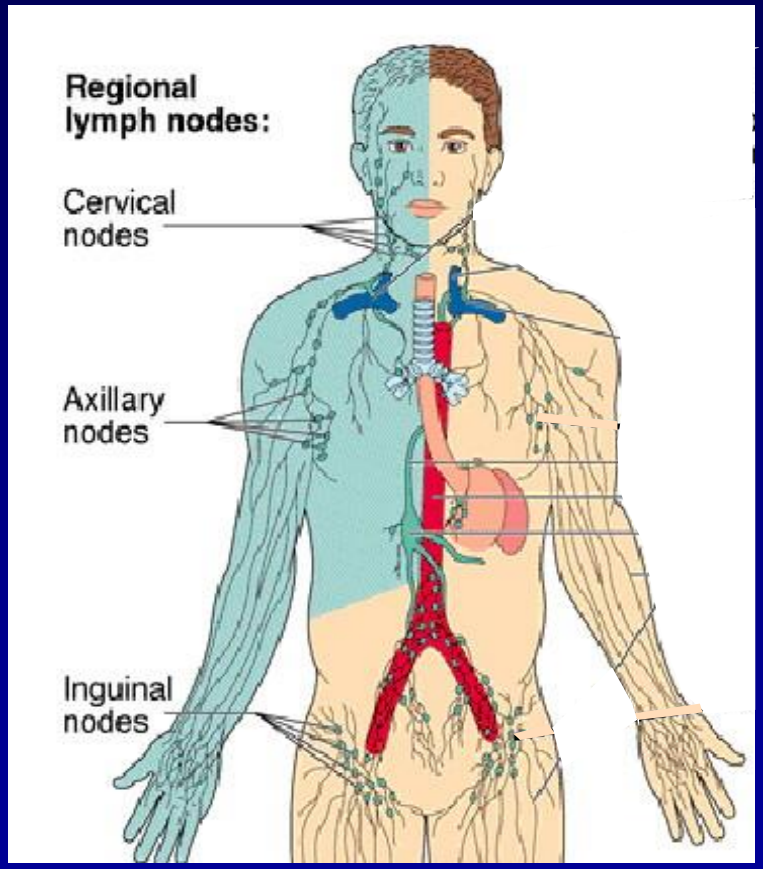
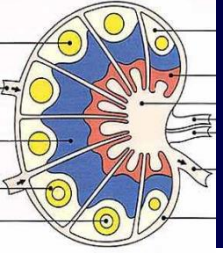


2. Live vaccines

- Minimal local retention / reaction
- Replication – dissemination - pathogen-specific pattern

Multifocal lymph node activation ↔ stronger responses!



How do vaccine induce protection ?

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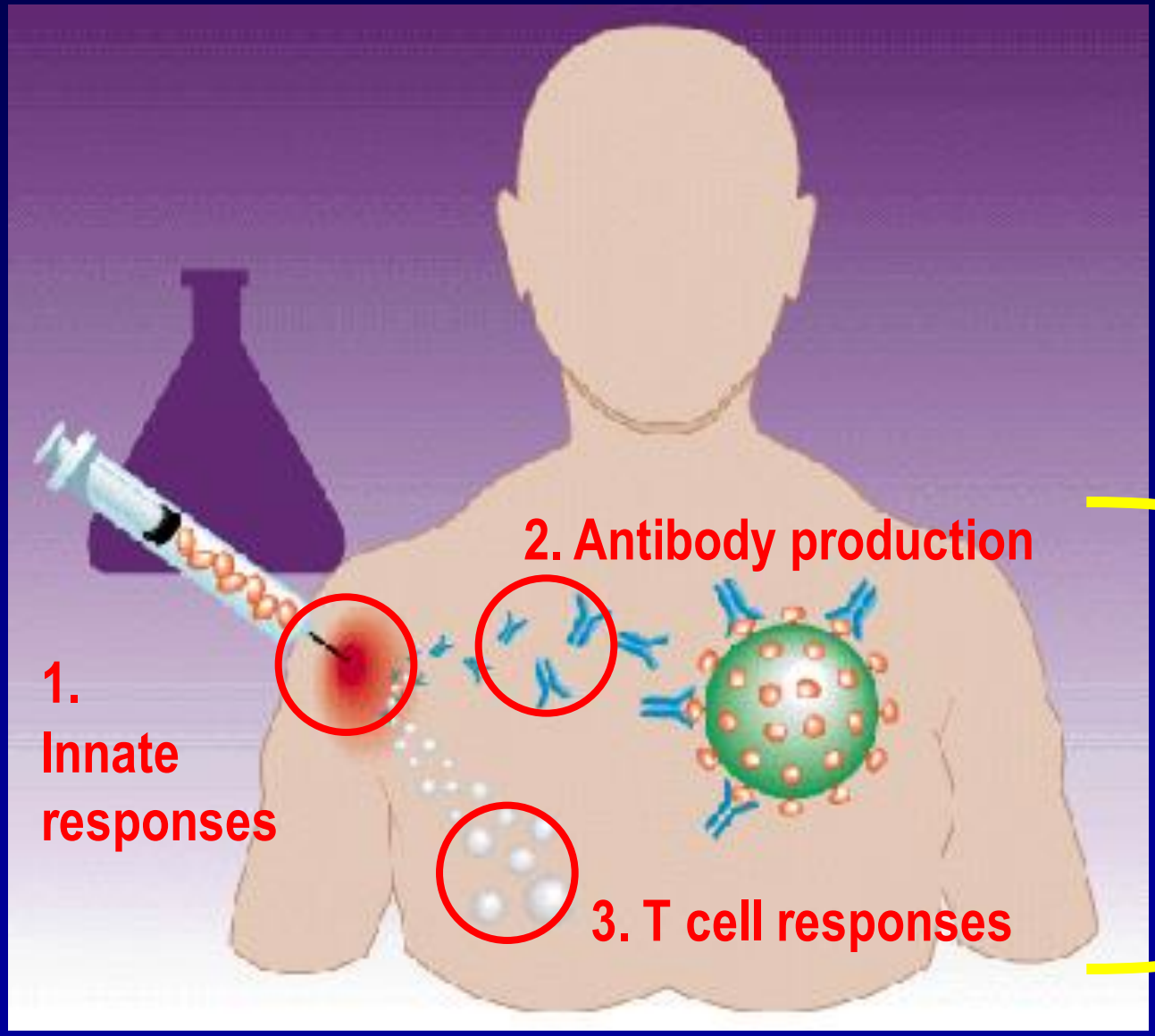
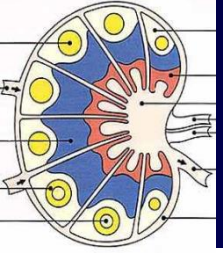
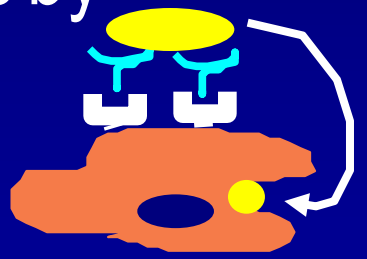




How do vaccine induce protection ?

1. Vaccine antibodies :

- Binding to the enzymatic active sites of toxins or preventing their diffusion
- Neutralizing viral replication, e.g. preventing viral entry into cells
- Promoting opsonization and phagocytosis by macrophages and neutrophils
- Activating the complement cascade



- Early reduction of pathogen load

- Clearance of extracellular pathogens

Table 2-2 Correlates of Vaccine-Induced Immunity

Vaccines	Vaccine type	Serum IgG	Mucosal IgG	Mucosal IgA	T cells
Diphtheria toxoid	*Toxoid*	++	(+)		
Hepatitis A	*Killed*	++			
Hepatitis B (HBsAg)	Protein	++			
Hib PS	PS	++	(+)		
Hib glycoconjugates	PS-protein	++	++		
Influenza	Killed, subunit	++	(+)		
Influenza intranasal	Live attenuated	++	+	+	+ ($CD8^+$)
Japanese encephalitis	Killed	++			
Measles	Live attenuated	++			+ ($CD8^+$)
Meningococcal PS	PS	++	(+)		
Meningococcal conjugates	PS-protein	++	++		
Mumps	Live attenuated	++			
Papillomavirus (human)	VLPs	++	++		
Pertussis, whole cell	Killed	++			
Pertussis, acellular	Protein	++			+?($CD4^+$)
Pneumococcal PS	PS	++	(+)		
Pneumococcal conjugates	PS-protein	++	++		
Polio Sabin	Live attenuated	++	++	++	
Polio Salk	Killed	++	+		
Rabies	Killed	++			
Rotavirus	VLPs	(+)	(+)	++	
Rubella	Live attenuated	++			
Tetanus toxoid	Toxoid	++			
Tuberculosis (BCG)	Live mycobacteria				++($CD4^+$)
Typhoid PS	PS	+	(+)		
Varicella	Live attenuated	++			+?($CD4^+$)

Essential role for Antibodies in most current vaccines !

Vaccines – as seen by the immune system

Polysaccharides

and/or

Proteins

and

"Danger signals" activating the innate immune system → initiating and shaping B and T cell responses

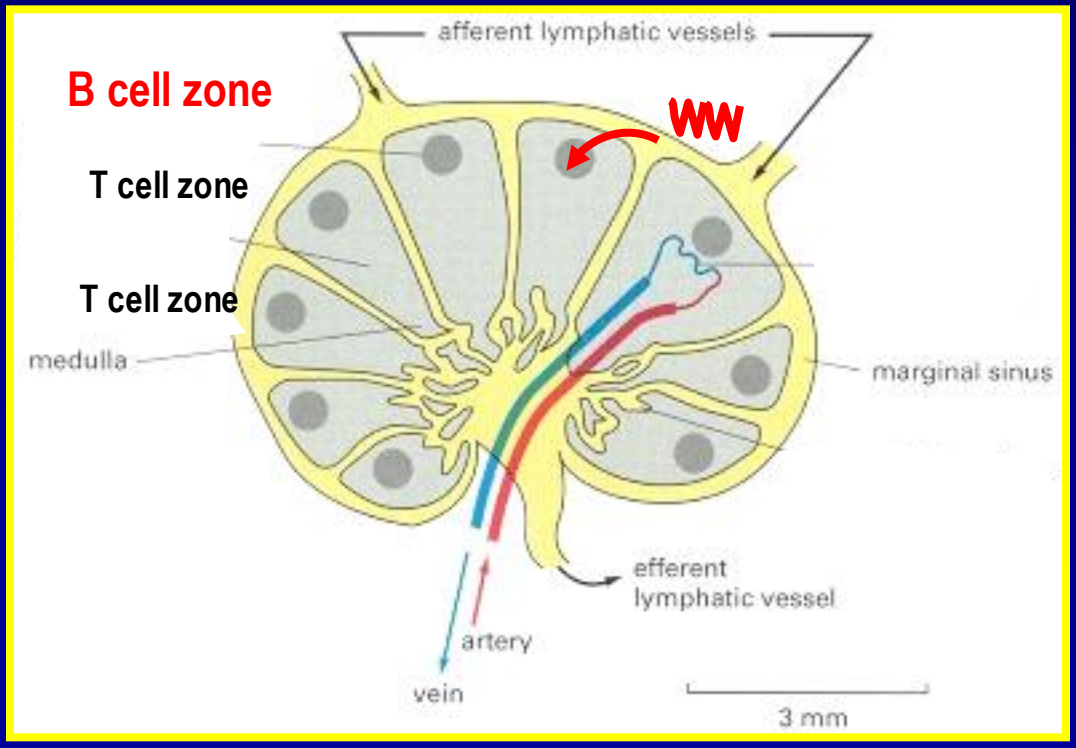
Exposure to polysaccharides induces a wave of short-lived Ab-secreting plasma cells

Lymph nodes

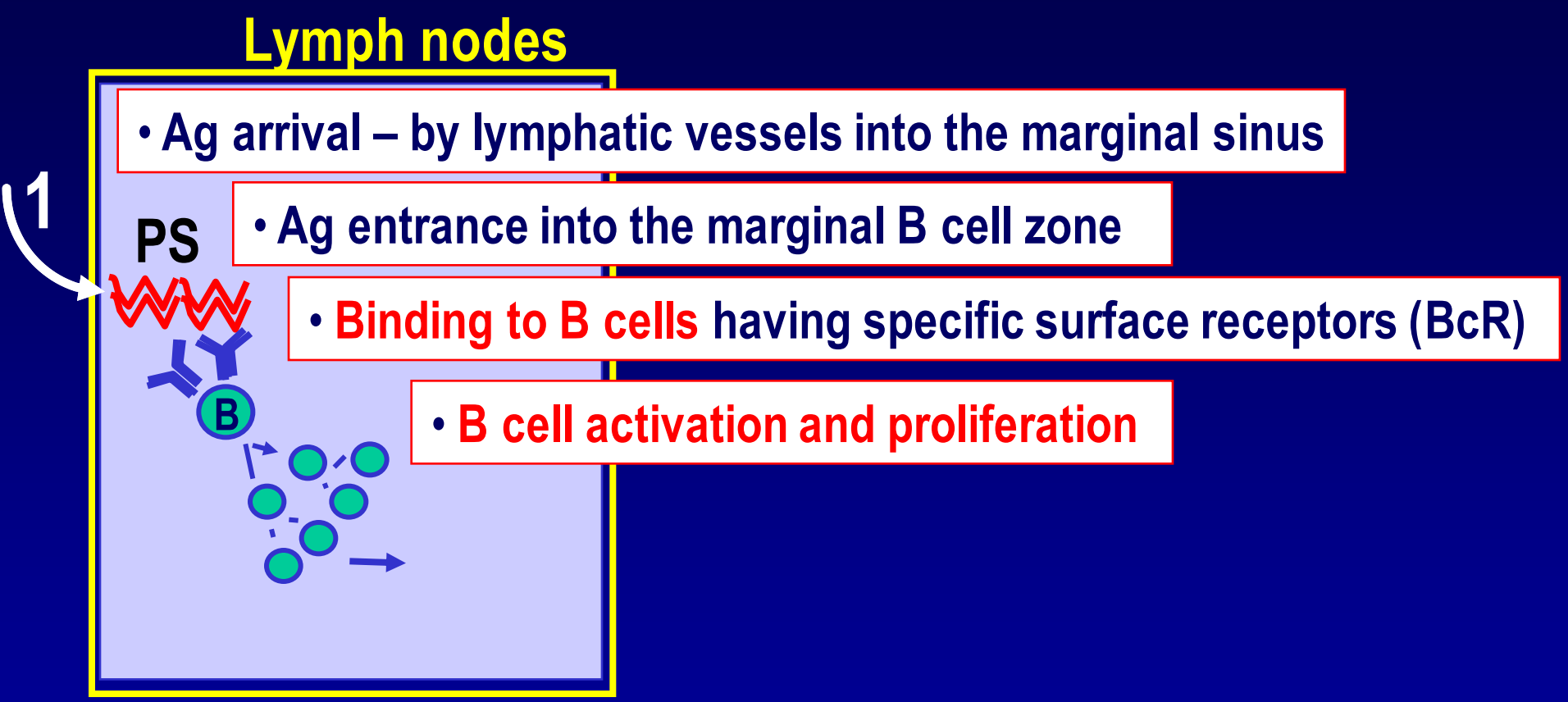
1

PS

- Ag arrival – by lymphatic vessels into the marginal sinus
- Ag capture by subcapsular sinus macrophages and translocation into the marginal B cell zone



Exposure to polysaccharides induces a wave of short-lived Ab-secreting plasma cells



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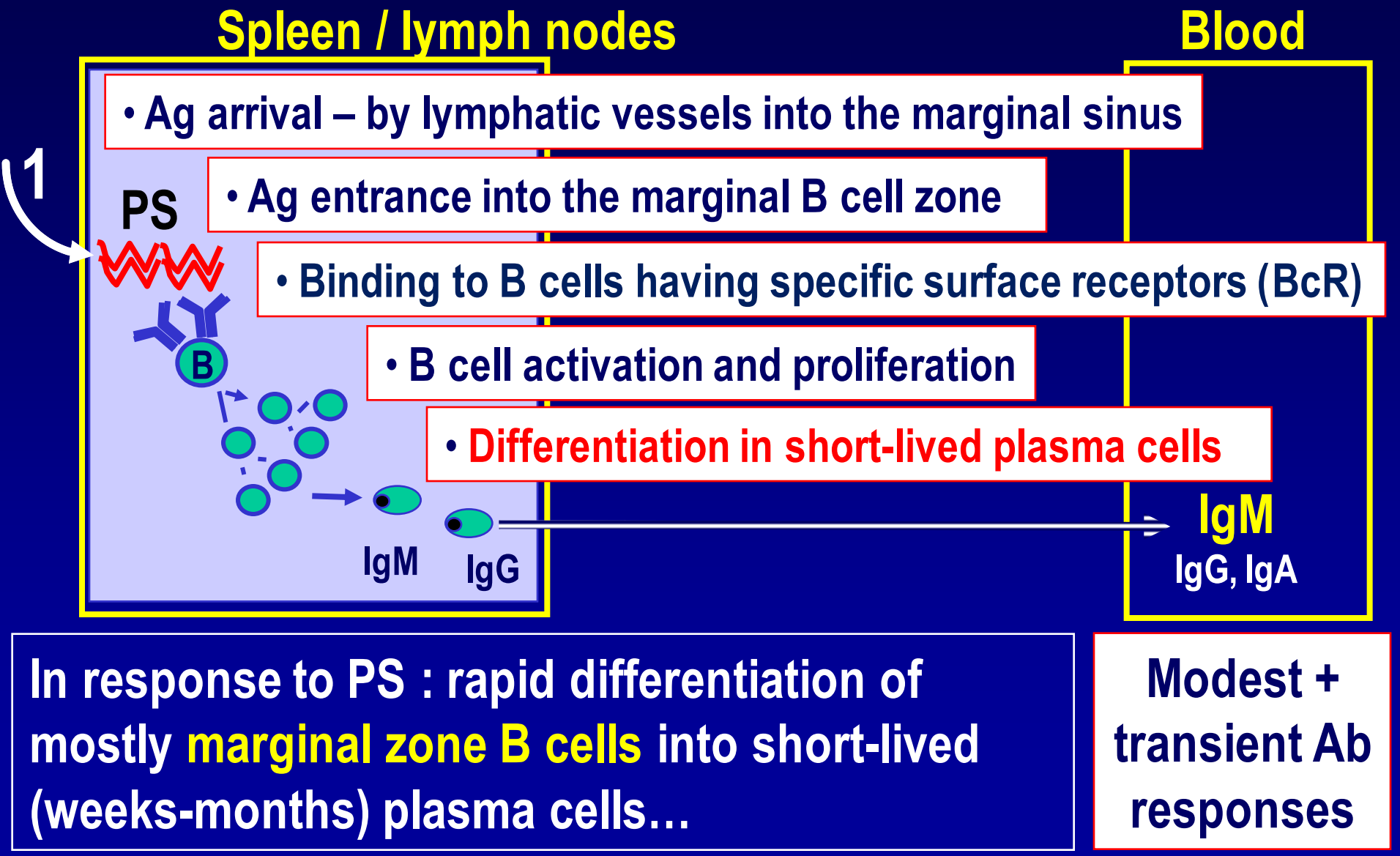
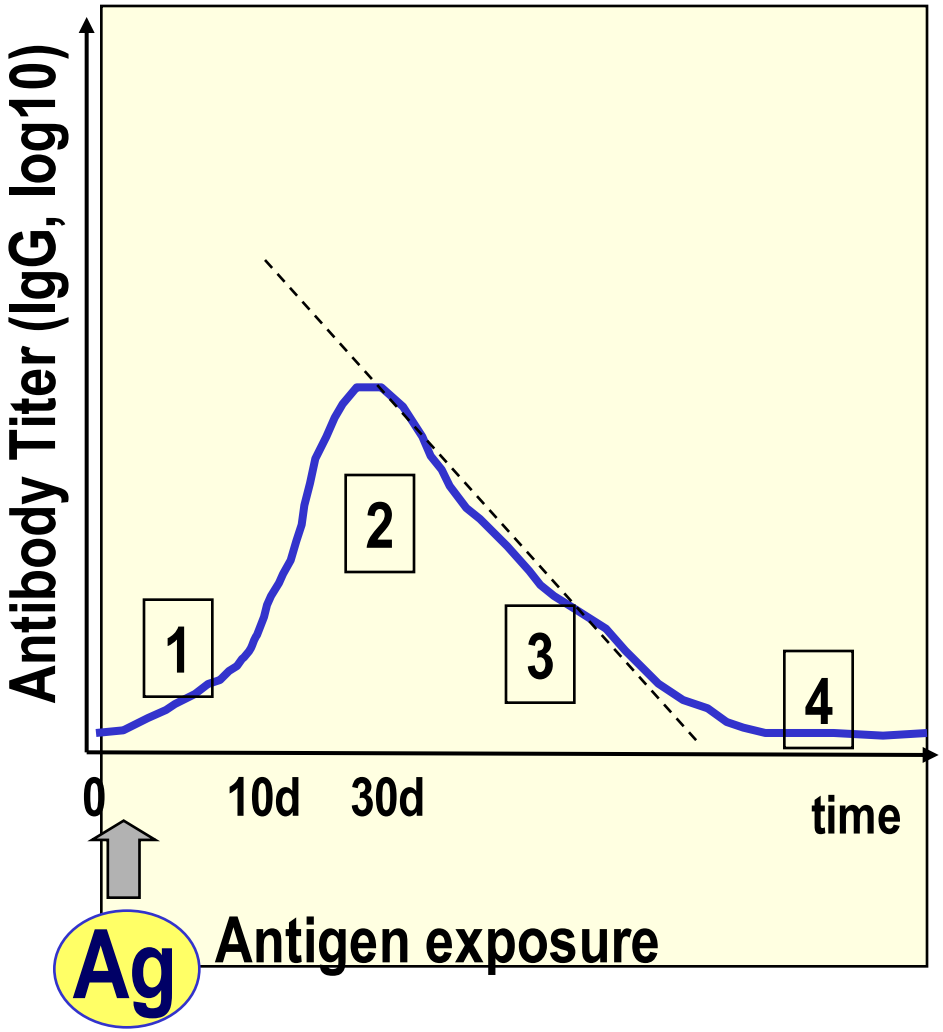


In response to PS : rapid differentiation of mostly marginal zone B cells into short-lived (weeks-months) plasma cells…

Modest + transient Ab responses

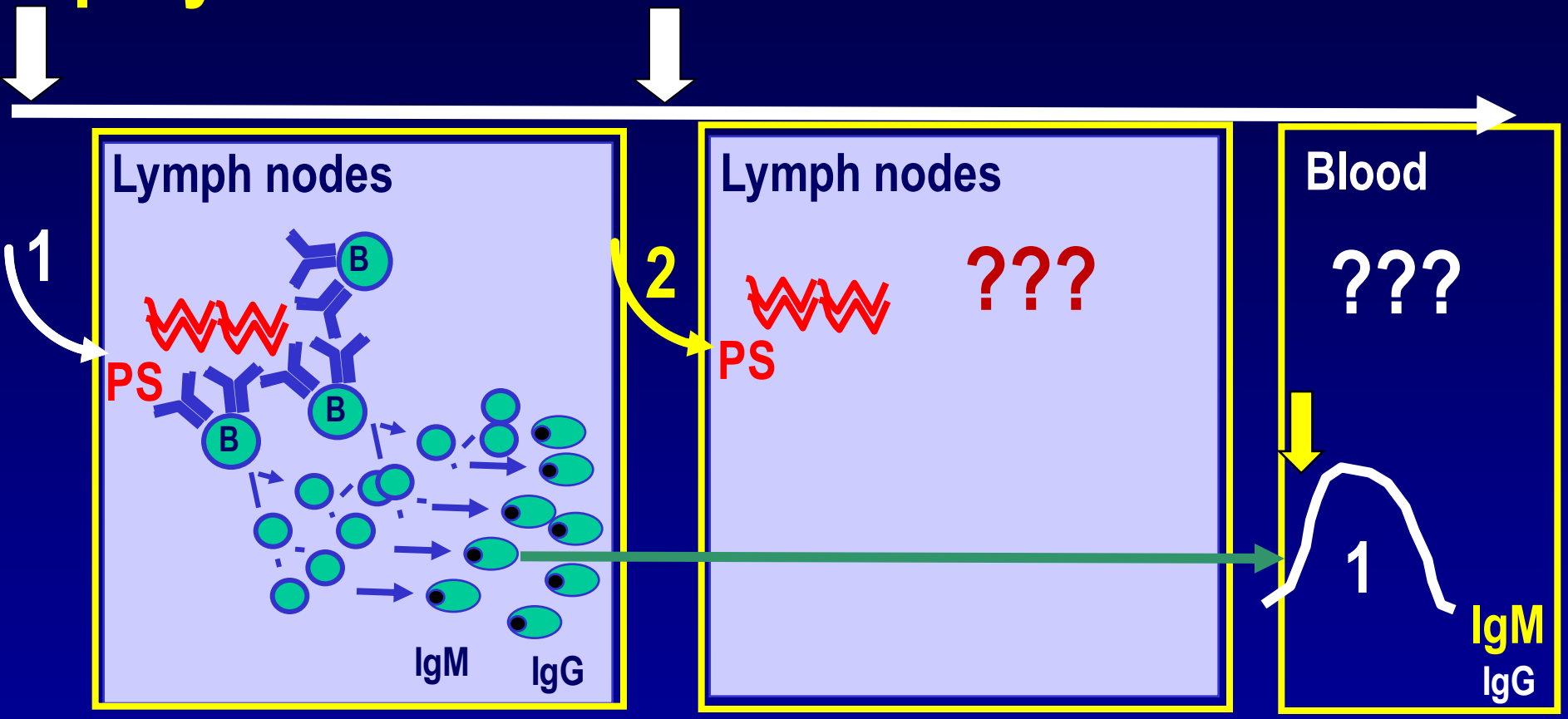
Induction of primary Ab responses to polysaccharide antigens



1. B cell response *(extrafollicular)*
2. Peak IgG titers ~ 2-4 weeks after immunization.
3. Short PC life span in lymph nodes (weeks): rapid decline of Ab titers.
4. Rapid return (months) to baseline levels.

No induction of immune memory…

What happens after repeat exposure to polysaccharides ?



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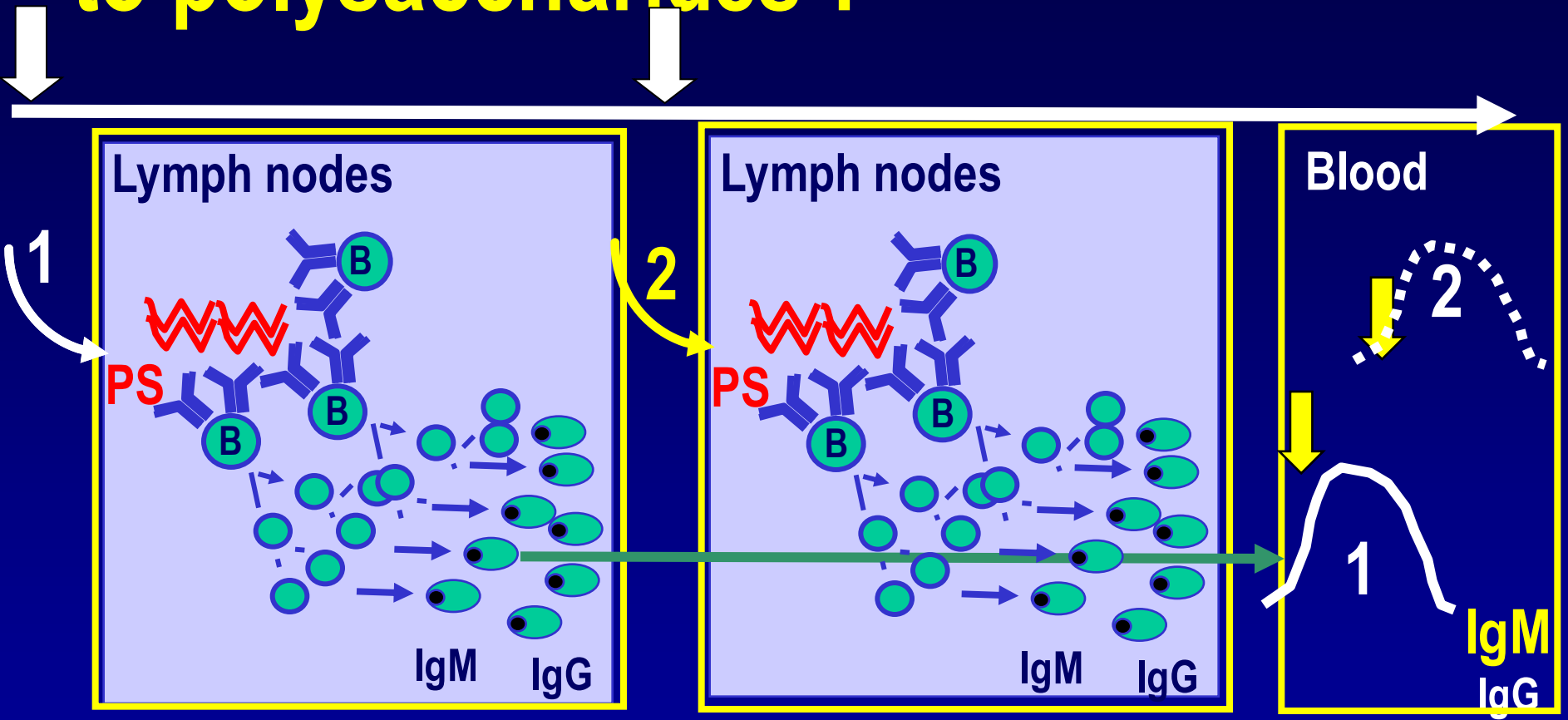
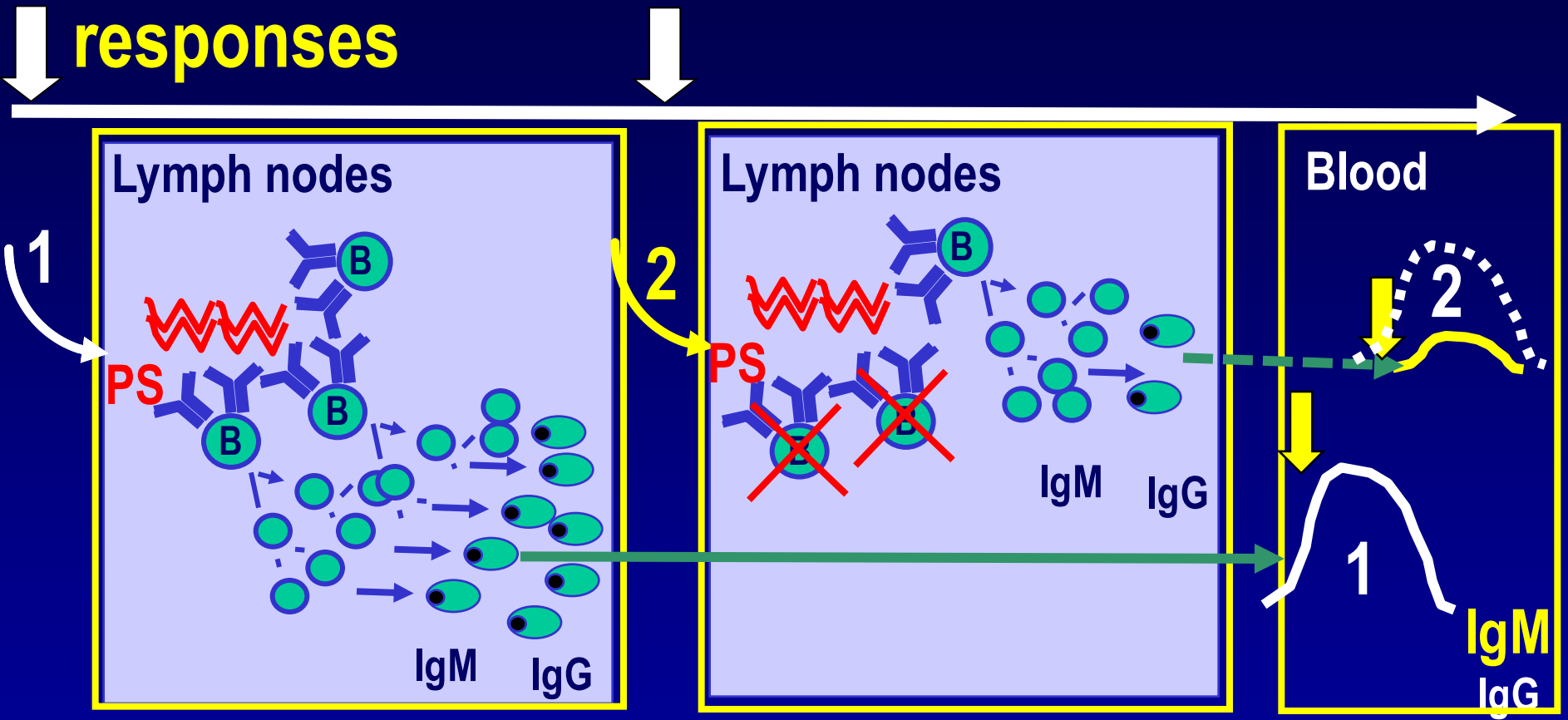


1) A second primary response, similar to the first one *(no induction of memory)*...

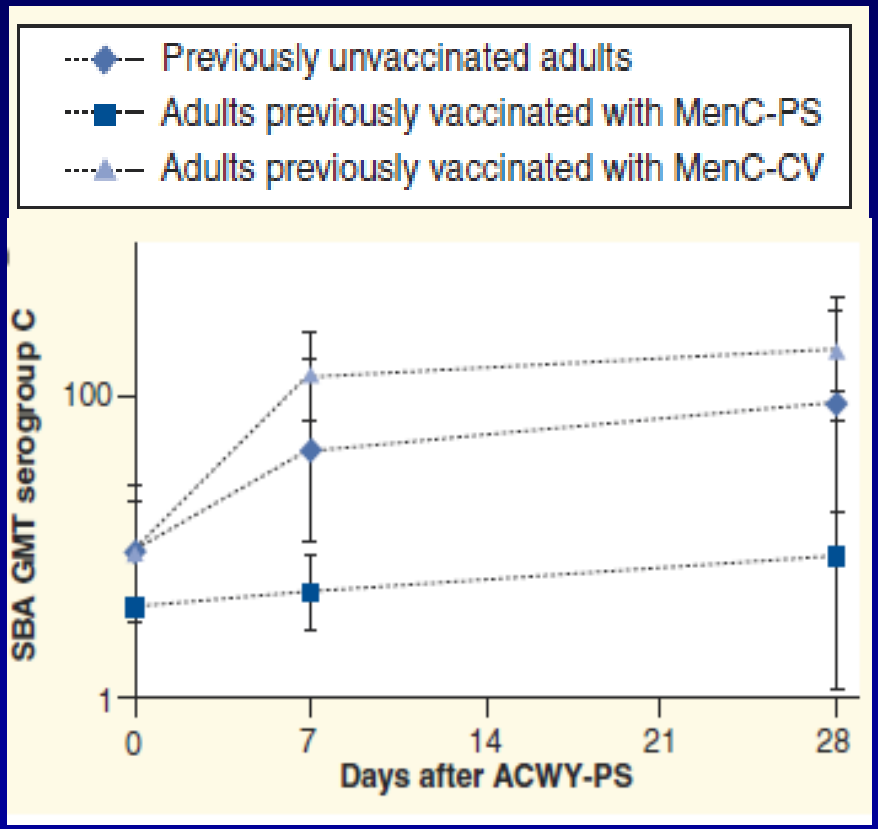
Repeat exposure to polysaccharides may induce similar or lower repeat than primary responses



2) A weaker response (B cell hyporesponsiveness)
by exhaustion of the Ag-specific B cell reservoir which is only slowly reconstituted after its mobilization

Repeat exposure to polysaccharides may induce lower than primary responses

Impaired responses to MenC polysaccharides by prior immunization with MenC PS



Impaired responses to pneumococcal conjugate vaccine (PCV-7) by prior PS immunization

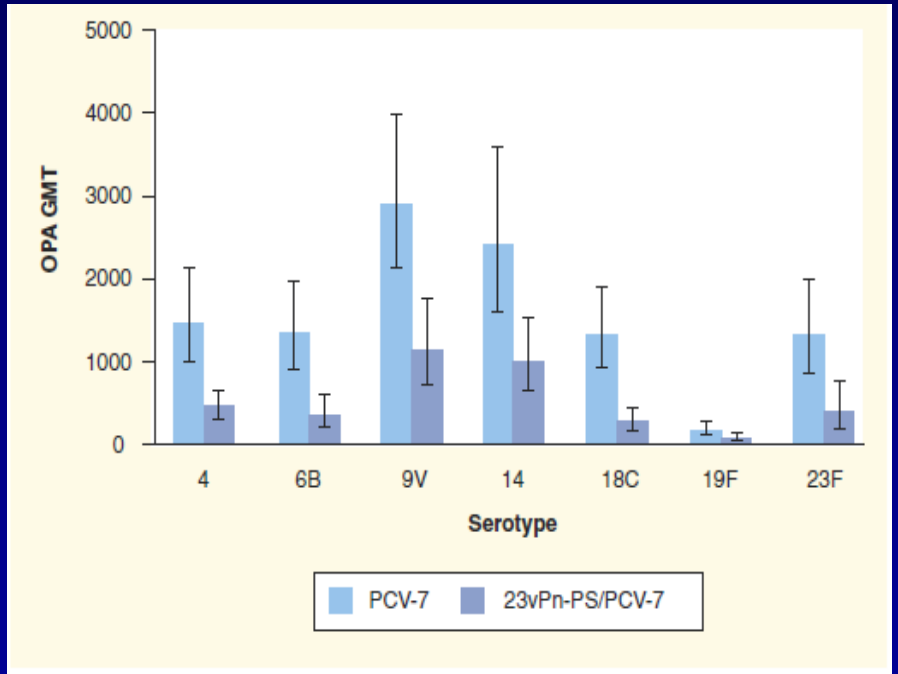
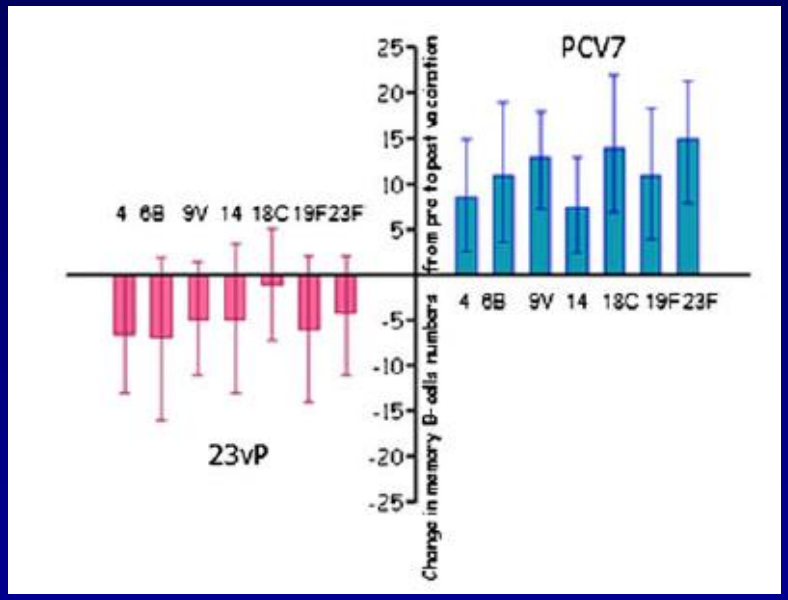


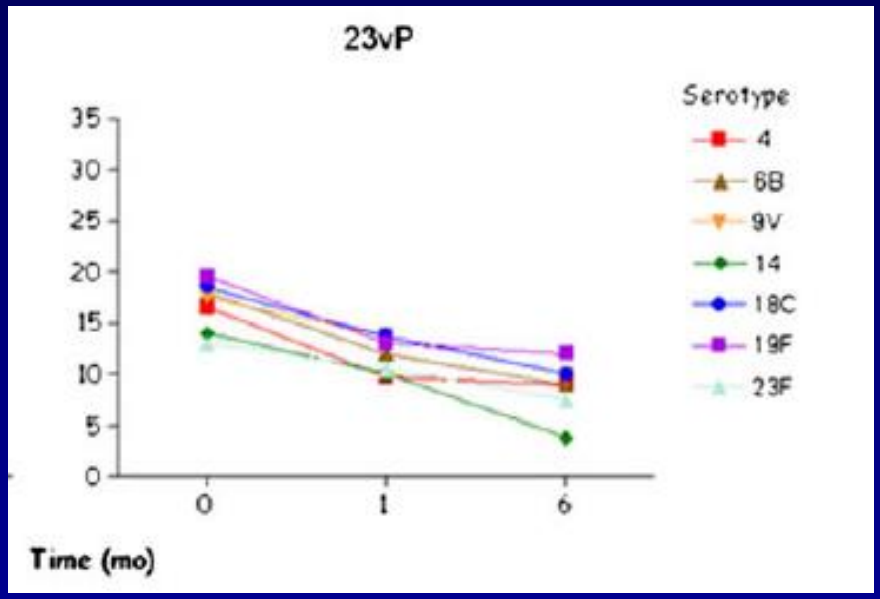
Figure 4. Antipneumococcal antibody GMCs (A) and opsonophagocytic activity GMTs (B) in adults ≥70 years of age administered PCV-7 (n = 110) or 23vPn-PS followed 1 year later by PCV-7 (n = 78). Error bars represent the 95% CIs. Differences between the groups were statistically significant ($p < 0.01$) for all serotypes except OPA titers for serotype 19F.

Poolman J Expert Rev Vaccines 2011; 10(3), 307; Brynjolfsson SF, J Infect Dis. 2012 Feb;205(3):422-30.

Exposure to polysaccharides may reduce preexisting Ag-specific B cells

Reduction of « memory » B cells following 1 dose of polysaccharide vaccine in adults





Clutterbuck EA et al (Oxford Vaccine Group), J Inf Dis 28.03.2012

- **Observed for all serotypes – duration ≥ 6-12 months**
- **Proposed mechanism: induction of B cell apoptosis by PS binding without additional activation signals** *(mouse: Brynjolfsson SF J Inf Dis 2012)*

Polysaccharide vaccines
(S. pneumoniae, N. meningitidis)

- **Recruit PS-specific "memory" B cells** *(elicited by prior colonisation or immunization)*
- **Drive their differentiation into short-lived Ab secreting PCs**

→ short-lived antibody responses ↔ transient protection ↔ limited benefit, no population impact (UK)

Boosters recommended in numerous countries
(example : splenectomy, hemoglobinopathies)

3 - 5 years ***3 - 5 years*** ***3 - 5 years*** ***3 - 5 years***

But NO induction of immune memory AND risks of B cell depletion ↔ toward the end of PS vaccines?

Vaccines – as seen by the immune system

Polysaccharides

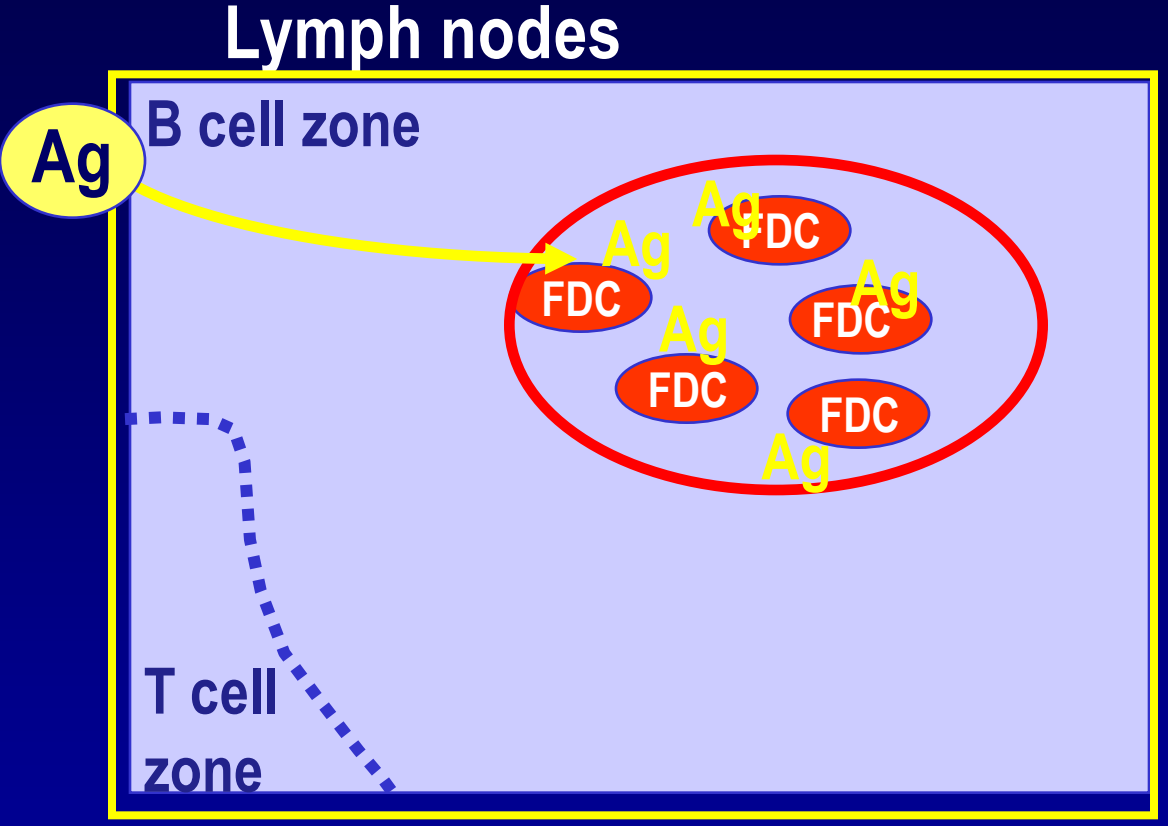
and/or

Proteins

and

"Danger signals" activating the innate immune system → initiating and shaping B and T cell responses

Responses to protein-containing vaccines :
1. Antigen delivery to B cells + T cells



1. Soluble antigens drain from the site of injection to the capsular sinus of the lymph nodes and are translocated (by specific subcapsular macrophages) to **follicular dendritic cells (↔ antigen depot in the B cell zone)**

Responses to protein-containing vaccines :

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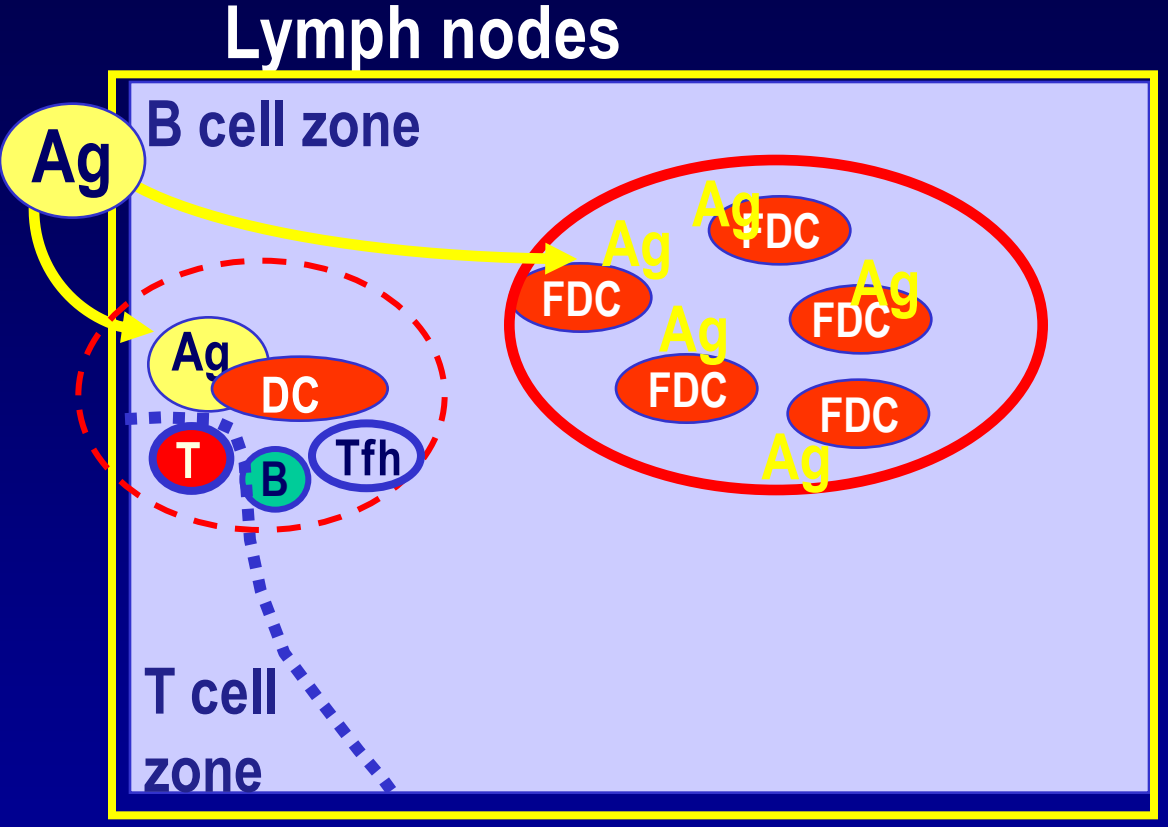
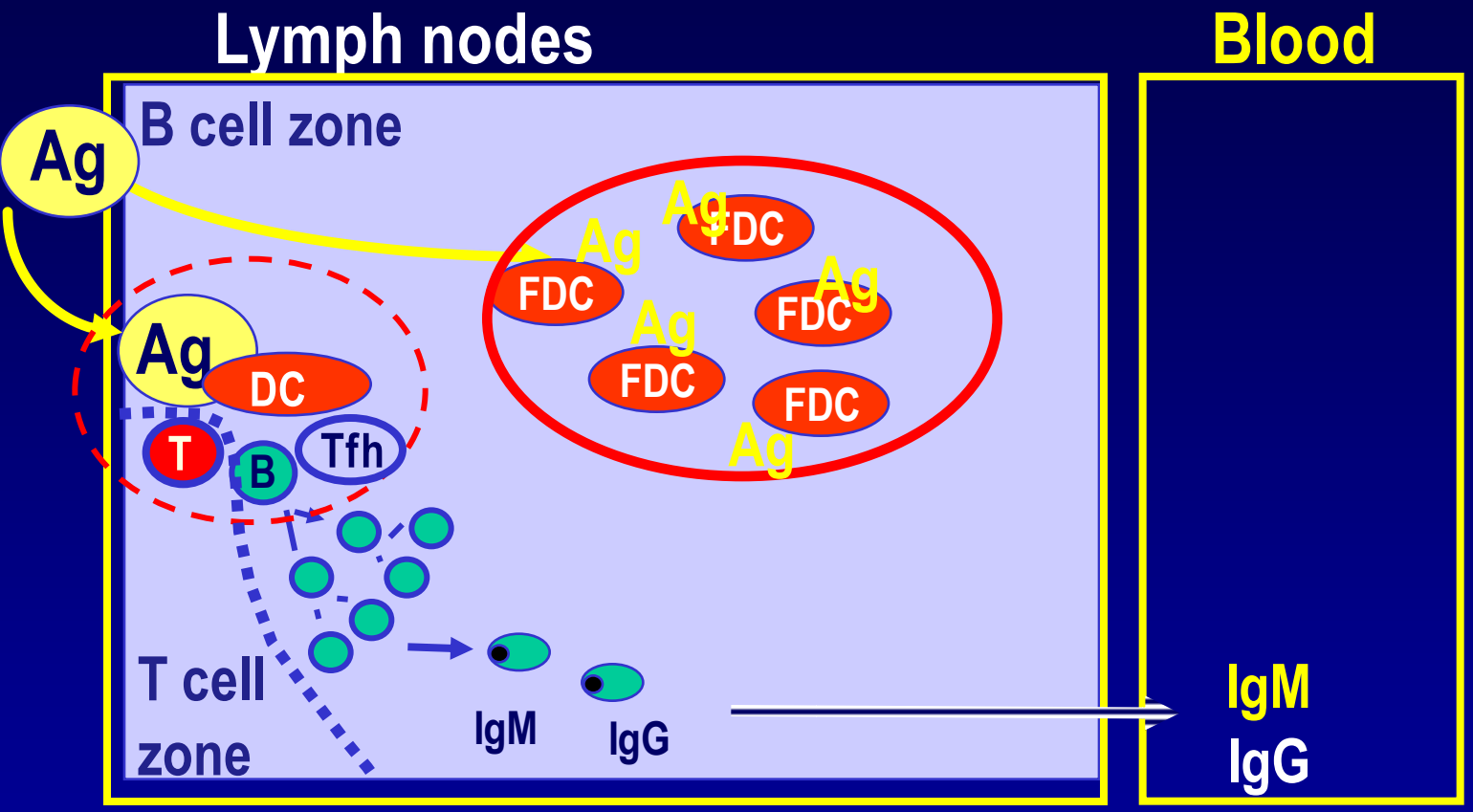


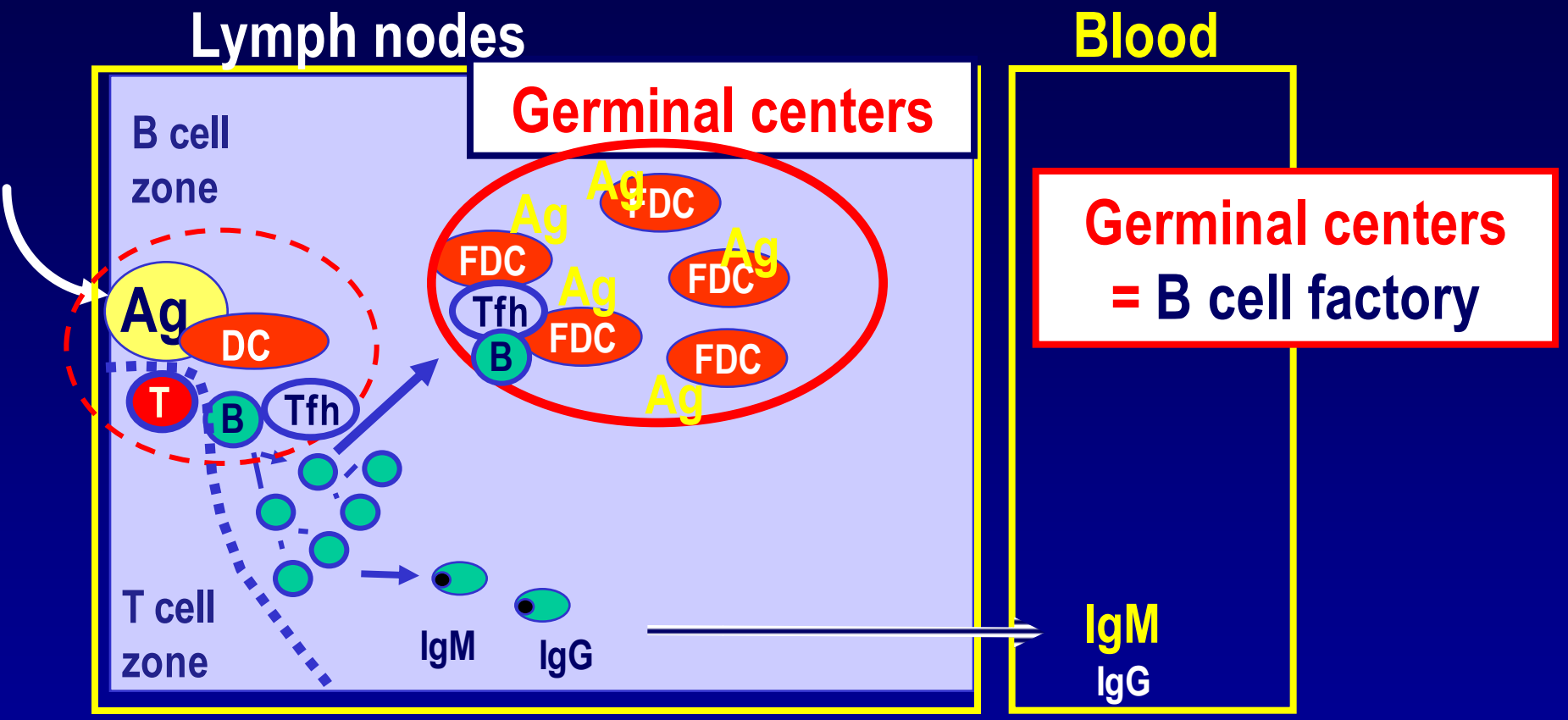
2. Antigens retained at the site of injection (depot formulations) are captured by circulating monocytes / dendritic cells which migrate **to the border of the T:B cell zone**

Responses to protein-containing vaccines :
2. Activation of APC → T cells + B cells



- Ag-transporting Dendritic cells activate Ag-specific B cells + Ag-specific CD4 T helper cells
- B cell proliferation – differentiation = extrafollicular response

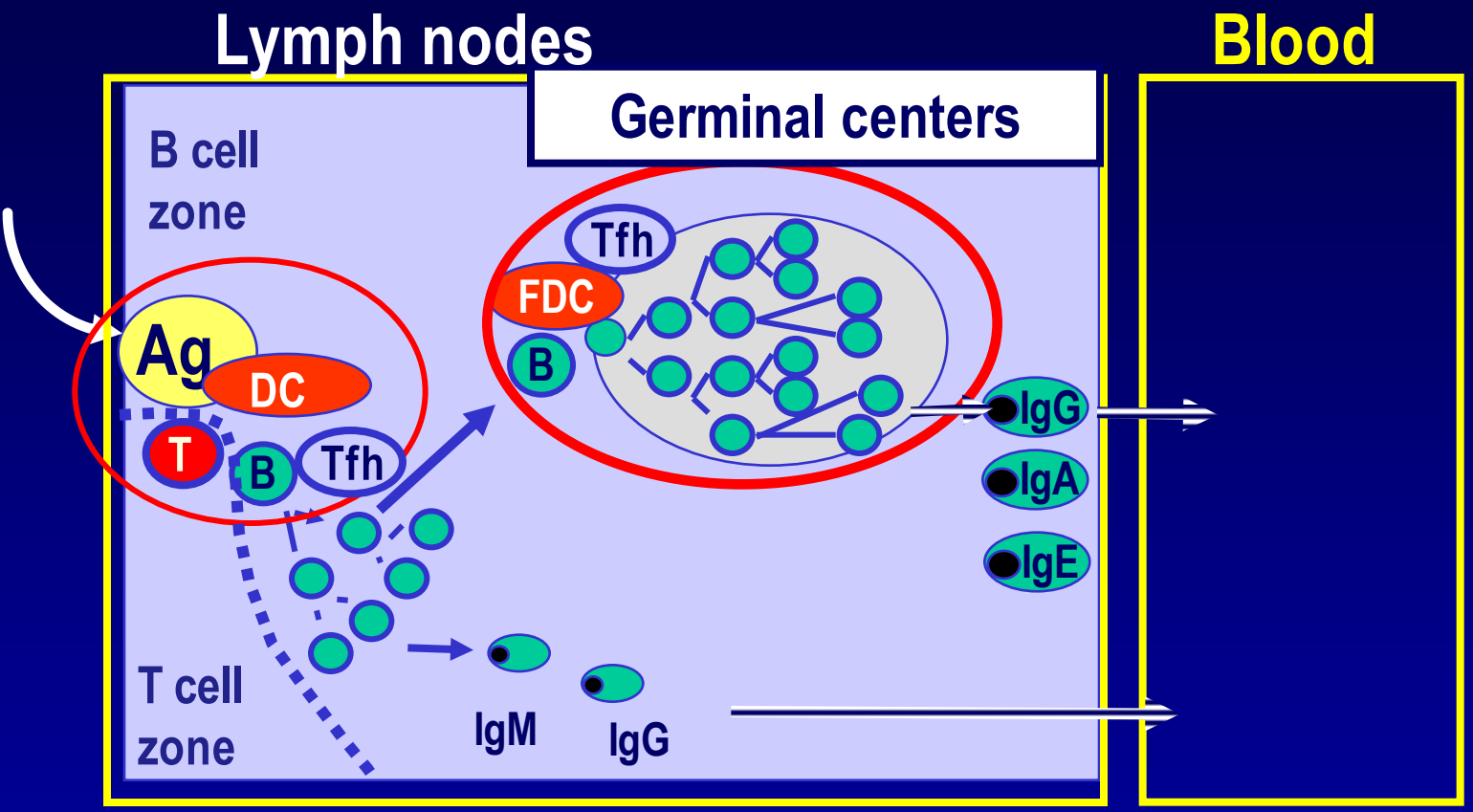
Responses to protein-containing vaccines :
3. Development of a Germinal Center reaction



- **Activated Ag-specific B cells** and **CD4 follicular T cells (Tfh) are attracted** by Ag-bearing **Follicular dendritic cells**
- Ag^+ FDCs + B cells + Tfh cells ↔ **induction of Germinal Centers**

Responses to protein-containing vaccines :

3. Development of a Germinal Center reaction

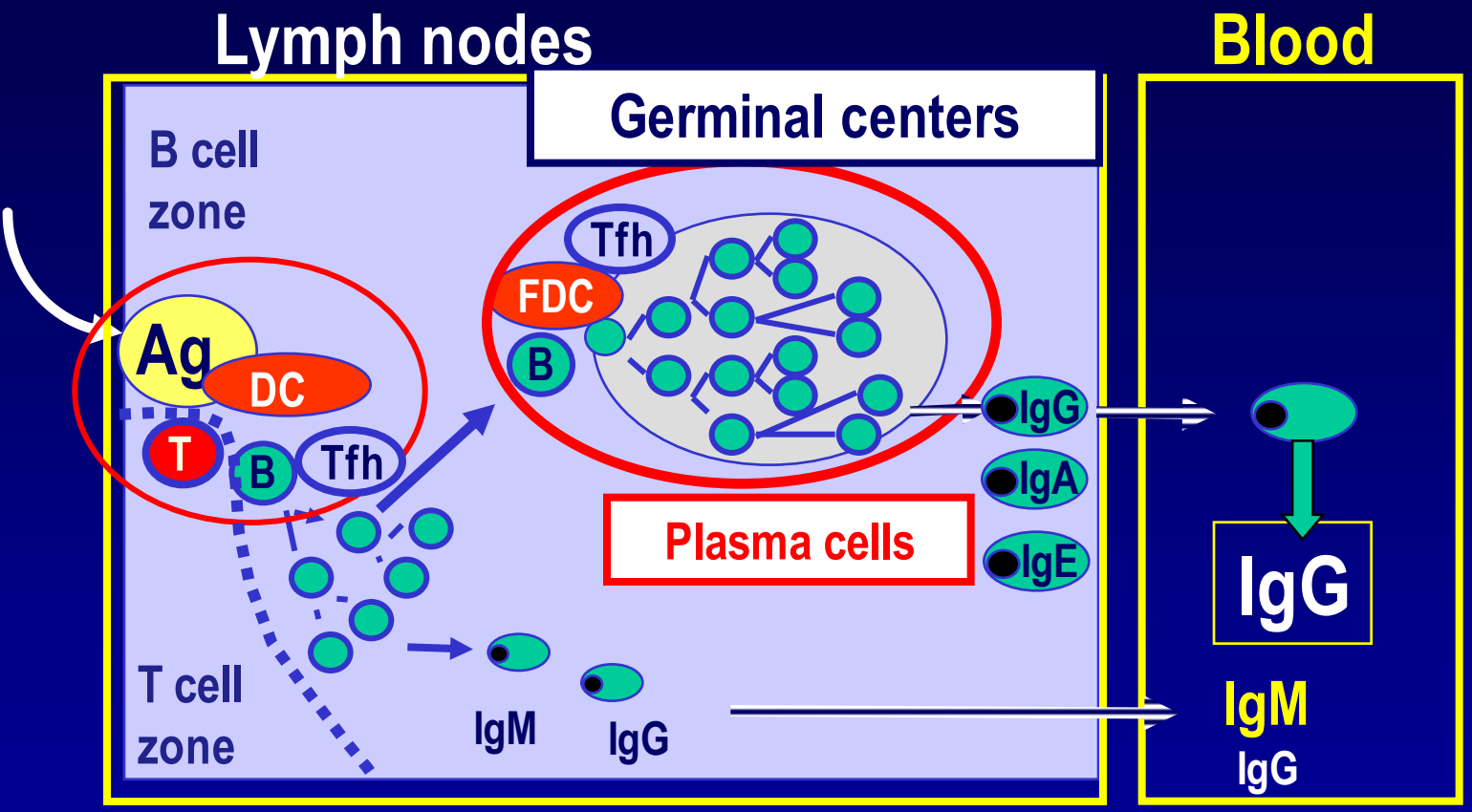


Proliferation and Ig switch IgM → **IgG*, IgA, IgE**

** IgG isotype ↔ cytokines produced by Tfh (IFNγ / IL-4)*

Responses to protein-containing vaccines :

3. Development of a Germinal Center reaction

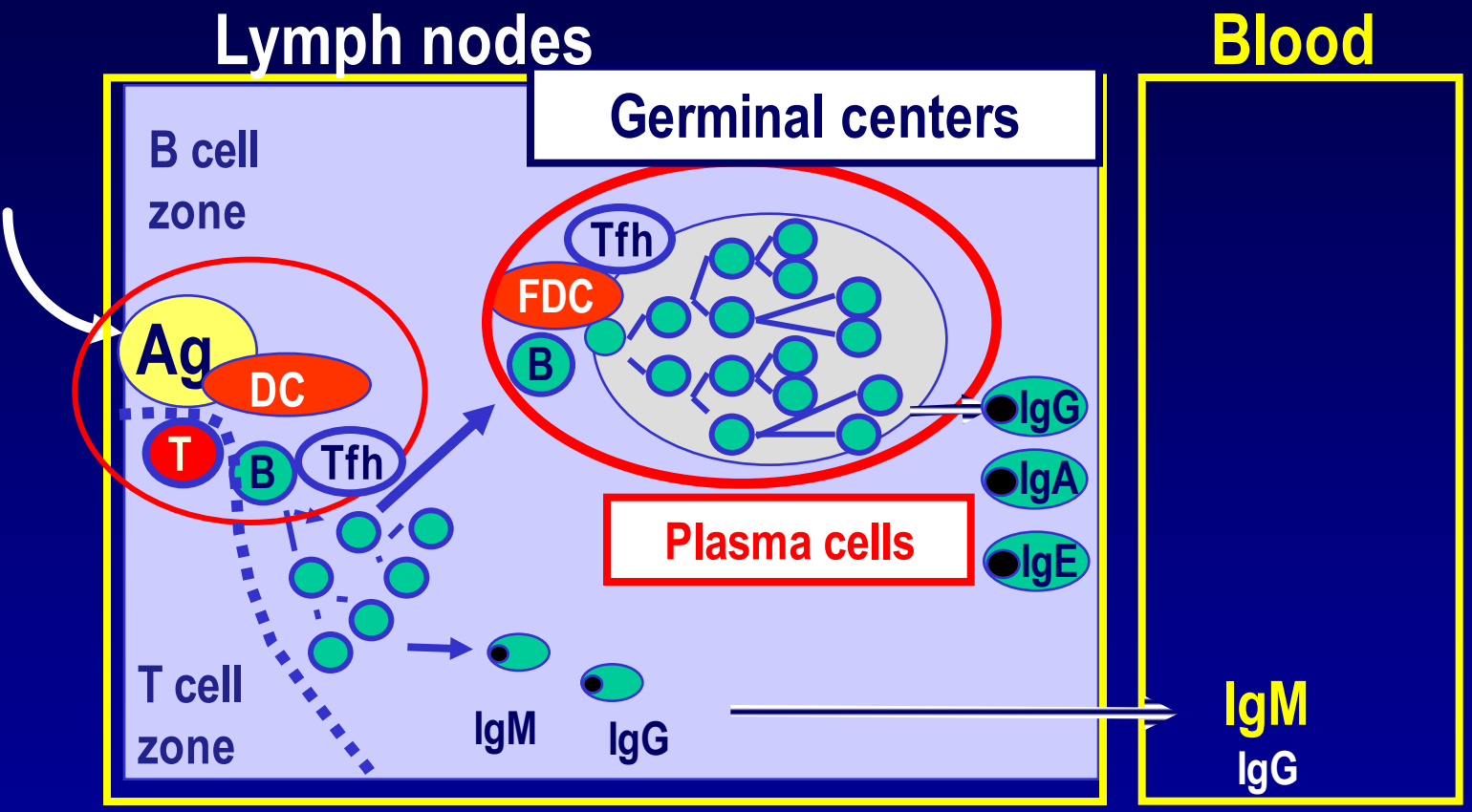


Proliferation and Ig switch IgM → IgG, IgA, IgE

Differentiation into plasma cells → ↑ Ab production / cell

Responses to protein-containing vaccines :

3. Development of a Germinal Center reaction

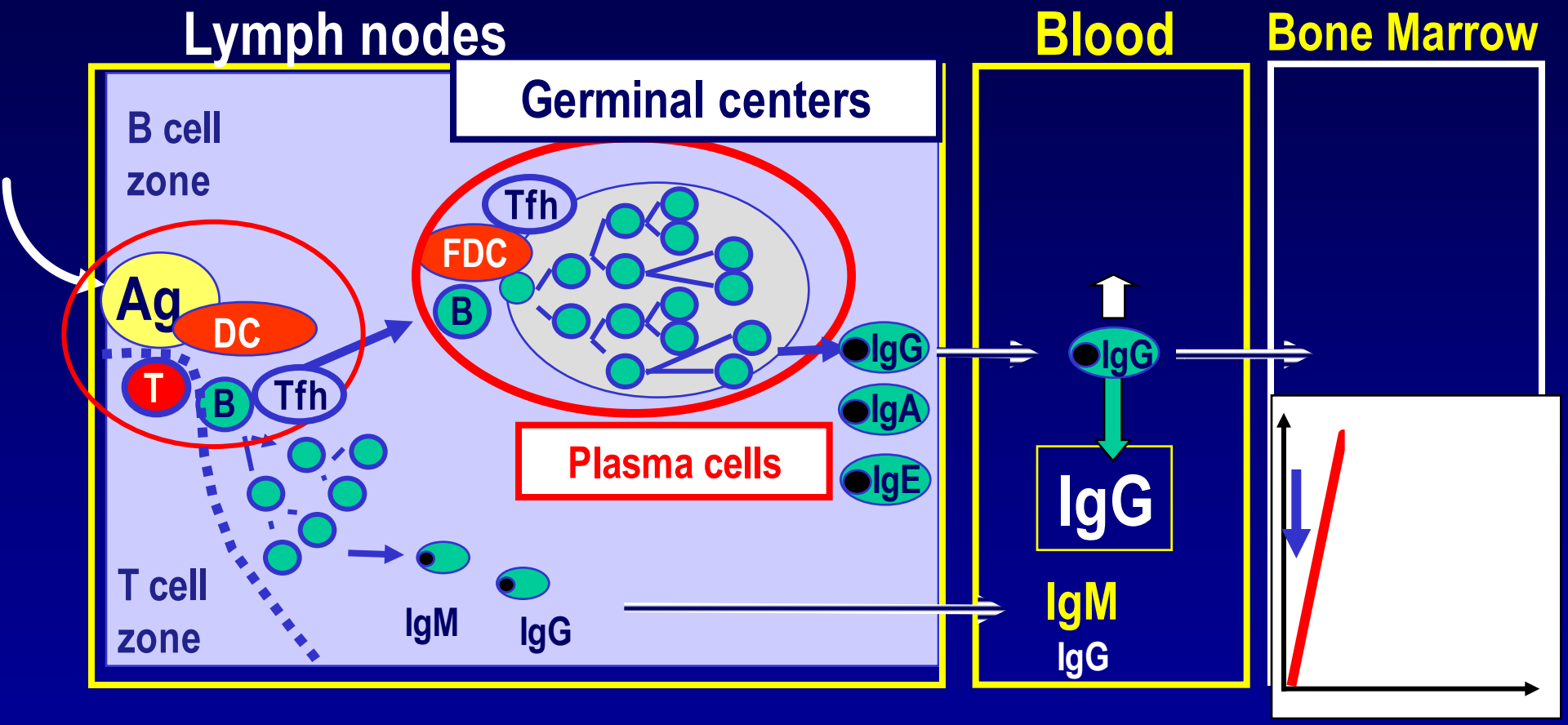


Proliferation and Ig switch IgM → IgG, IgA, IgE

Differentiation into plasma cells → ↑ Ab production / cell

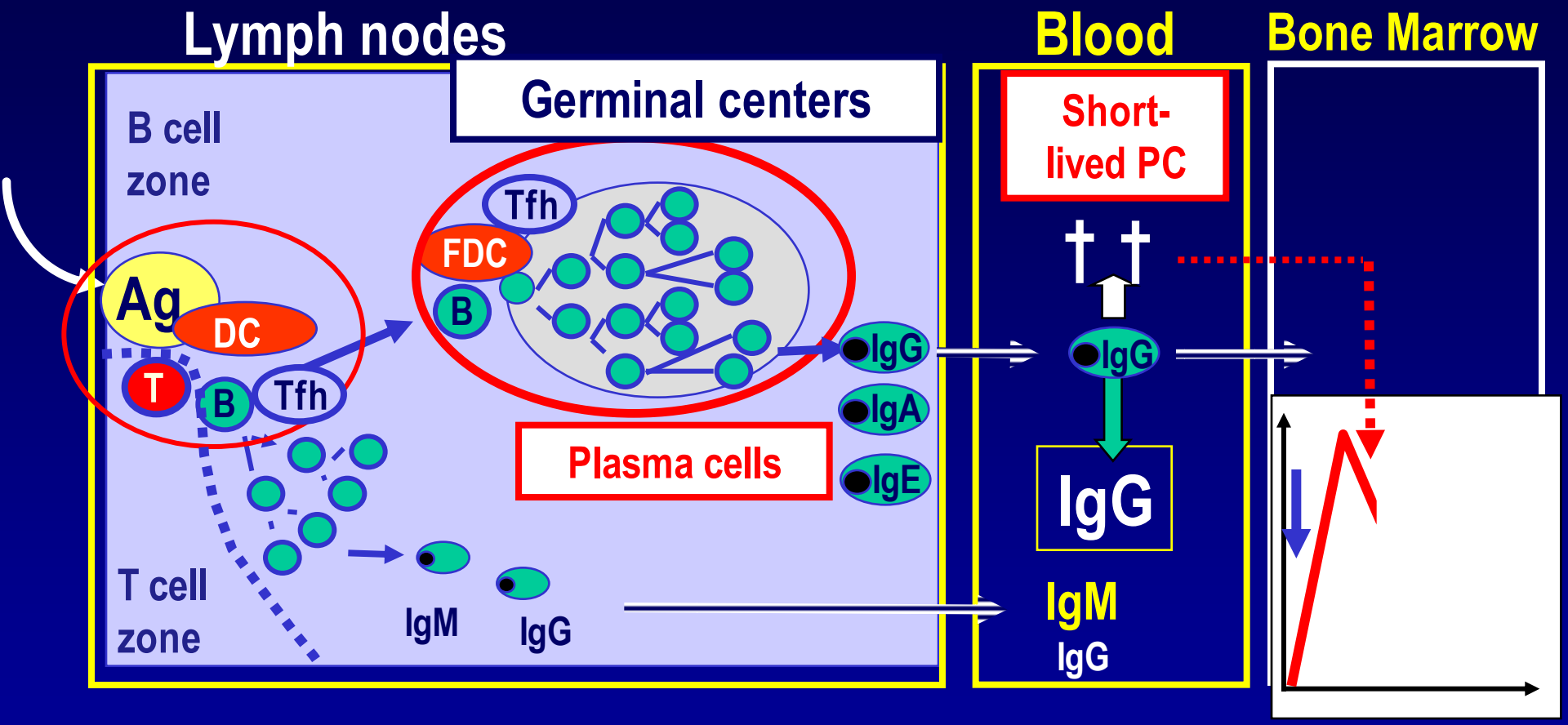
Mutations + clonal selection → Selection of the best PC!

Responses to protein-containing vaccines :
4. Induction and differentiation of plasma cells



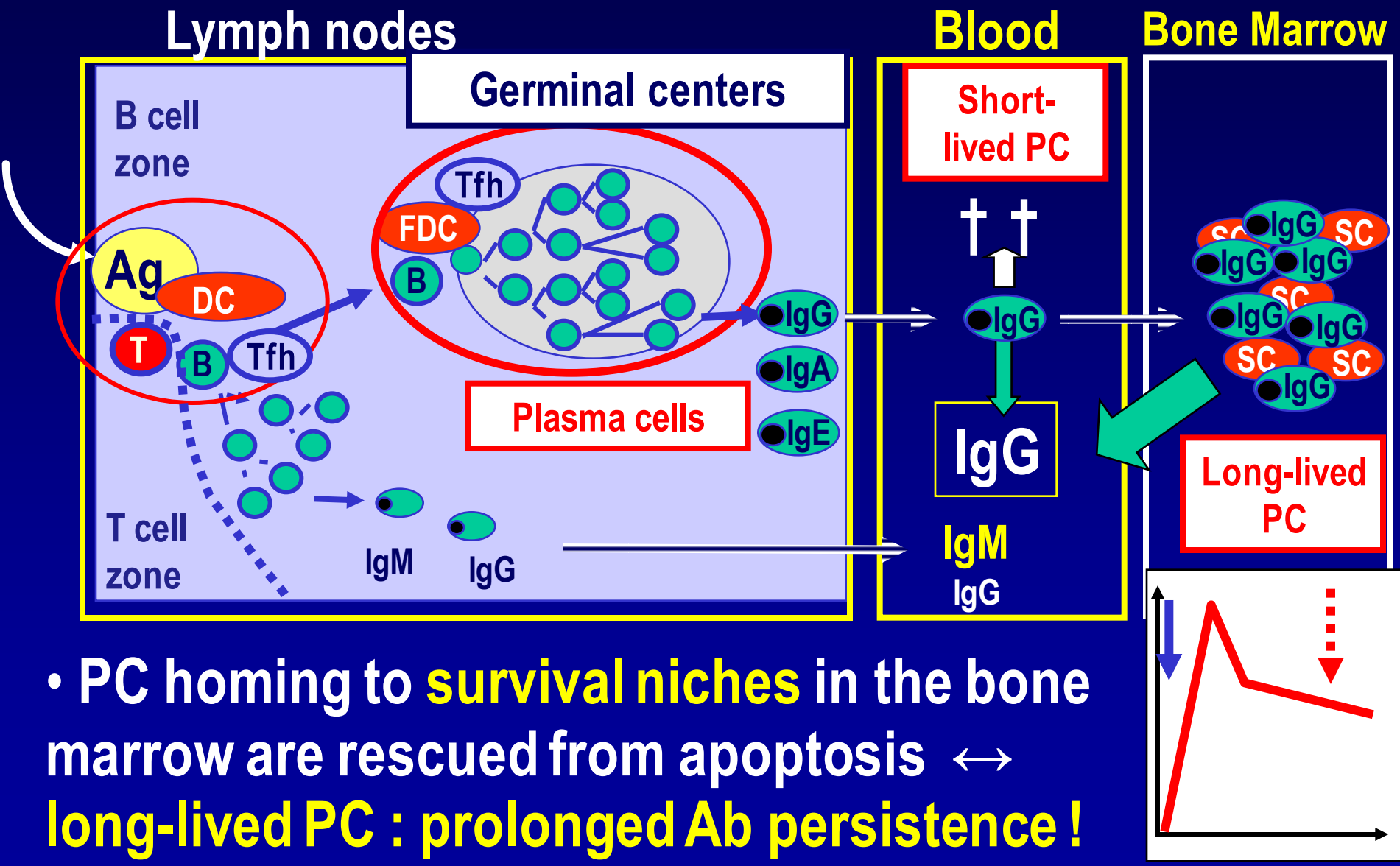
- Antigen-specific plasma cells in the blood after 10-14 days
- Peak Ab titers 4 weeks after injection.

Responses to protein-containing vaccines :
4. Induction and differentiation of plasma cells



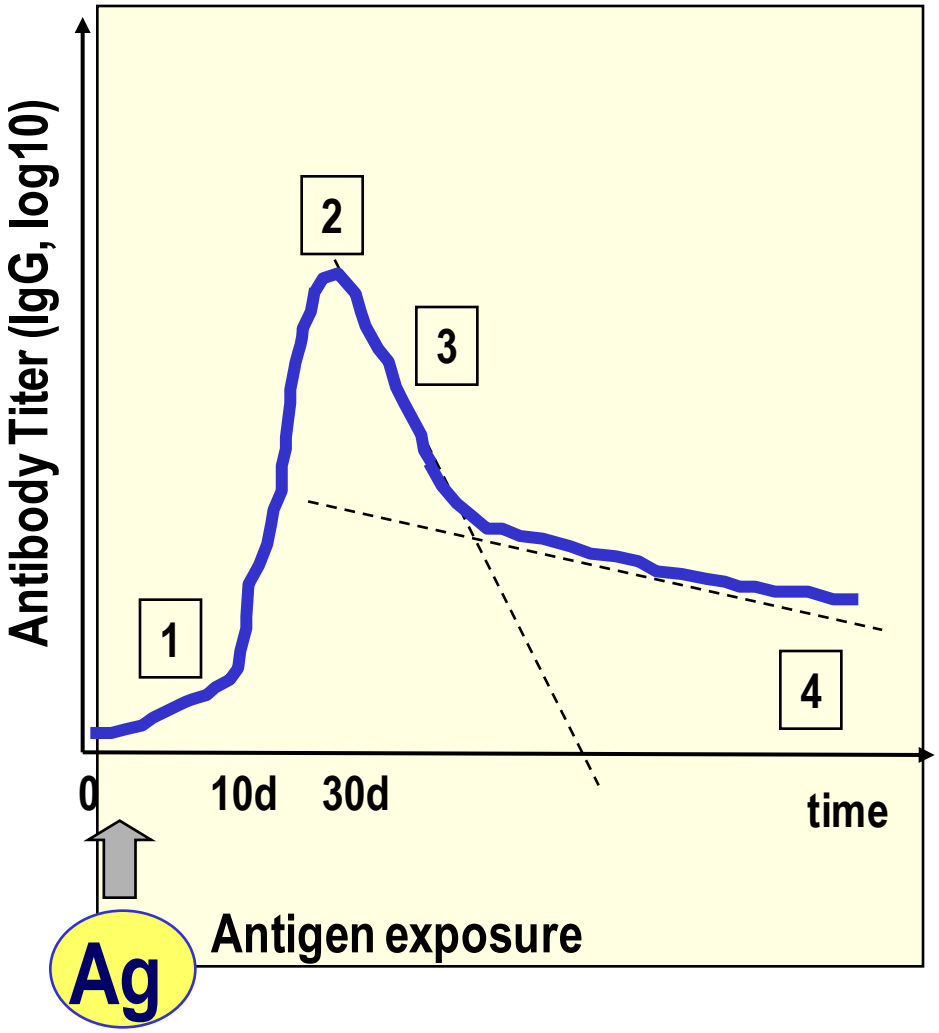
- Antigen-specific plasma cells in the blood after 10-14 days
- Peak Ab titers 4 weeks after injection.
- Early cell death (short-lived plasma cells) ↔ rapid Ab fall !

Responses to protein-containing vaccines :
5. Survival of plasma cells into survival niches



- PC homing to **survival niches** in the bone marrow are rescued from apoptosis ↔ **long-lived PC : prolonged Ab persistence !**

Induction of primary Ab responses to protein antigens



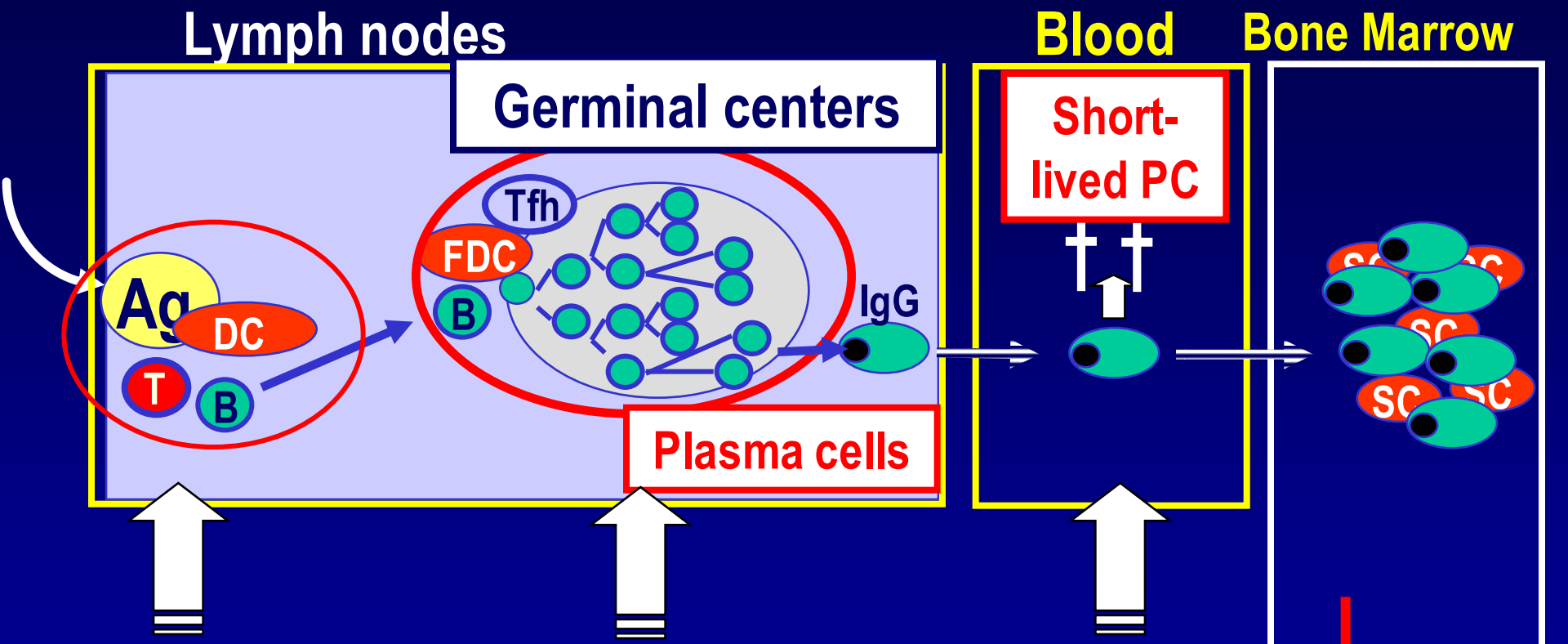
1. Initial early extrafollicular response

2. Higher peak of IgG Ab titers (GCs), ~ 4 wks after immunization.

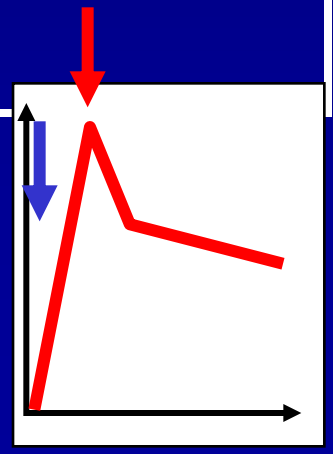
3. Short life span of PCs in spleen / nodes: rapid initial Ab decline.

4. Long-lived PC in the BM: slower decline of Ab titers (years).

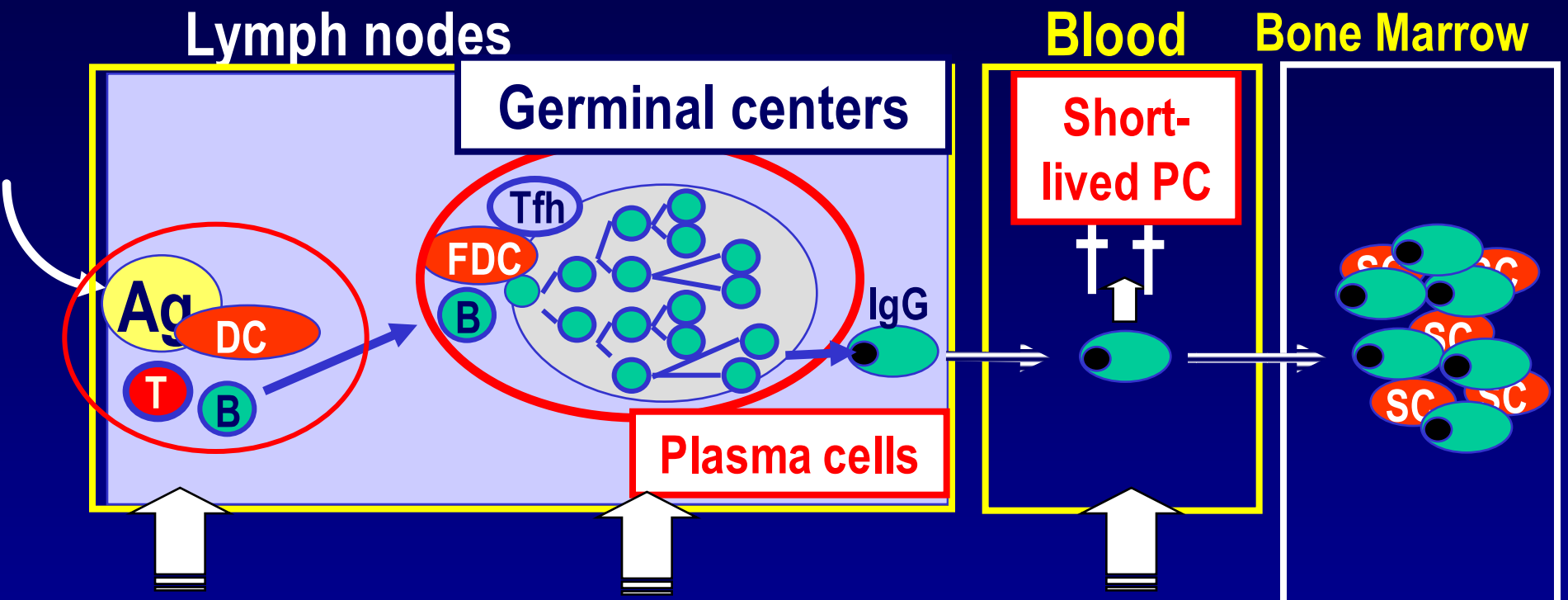
Determinants of peak primary Ab responses



Which are the essential factors that control peak Ab responses / Ab titers ?



Determinants of peak primary Ab responses



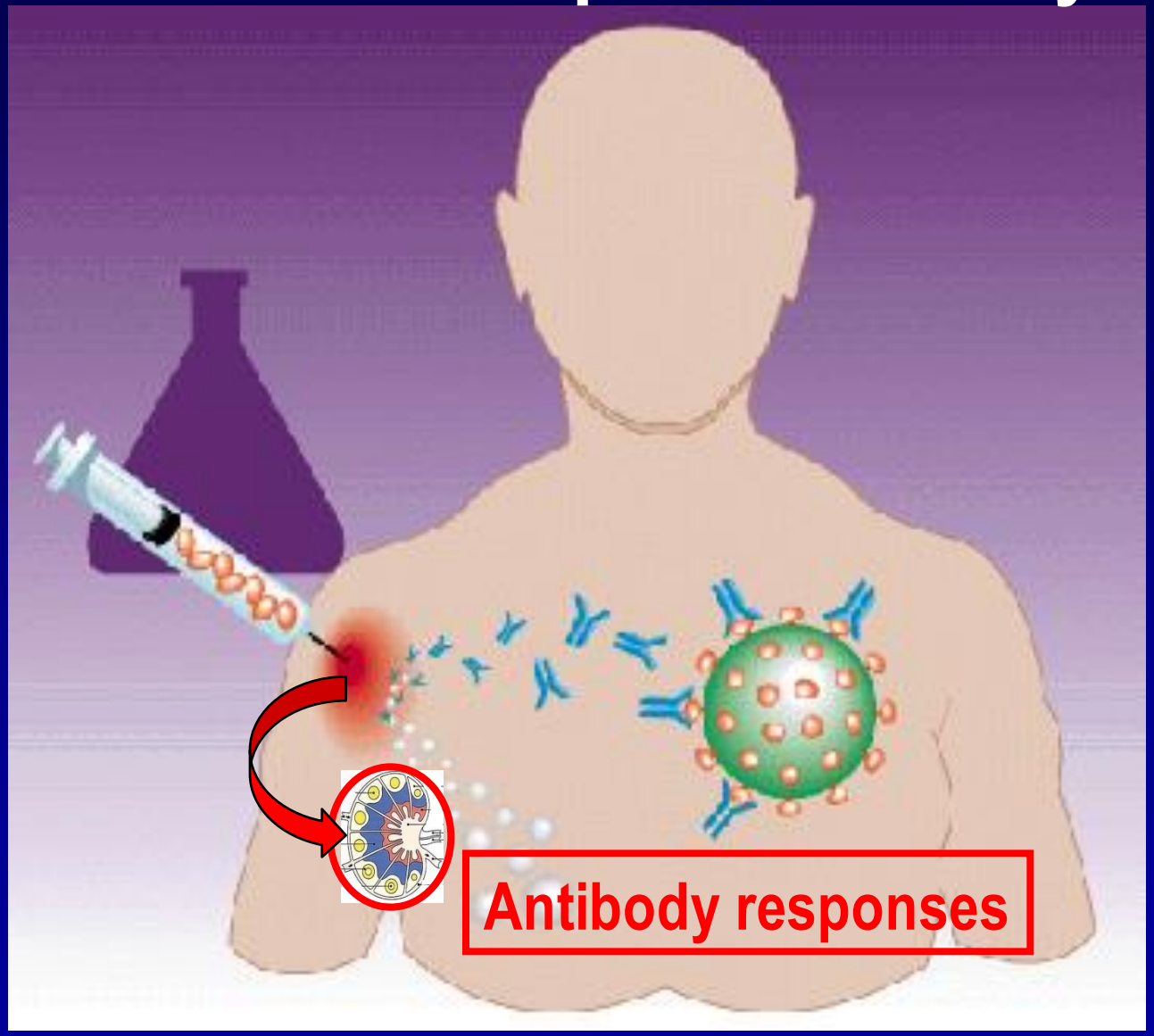
- Antigen nature (epitopes)
- Antigen dose
- B / T cell repertoire
- APCs: activation status
- Tfh cells : control GC responses

Vaccine antigen

Genetics

Innate immunity
PAMPs, adjuvants

How may adjuvants enhance peak antibody responses ?



By increasing :

Ag delivery to B cells

+

DC / Tfh / B cell activation

↓

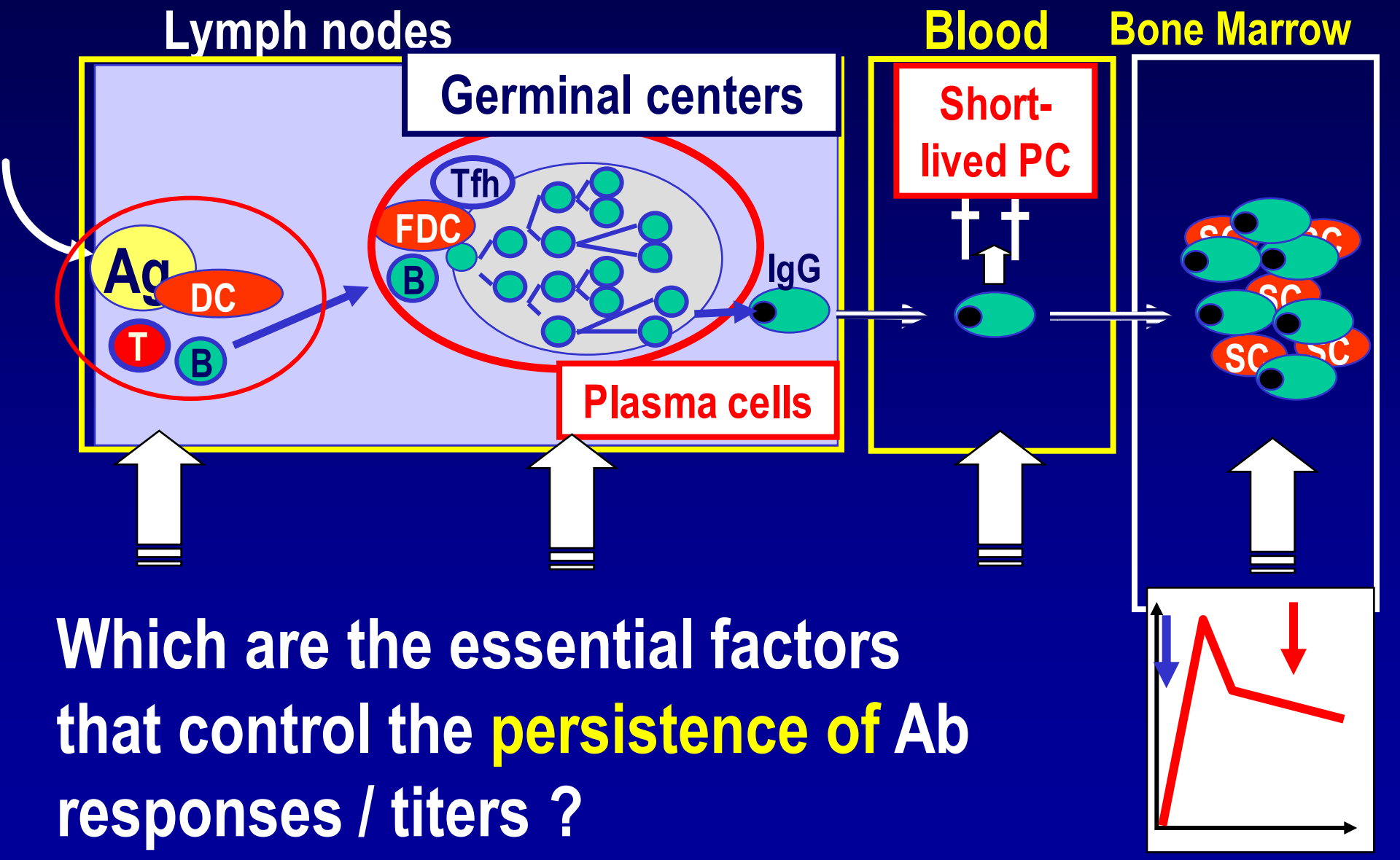
GC responses

↓

Plasma cells

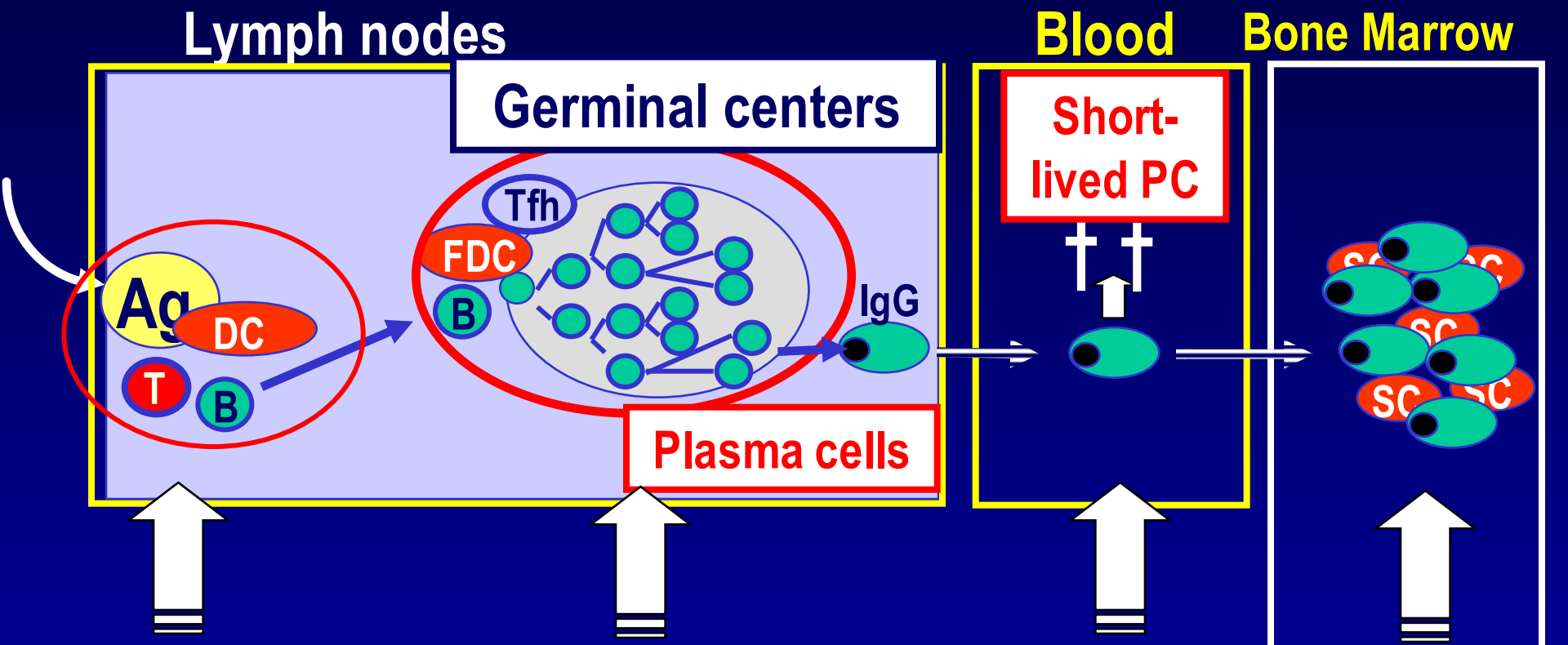
Ab titers

Determinants of the duration of antibody responses to protein-containing vaccines :



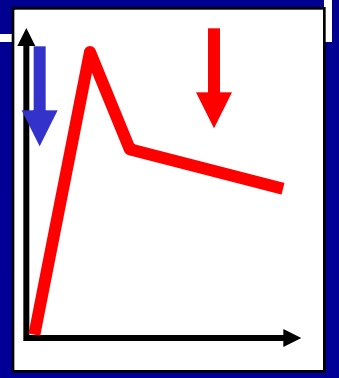
Which are the essential factors that control the persistence of Ab responses / titers ?

Determinants of the duration of antibody responses to protein-containing vaccines :



1. Numbers of long-lived plasma cells

2. PC persistence in BM survival niches



The persistence of HBsAg vaccine antibodies may be predicted based on initial Ab titers

- *Health care workers*
- *3 doses of HBsAg*
- *peak serology after the 3rd dose*
  - *10-99*
  - *100-999*
  - *≥ 1000*

Proportion with HBsAb >10 UI/l with time elapsed after adult immunization

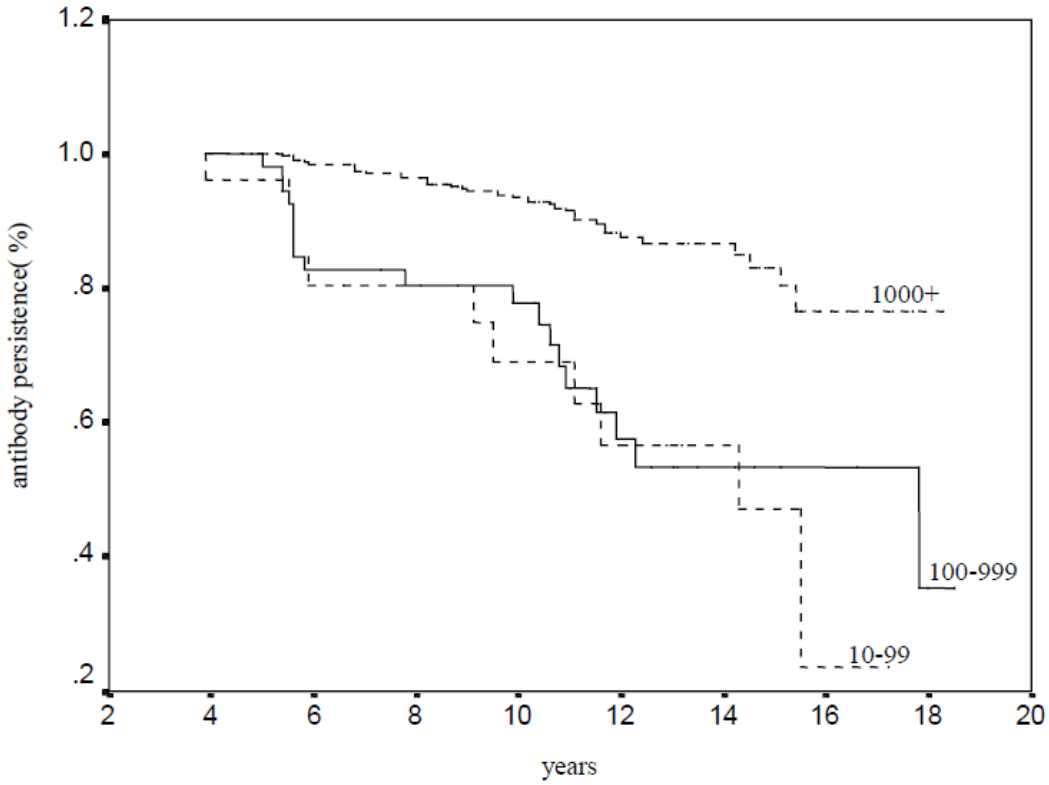
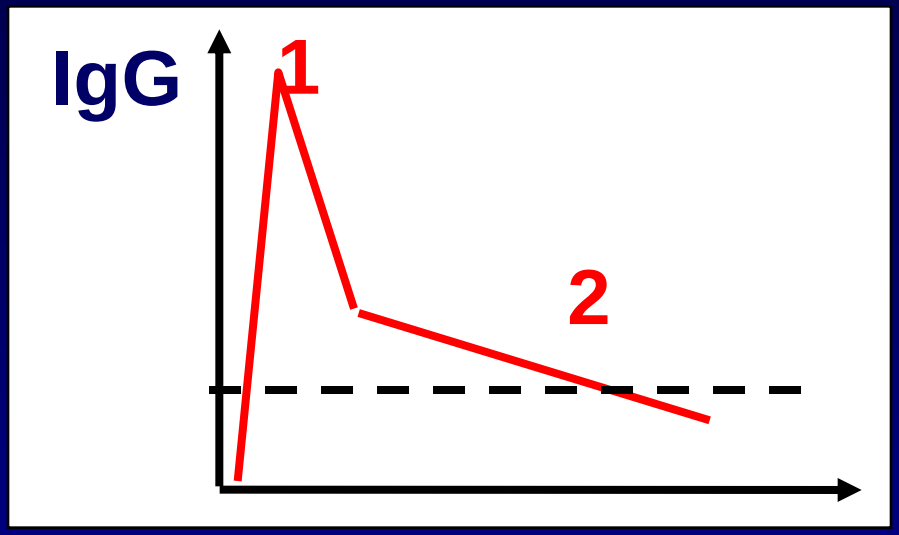


Fig. 2. Anti-HBs persistence according to post-vaccination anti-HBs titers.

A. Floreani et al. / Vaccine 22 (2004) 607–610

Antibodies eventually return to baseline…

How may vaccines confer long term Ab-mediated protection?



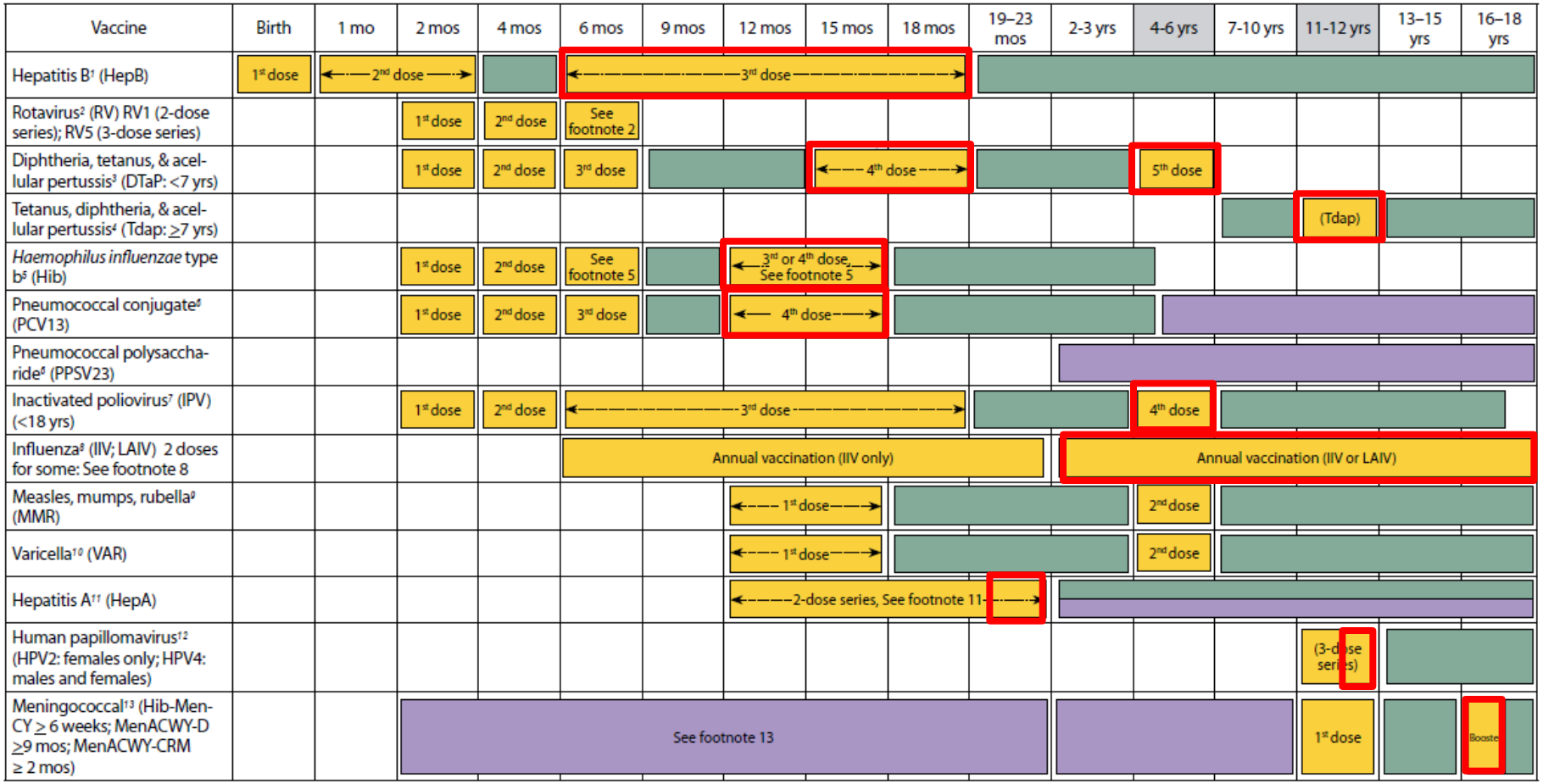
1. Induction of long-lived bone-marrow plasma cells

Reactivation of memory B cells

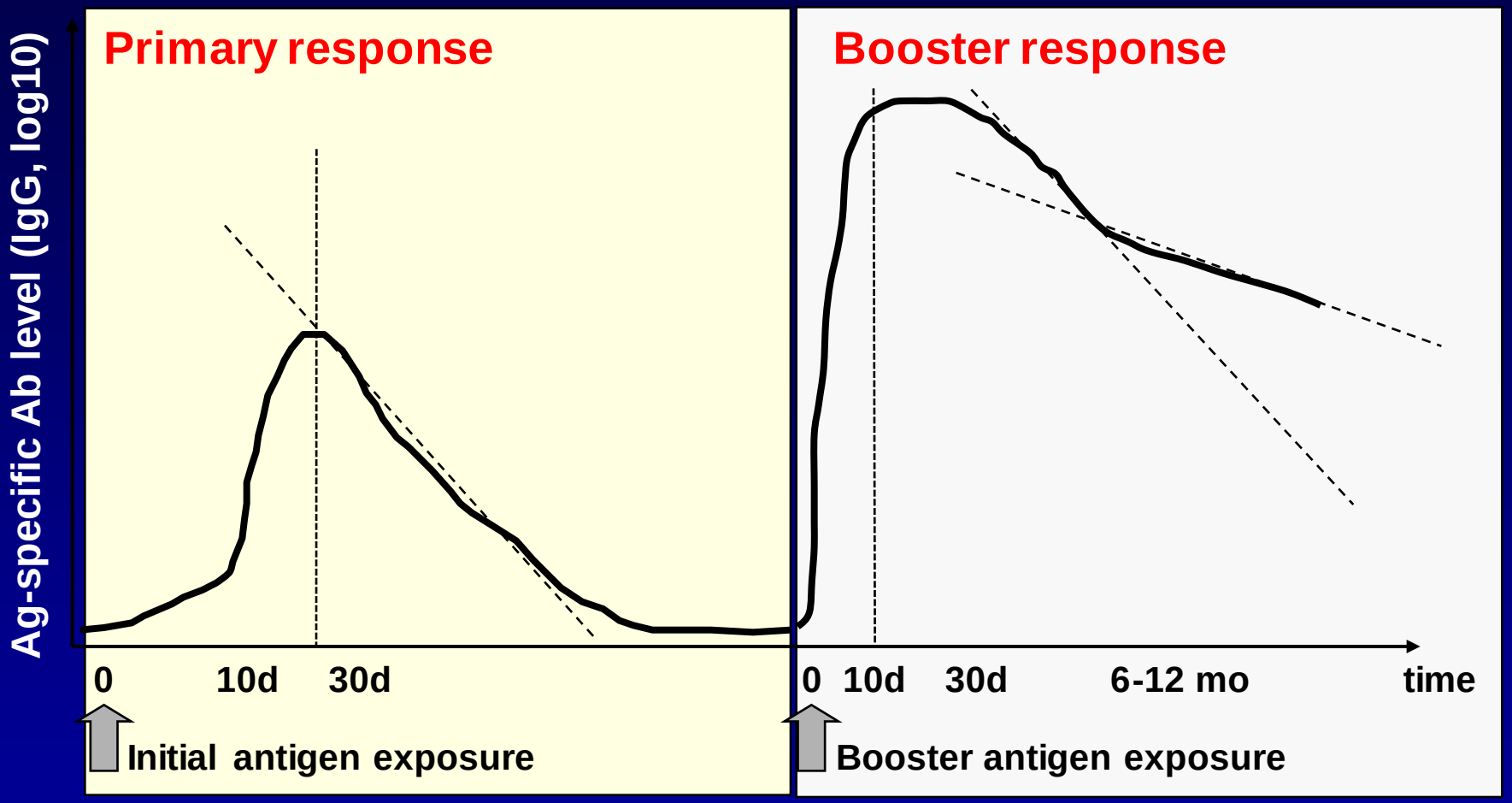
+Ag

Booster doses are recommended to maintain protective antibody titers

Figure 1. Recommended immunization schedule for persons aged 0 through 18 years – United States, 2014.
(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 2]).
These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are in bold.

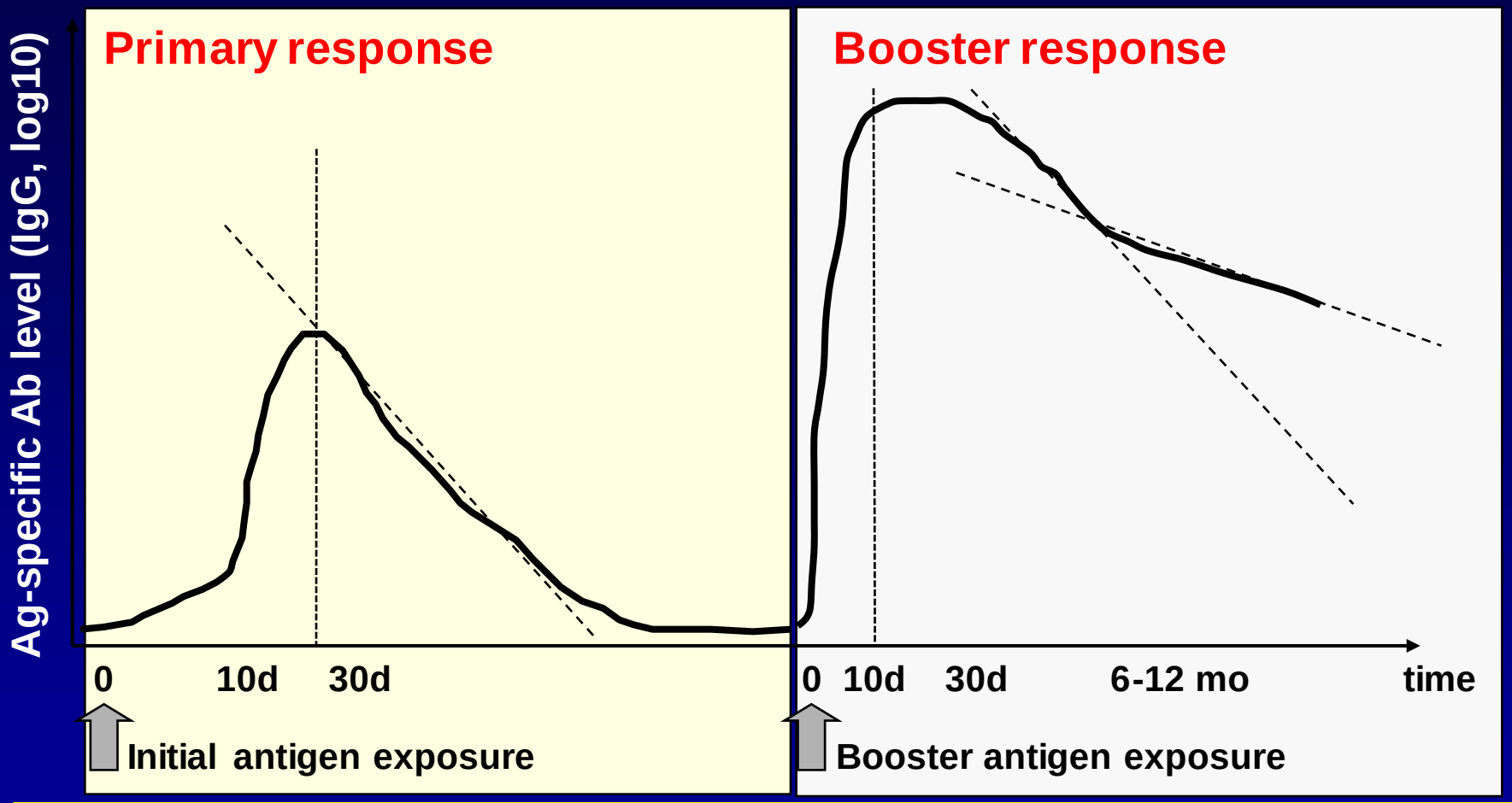


Comparison of primary and booster Ab responses to protein-containing vaccines



Which differences between primary and booster responses ?

Comparison of primary and booster Ab responses to protein-containing vaccines



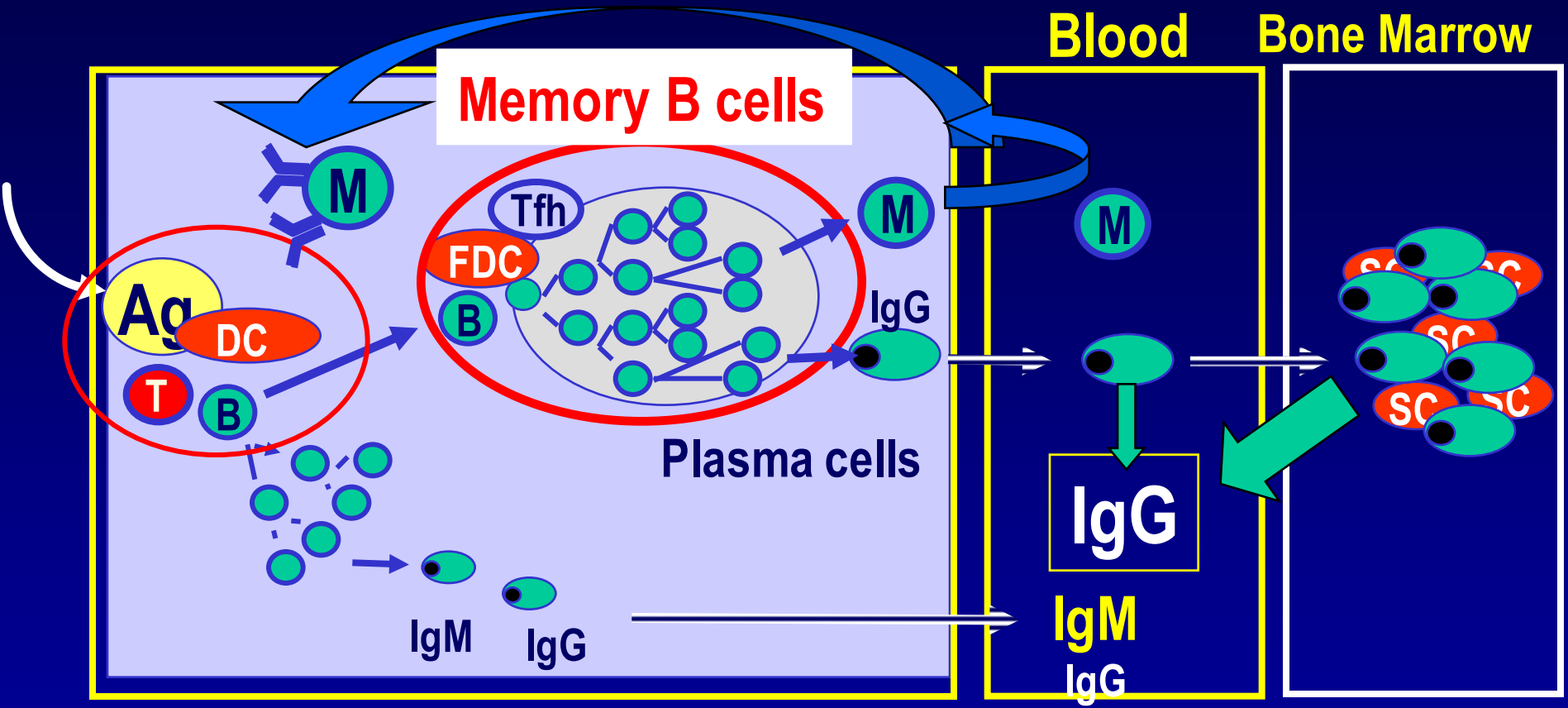
Booster Ab responses are faster (peak ~ at day 7), stronger (Ab titers), more prolonged (years) and of a higher neutralizing capacity (increased affinity).

Which vaccines induce memory ?

Which vaccines induce memory ?

	Induction of memory		
PS vaccines	**0**	**Protein-containing vaccines !**	
Diphtheria	+	Tetanus	+
Pertussis	+	Poliomyelitis	+
Hib	+	Pneumo conj.	+
MenC conj.	+	Influenza	+
Hepatitis A	+	Hepatitis B	+
HPV	+	TBE/FSME	+
MMR	+	VZV	+
Yellow fever	+	Rabies…	+

1- Induction of memory B cells by protein-containing vaccines

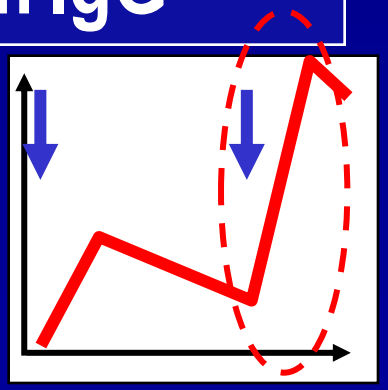


- **Induction in the same Ag-induced Germinal Centers as PCs**
- **Exit of GC, migration through blood – return to the B cell zones of lymph nodes where expect a new Ag encounter**

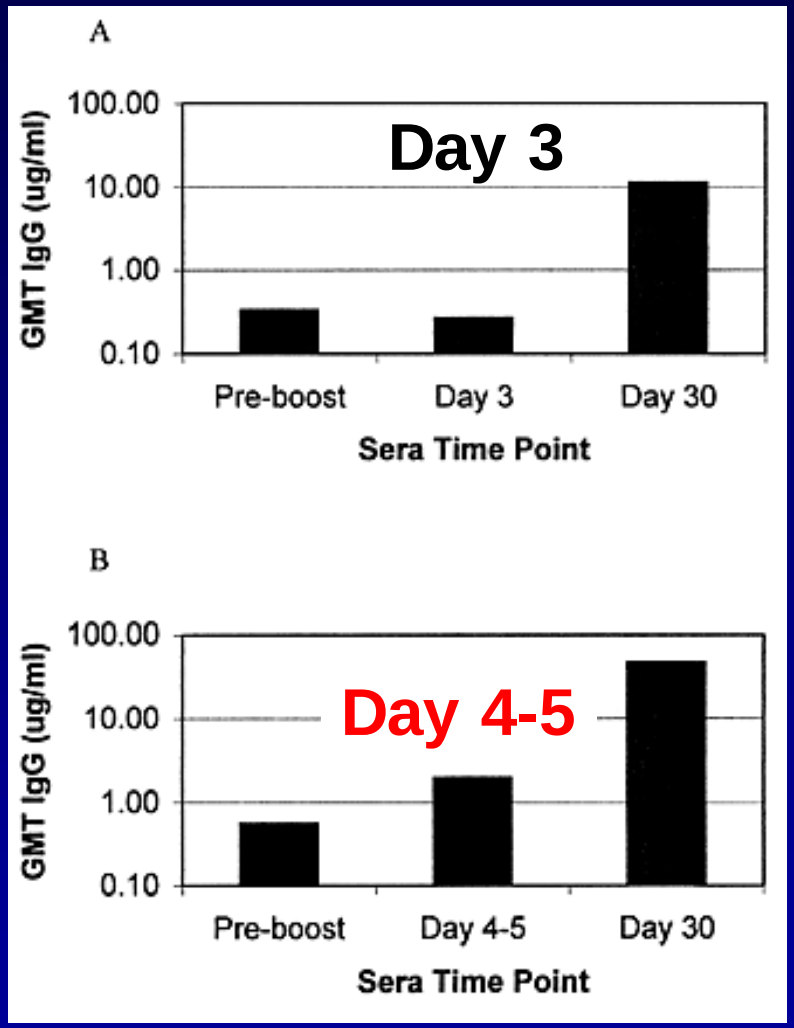
Reactivation of memory B cells upon contact with their specific antigen

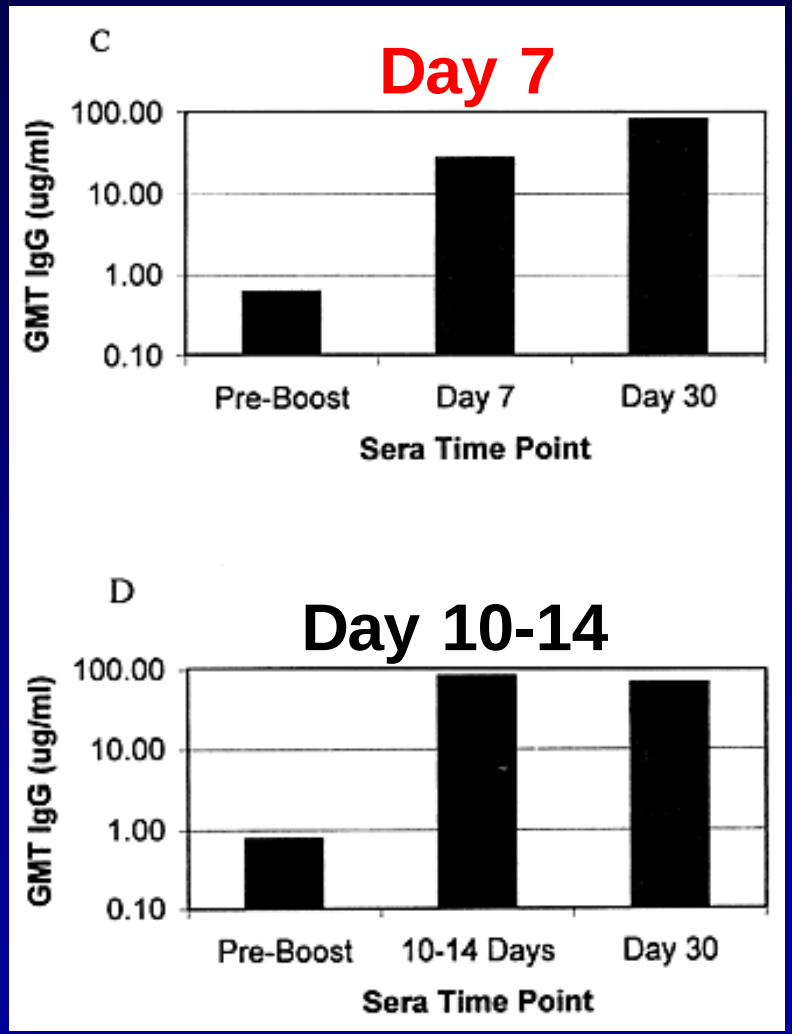
- Ag-specific memory B cells are only reactivated when exposed to their specific Ag :
  - natural microbial exposure **(colonization, infection)**
  - mimicry of microbial exposure **(ex: PS injection)**
  - booster vaccine doses

Kinetics of IgG responses : rapid (~ day 7) and strong increase of serum IgG



Kinetics of HIB responses to PS in children vaccinated as infants with conjugate vaccines



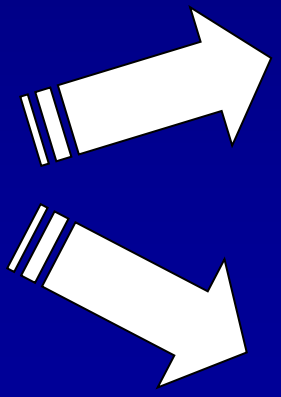


Pichichero M, Ped Inf Dis J 1999

4-7 days necessary ↔ no early protection !

Reactivation of memory B cells upon contact with their specific antigen

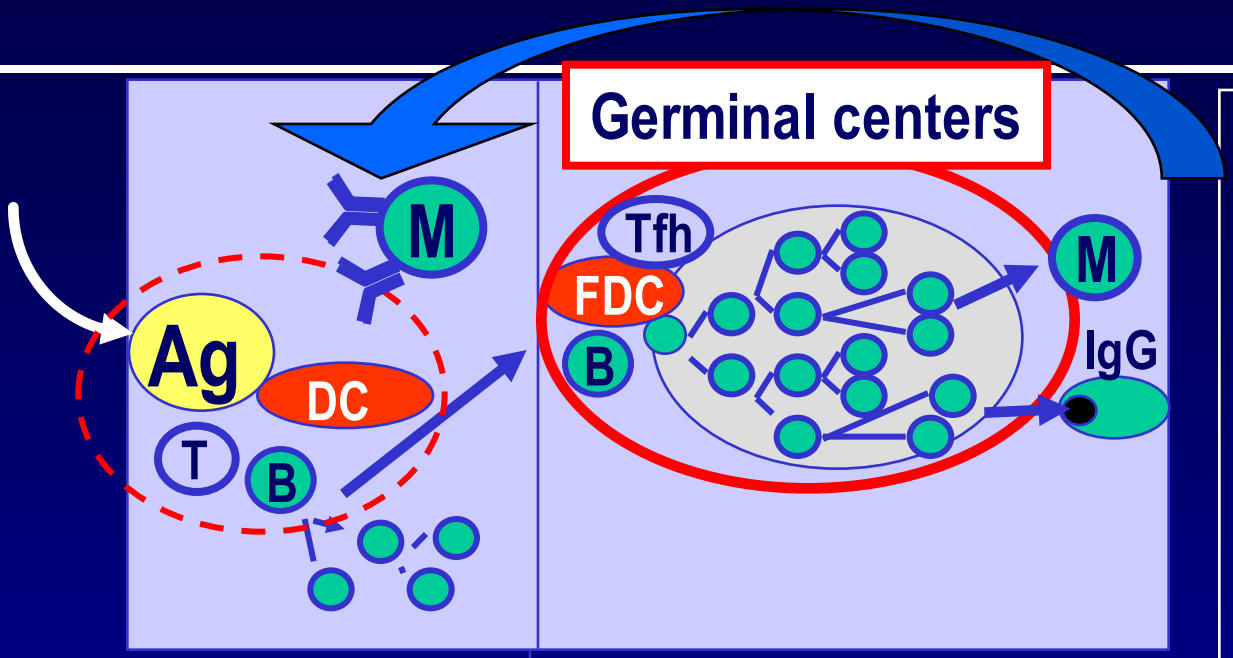
- Ag-specific memory B cells are only reactivated when exposed to their specific Ag :
  - natural microbial exposure **(colonization, infection)**
  - mimicry of microbial exposure **(ex: PS injection)**
  - booster vaccine doses



Kinetics of IgG responses : rapid (~ day 7) and strong increase of serum IgG

Increased Ag-binding capacity of IgG antibodies (higher affinity)

Affinity maturation of antigen-specific B cells

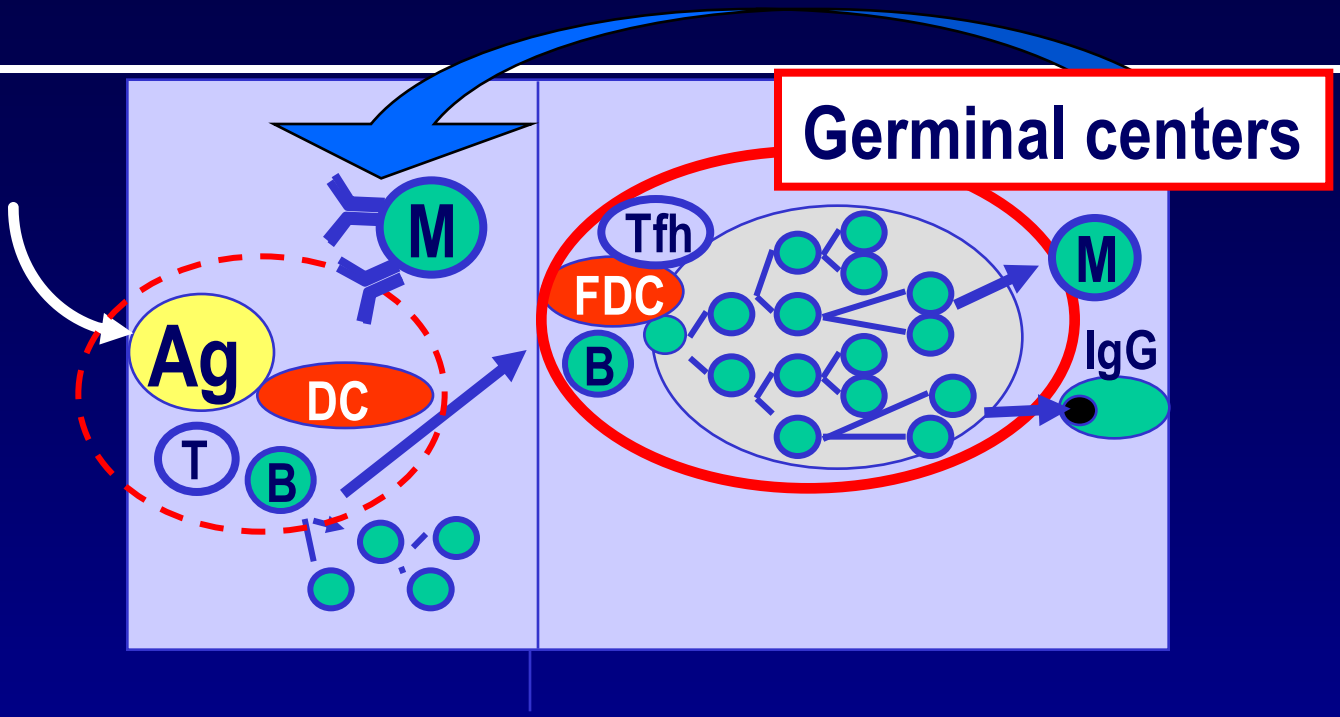


- Memory B cells undergo **affinity maturation during several months**
- This **increases the affinity for Ag** of their surface IgG
- **When reactivated, mB cells** thus produce **antibodies of higher affinity** – e.g. higher NT capacity

1. **Random mutations in B cell Ig genes:**
   - most deleterious
   - a few conferring better Ag binding capacity
2. **Limited availability of Ag : competition among B cells for Ag binding !**
3. **FDC survival signals** only to Ag-bound B cells

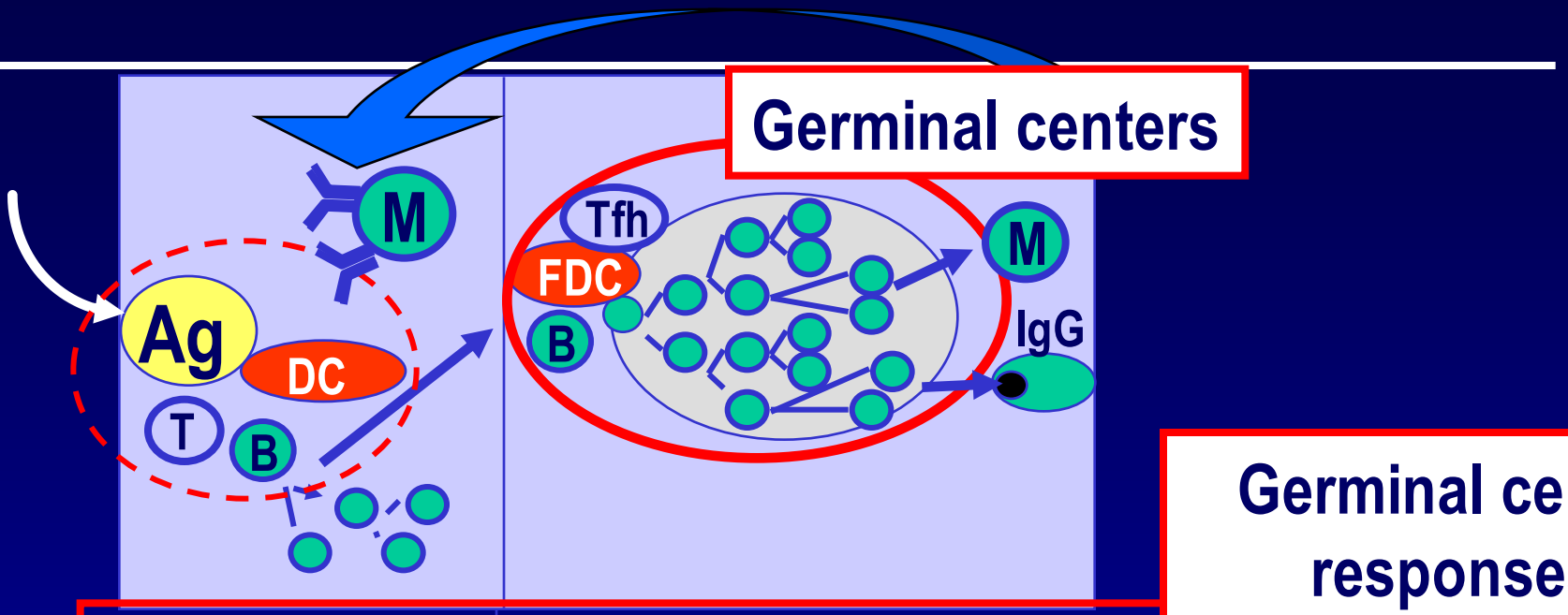
SURVIVAL OF THE FITTEST !

Induction and magnitude of memory responses



Which are the essential factors that control the induction and magnitude of memory responses ?

Induction and magnitude of memory responses



Germinal center responses

- Antigen nature (epitopes)
- Antigen dose
- B / T cell repertoire
- DC : state of activation
- Tfh cells : control GC responses

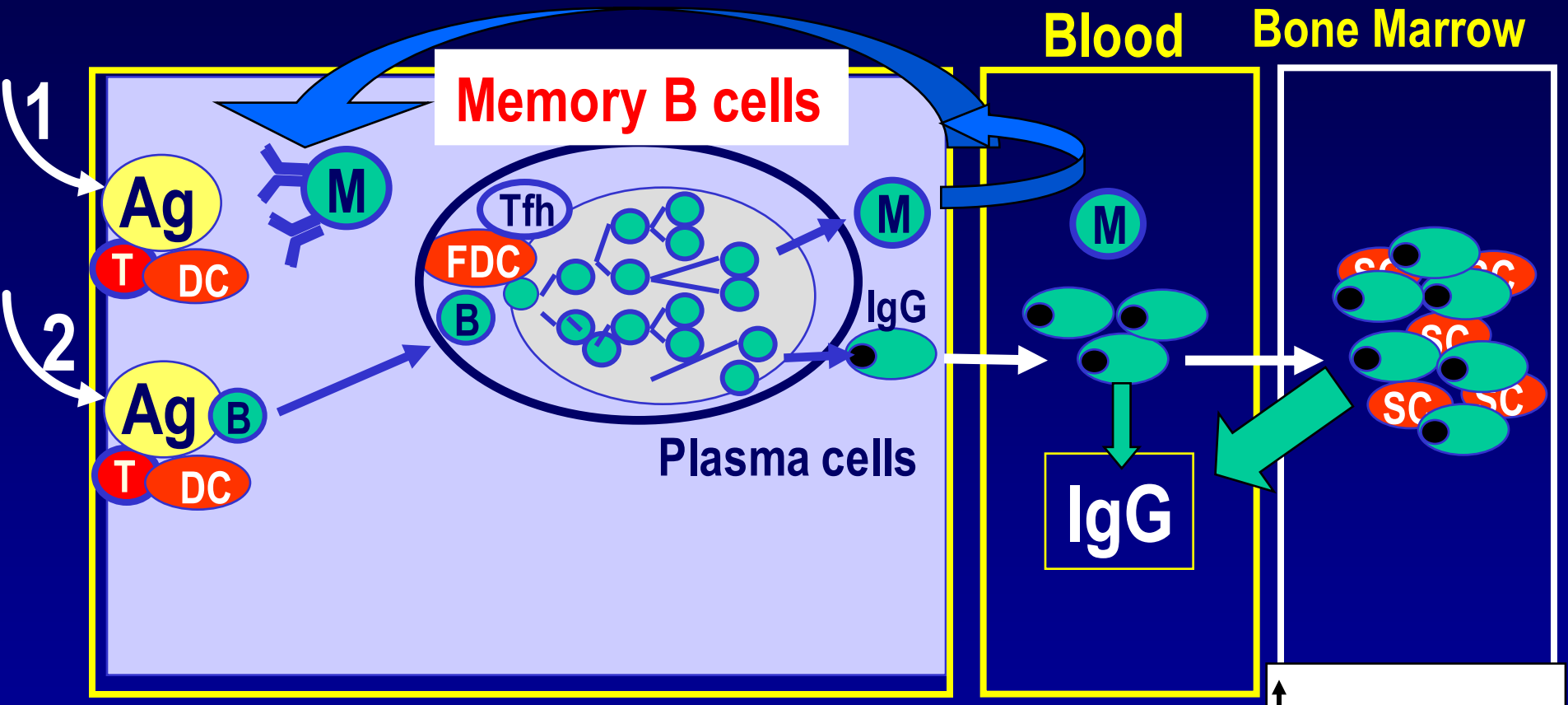
Vaccine antigen

Genetics

Innate immunity
PAMPs, adjuvants

+ vaccine schedule (↔ time for affinity maturation)!

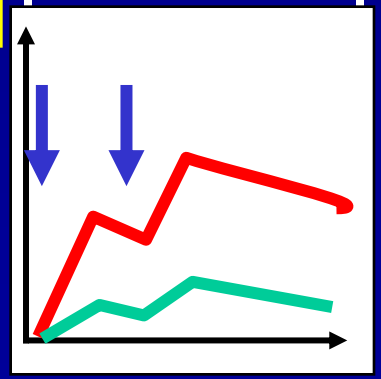
Influence of the vaccine schedule on the reactivation of memory responses



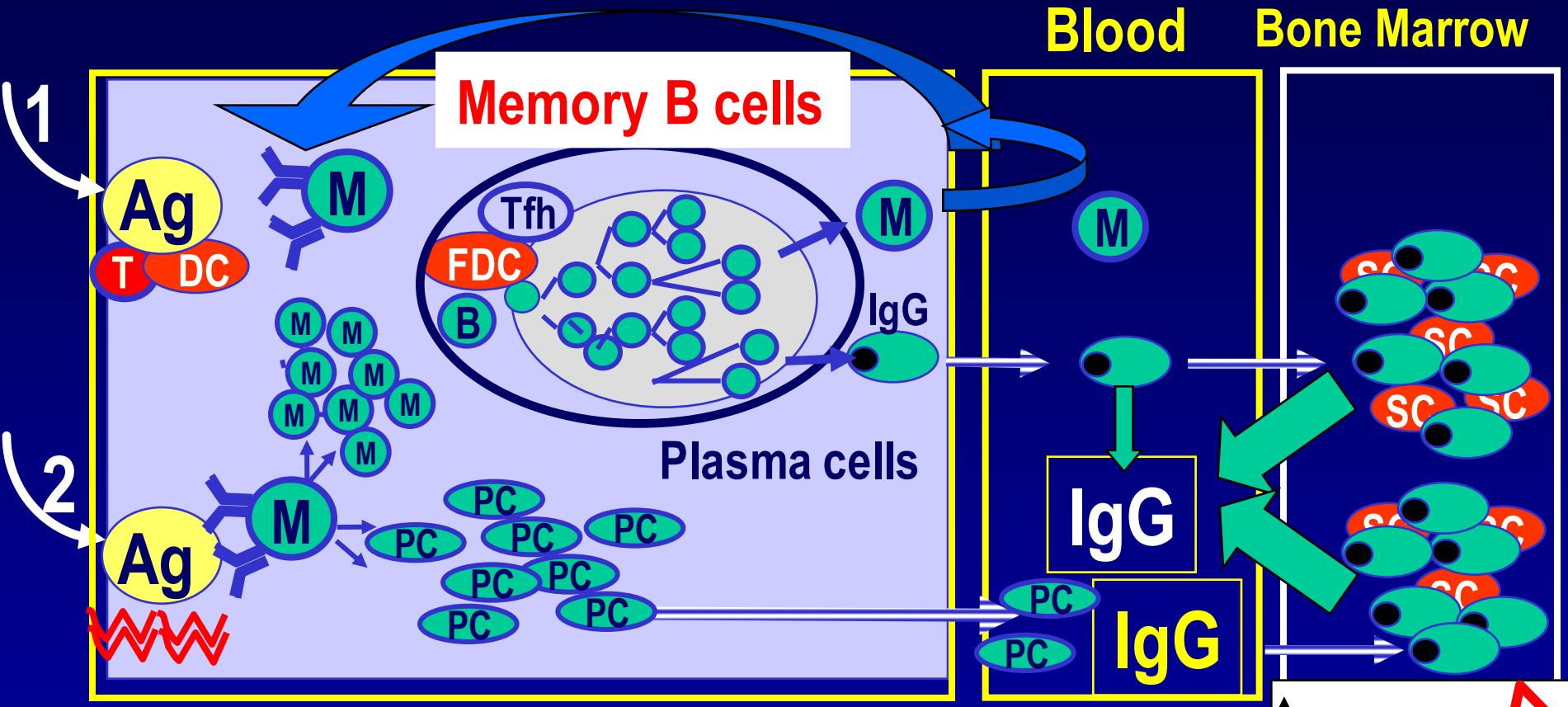
- **Short interval (weeks) btwn 2 doses:**

→ **2nd wave of primary responses…**

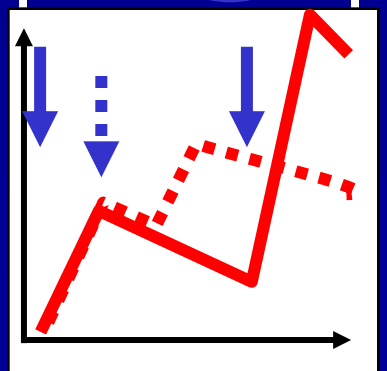
(memory B cells, plasma cells)



Influence of the vaccine schedule on the reactivation of memory responses



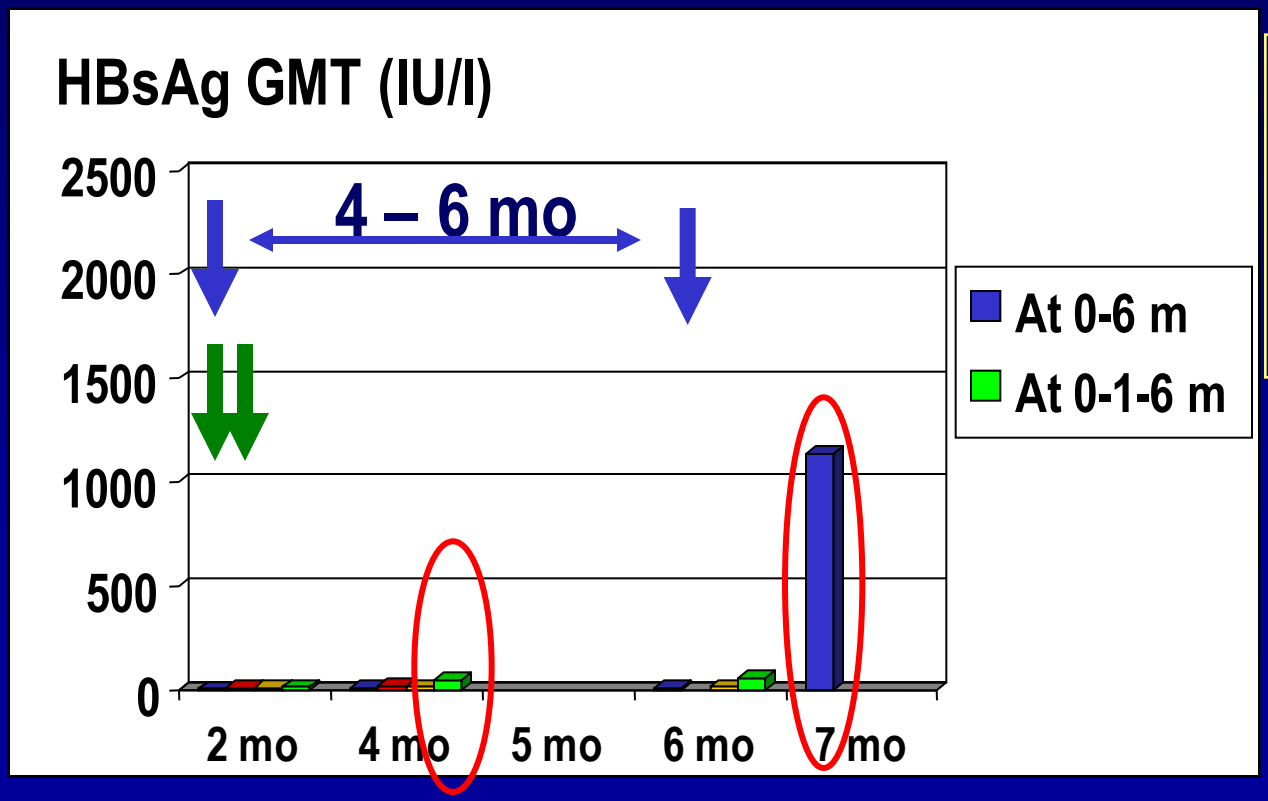
- **Long interval (≥4 months) btwn 2 doses:**
  → affinity maturation of memory B cells – enhanced capacity to respond to Ag !



Influence of vaccine schedules on booster responses

Adolescents randomized to receive **5µg of Recombivax HB®** at a 0-6 months or a 0-1-6 months interval

(Cassidy WM, Pediatrics 2001)



1 month between two doses of HBV vaccine: **WEAK responses to the 2nd dose of HBsAg !**

≥ 4 months btwn two doses ↔ **booster** response to the 2nd dose !

Influence of vaccine schedules on booster responses

- Cervarix® (HPV, GSK)
- 3 doses (0-1-6 mo) @ 15-25 years

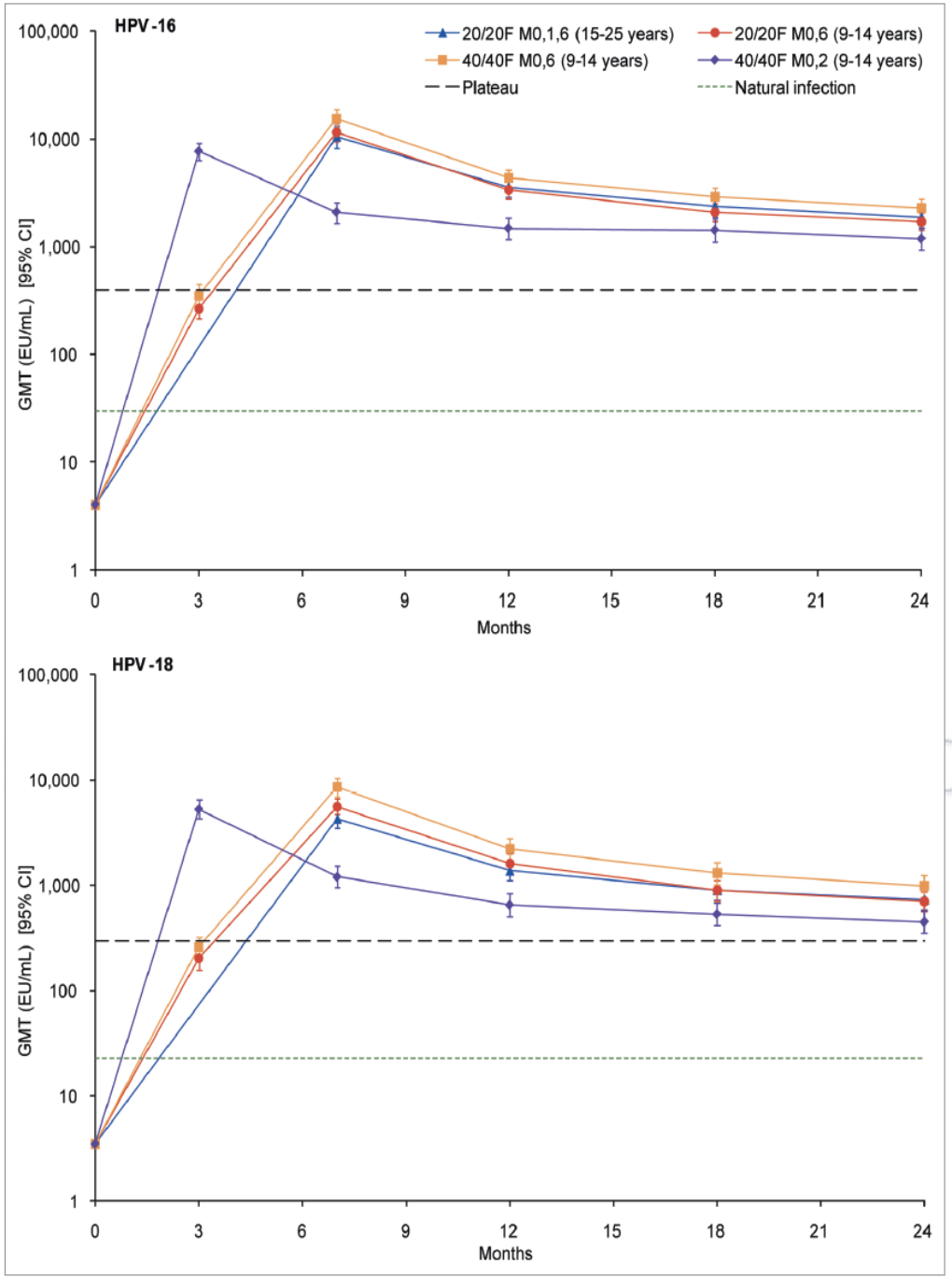
=

- 2 doses (0-6 mo) @ 9-14y

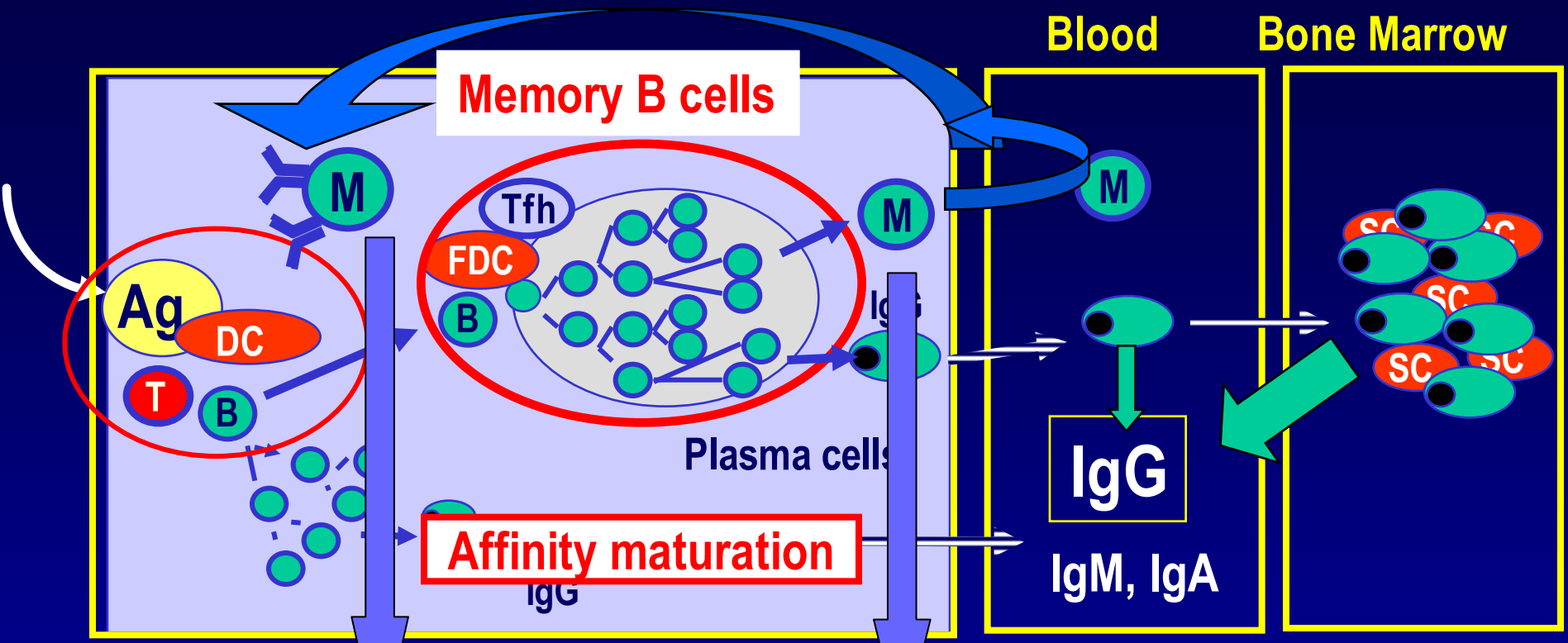
>>>

- 2 double doses (0-2 mo) @ 9-14y

(Romanovski B., Human Vaccines 2011)



0 -1- 6 : the “classical” immunization schedule !



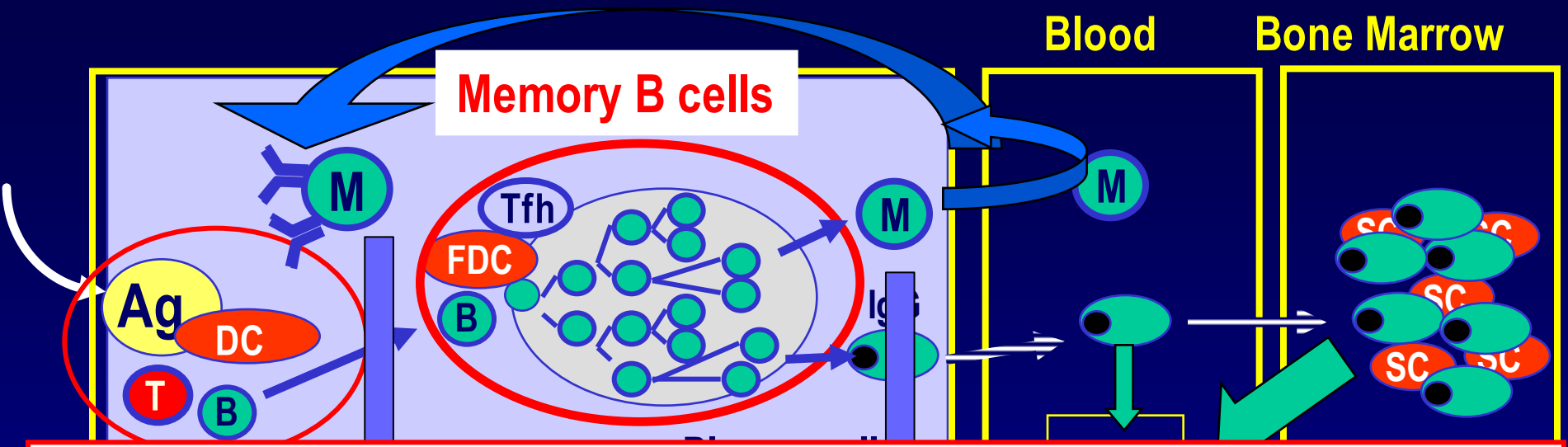
1(-2) doses for priming

Affinity maturation and clonal selection of the fittest B cells

1 booster dose to reactivate memory cells

≥ *4 months*

0 -1- 6 : the “classical” immunization schedule !



- When may vaccines be used with a 2-dose schedule ?
- Why does the EPI schedule include 3 primary doses ?
- Why is a 4th dose needed for accelerated schedules ?

1(-2) doses for priming

Affinity maturation and clonal selection of the fittest B cells

1 booster dose to reactivate memory cells

≥ *4 months*

Which B cell responses may be assessed in vaccine studies ?

Quantification

Ag-specific IgG/M/A

- ELISA, Ag-binding assay
- Western Blot
- Immunoprecipitation

Ag-specific B cells

- FACS analyses
- ELISPOTs for Ab-secreting plasma cells
- ELISPOTs (+ Ag) for reactivated memory cells

Function

Ag-specific IgG/M/A

- Serum neutralization titers
- Serum bactericidal activity
- Opsonophagocytosis
- Hemagglutination inhibition (flu)
- Avidity index

Which B cell responses should be assessed in vaccine studies ?

Quantification

Ag-specific IgG/M/A

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Ag-specific B cells

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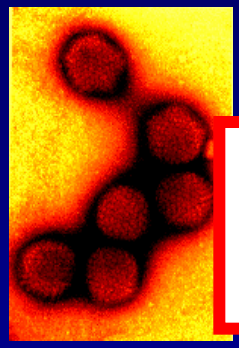
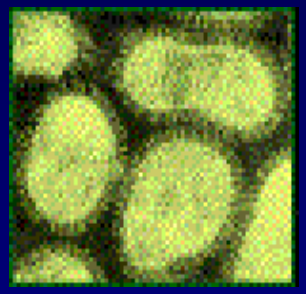
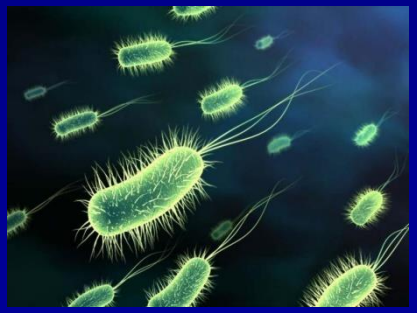




Pathogen specific !



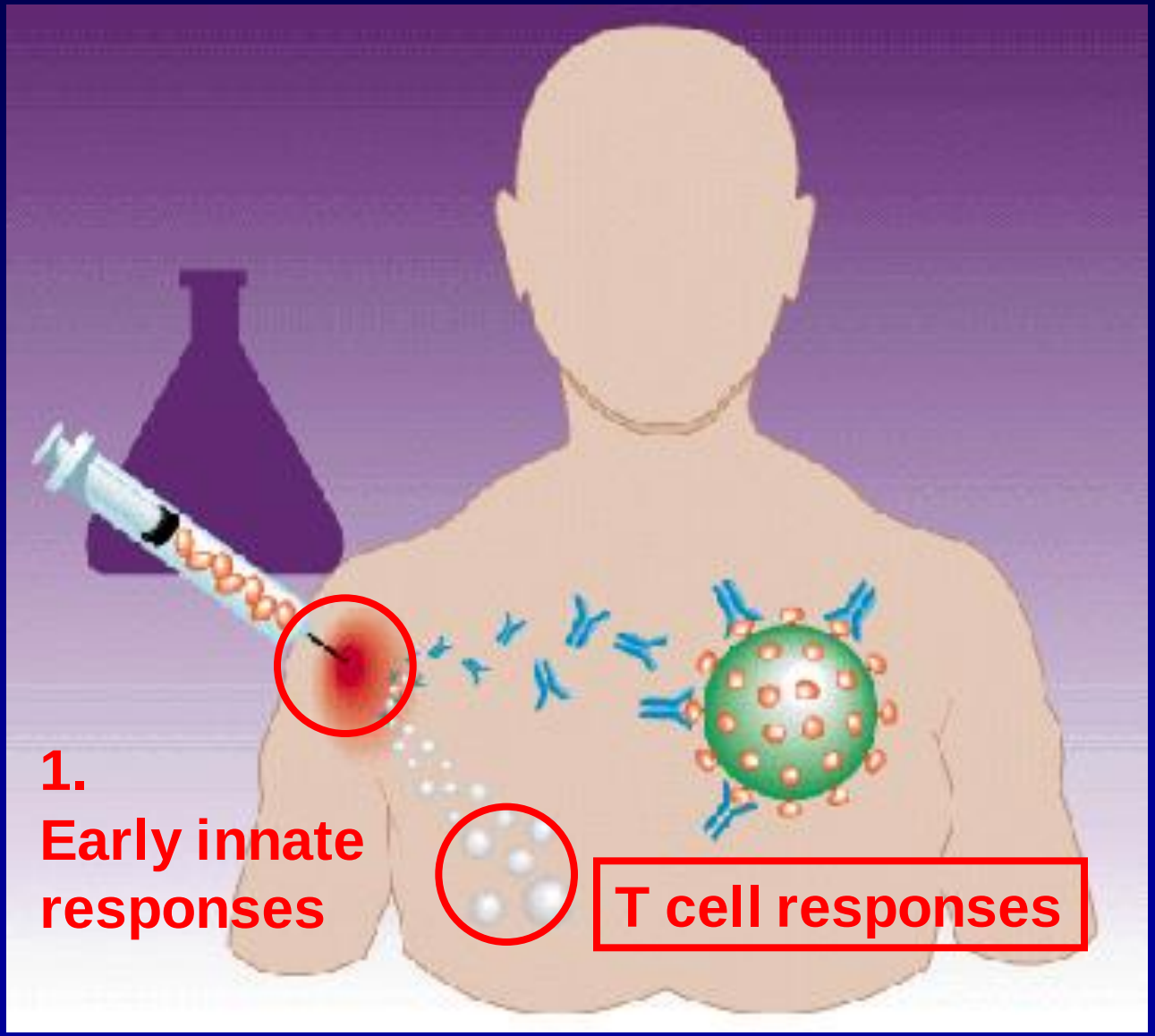
Function

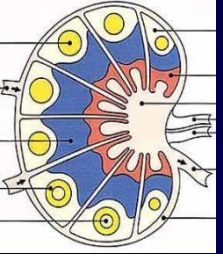
Ag-specific IgG/M/A

- Serum neutralization titers
- Serum bactericidal activity
- Opsonophagocytosis
- Hemagglutination inhibition (flu)

Correlates of protection!

How do vaccine induce protection ?





How do vaccine induce protection ?

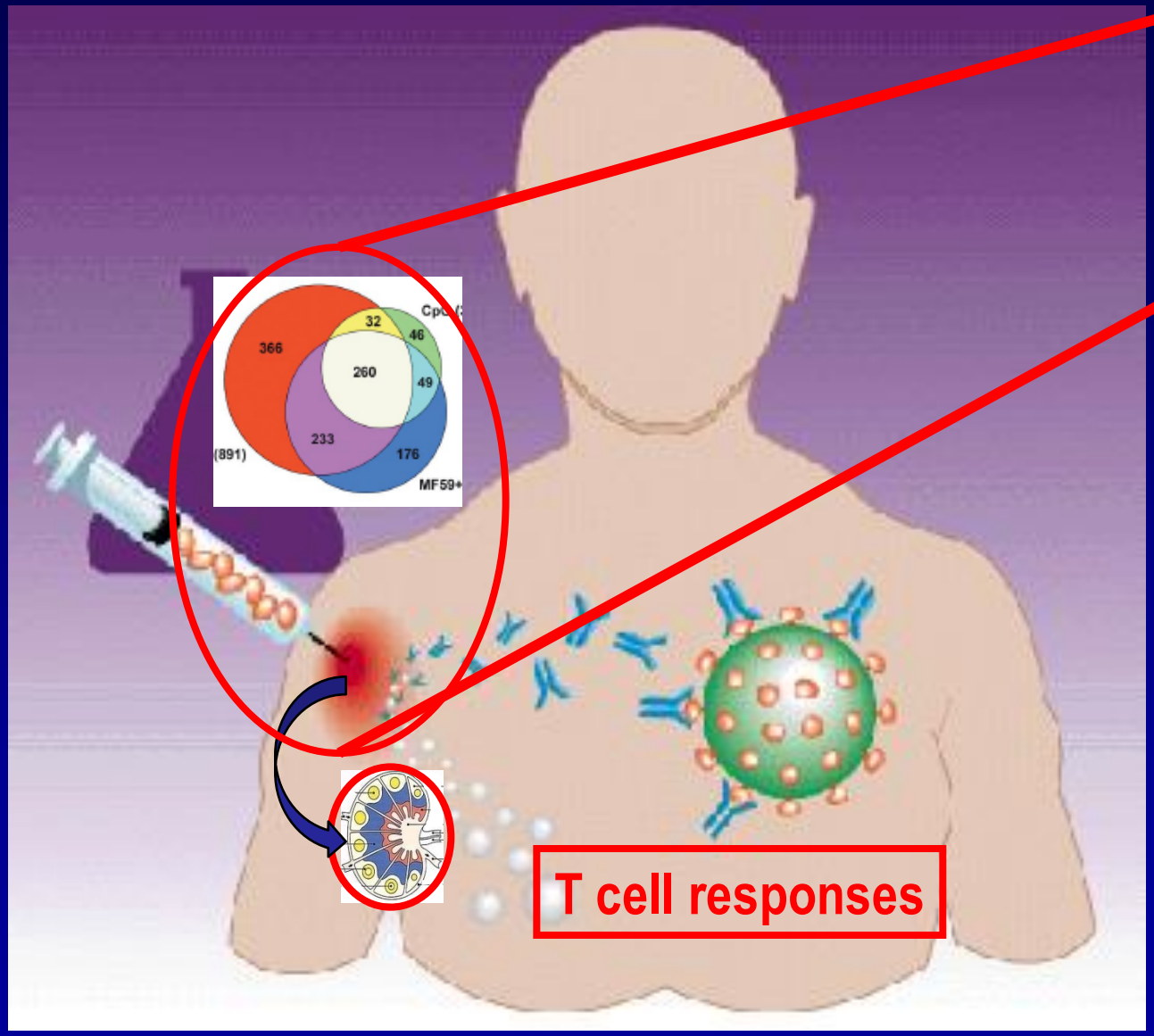
2. Vaccine-specific CD4 T cells do not prevent infection but participate in pathogen reduction, control and clearance by:

- Supporting antibody responses *(T-dep. antigens)*
- Producing cytokine / cytolytic activities :
  - IFN-γ, TNF-α/TNF-β, IL-2… (Th1 cells)
  - IL-4, IL-5, IL-14, IL-6, IL-10… (Th2 cells)
  - IL-17, IL-21, IL-22… (Th17 cells)

⇨ ***Clearance of intra- and extracellular pathogens***

Essential role for T cells in BCG, in pertussis (after Ab waning), in specific future vaccines (Mtb)…

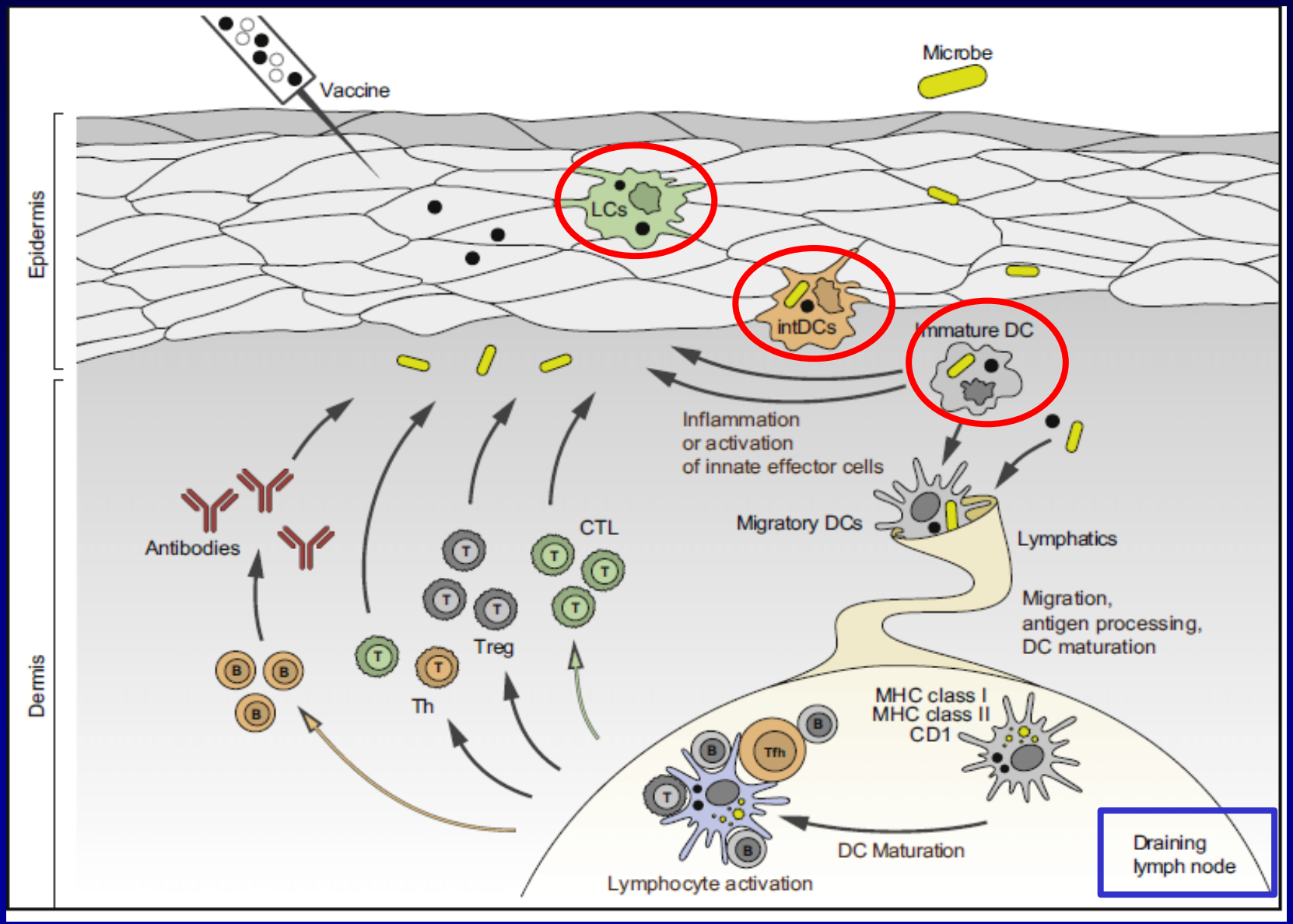
How do we expect vaccines to elicit potent specific T cell responses ?



Injection-site innate activation

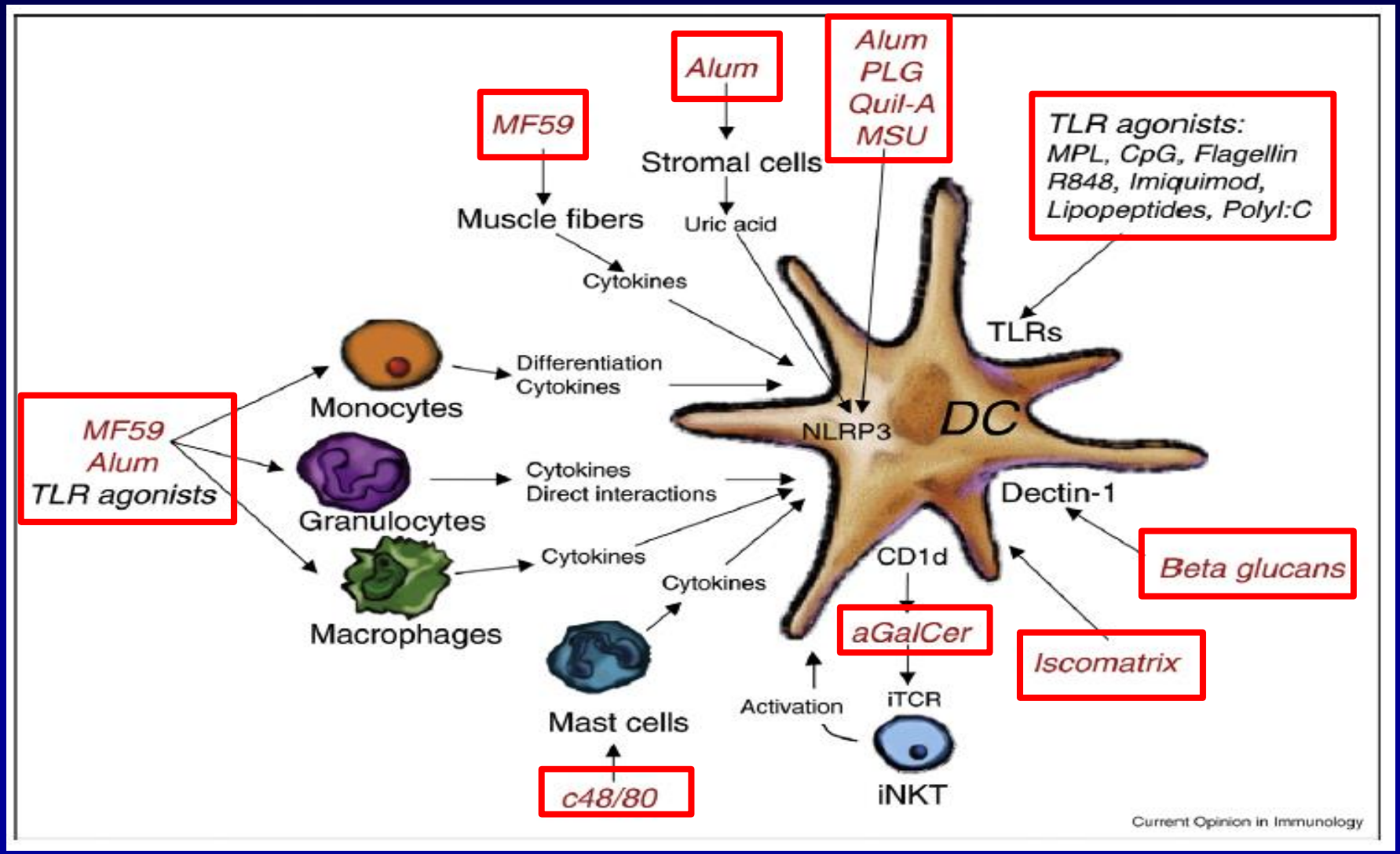
Recruitment and activation of professional APCs (DCs)

How do vaccines induce specific T cells ?



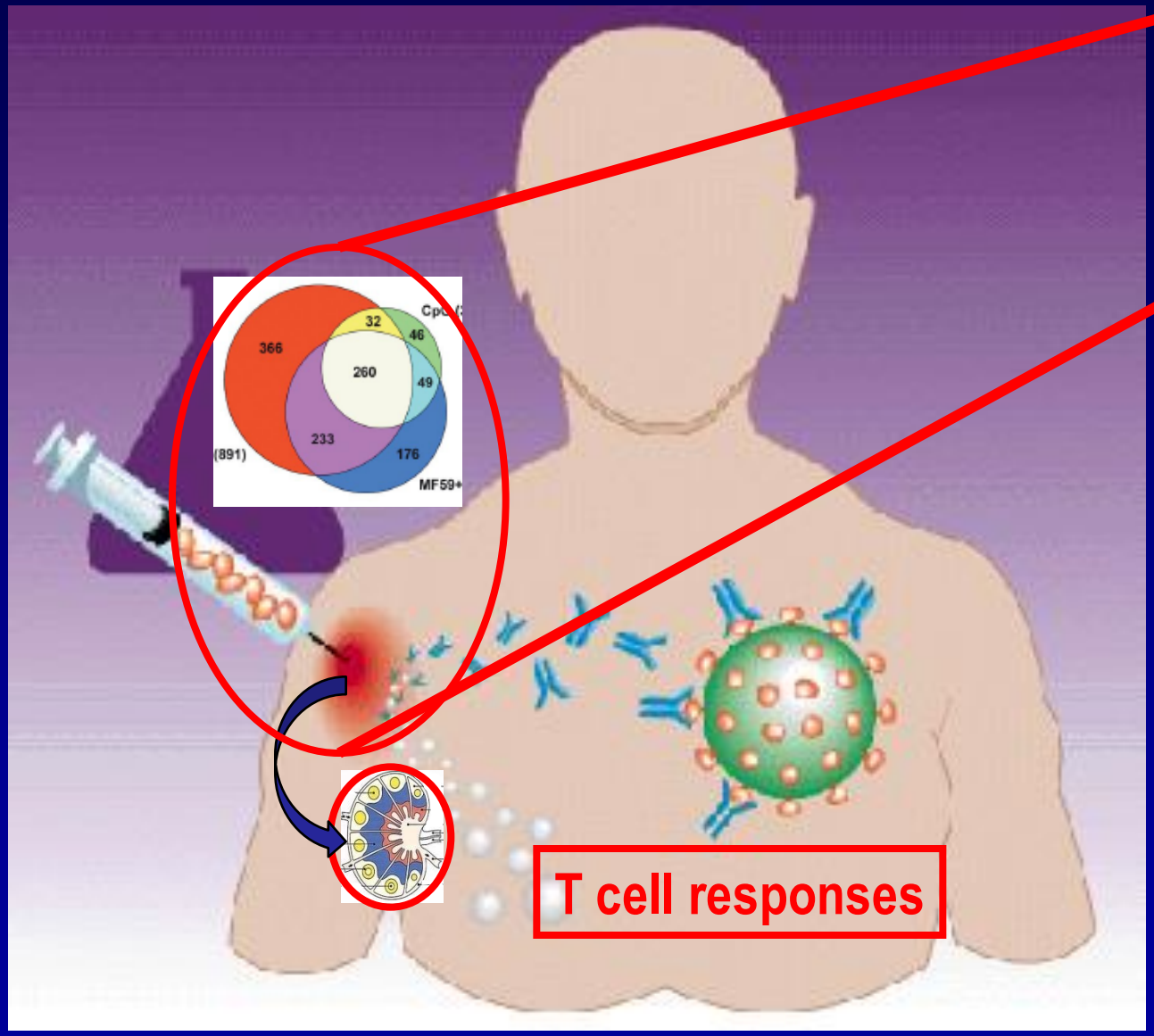
Karolina Palucka, Immunity *33*, October 29, 2010

“Danger signals” / adjuvants activate dendritic cells directly or indirectly



De Gregorio E, Current Opin Immunol 2009;21:339

How do we expect vaccines to elicit potent specific T cell responses ?



Injection-site innate activation

Recruitment and activation of professional APCs (DCs)

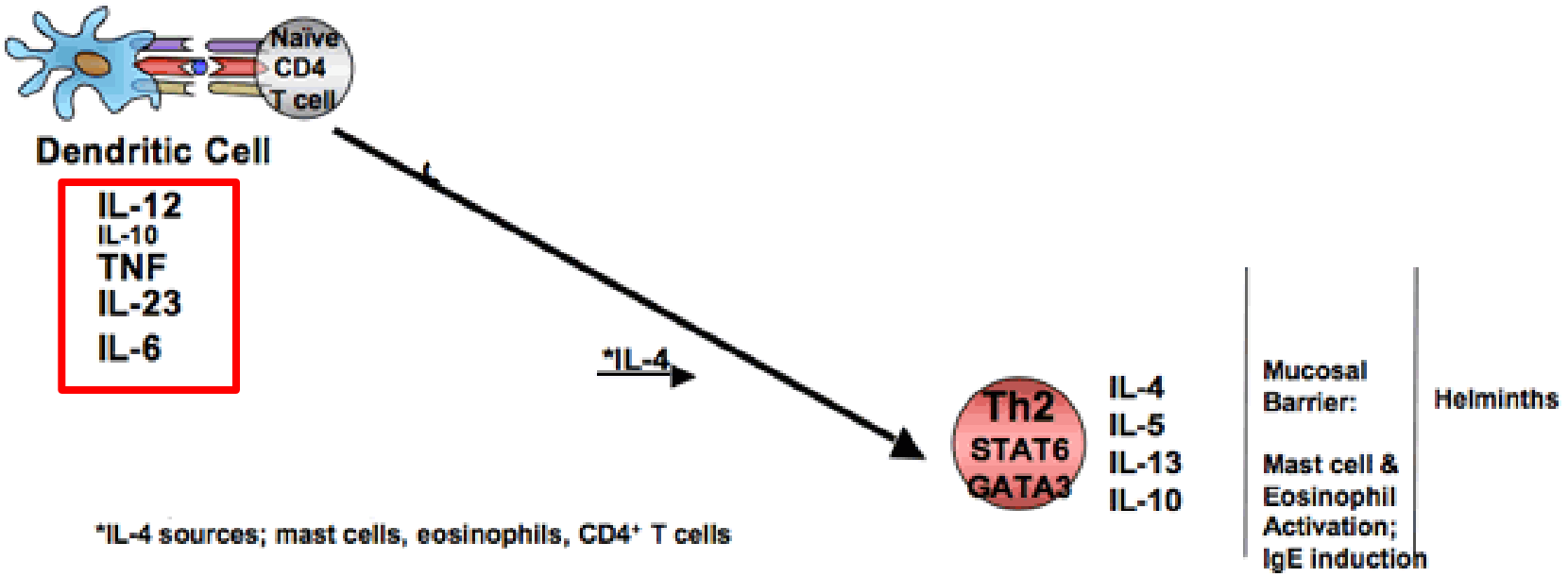
↑ Migration

Draining LN

Ag-specific polarized T cells

How do vaccines induce specific T cells ?

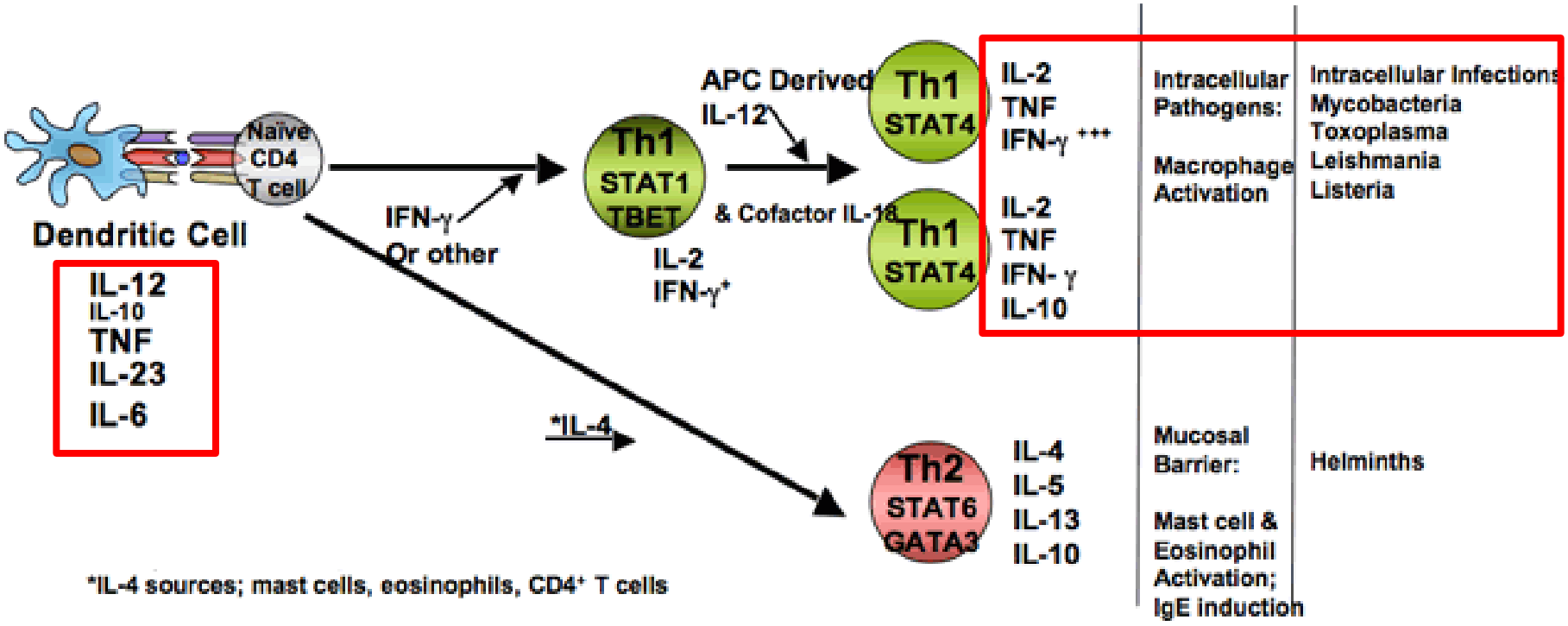
1. In the absence of specific danger signals, activated DC induce naïve CD4⁺ T cells towards T helper 2 → IgE, IgG



How do vaccines induce specific T cells ?

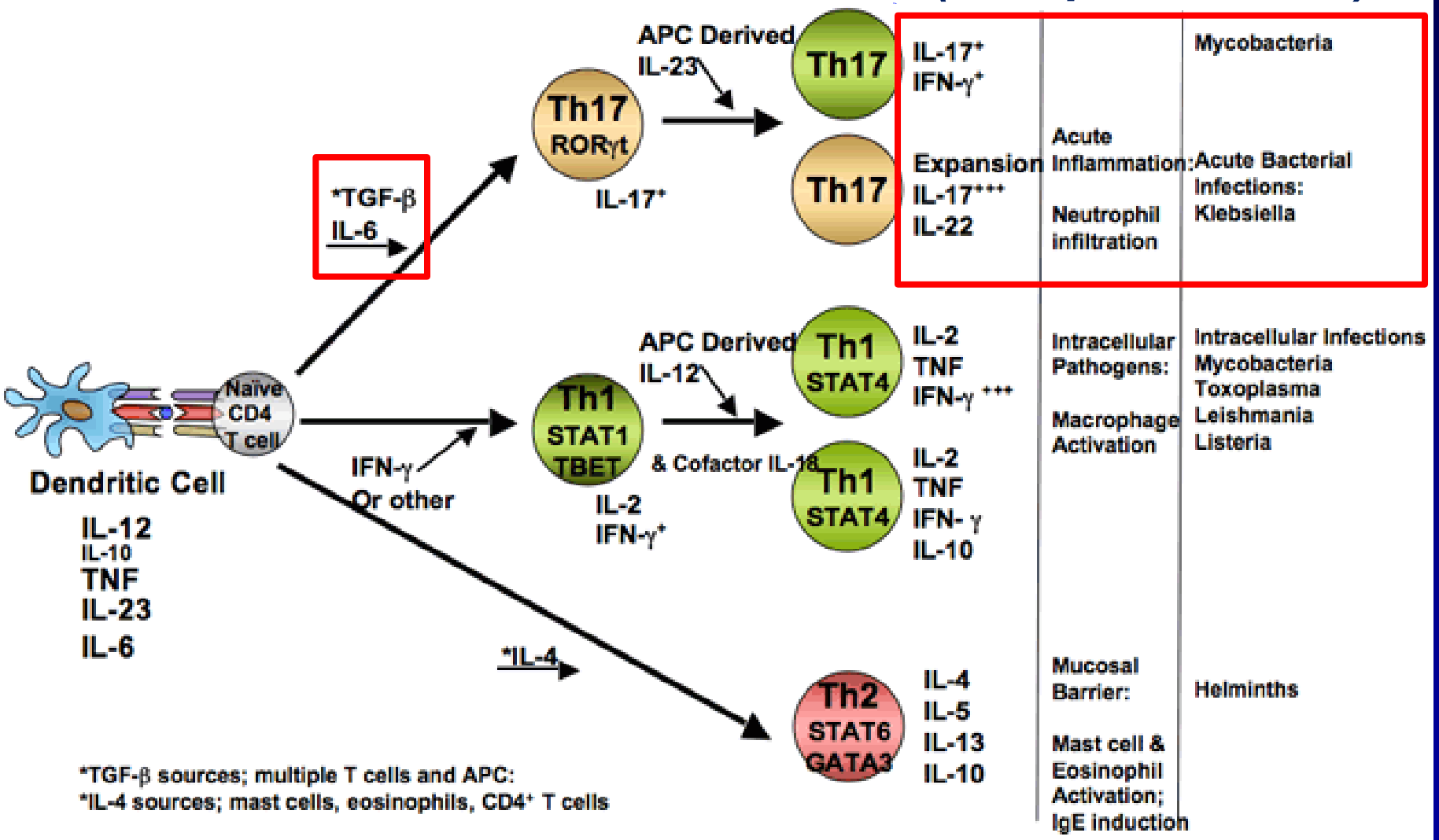
1. In the absence of specific danger signals, activated DC induce naïve CD4⁺ T cells towards T helper 2 → IgE, IgG

2. In the presence of inflammatory signals, naïve CD4⁺ T cells differentiate towards Th1 cells → IL2, TNF, IFN-γ



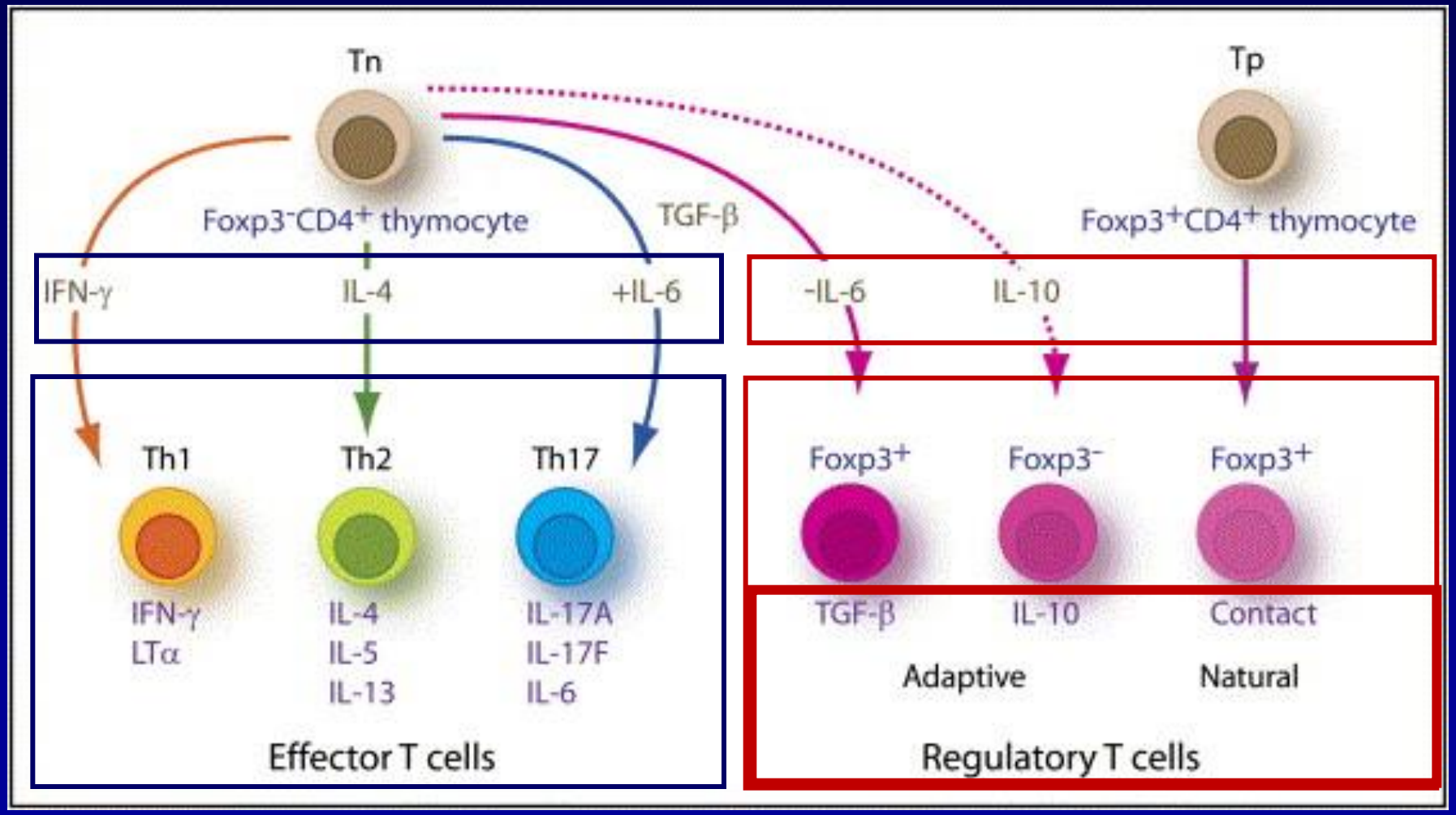
How do vaccines induce specific T cells ?

3. IL-6 / TGF-β induceTh17 cells with a major role in tissue inflammation and on mucosal surfaces *(Mtb, pertussis,…)*



$CD4^+$ T cells may also differentiate into regulatory T cells - which inhibit T cell proliferation / activation

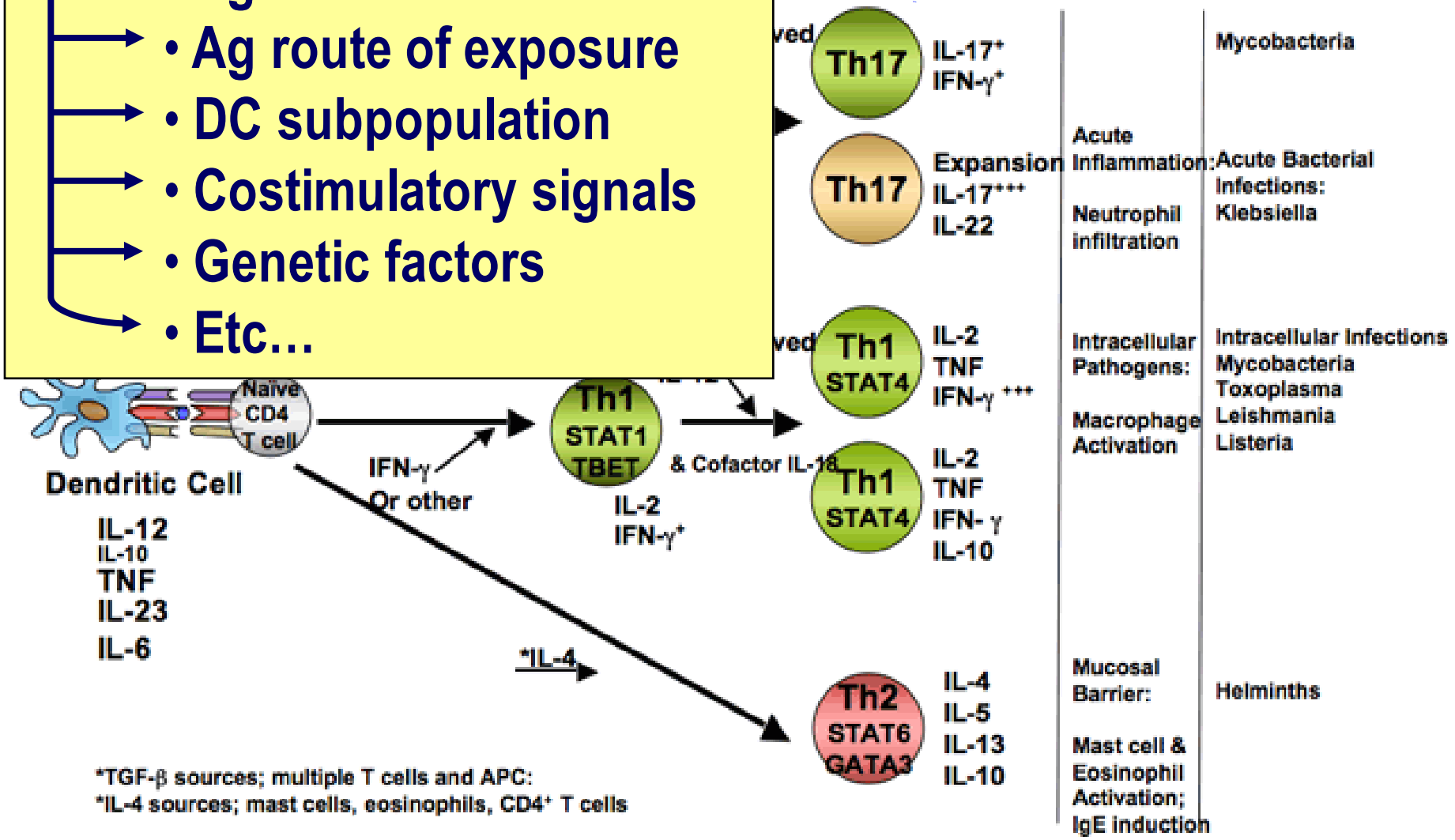
(biofeedbacks – termination of immune responses)



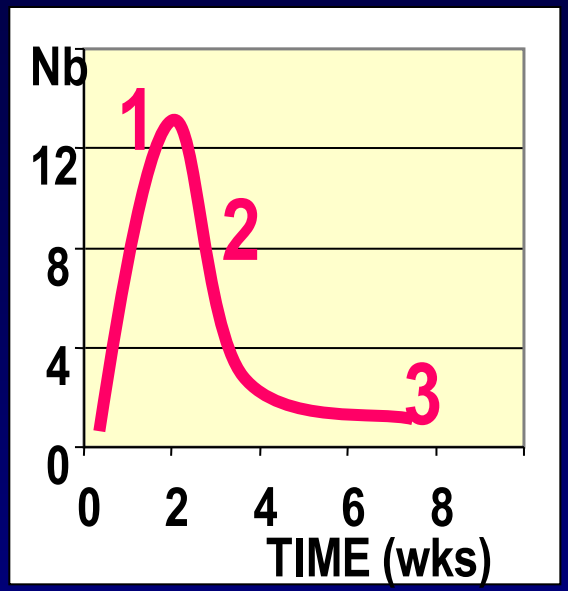
Weaver CT, Immunity. 2006 Jun;24(6):677-88

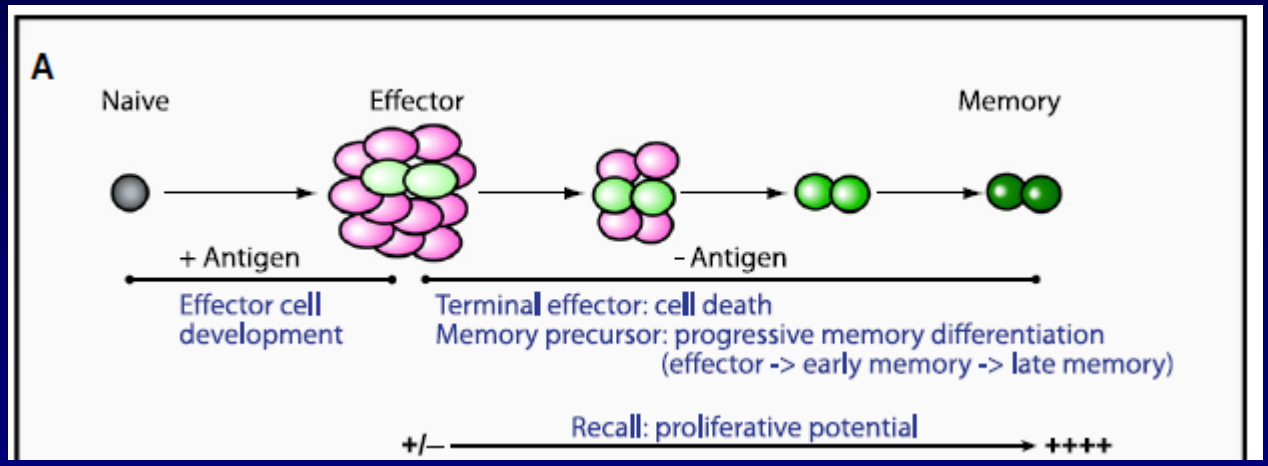
How do vaccines induce specific T cells ?

- Ag nature / dose
- Ag route of exposure
- DC subpopulation
- Costimulatory signals
- Genetic factors
- Etc…



T cell responses and induction of T cell memory





1. **T CELL DIFFERENTIATION IN THE THYMUS** – self / non-self education
2. **EXPANSION OF EFFECTOR T CELLS** – driven by Ag (days)
3. **DEATH OF EFFECTOR T CELLS** (>90%) – when Antigen is cleared
4. **DIFFERENTIATION OF PRECURSOR MEMORY T CELLS INTO :**
   - Central memory T cells : resting, reservoir in lymph nodes, BM, etc.
   - Effector memory T cells : pre-activated, in tissues

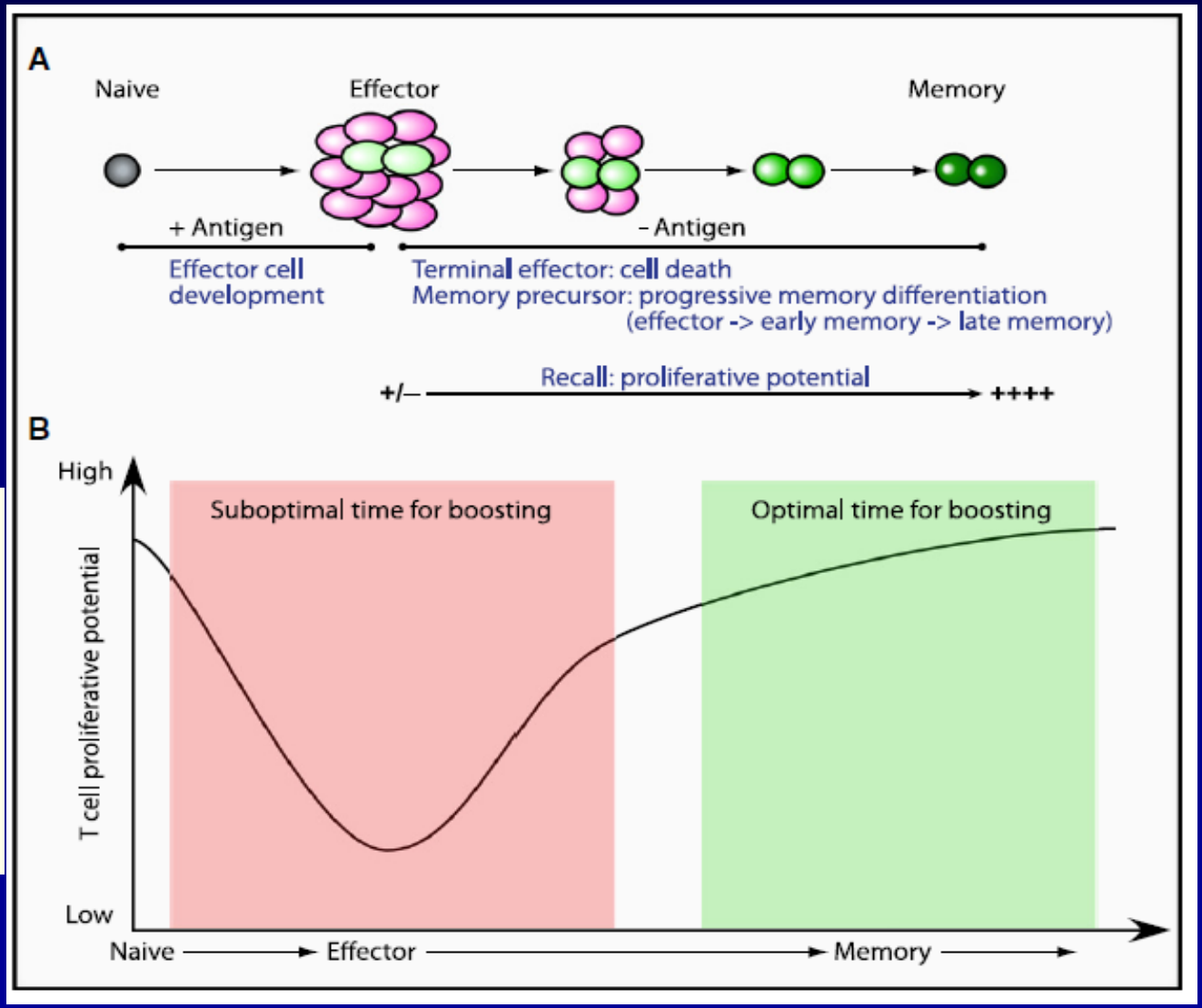
Federica Sallusto,[1,*] Antonio Lanzavecchia,[1,2] Koichi Araki,[3] and Rafi Ahmed[3,*]

Immunity *33*, October 29, 2010

Influence of vaccine schedule on the induction of memory T cells

T cell responses are lower

if boosters are given too early!



Federica Sallusto,[1,*] Antonio Lanzavecchia,[1,2] Koichi Araki,[3] and Rafi Ahmed[3,*]

Immunity *33*, October 29, 2010

*Which parameters of T cell responses **may be assessed** in vaccine studies ?*

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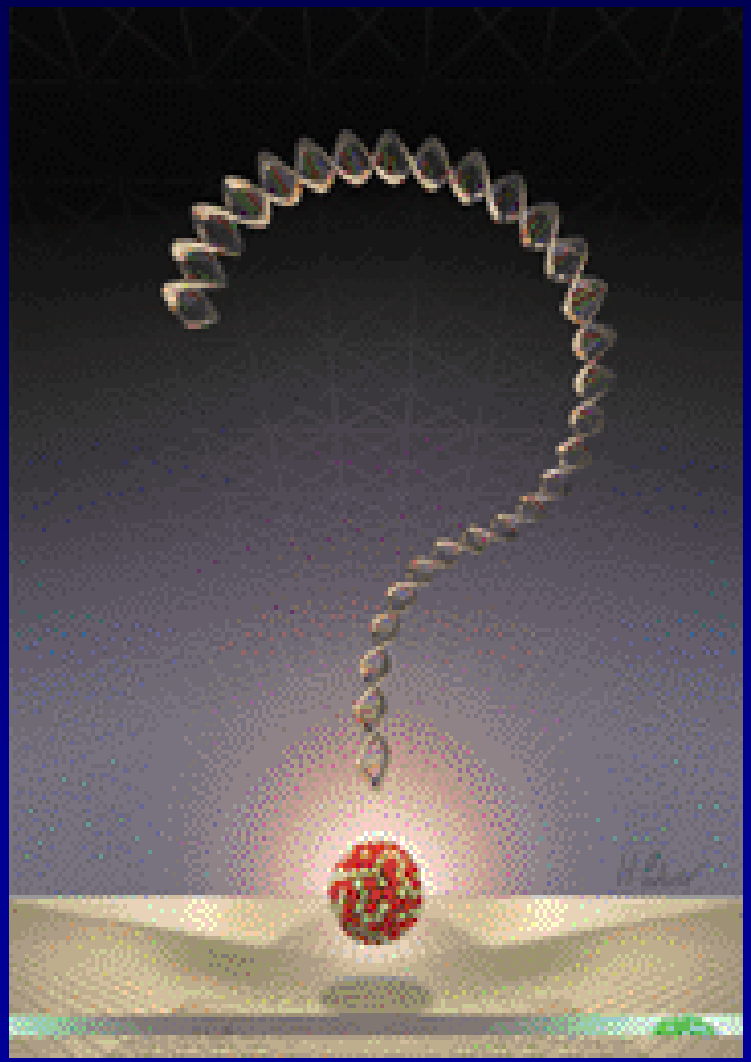
- Nb of CD8 T cells **binding** to a specific Ag : tetramers
- **T cell proliferation** following Ag recognition (3H thymidine, CSFE dye + FACS, others)



Function

- Nb of **cytokine producing** CD4/CD8 T cells: ELISPOTs, flow cytometry
- **Cytokine** detection in T cell supernatants
- **Cytotoxicity** : in vivo (animal), in vitro

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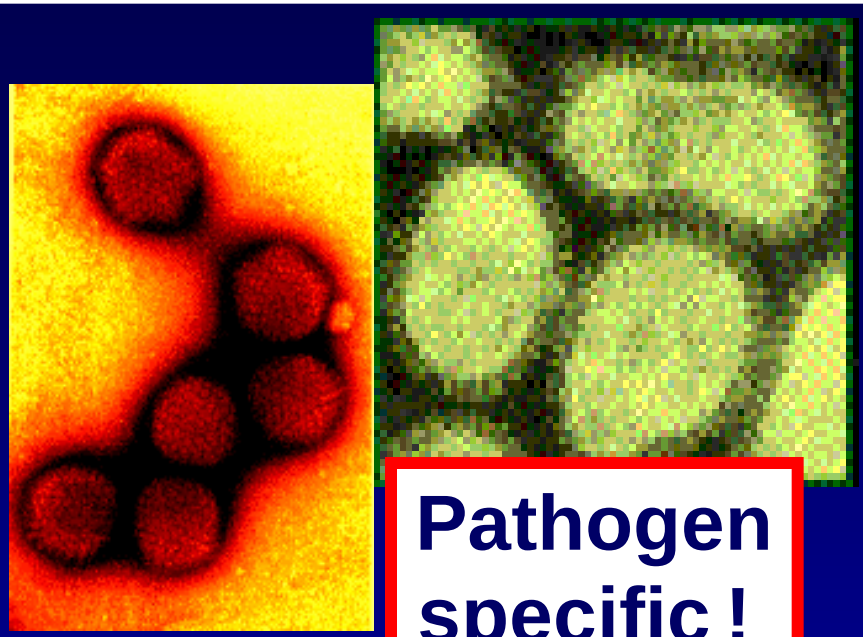

Pathogen specific !

Correlates of protection!

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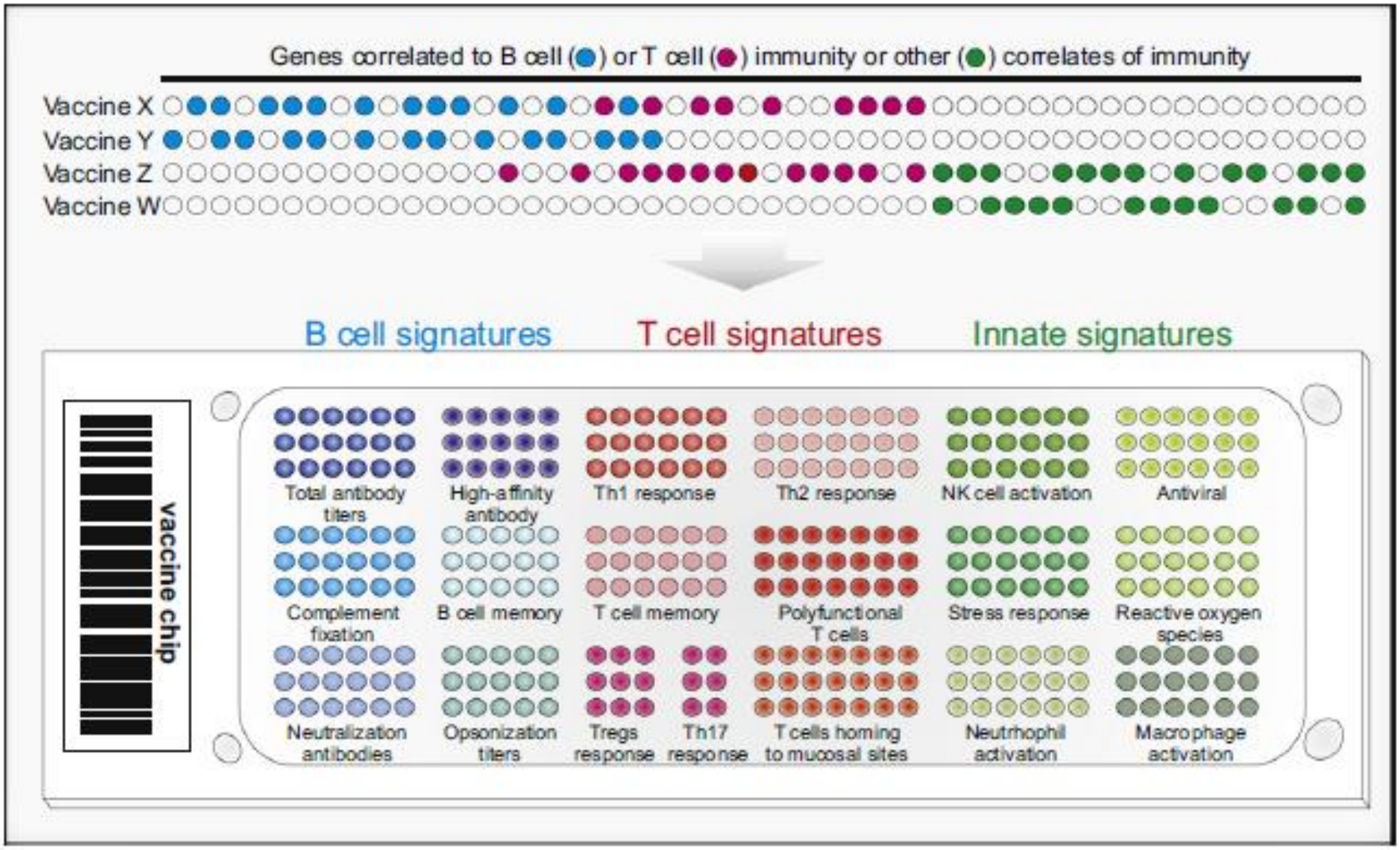
System vaccinology : towards vaccine chips !



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What is elicited by vaccination ?

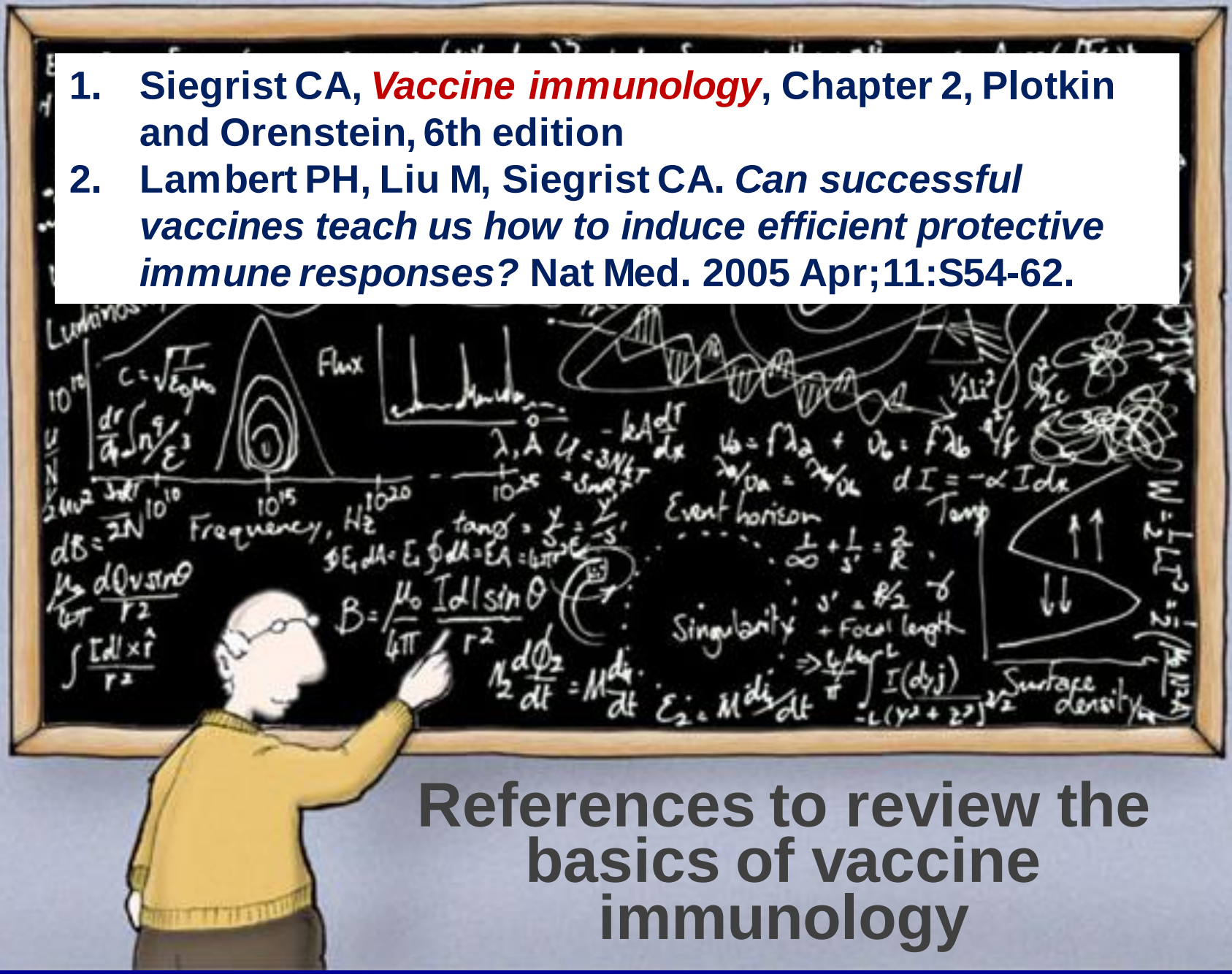
- **Antibodies :**
  - *magnitude, persistence, functional capacity ?*
- **T cells :**
  - *characteristics ? persistence ?*
- **Duration of protection :**
  - Long term effectors
  - Memory cells
    - *induction ?*
    - *reactivation kinetics ?*
    - *persistence?*

What is needed for protection ?

- **Antibodies ?**
  - *Protective threshold ?*
- **T cells ?**
  - *Pattern of responses ?*
- **Long term protection ?**
  - *Effector mechanisms ?*

Pathogen specific !

Correlates of immunity !


1. Siegrist CA, *Vaccine immunology*, Chapter 2, Plotkin and Orenstein, 6th edition
2. Lambert PH, Liu M, Siegrist CA. *Can successful vaccines teach us how to induce efficient protective immune responses?* Nat Med. 2005 Apr;11:S54-62.
References to review the basics of vaccine immunology