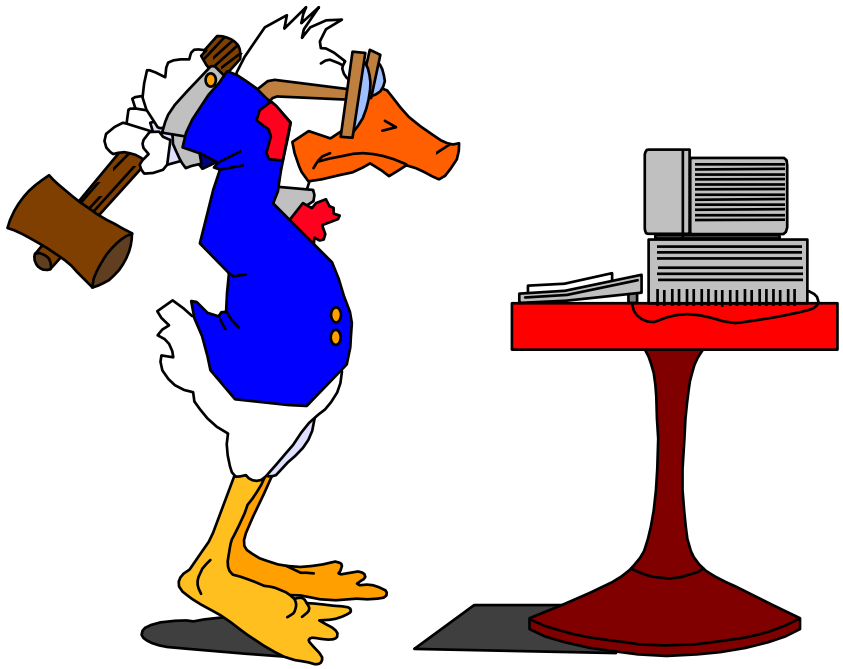
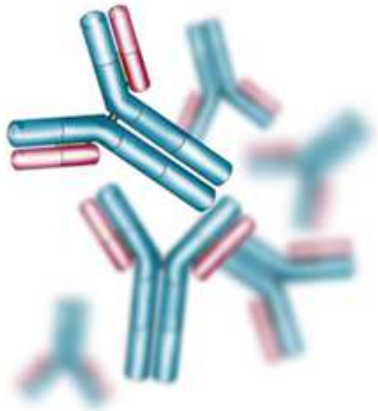


INMUNOLOGÍA CLÍNICA 2009

BIOQ GRACIELA R SVIBEL DE MIZDRAJI



La comprensión y manipulación del sistema inmune tiene un enorme potencial preventivo y terapéutico

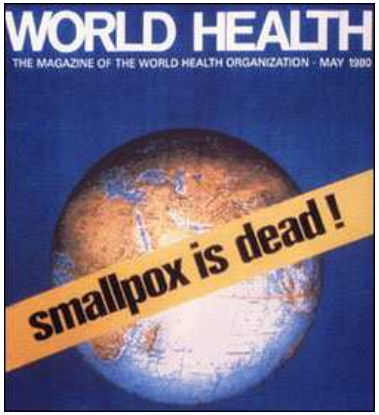
VACUNAS

- Edward Jenner primer vacuna contra viruela

1885 Pasteur: atenuación artificial de microorganismos, colera, antrax. Vacuna antirábica (aplicada a J. Meister)

Siguieron: B. pertussis, BCG, Difteria, Tifus, Tétanos, Fiebre amarilla, Gripe, Polio,Sarampión, etc.

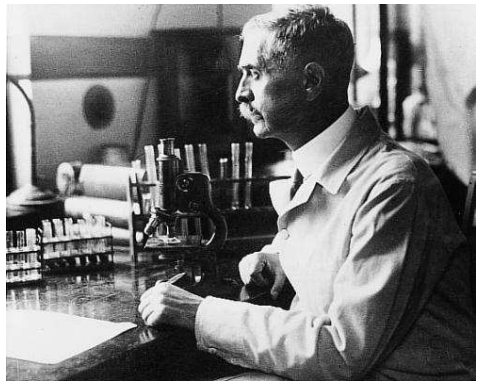
Vacunación masiva contra la viruela



1979: dos años después del último caso en Somalia

1991 – Luis Fermin, último caso de polio en las Americas (Peru)

La comprensión y manipulación del sistema inmune tiene un enorme potencial preventivo y terapéutico



TRANSPLANTES

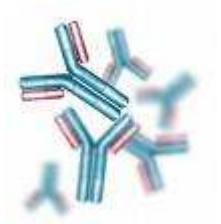
1900’ K. Landsteiner: Transfusiones seguras descubrimiento de los mayores grupos sanguíneos

1950’ George Snell: Descubrimiento del MHC, lo que permitió mejorar las posibilidades de éxitos de los transplantes.

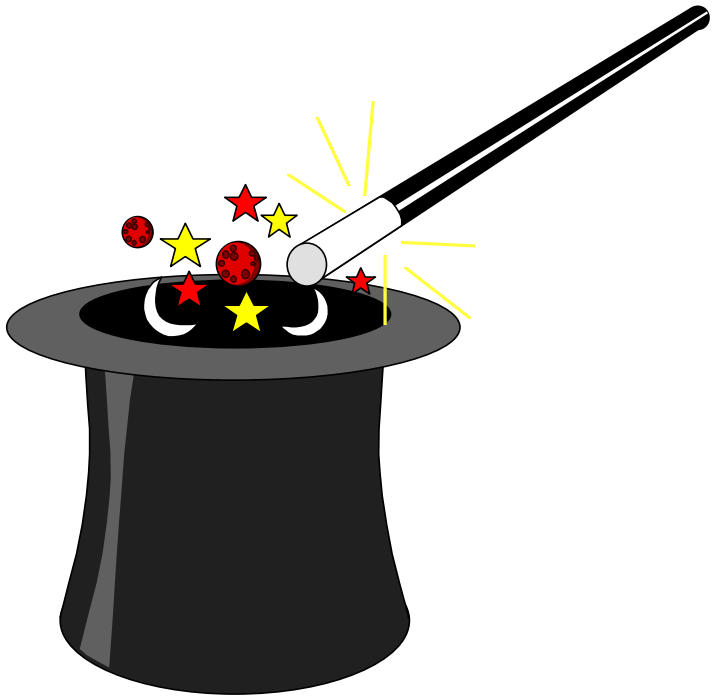
ANTICUERPOS TERAPÉUTICOS

Fin del siglo XIX: Los anticuerpos preparados en animales se inyectan en humanos para neutralizar toxinas y venenos.

1990’ Los avances en la tecnología de producción de anticuerpos permite la aparición de los anticuerpos terapéuticos

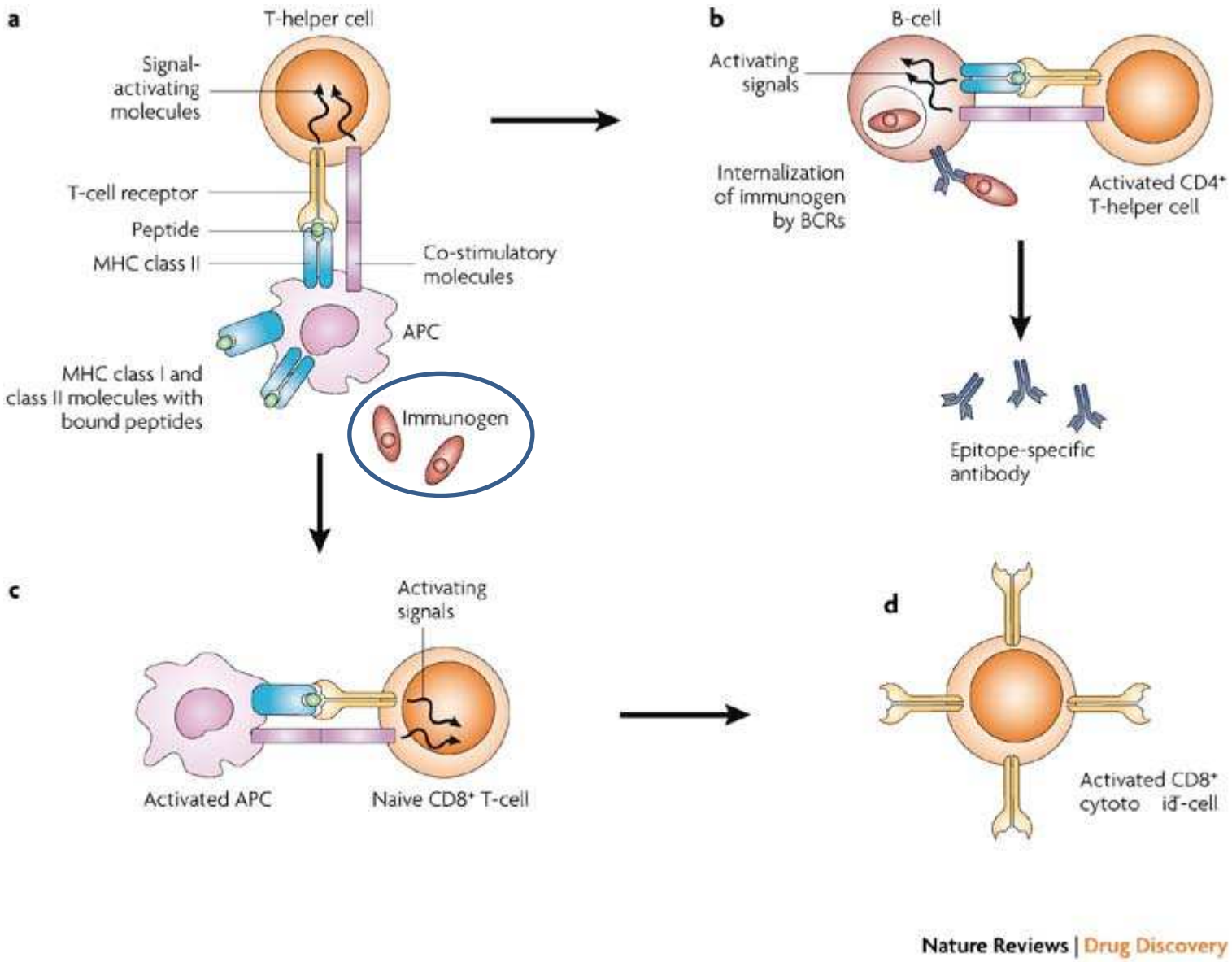


In 1899 Ladislas Deutsch (Detre) (1874-1939) named the hypothetical substances halfway between bacterial constituents and antibodies "substances immunogenes or antigenes". He originally believed those substances to be precursors of antibodies, just like zymogen is a precursor of zymase. But by 1903 he understood that **an antigen induces the production of immune bodies (antibodies) and wrote that the word antigen was a contraction of "Antisomatogen** = Immunkö rperbildner". The Oxford English Dictionary indicates that the logical construction should be "anti(body)-gen"



ANTÍGENOS : ANTIBODY GENERATION

INMUNÓGENOS



Nature Reviews Drug Discovery 6, 404-414 (May 2007)

Antígeno (Ag)

Molécula que se **combina específicamente** con la **inmunoglobulina libre o el BCR o con el TCR cuando se encuentra en forma de complejo con MHC….**

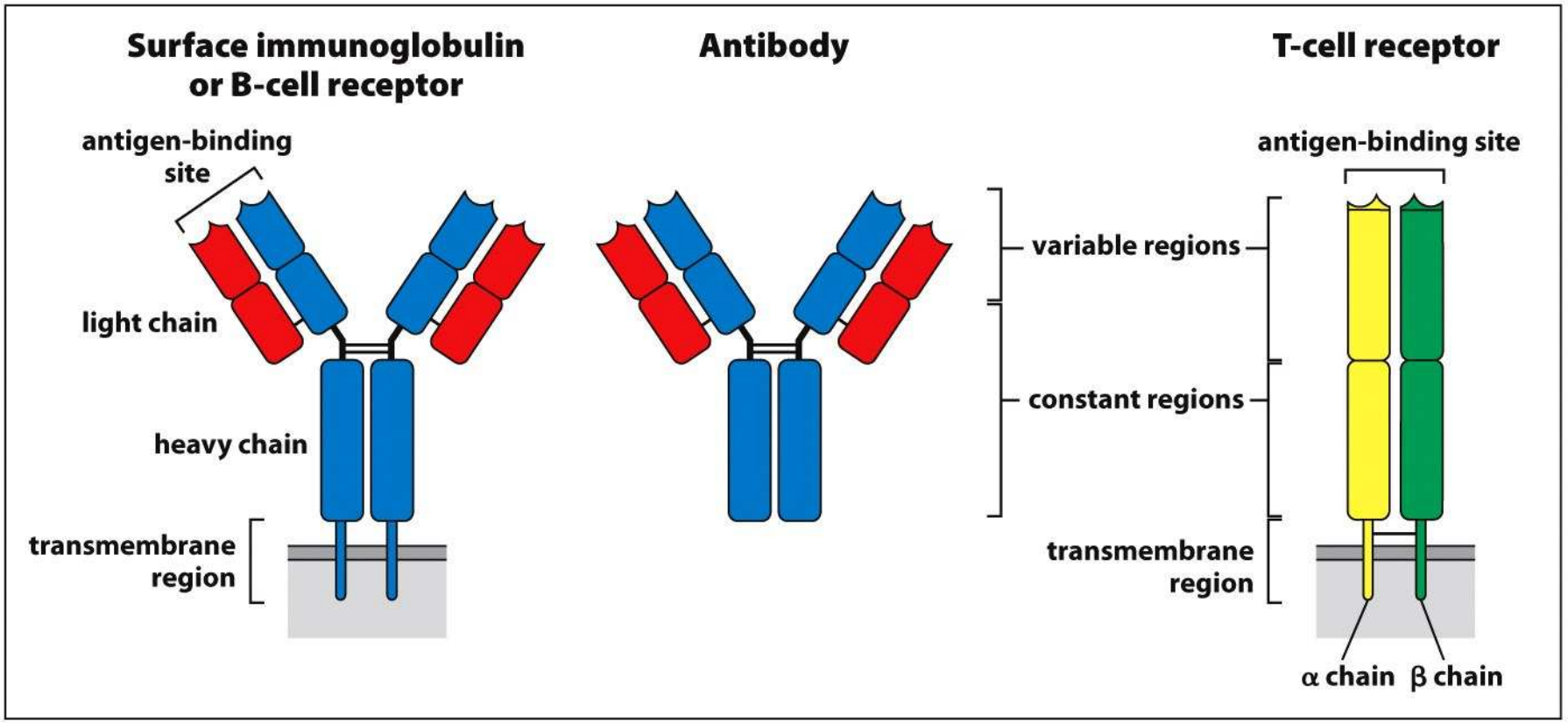
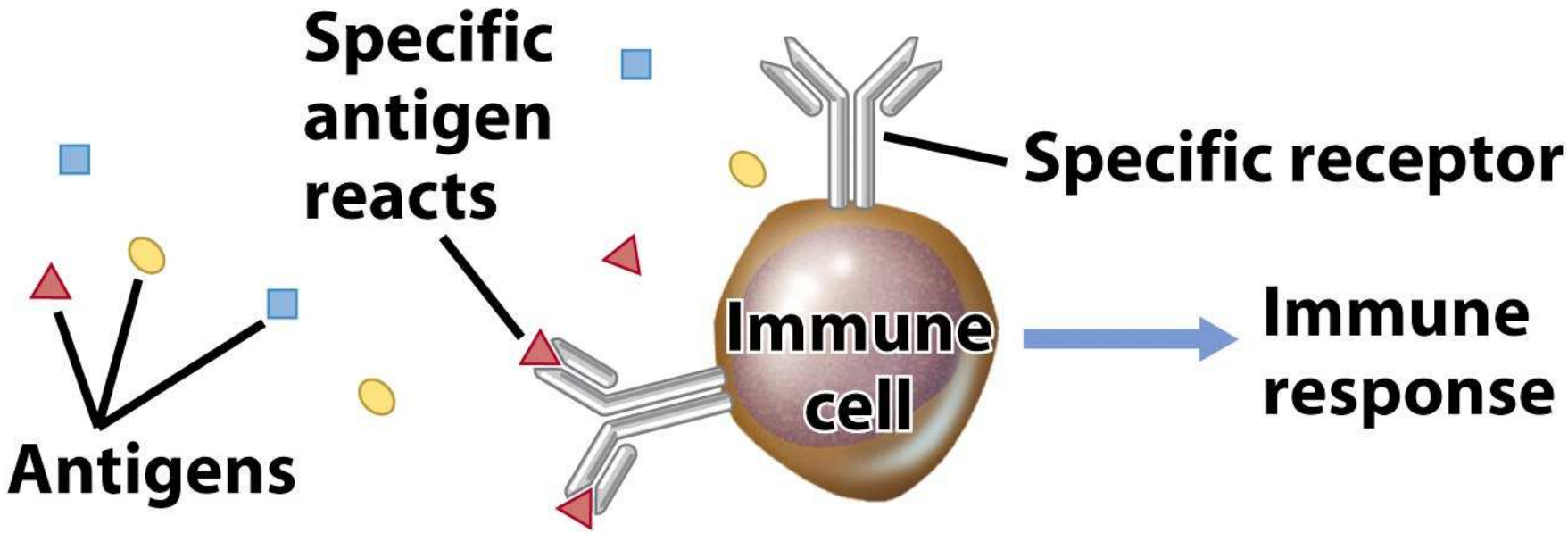
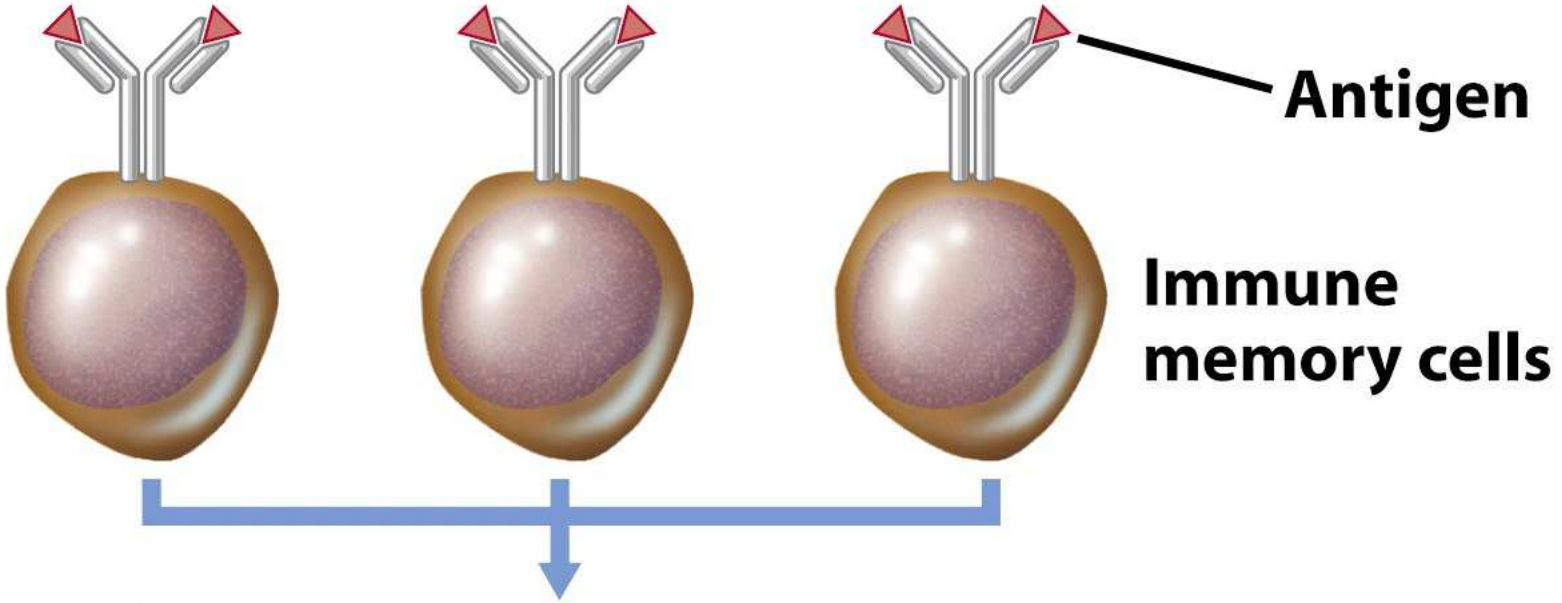


Figure 3.1 The Immune System, 3ed. (© Garland Science 2009)



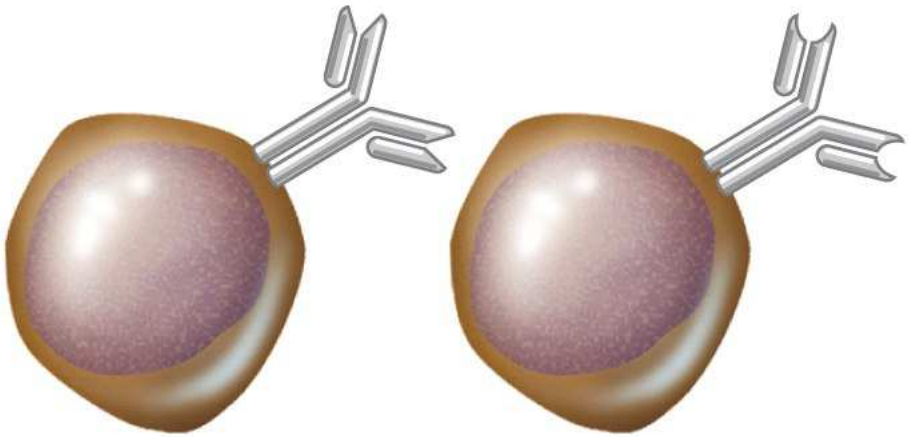
Specificity: Immune cells recognize and react with individual molecules (antigens) via direct molecular interactions.

Figure 22-8 part 1 Brock Biology of Microorganisms 11/e



Memory: The immune response to a specific antigen is *faster* and *stronger* upon subsequent exposure because the initial antigen exposure induced growth and division of antigen-reactive cells, resulting in multiple copies of antigen-reactive cells.

Figure 22-8 part 2 Brock Biology of Microorganisms 11/e



■ Self antigen

Immune cells specific for nonself antigens

Tolerance: Immune cells are not able to react with self antigen. Self-reactive cells are destroyed during development of the immune response.

Figure 22-8 part 3 Brock Biology of Microorganisms 11/e

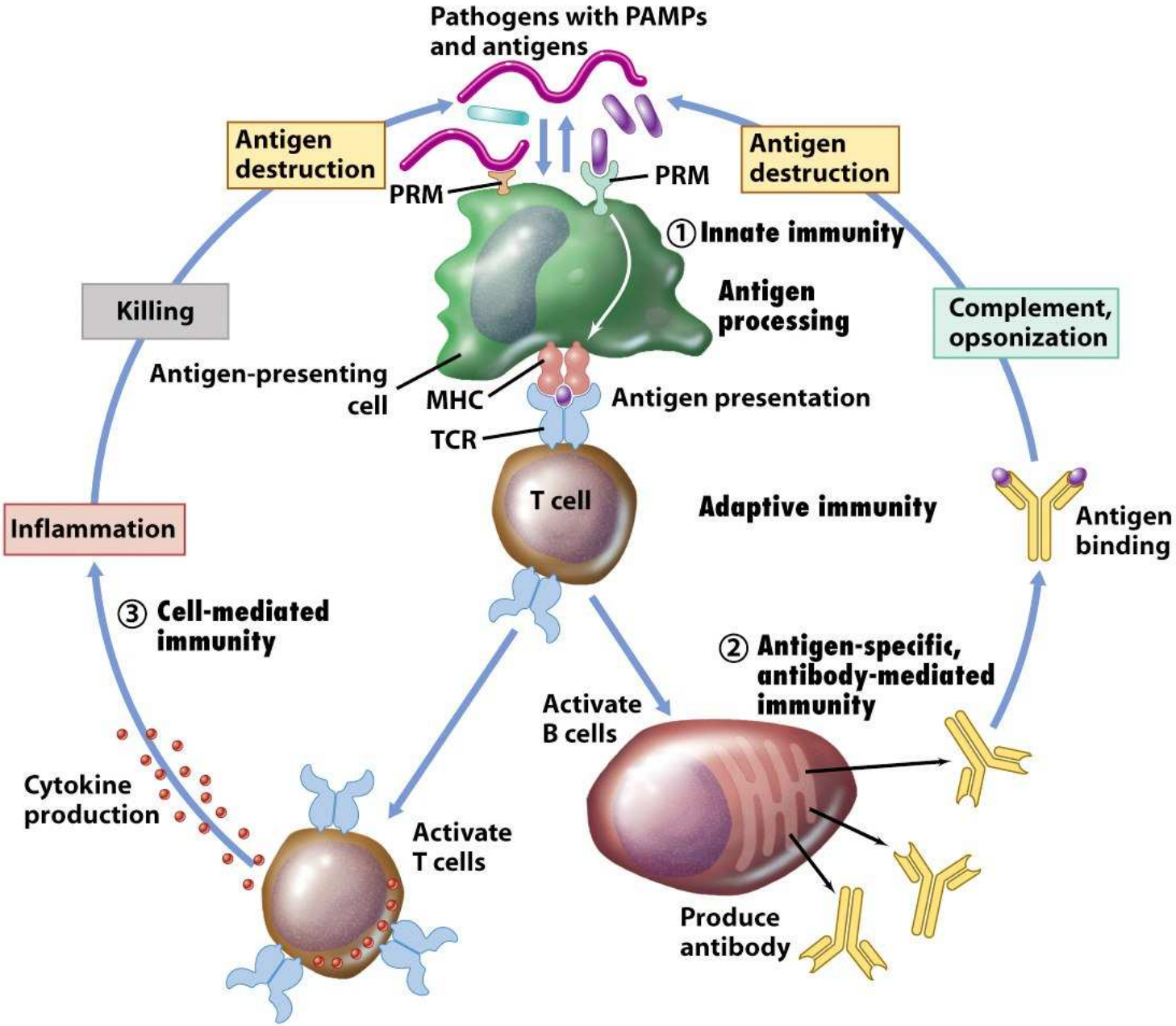


Figure 22-5 Brock Biology of Microorganisms 11/e

La molécula de antígeno tiene generalmente dos propiedades:

1. Immunogenicidad
2. Immunoreactividad o antigenicidad

Inmunogenicidad vs antigenicidad

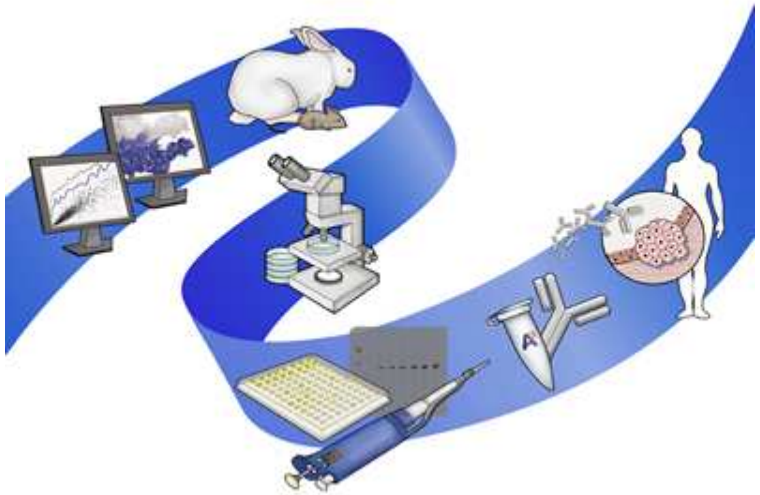
- …es la habilidad de **inducir** una respuesta inmune humoral o celular, o ambas…..

- ….es la habilidad de **combinarse específicamente** con el producto final de las respuestas anteriores (anticuerpos secretados, receptores de superficie en las células T, o ambas

Todo inmunógeno se va a comportar como antígeno, pero no todo antígeno va a ser inmunógeno.

EPÍTOPOS O DETERMINANTES ANTIGÉNICOS

Valencia antigénica



..el **número de determinantes antigénicos funcionales** que pueden unirse al anticuerpo.

Hapteno es UNIVALENTE.

Antígeno natural es POLIVALENTE…múltiples determinantes antigénicos se unen a diferentes moléculas de anticuerpos.

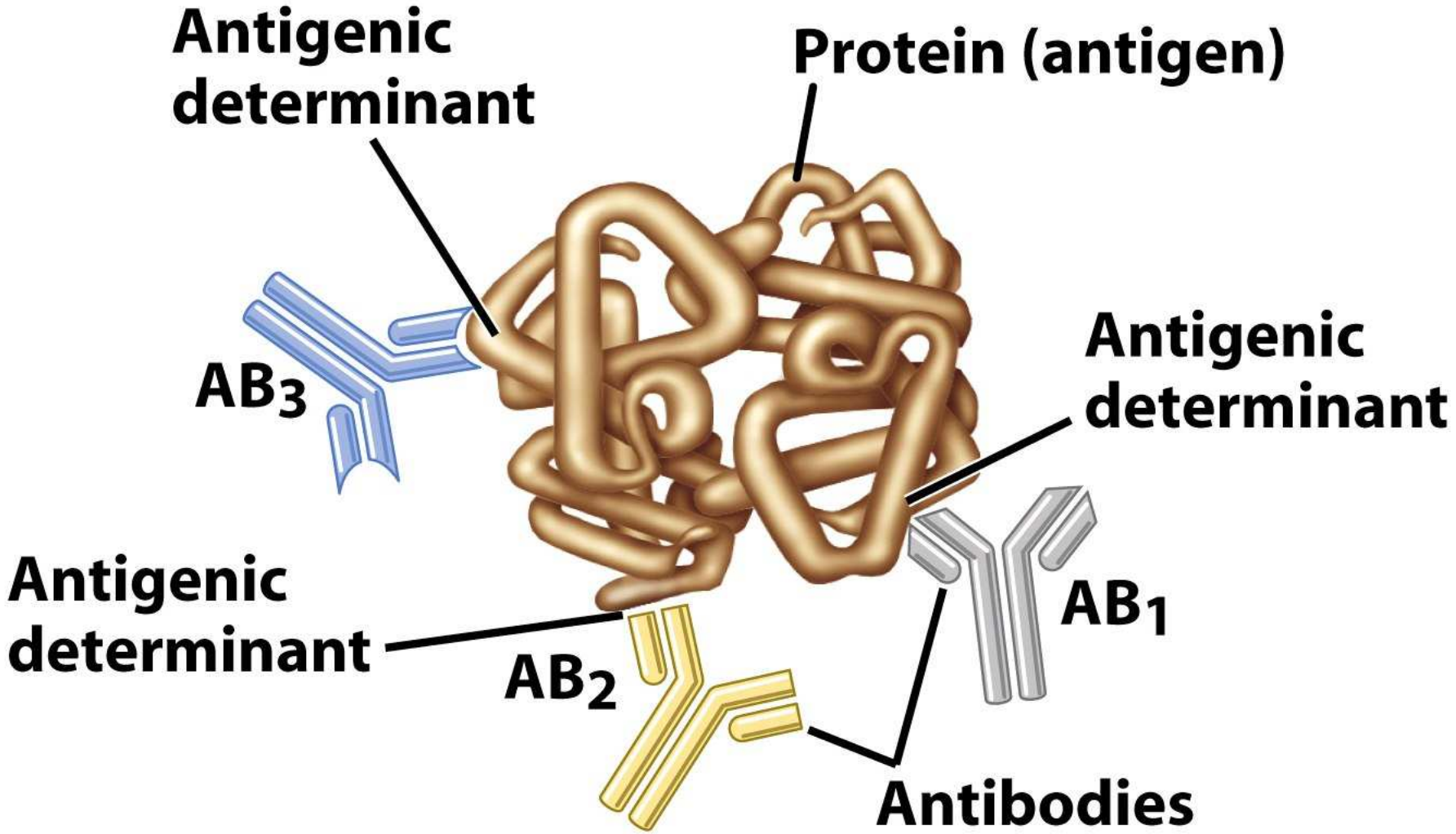
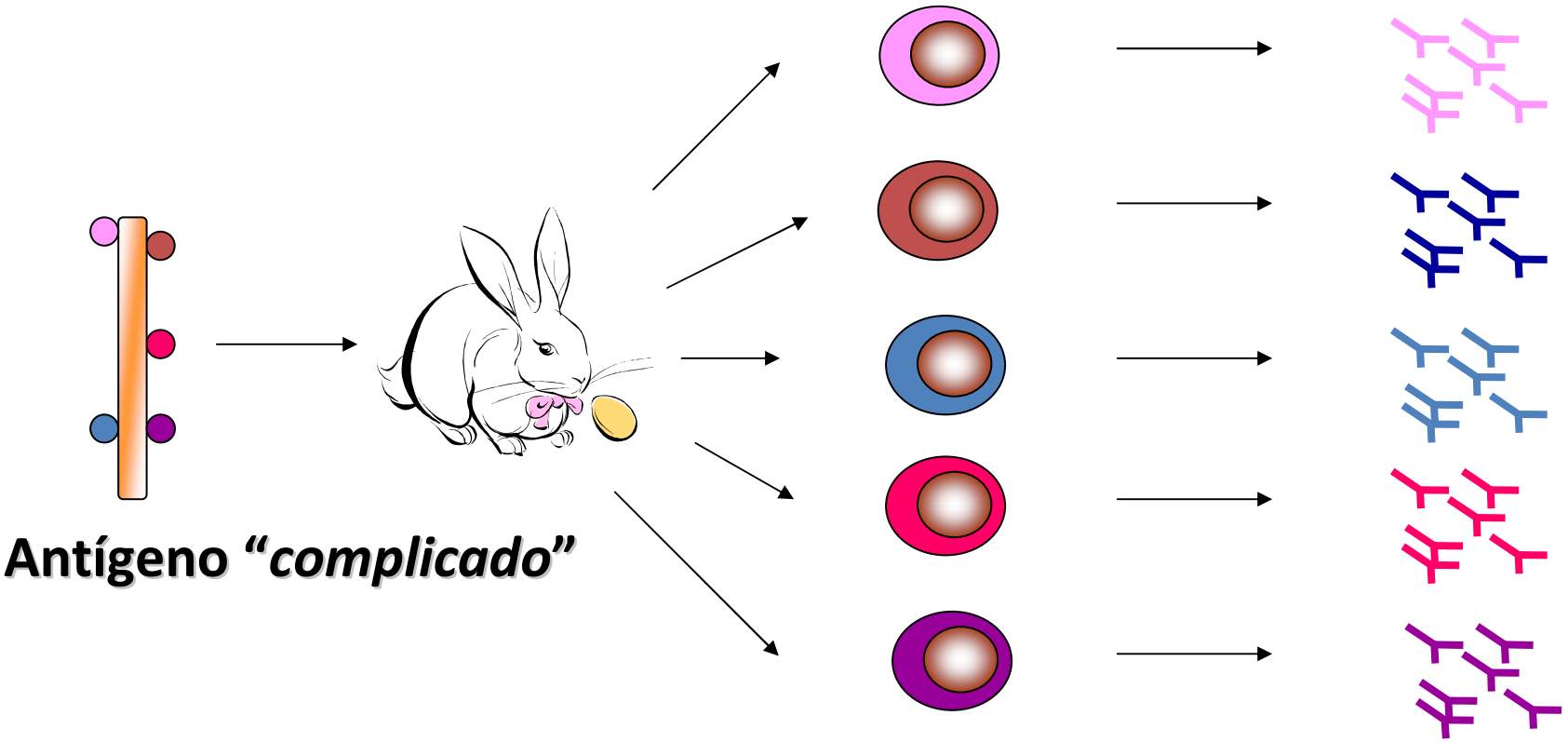


Figure 22-9 Brock Biology of Microorganisms 11/e

Cada **determinante antigénico de CÉLULA B** induce la producción de **UN** anticuerpo específico

Un antígeno "*complicado*" puede inducir la producción de múltiples.



Especificidad epítope-anticuerpo

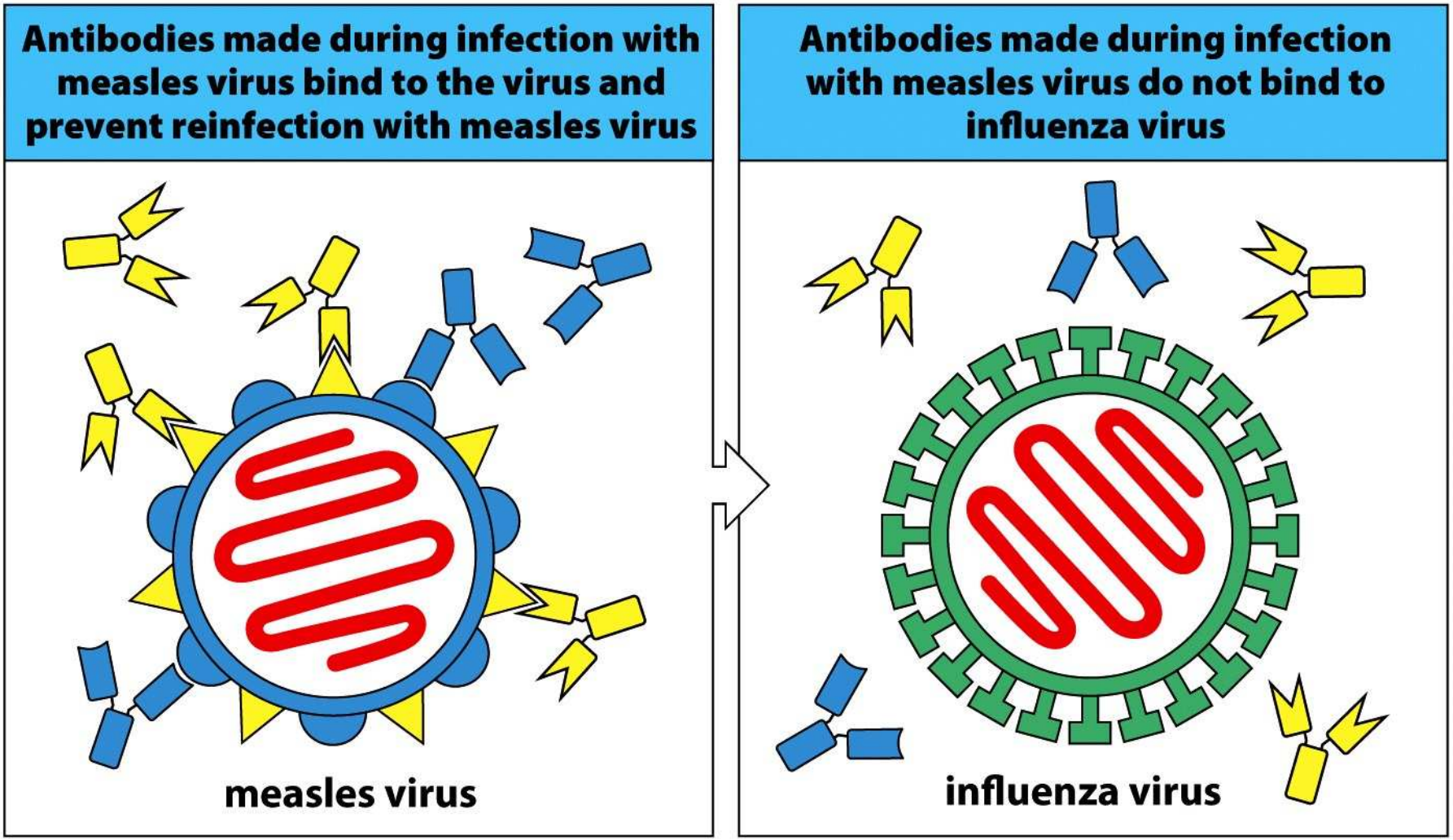
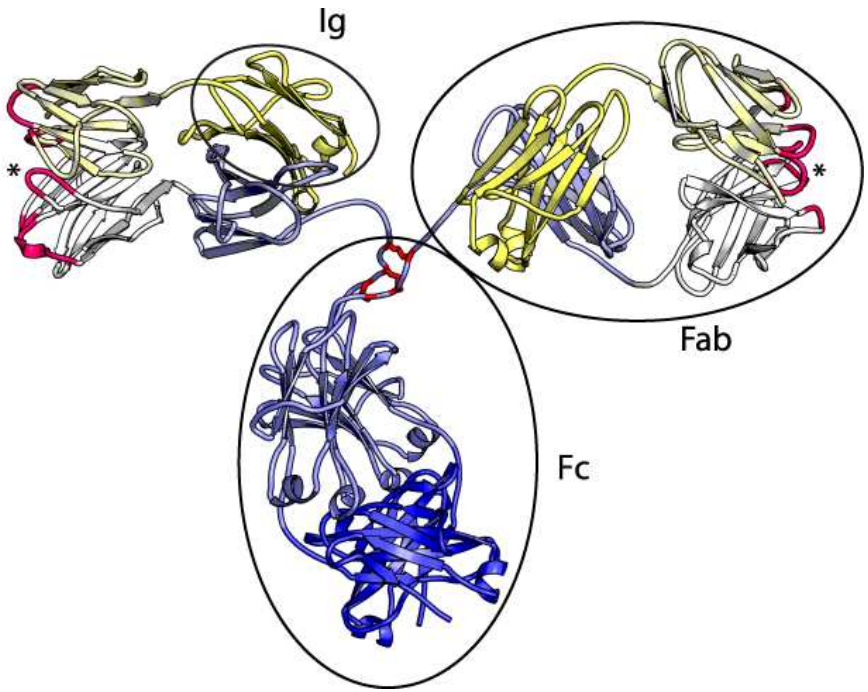
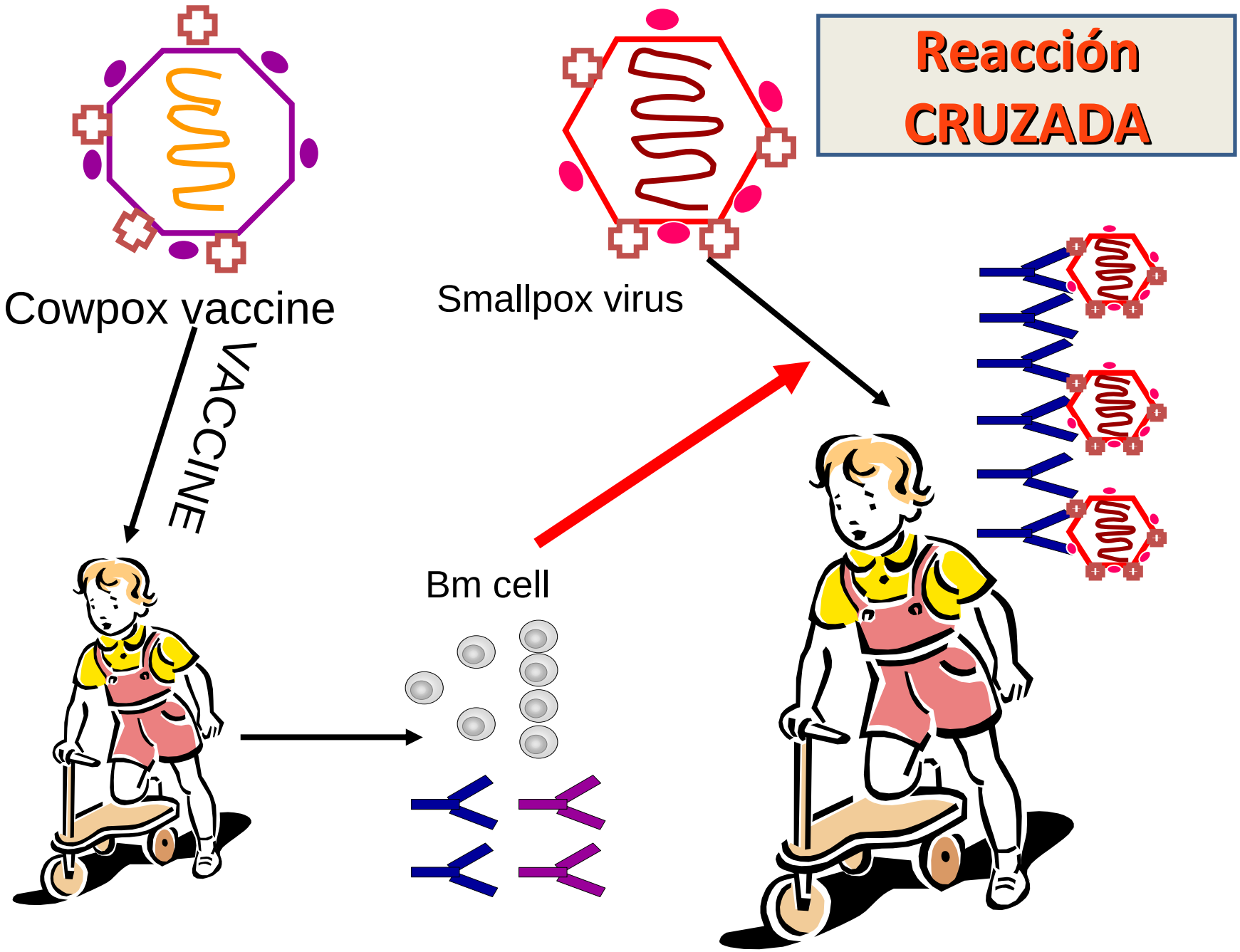
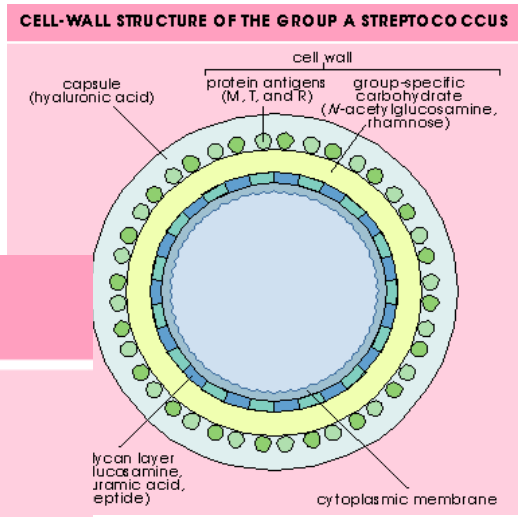


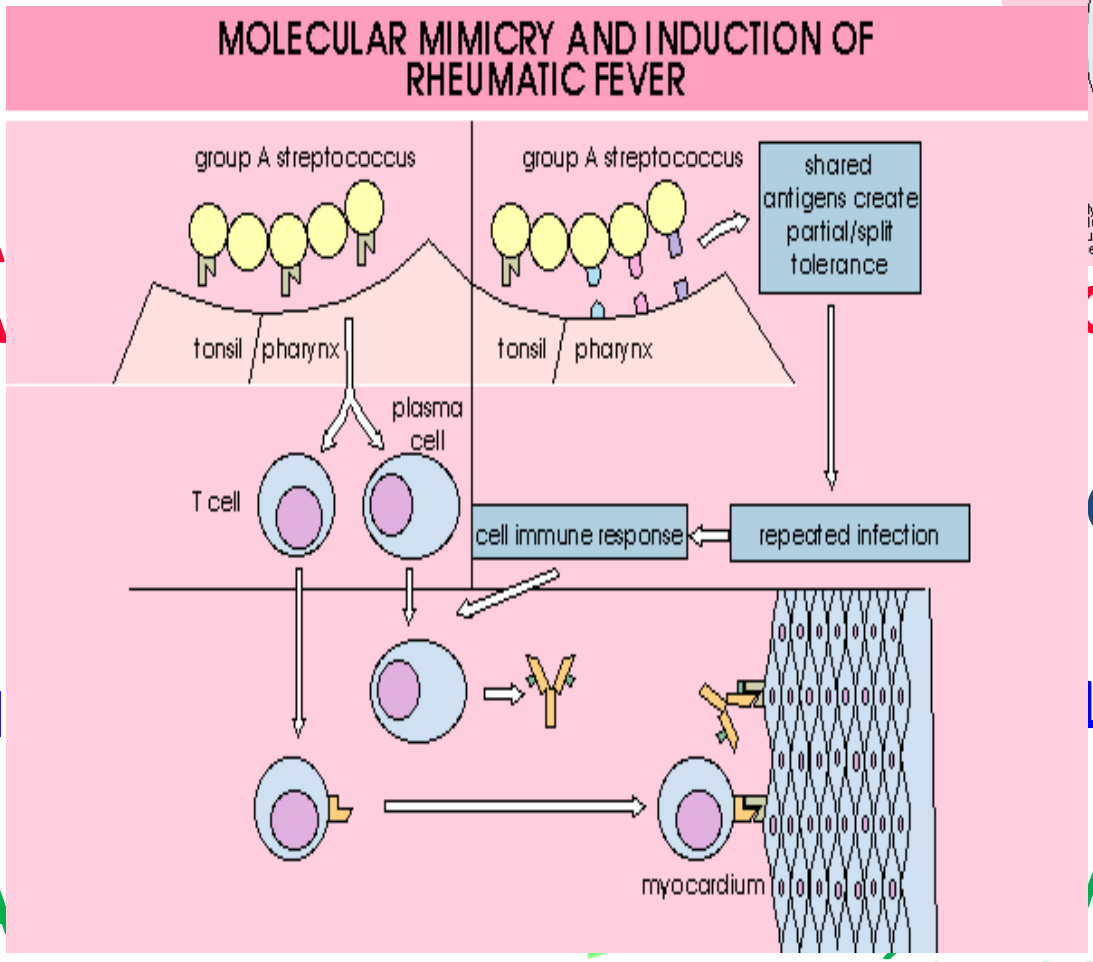
Figure 3.2 The Immune System, 3ed. (© Garland Science 2009)


Ig
Fab
Fc
*
*


Reacción
CRUZADA
Cowpox vaccine
VACCINE
Smallpox virus
Bm cell

Streptococcus grupo A





CÁPSULA

AC.HIA

CIÓN

PROT.M,

O

CARBOHI

LVULAR

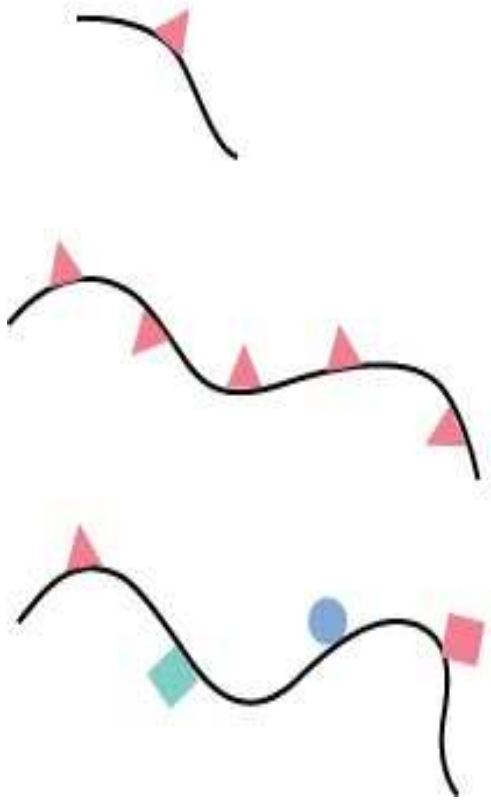
MEMBRA

MA,

PROTOPLASMA

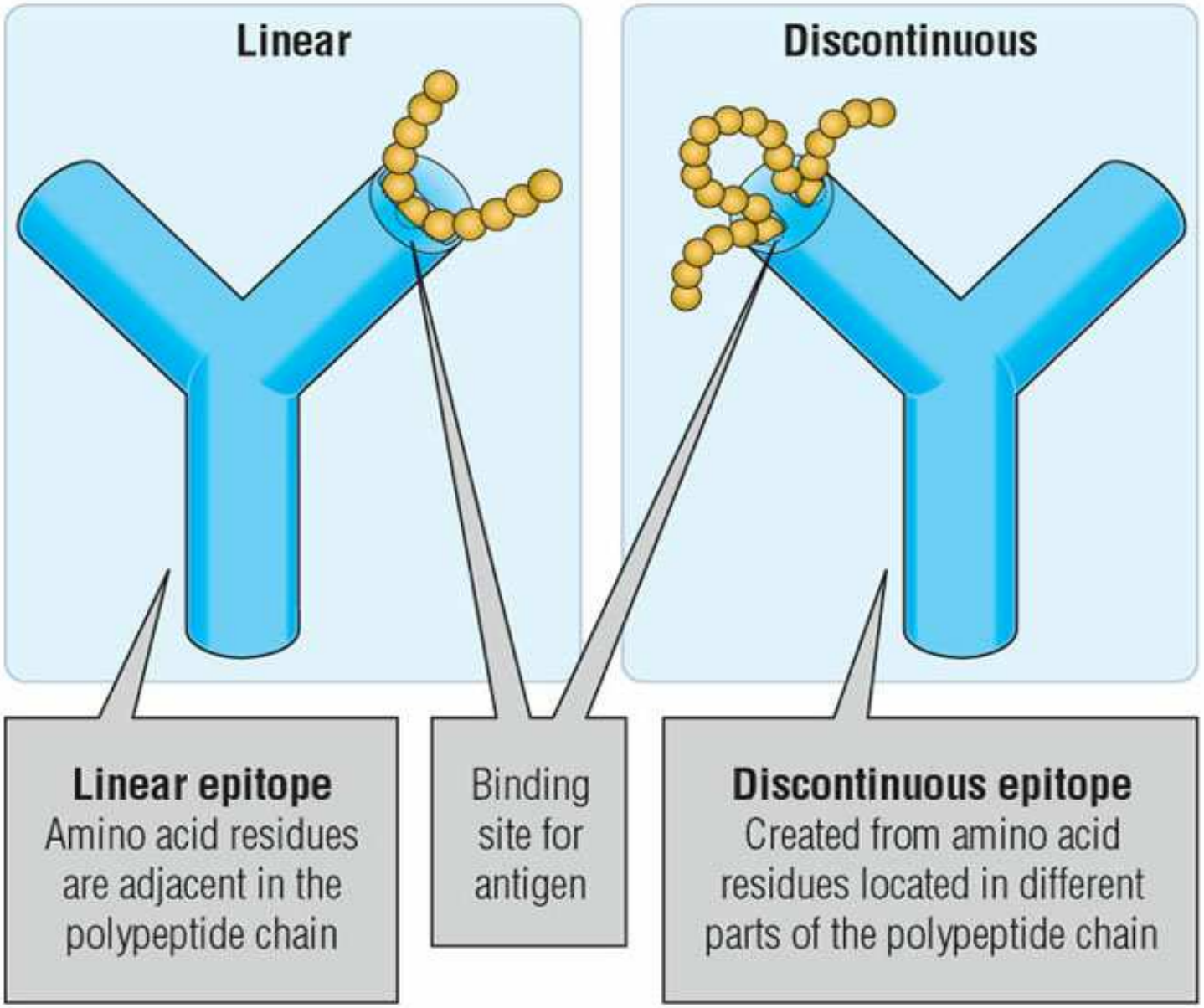
NÚCLEOS SNC.

EPÍTOPE: porción específica del antígeno que se une a la INMUNOGLOBULINA libre o al BCR / TCR.



Description	Example
One epitope	Haptens
Many epitopes of the same specificity	Many polysaccharides, homopolymers
Many epitopes of different specificities	Proteins

Epítope lineal vs discontinuos



Los anticuerpos libres o la inmunoglobulina del BCR reconocen proteínas nativas, mientras que el TCR reconoce péptidos específicos en el contexto del MHC.

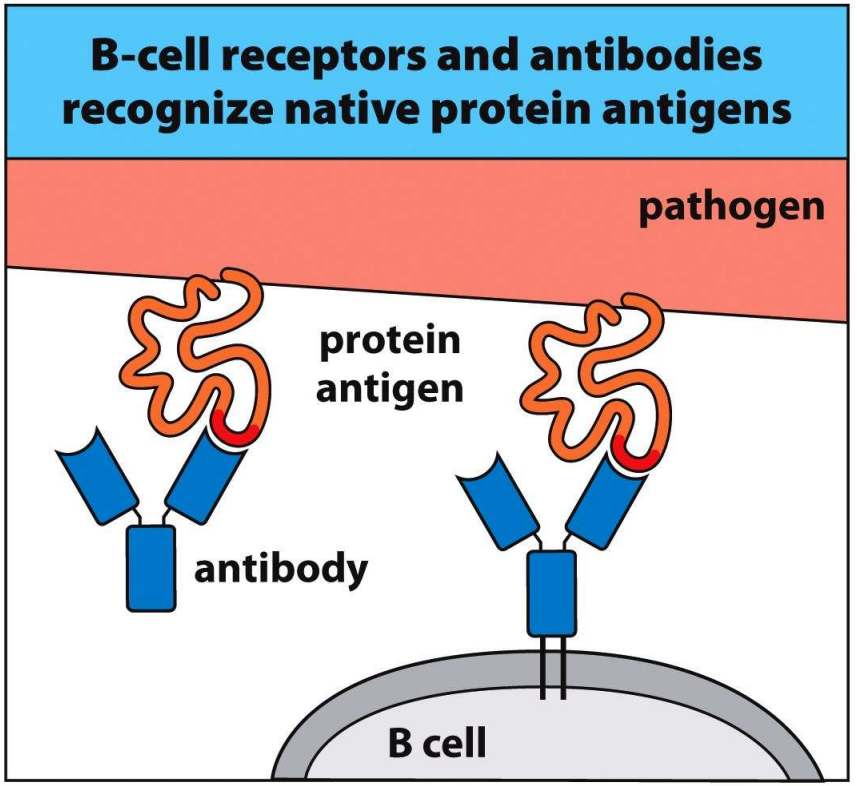


Figure 3.12 The Immune System, 3ed. (© Garland Science 2009)

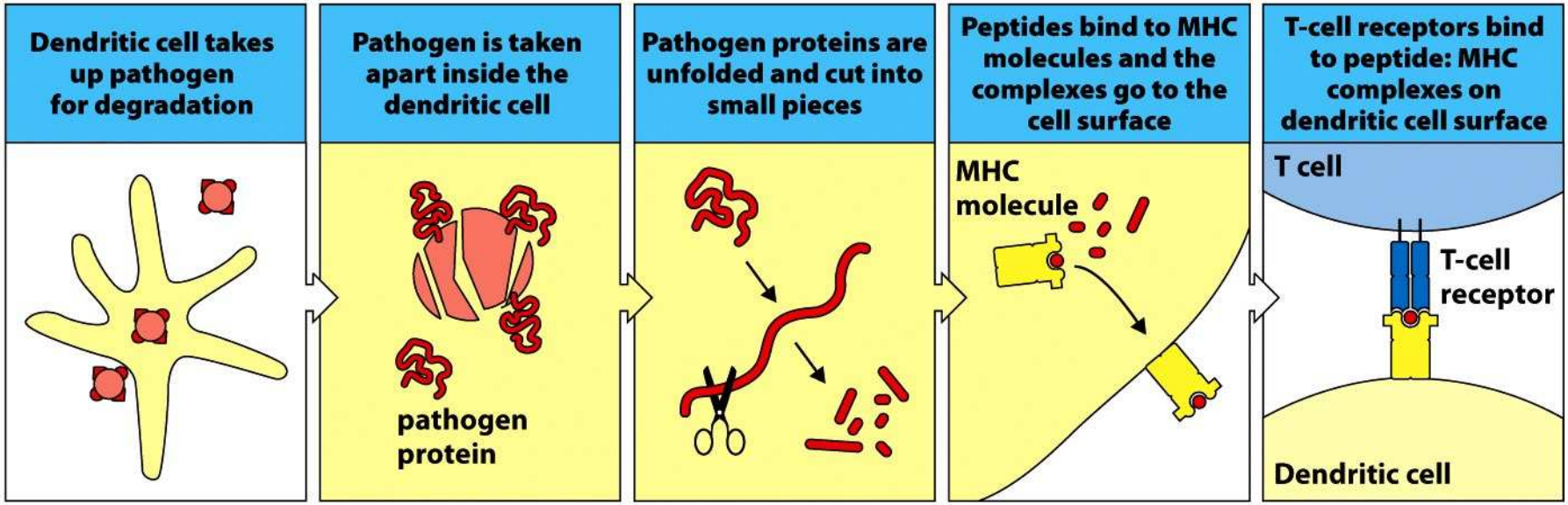


Figure 3.7 The Immune System, 3ed. (© Garland Science 2009)

MHC- I y MHC-II

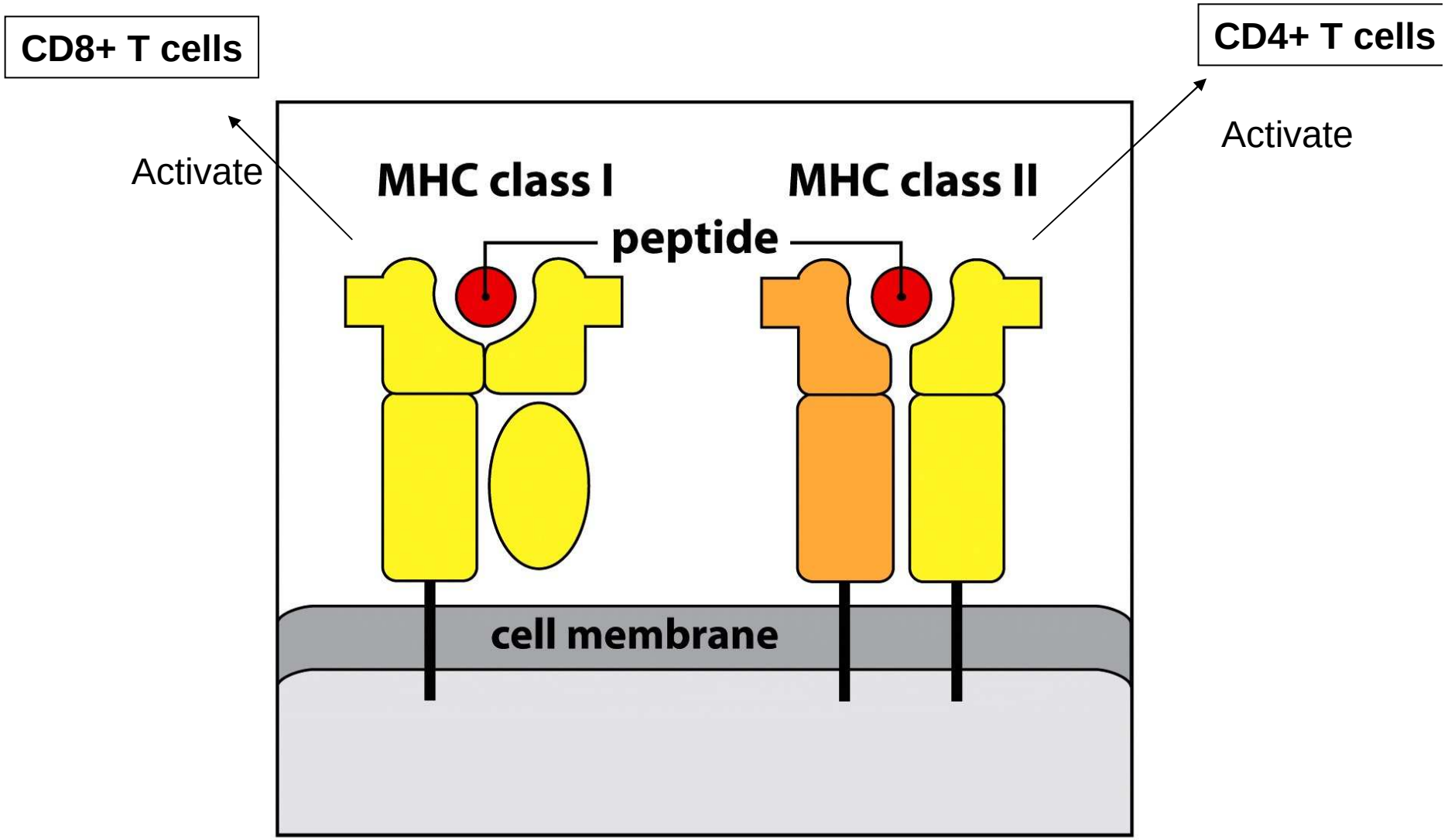
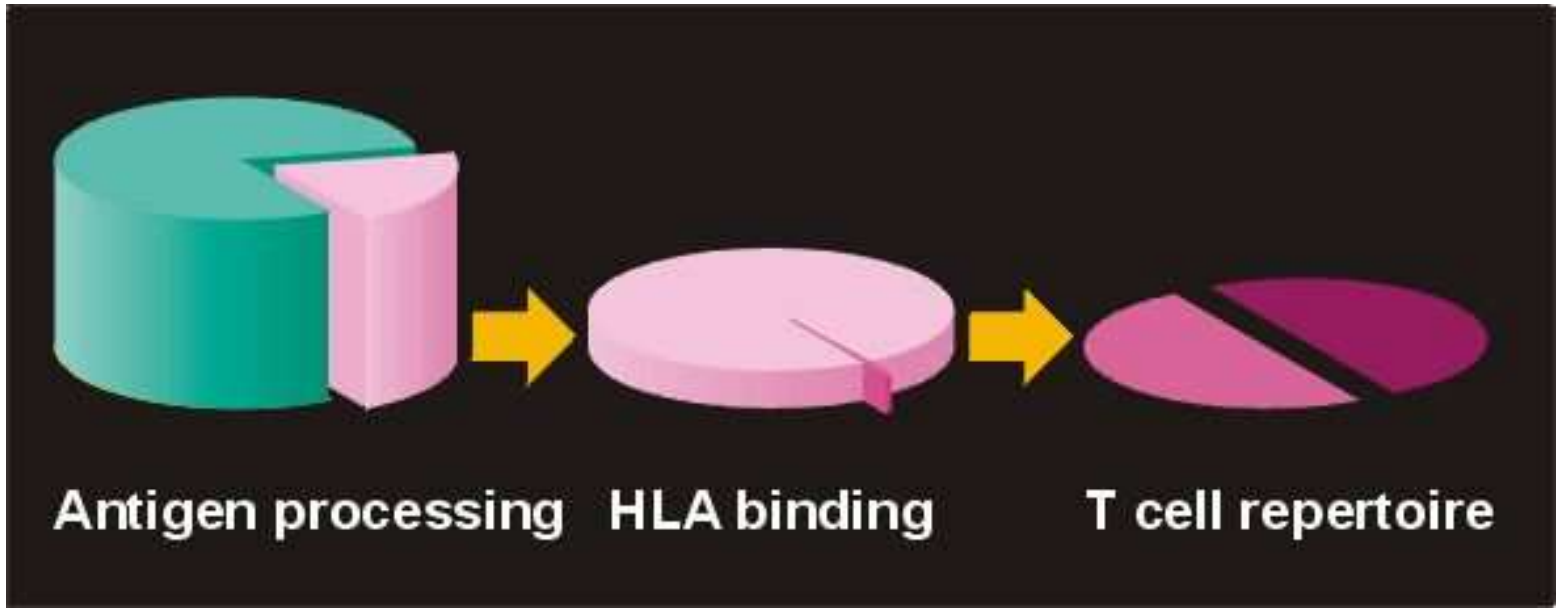


Figure 3.8 The Immune System, 3ed. (© Garland Science 2009)

Desde proteínas a immunógenos

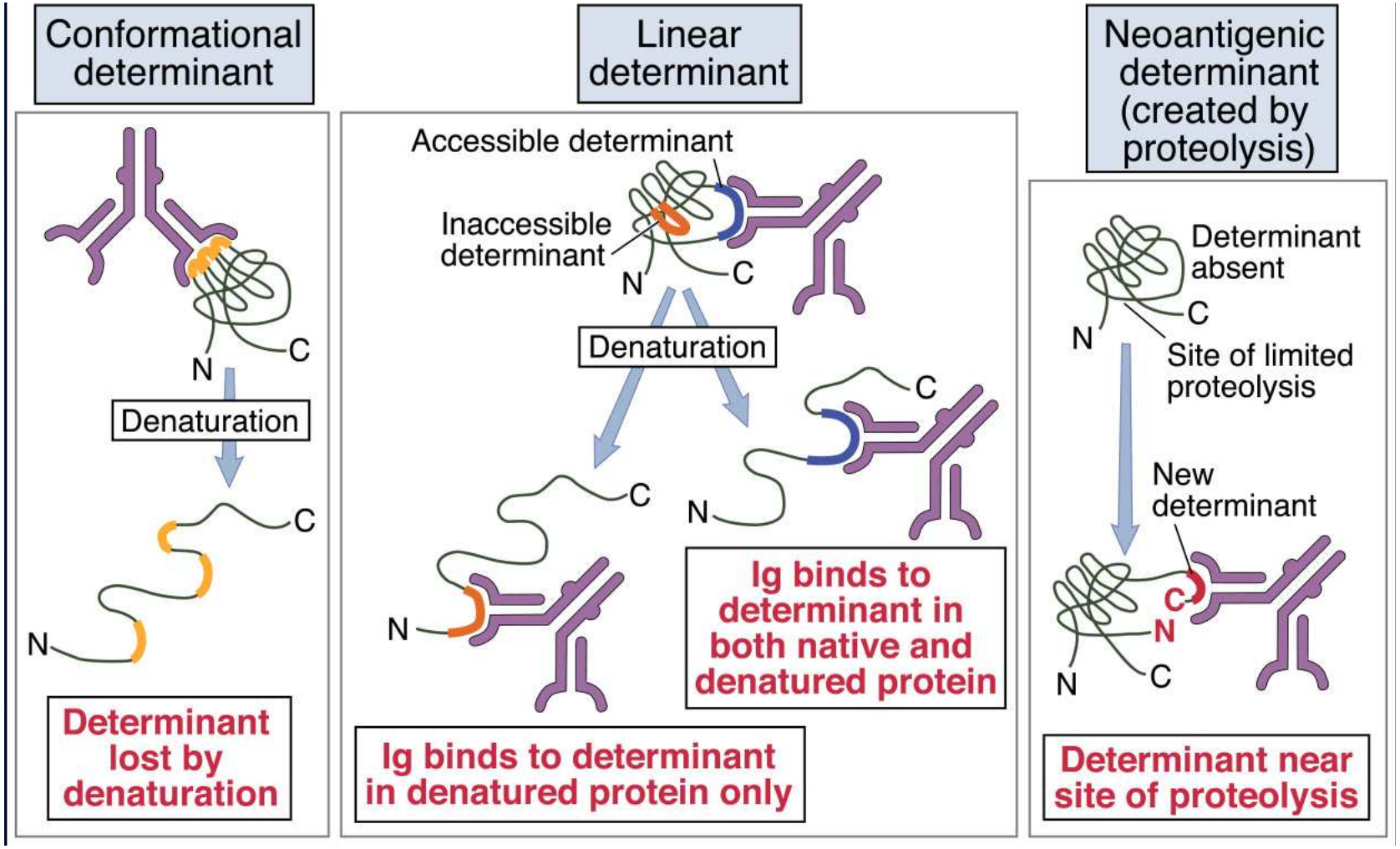
20% procesado 0.5% une a MHC 50% CTL responden



=> 1/2000 péptidos son immunogénicos

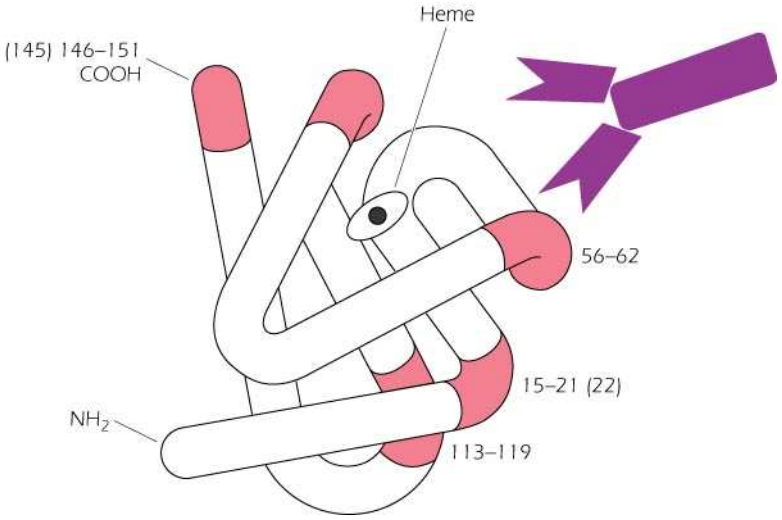
Lauemøller et al., 2000

PROPIEDADES DE LOS DETERMINANTES ANTIGÉNICOS

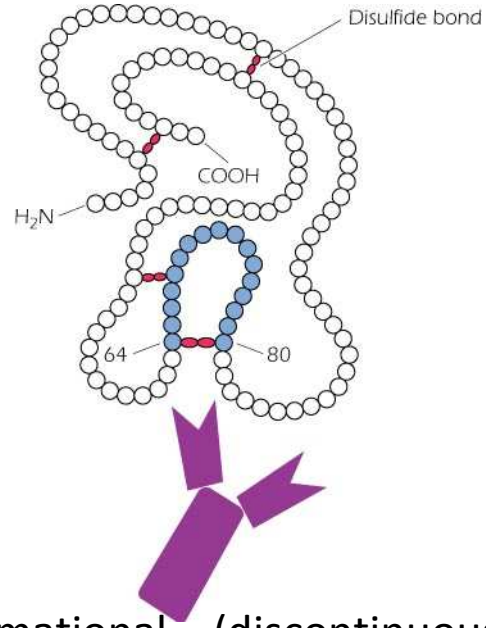


EPÍTOPES DE CÉLULAS B

LA CÉLULA B reconoce y se une al antígeno libre soluble.
Los epítopes pueden ser LINEALES O DISCONTINUOS.
Deben estar ACCESIBLES, sobre la superficie externa del antígeno.

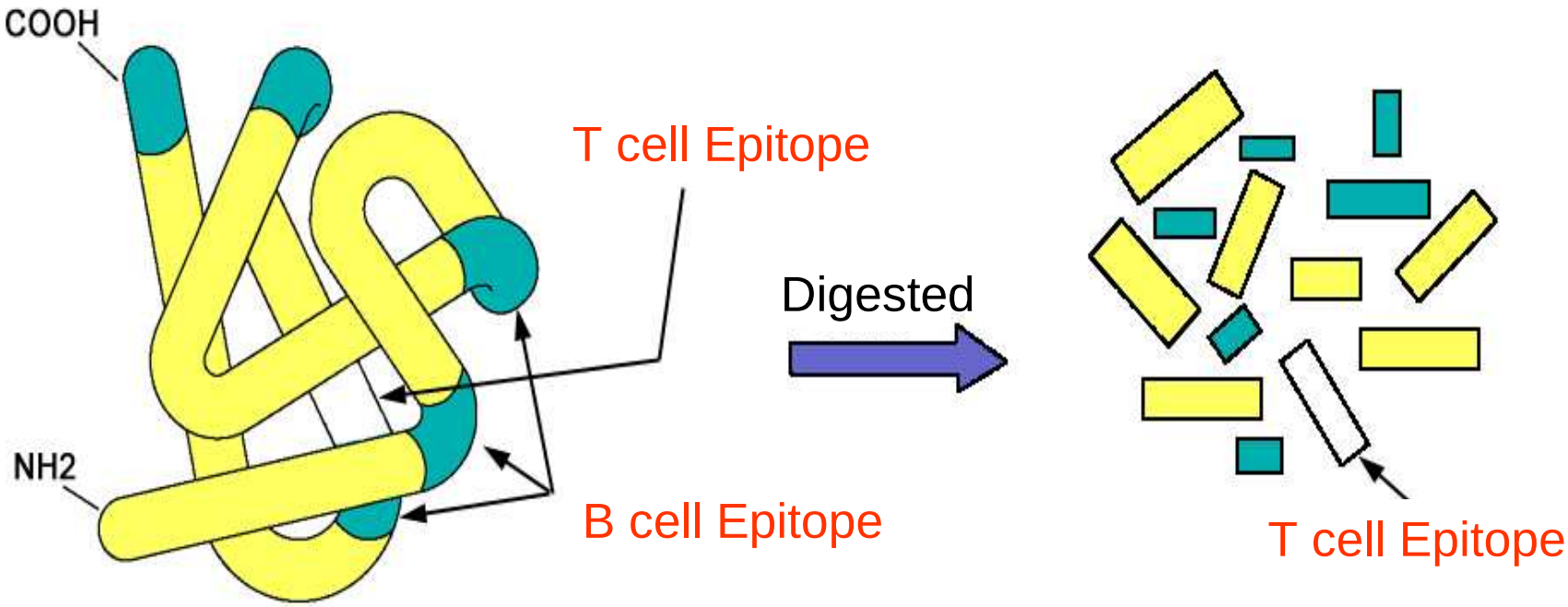


5 linear B cell epitopes (sequential amino acids)



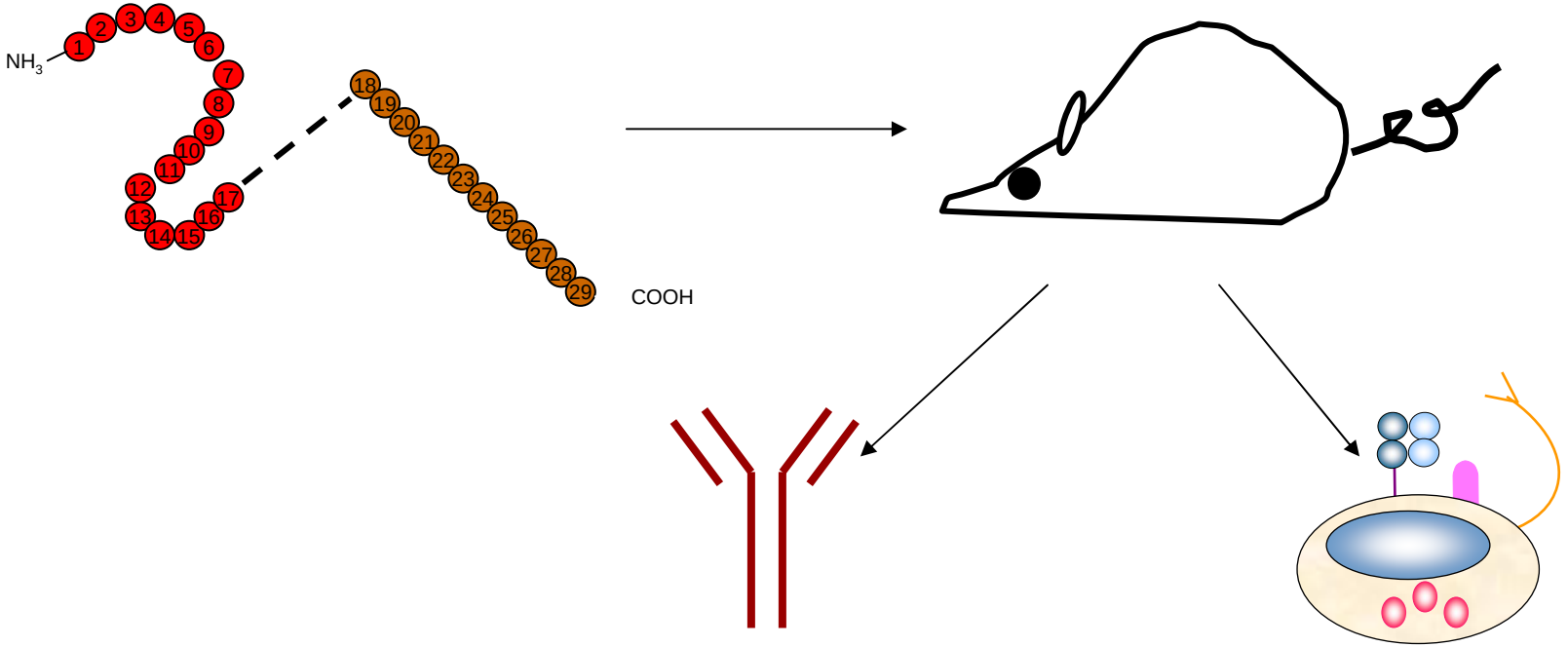
A conformational (discontinuous) B cell epitope (nonsequential amino acids)
~**90% of epitopes in globular proteins are discontinuous** (Thornton et. al. 1986, Barlow et al. 1986)

Epítope de célula B y célula T



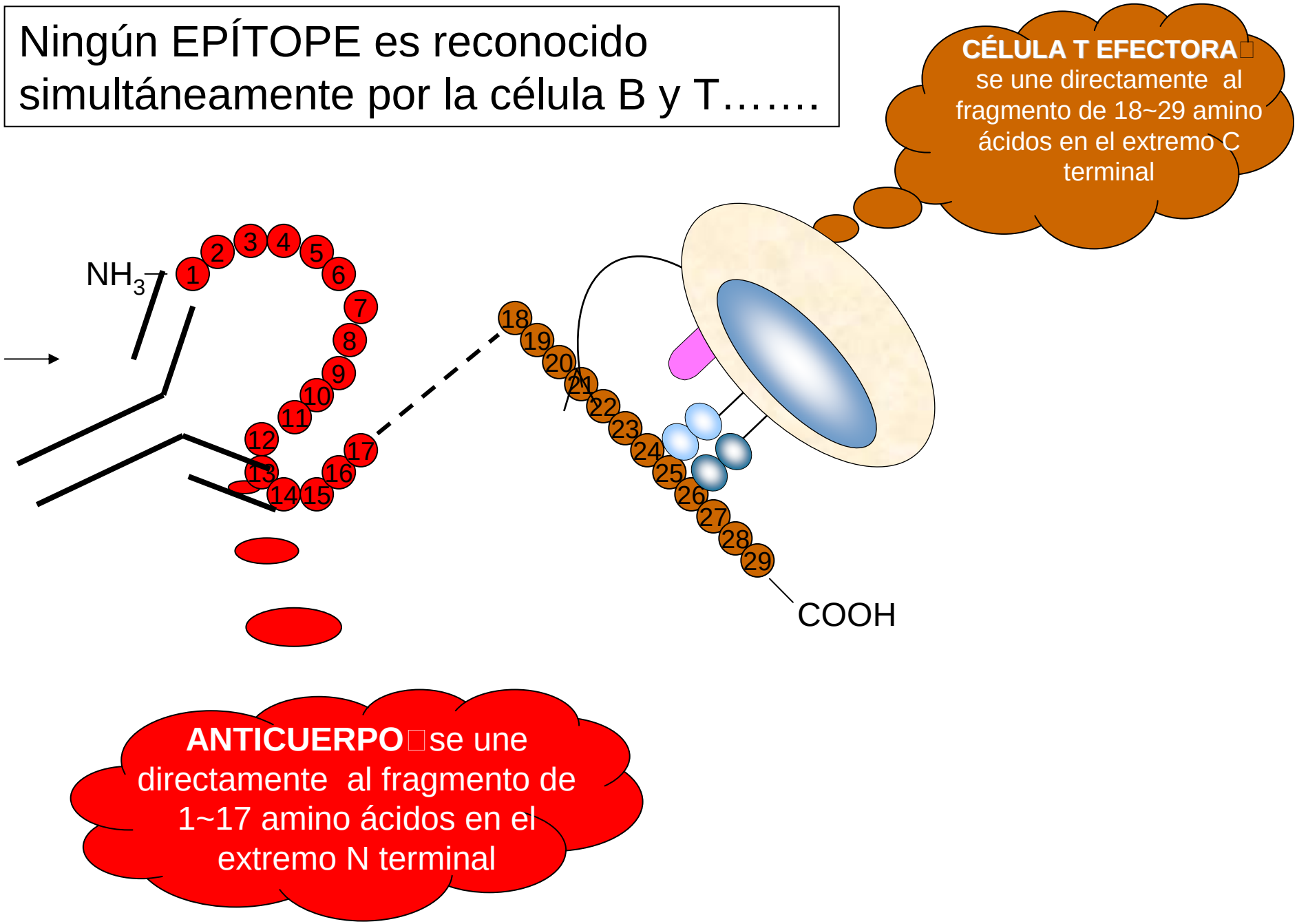
Epítope de célula B y célula T

□1□Se inocula el ratón con glucagon pancreático humano….



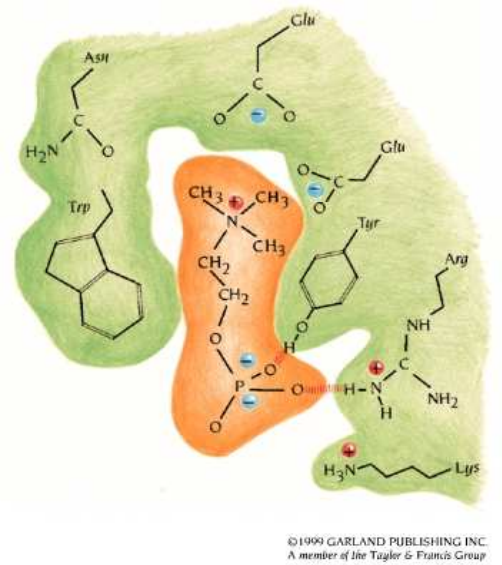
□2□Se induce la producción de anticuerpo específico y células T efectoras…..

Ningún EPÍTOPE es reconocido simultáneamente por la célula B y T…….



COMPARACIÓN DE LOS ANTÍGENOS RECONOCIDOS POR CÉLULAS B Y T

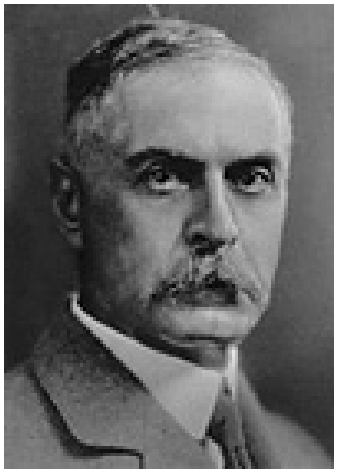
Characteristic	B cells	T cells
Interaction with antigen	Involves binary complex of membrane Ig and Ag	Involves ternary complex of T-cell receptor, Ag, and MHC molecule
Binding of soluble antigen	Yes	No
Involvement of MHC molecules	None required	Required to display processed antigen
Chemical nature of antigens	Protein, polysaccharide, lipid	Mostly proteins, but some lipids and glycolipids presented on MHC-like molecules
Epitope properties	Accessible, hydrophilic, mobile peptides containing sequential or nonsequential amino acids	Internal linear peptides produced by processing of antigen and bound to MHC molecules



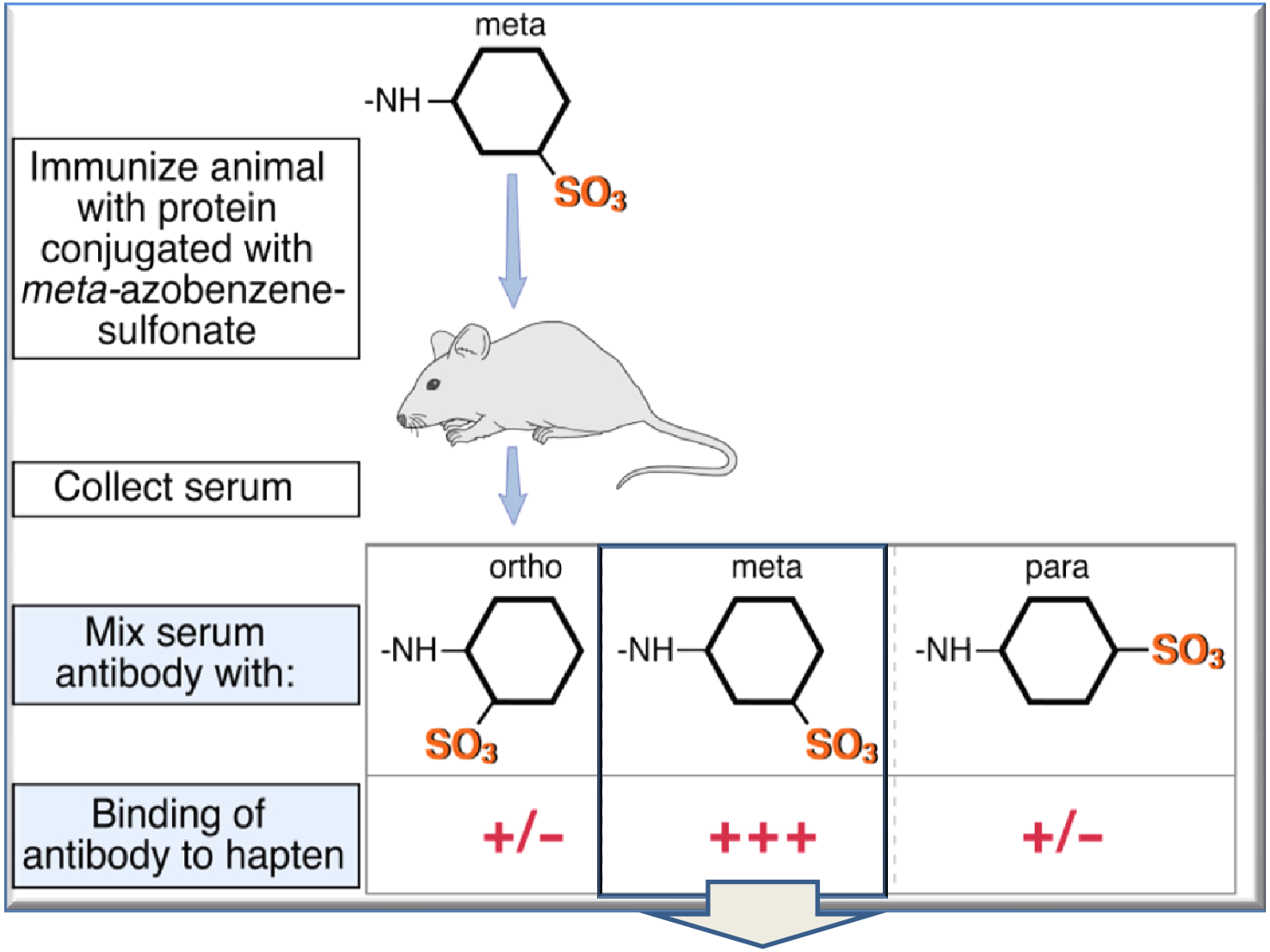
Moléculas pequeñas que si bien son antigénicas son incapaces de inducir por sí mismas una respuesta inmune……

HAPTENOS

Landsteiner observó que la CONFIGURACIÓN GLOBAL DE UN HAPTENO tiene un papel importante para determinar si podrá reaccíonar específicamente con un anticuerpo dado.



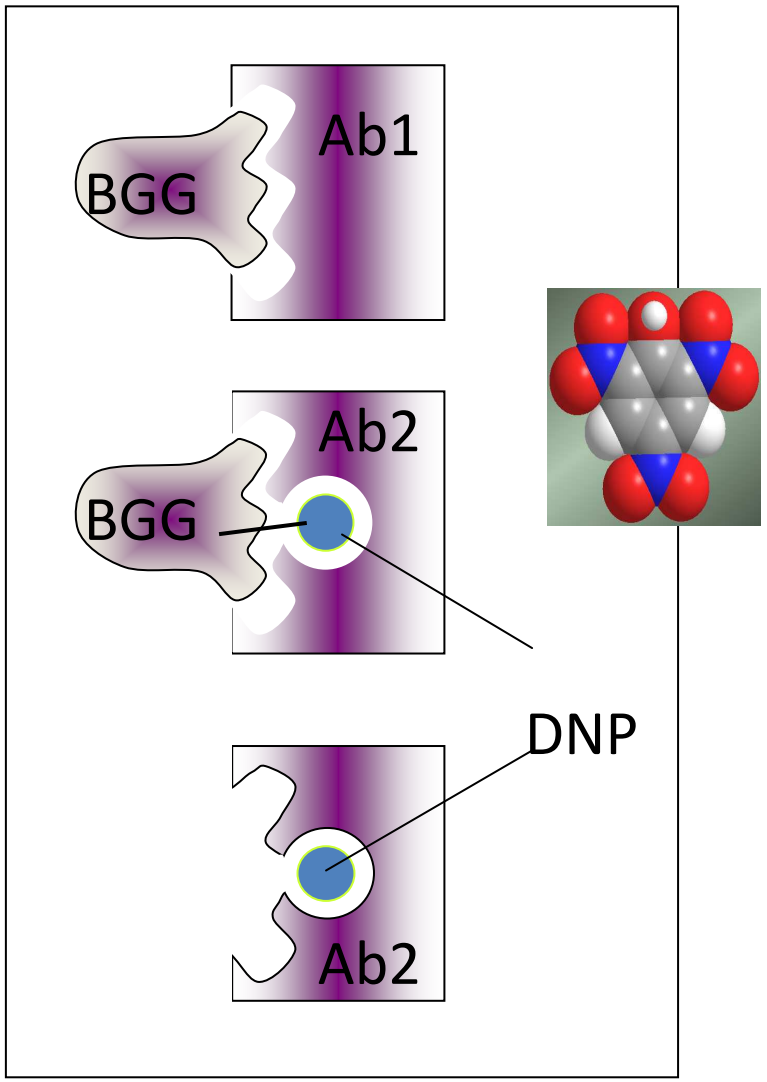
Landsteiner



Hapteno: normalmente una molécula orgánica de bajo peso molecular, como DINITROFENOL□DNP□.

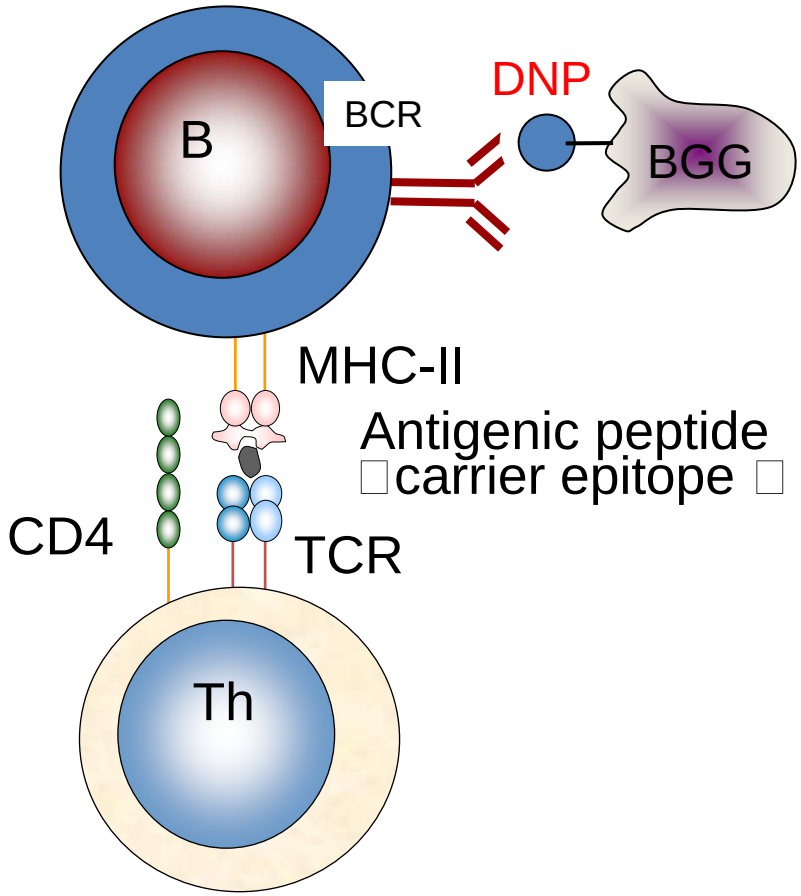
Chemical coupling of a DNP to a large protein, bovine gamma globulin (BGG) or egg albumin (EA), yields an immunogenic hapten-carrier conjugate.

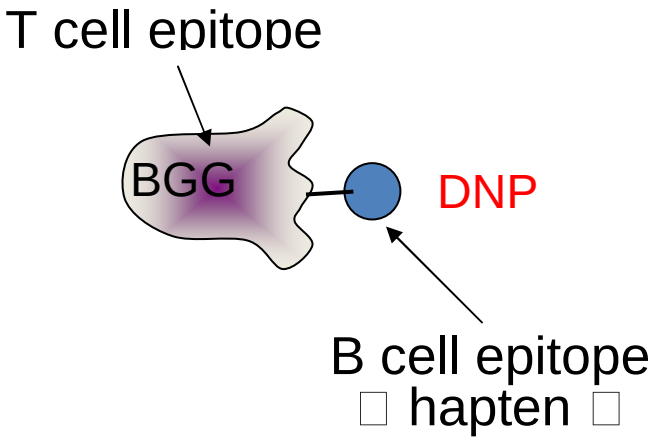
Mice immunized with such a conjugate produce antibodies specific for DNP.



EFECTO DEL PORTADOR.

The T cell stimulate the B cell , which is called carrier effector.





ANTICUERPOS ESPECÍFICOS ANTI HAPTENO

First immunized	Secondary immunized	Antibody for DNP
DNP	DNP	□
DNP	BGG-DNP	□ □
BGG	BGG-DNP	□ □ □ □
EA	BGG-DNP	□ □
EA	EA-DNP	□ □ □ □

hapten------B cell
carrier------Th cell

EL HAPTENO ES EL EPITOPO INMUNODOMINANTE

Conclusión: la respuesta de la célula Th inducida por la PROTEÍNA CARRIER juega un rol importante en la producción de ANTICUERPOS ESPECÍFICOS ANTI-HAPTENO.

¿QUÉ RESPUESTA INDUCEN LAS DIFERENTES DROGAS???

Penicilina: hapteno

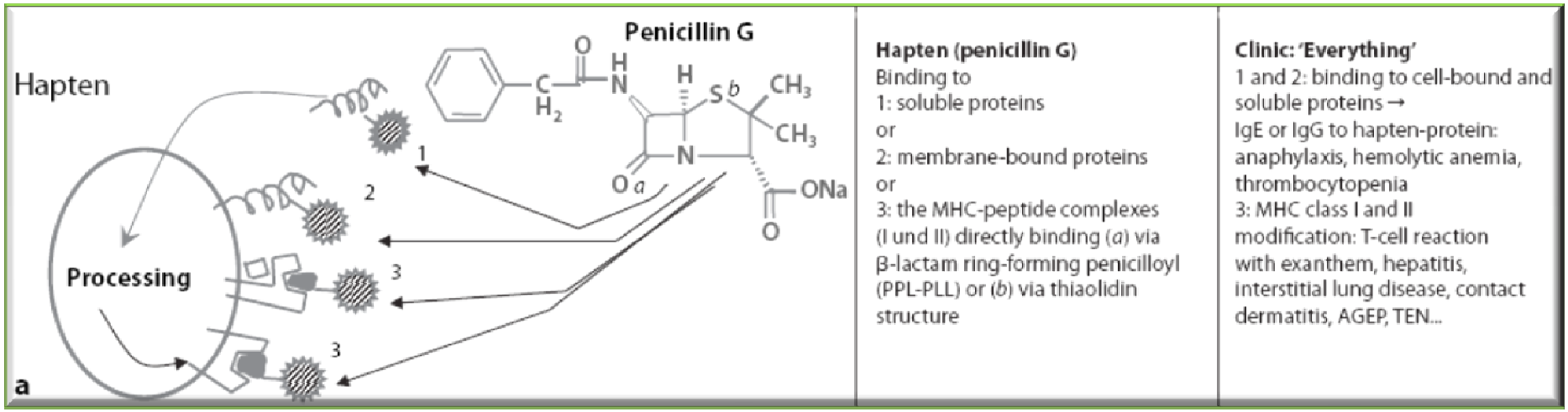
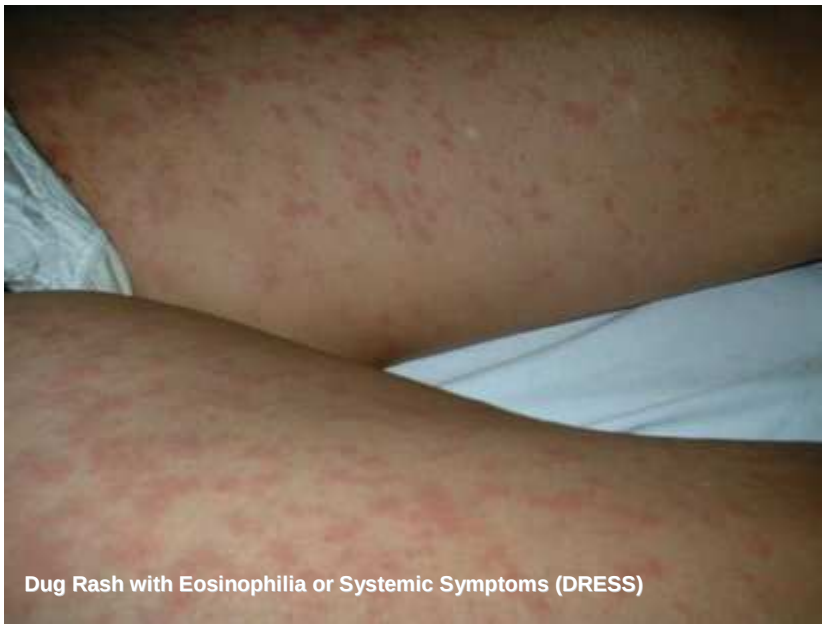


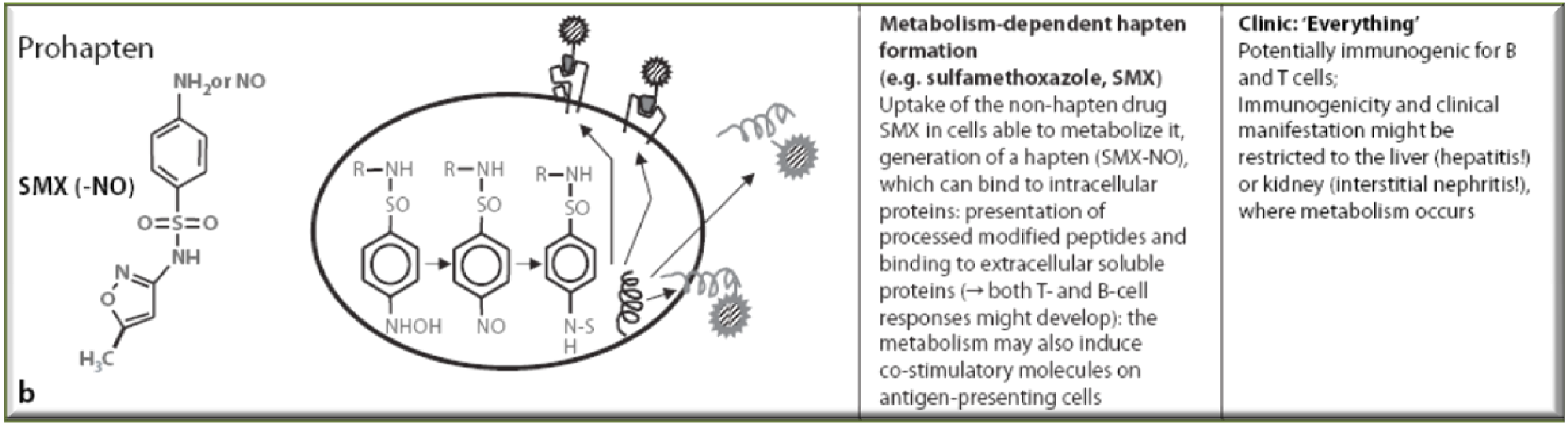
Fig. 1. Hapten and prohapten concept and the non-covalent drug presentation to T cells. **a** Haptens: Drugs are haptens if they can bind covalently to molecules, be they soluble or cell bound (e.g. penicillin G). They can even bind directly to the immunogenic major histocompatibility complex (MHC)/peptide complex on antigen-presenting cells (APC), either to the embedded peptide or to the MHC molecule itself. Thus, the chemical reactivity of haptens leads to the formation of many distinct antigenic epitopes, which can elicit both humoral and cellular immune responses. Some examples of a B- or T-cell-mediated immune response are listed on the right side.



Pichler WJ (ed): Drug Hypersensitivity. Basel, Karger, 2007, pp 168–189

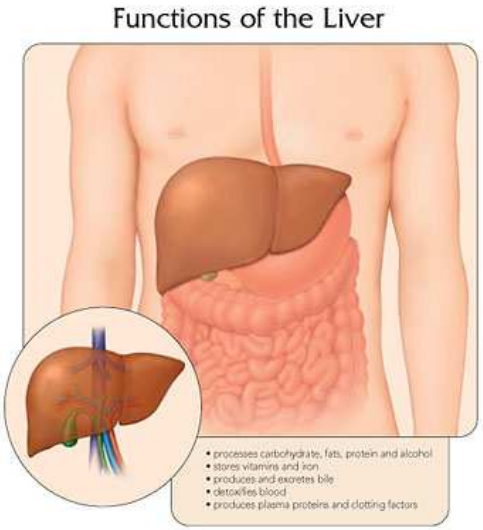
- Most drugs *not* chemically or immune reactive
- Drug is metabolized to a reactive intermediate
- **Reactive intermediate covalently binds to proteins**
- **Metabolite-protein adduct activates immune cells**
- **Immune system activation leads to cytokine release and development of symptoms**

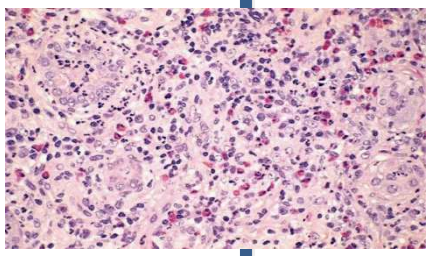
Sulfametoxazol: pro-hapteno



Metabolism-dependent hapten formation
(e.g. sulfamethoxazole, SMX)
Uptake of the non-hapten drug SMX in cells able to metabolize it, generation of a hapten (SMX-NO), which can bind to intracellular proteins: presentation of processed modified peptides and binding to extracellular soluble proteins (→ both T- and B-cell responses might develop): the metabolism may also induce co-stimulatory molecules on antigen-presenting cells

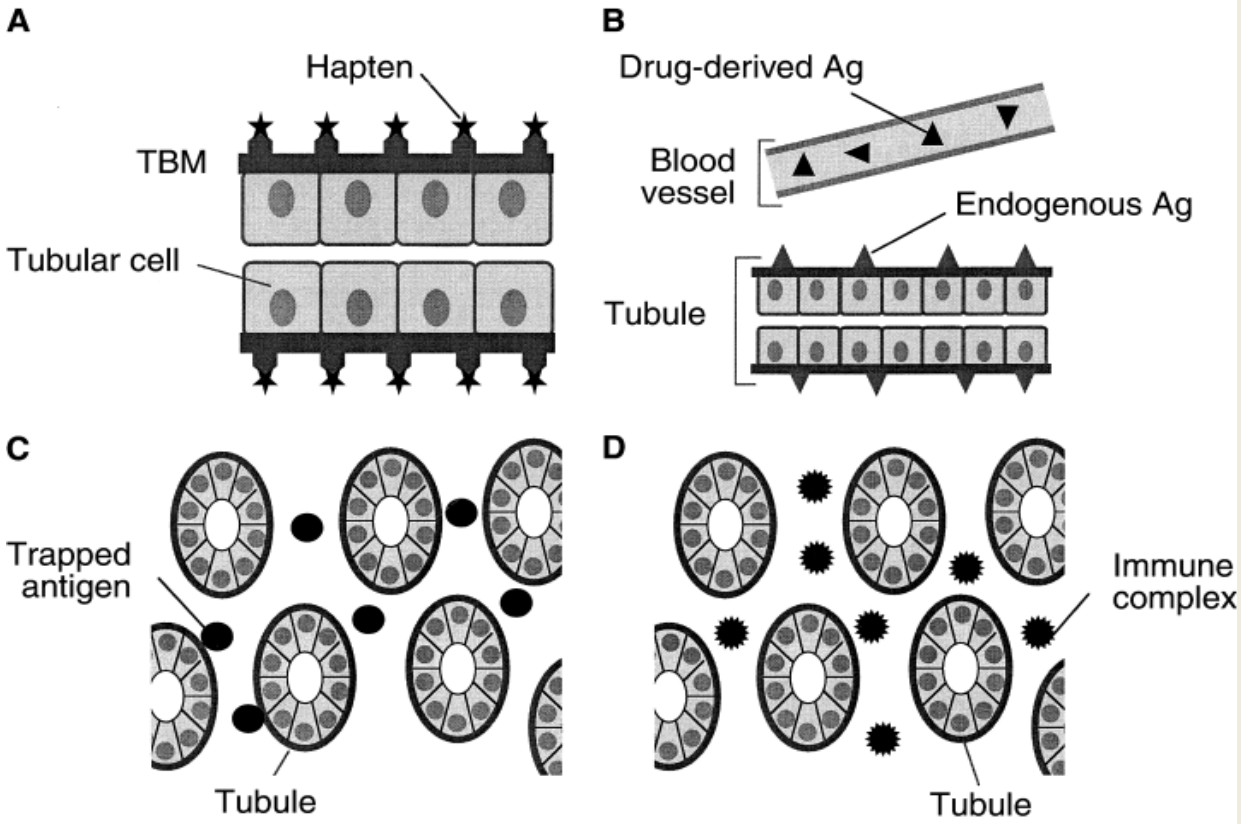
Clinic: 'Everything'
Potentially immunogenic for B and T cells;
Immunogenicity and clinical manifestation might be restricted to the liver (hepatitis!) or kidney (interstitial nephritis!), where metabolism occurs





Diagnostic group	Common	Uncommon
Systemic infection	Diphtheria Streptococci	Leprosy *Rickettsia* *legionella* Syphilis Leptospira Toxoplasma Brucella Mycoplasma Measles virus
Drug reaction	Antibiotics Methicillin Penicillin Ampicillin Cephalosporins Sulfonamides Rifampin Phenindione Nonsteroidals	Antibiotics Oxacillin Nafcillin Tetracycline Diuretics Thiazides Furosemide Triamterene Ethacrynic acid Phenytoin Allopurinol Cimetidine
Immune or immune-like inflammation	Sarcoidosis	Anti-TBM disease Sjögren's syndrome TINU syndrome

Mecanismo de inducción de AIN



http://www.nature.com/ki/journal/v60/n2/fig_tab/4492487f1.html#figure-title

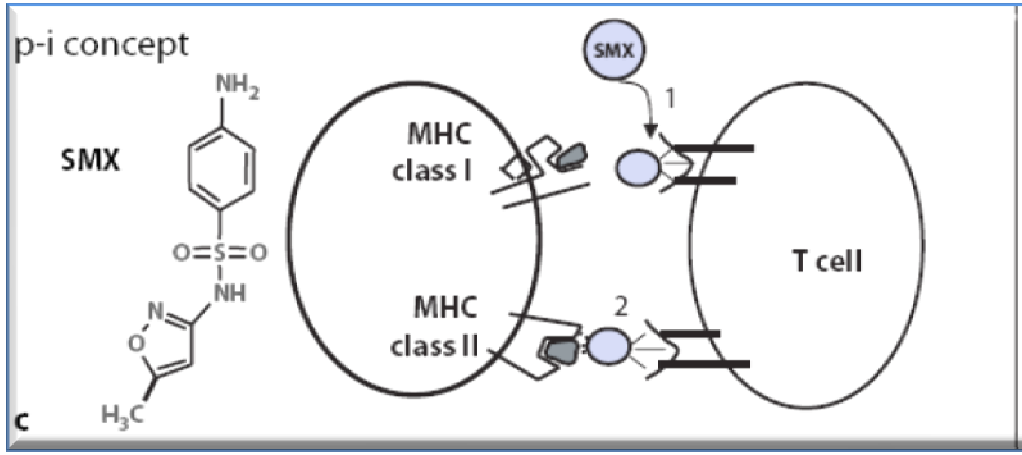
- Drug-induced AIN is secondary to immune reaction
- AIN occurs only in a small percentage of individuals taking the drug
- **AIN is not dose-dependent**
- Association with extrarenal manifestations of hypersensitivity
- Recurrencence after re-exposure to the drug
- Experimental models suggest that drugs responsible for AIN induce an immune reaction directed against endogenous renal antigens

p-i concept

(*pharmacological* interaction with immune receptors)

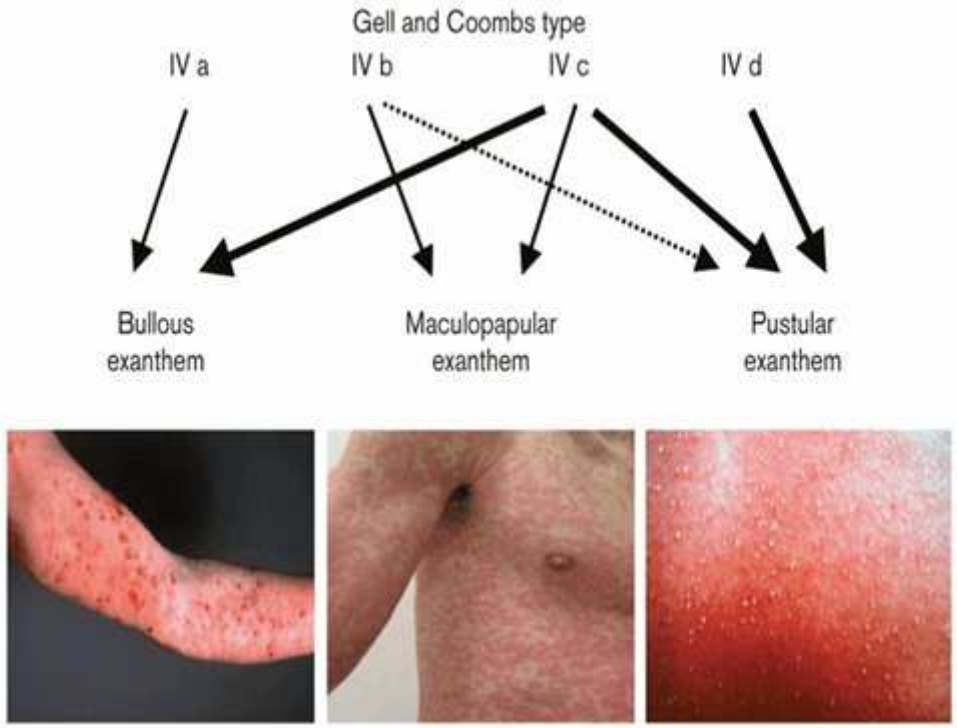
…las DROGAS pueden actuar como SUPERANTÍGENOS

- The **p-i concept** postulates a bypassing of the development of a normal immune response, as **a direct, pharmacological stimulation of memory and effector T cells is implied;**
- Therefore, it does *not follow the normal rules* of an immune response, which may already explain some as 'bizarre' classified clinical features;
- **It could appear at the first encounter with the drug, as no sensitization is required**;
- **Those T cells which happen to be stimulated by drugs are assumed to actually have a peptide specificity (to which they were primed); however, which peptides are recognized is unknown.**

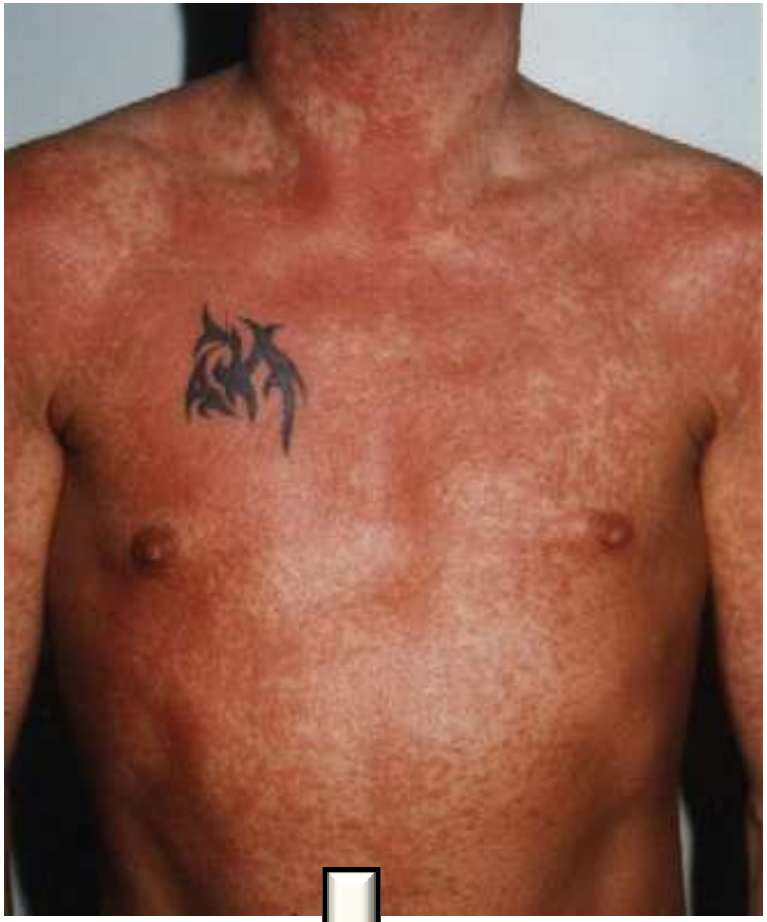


p-i concept
The drug happens to fit into some TCR (1) with sufficient affinity to cause a signal. This drug-TCR interaction is supplemented by MHC interaction (2); the T cells react and proliferate. No metabolism of drugs required. The reacting T cells are probably preactivated and have an additional peptide specificty

Clinic: Only T cells
An exclusive T-cell response might develop with exanthems, hepatitis, etc.
Whether B cells (by drug binding to Ig) can similarily be stimulated, remains unclear

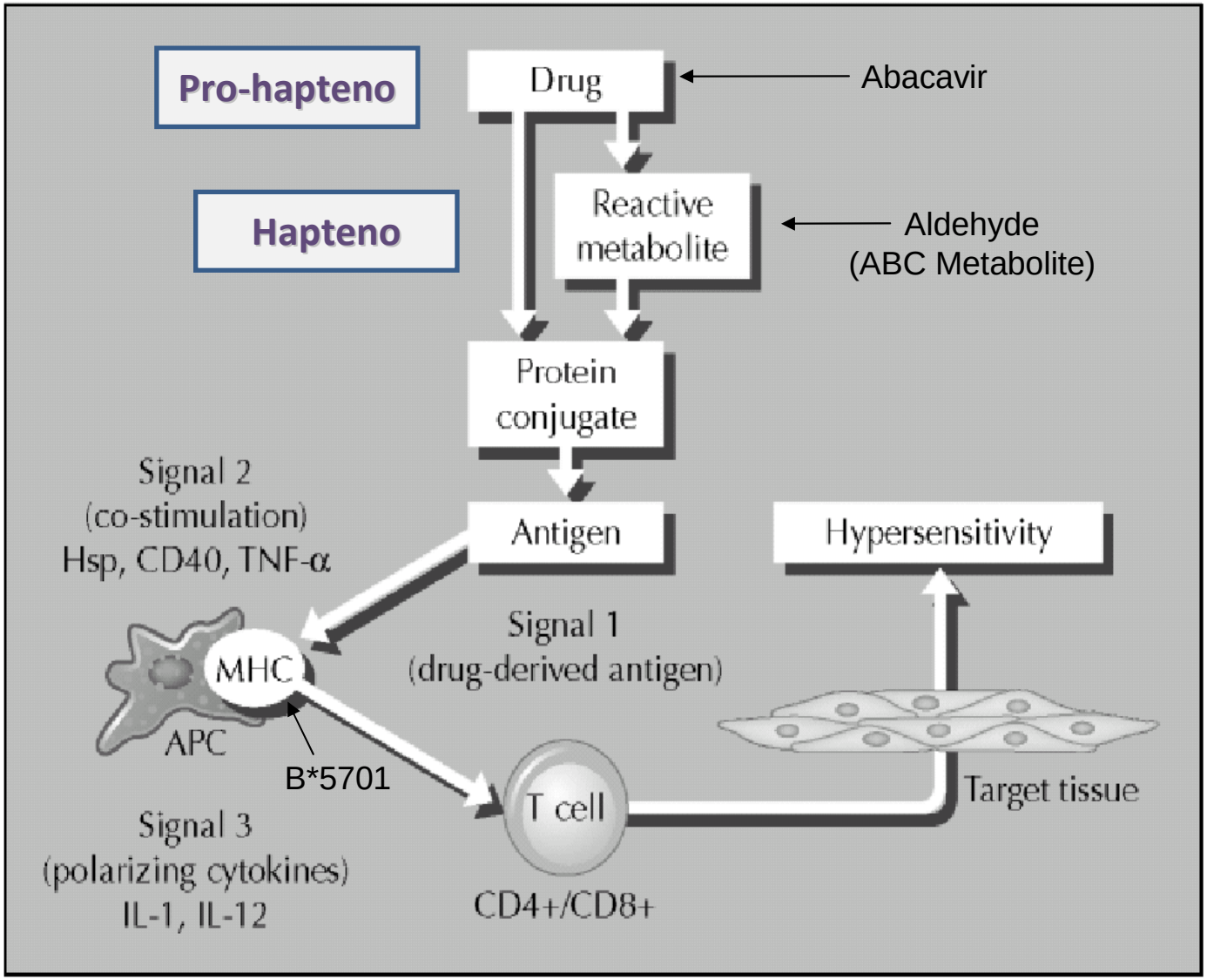


Abacavir



- Nucleoside analogue
- **Reverse transcriptase inhibitor**
- Hypersensitivity 5%
- Fever, skin rash, gastro-intestinal symptoms
- Within 6 weeks

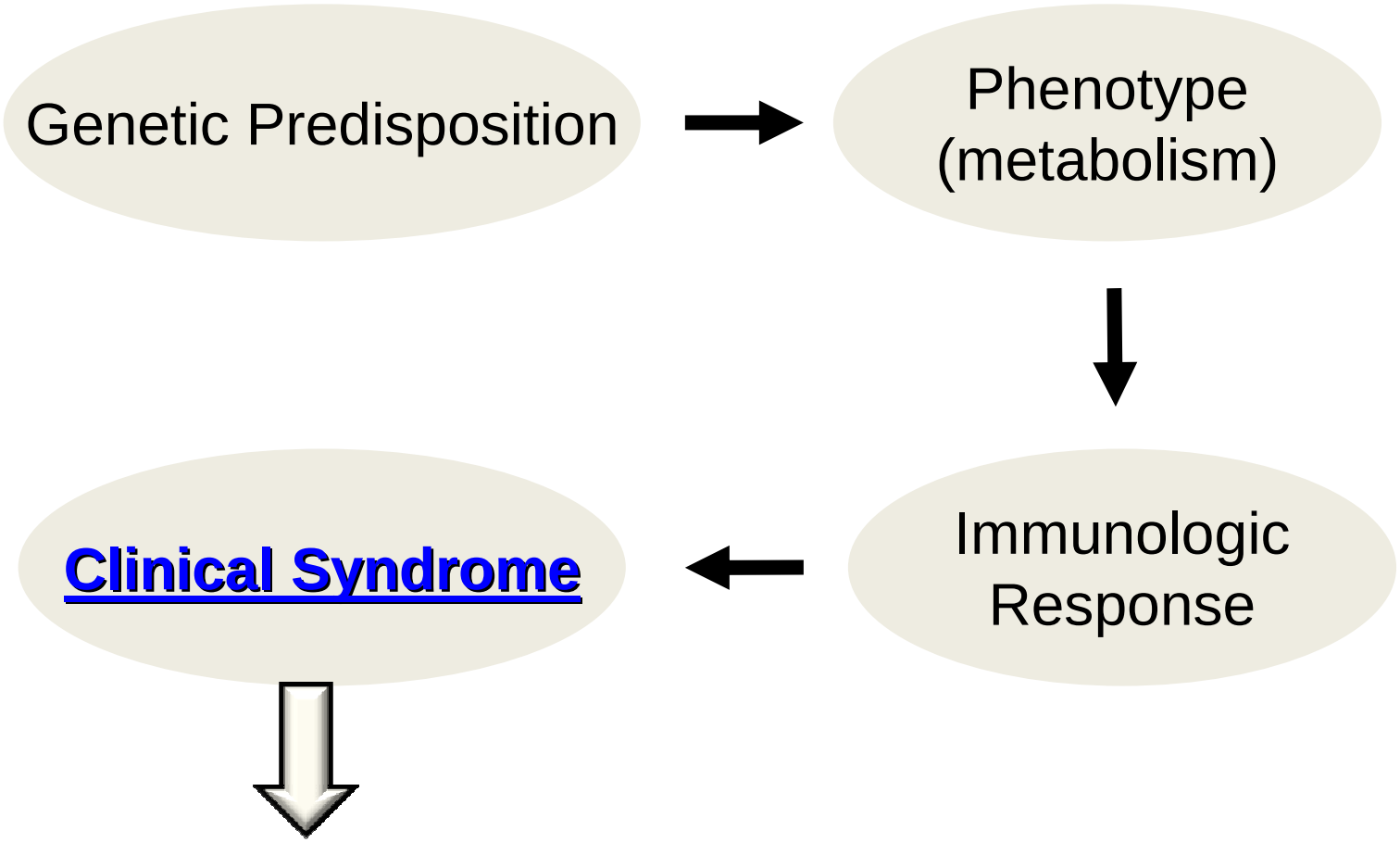
Hipótesis razonable…..



Naisbitt DJ, Pirmohamed M, Park BK, Current Allergy and Asthma Reports 2003;3:22-29

HIPÓTESIS DEL SINDROME DE HIPERSENSIBILIDAD POR DROGAS

Human genetic variation known as **HLA-B*5071** is strongly associated with susceptibility to abacavir hypersensitivity



Níquel: se comporta como SA

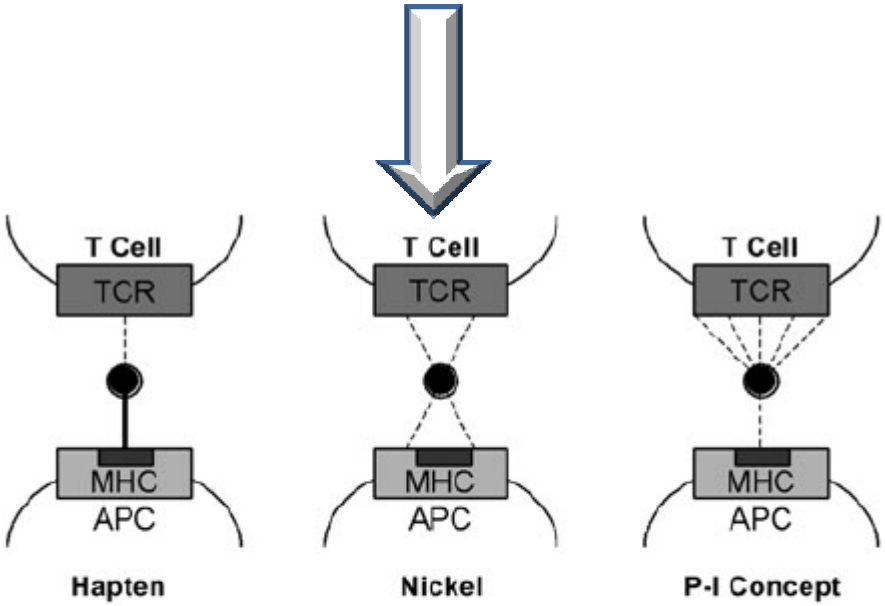
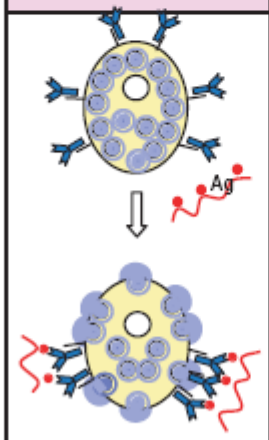
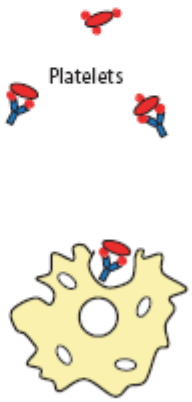
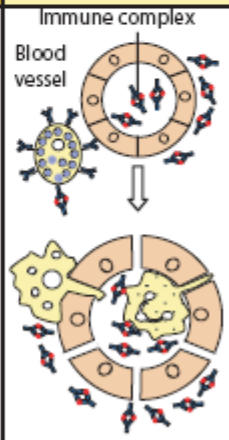
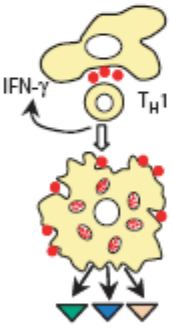
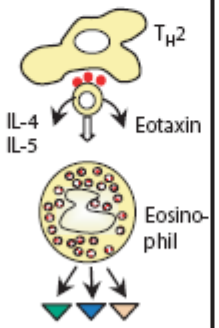
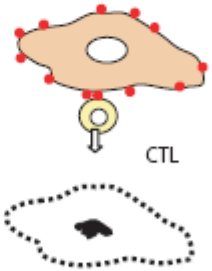
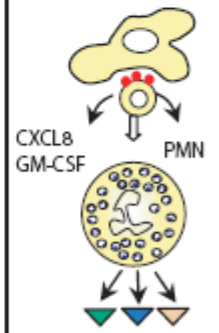


Figure 1. A schematic representation of how the TCR and the MHC might accommodate an antigen according to different models. The antigen (metal ion or drug) is depicted as a black ball, covalent bonds are indicated by bold lines, and noncovalent interactions by thin, dashed lines.

Nickel ions (Ni) are generally considered haptens even though they do not bind to proteins covalently but rather by forming reversible coordination complexes.[42] Weltzien and coworkers identified and characterized an HLA-DR-promiscuous, Ni-specific TCR in which Ni interacts simultaneously with the MHC and TCR by making contacts with a conserved His81 in the HLA-DR α-chain as well as Tyr29 and Tyr94 in CDR1α of the TCR. Thus, Ni forms a bridge between both receptors, much like a superantigen, even though requiring idiotypic residues in the TCR.[13] Ni has 6 coordination sites, of which only 3 are known for this complex at present. Nevertheless, a substantial part of its binding energy will be derived by the 2 (at least) contacts with the TCR of this complex. In fact, Ni binding may represent a "compromise" between how a typical hapten and a small antigen incapable of covalent binding may interact with the MHC and the TCR (see Figure 1 and legend for a detailed explanation).

Antibody (I–III) and T-cell orchestrated hypersensitivity reactions (IV a–d)

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IIFN-γ, TNF-α (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ granzyme B (CTL)	CXCL8, GM-CSF (T cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
Example of hypersen-sitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Hemolytic anemia, thrombocyto-penia (e.g., penicillin)	Serum sickness, Arthus reaction	Tuberculin reaction, contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis Maculopapular exanthema with eosinophilia	Contact dermatitis Maculopapular and bullous exanthema Hepatitis	AGEP Behçet's disease

FACTORES QUE INFLUYEN EN LA INMUNONEGENICIDAD

Relacionados al ANTÍGENO

1. Alteridad (distancia genética)
2. Tamaño molecular
3. Composición y complejidad químicas
4. Forma de presentación
5. Degradabilidad

Relacionados al HUÉSPED

1. Genotipo del receptor
2. Dosis y vía de administración
3. Adyuvantes
4. Edad
5. Nutrición
6. Factores ambientales

Vías de inoculación más efectivas

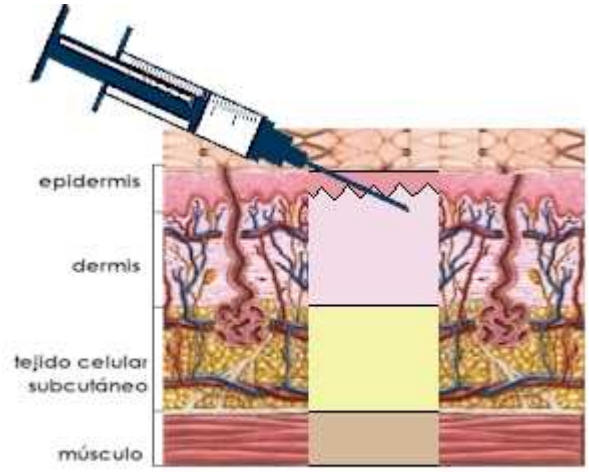


Figura 1.- Vía intradérmica

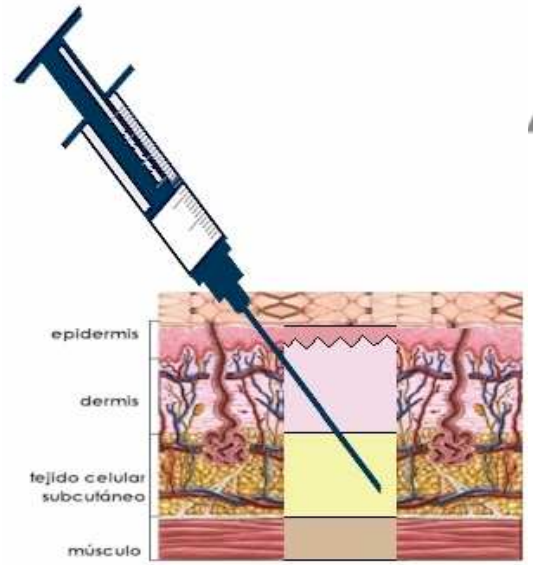


Figura 2.- Vía subcutánea o hipodérmica

Inmunogenicidad

Vía parenteral no i.v.

Subcutánea
Intradérmica
Intramuscular

Vía oral

Vía intravenosa

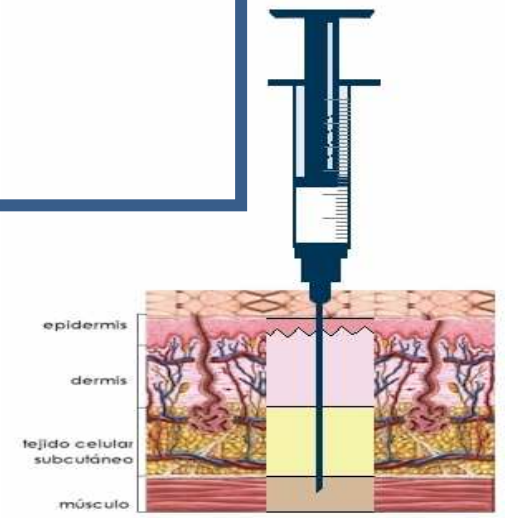


Figura 3.- Vía intramuscular

Factores que influencian la INMUNOGENICIDAD de las PROTEÍNAS

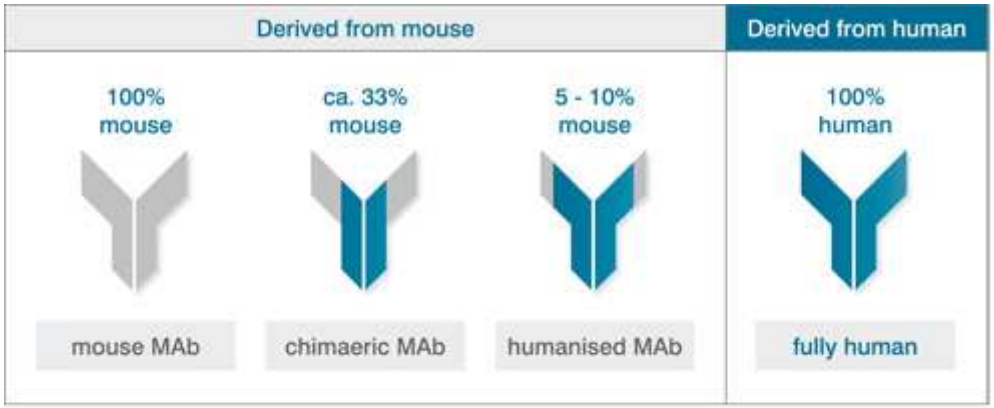
Parameter	Increased immunogenicity	Decreased immunogenicity
Size	Large	Small (MW<2500)
Dose	Intermediate	High or low
Route	Subcutaneous > intraperitoneal > intravenous or intragastric	
Composition	Complex	Simple
Form	Particulate	Soluble
	Denatured	Native
Similarity to self protein	Multiple differences	Few differences
Adjuvants	Slow release	Rapid release
	Bacteria	No bacteria
Interaction with host MHC	Effective	Ineffective

Figure A-2 Immunobiology, 6/e. (© Garland Science 2005)

Kids get Arthritis too

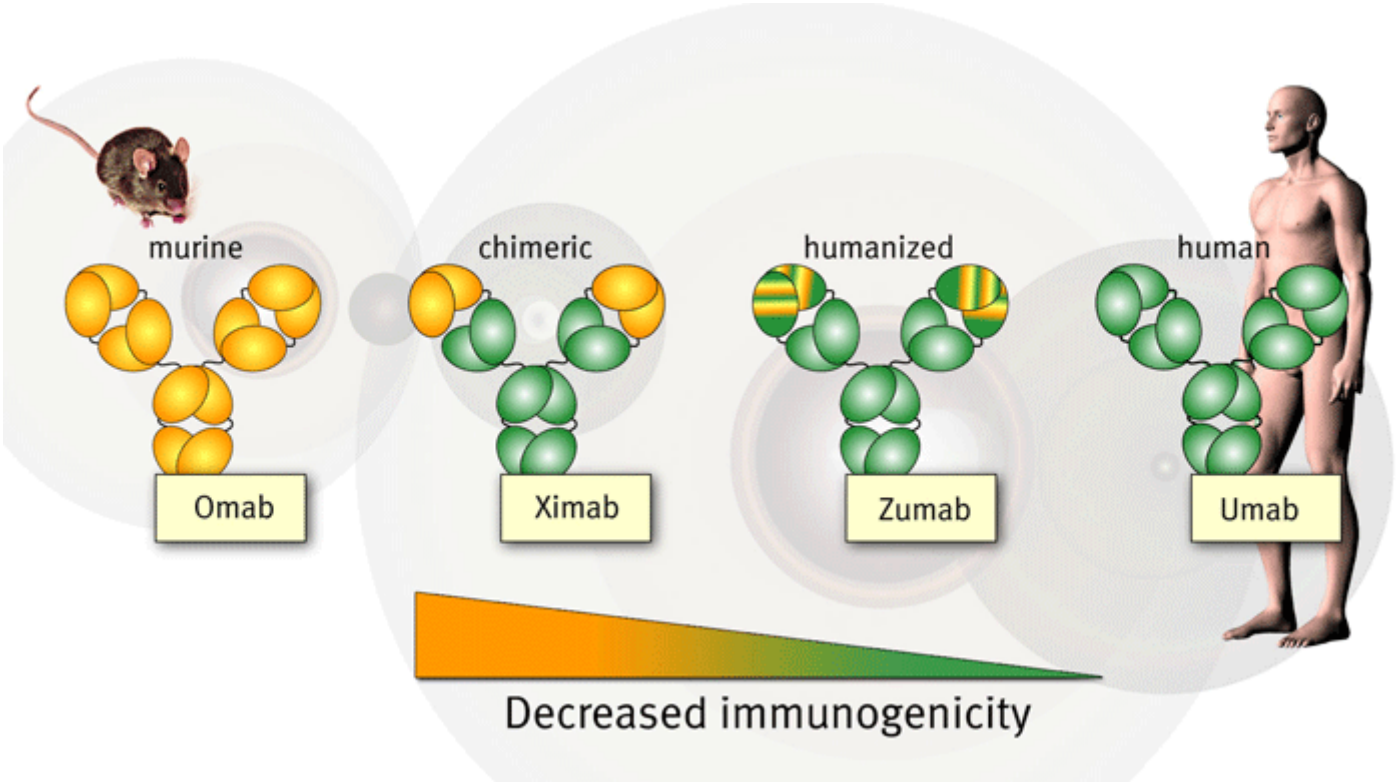
Arthritis Foundation®

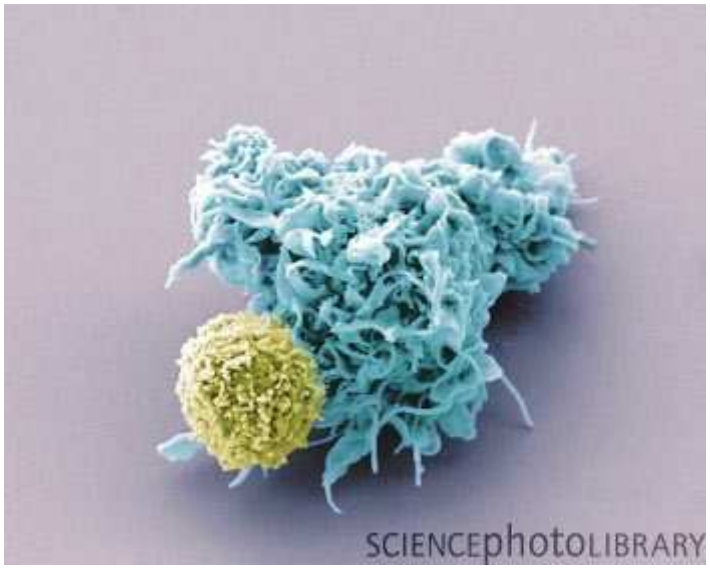
Generic names for mAbs reveal their genetic origins. MAb generic names end with the suffix -mab, but the preceding one or two letters indicate the animal genetic source: o = mouse, xi = chimeric, zu = humanized, u = human. For example, tositumomab is murine, rituximab is chimeric, bevacizumab is humanized, and panitumumab is human. In general, the immunogenicity of mAbs decreases with an increase in the amount of human-derived protein sequence.



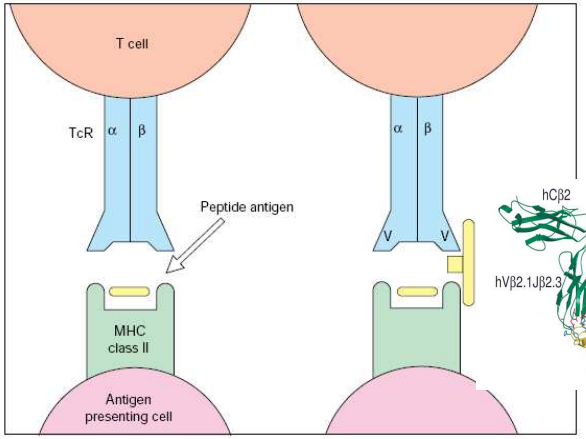
Advantages of fully human antibodies:

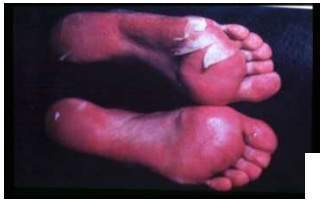
- Minimized immunogenicity
- Multiple treatments possible
- Improved serum half-life

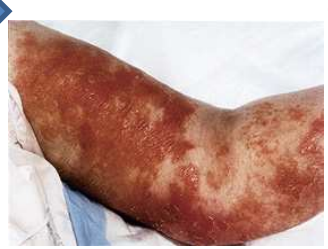




TIPOS DE ANTÍGENOS



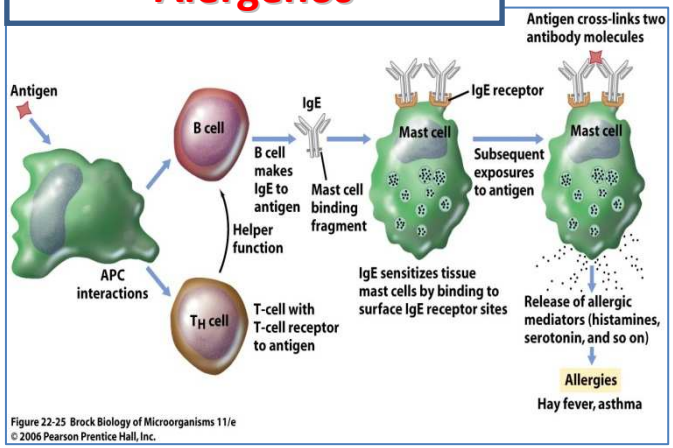


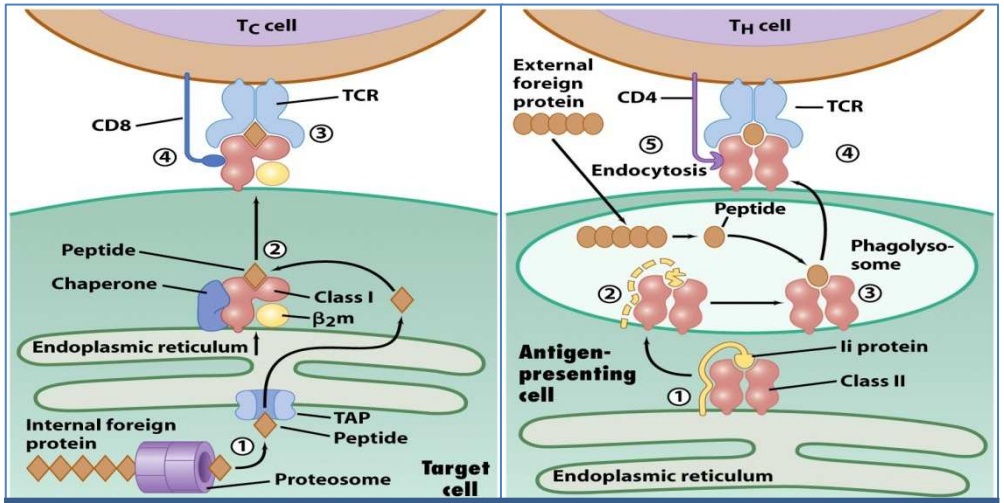


Superantígenos

Normally less than 0.01% of T-cells respond to a particular antigen, but 5% to 25% of T-cells can be activated by a SA

Alergenos

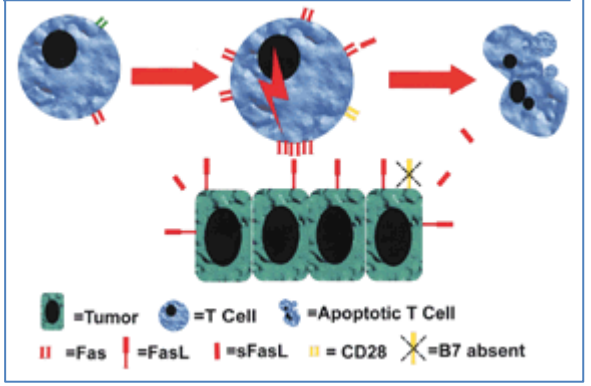




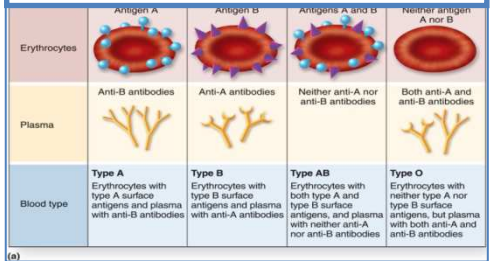
Endoantígenos

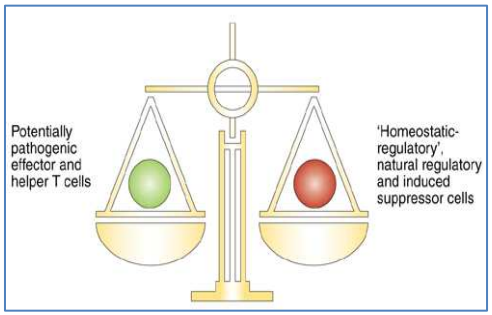
Exoantígenos

Antígenos Tumorales



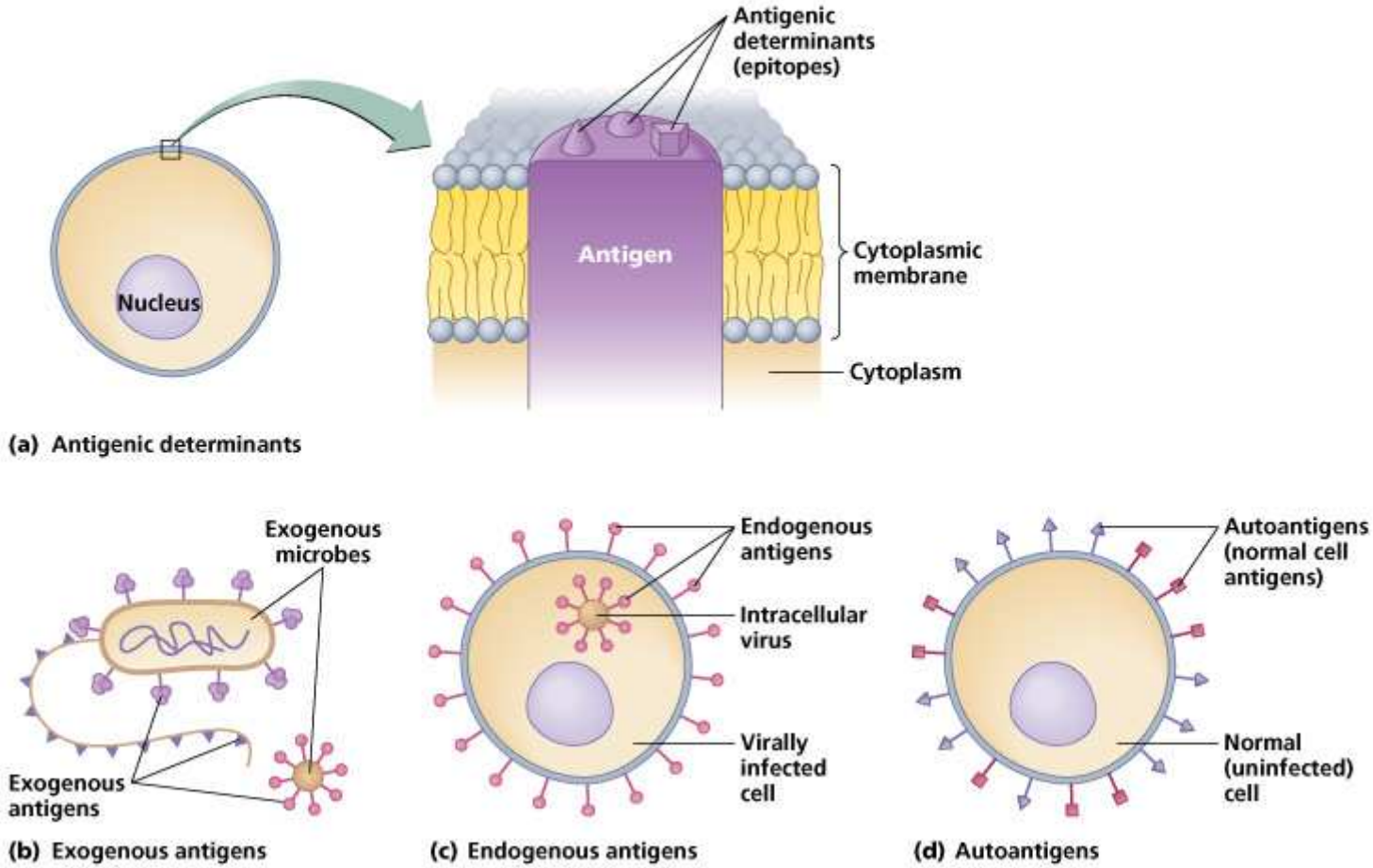
Antígenos ABO





- **Exógenos** (microorganismos, alergenos)
- **Endógenos** (microorganismos, productos metabólicos)
- **Autoantígenos** (aloantígenos, xenontígenos)
- **Antígenos crípticos**
- **Antígenos tumorales**
- **Superantígenos**
- **Mitógenos**

TIPOS DE ANTÍGENOS según su ORIGEN



SON AQUELLOS QUE HAN INGRESADO AL ORGANISMO DESDE EL EXTERIOR, POR EJEMPLO POR VÍA RESPIRATORIA, DIGESTIVA, SANGUÍNEA…….

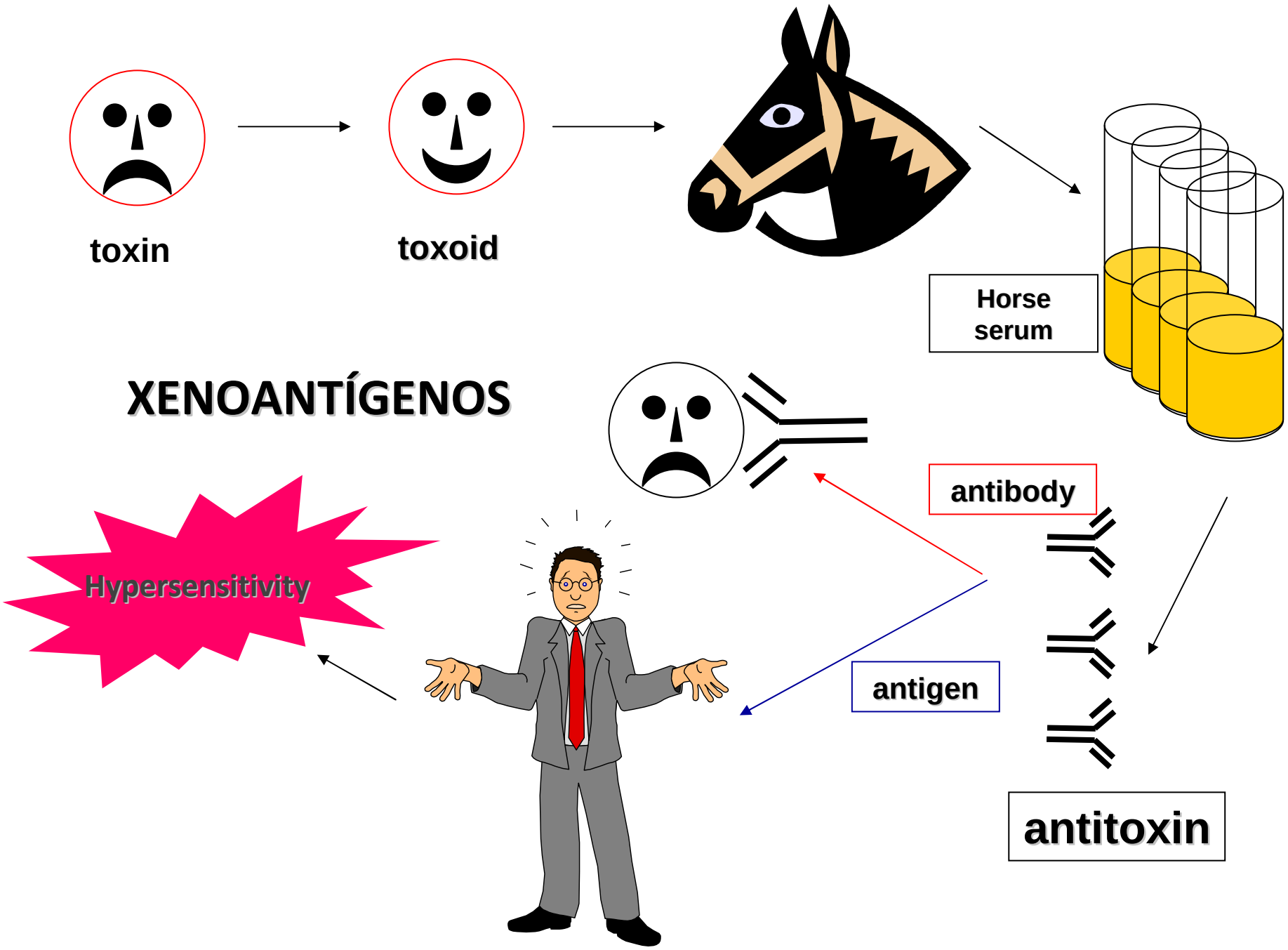
ANTIGENOS EXÓGENOS

Son aquellos que han sido generados dentro de la célula, como consecuencia del metabolismo celular normal, o bien tras una infección microbiana.

ANTÍGENOS ENDÓGENOS

Usualmente son proteínas normales o complejos de proteínas-DNA (DNP) que son reconocidas por el sistema inmune de un paciente que padece una **enfermedad autoinmune.**

AUTOANTÍGENOS


toxin
toxoid
Horse serum
XENOANTÍGENOS
antibody
Hypersensitivity
antigen
antitoxin

…expresados en distintas especies

ANTITOXINAS

(1) **ESPECIFICIDAD**: NEUTRALIZAN LA TOXINA

(2) **ANTÍGENO XENOGENEICO**: ESTIMULA LA PRODUCCIÓN DE ANTICUERPOS CONTRA LAS PROTEÍNAS DEL SUERO EQUINO

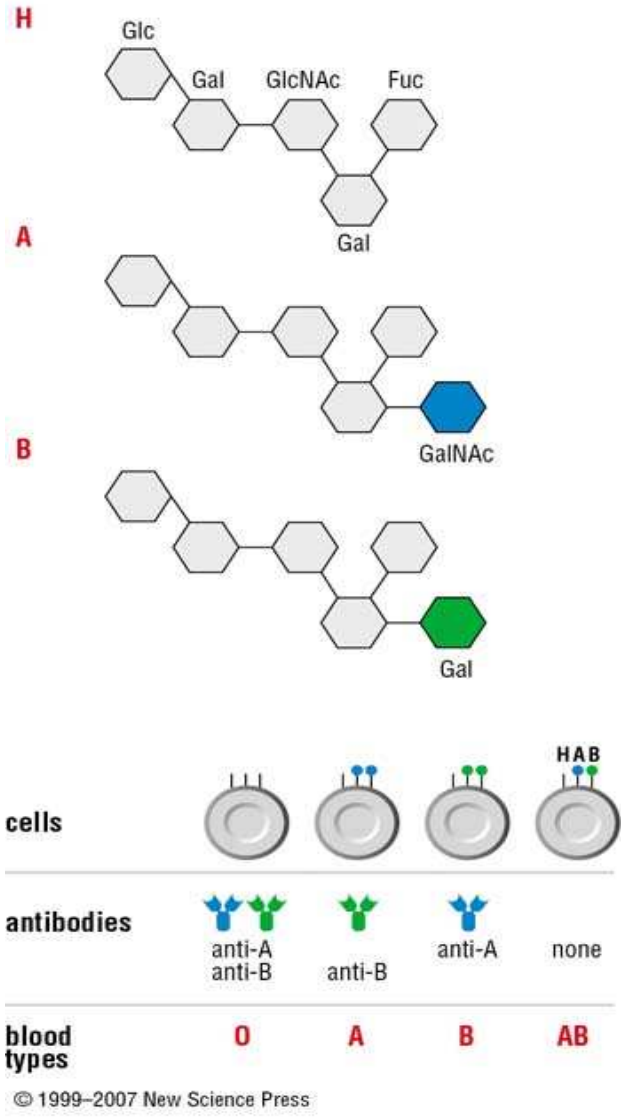
ALOANTÍGENOS

- **Antígenos expresados en diferentes individuos de la misma especie:**

❖ **Antígenos ABO**

❖ **Antígenos de HISTOCOMPATIBILIDAD**

ANTÍGENOS ABO



The ABO Blood System

Blood Type (genotype)	Type A (AA, AO)	Type B (BB, BO)	Type AB (AB)	Type O (OO)
Red Blood Cell Surface Proteins (phenotype)	A agglutinogens only	B agglutinogens only	A and B agglutinogens	No agglutinogens
Plasma Antibodies (phenotype)	b agglutinin only	a agglutinin only	NONE. No agglutinin	a and b agglutinin

ISOHEMAGLUTININAS

A antigen

Anti-A antibody

RBC

Type A

Type B

Anti-A antibody

complement

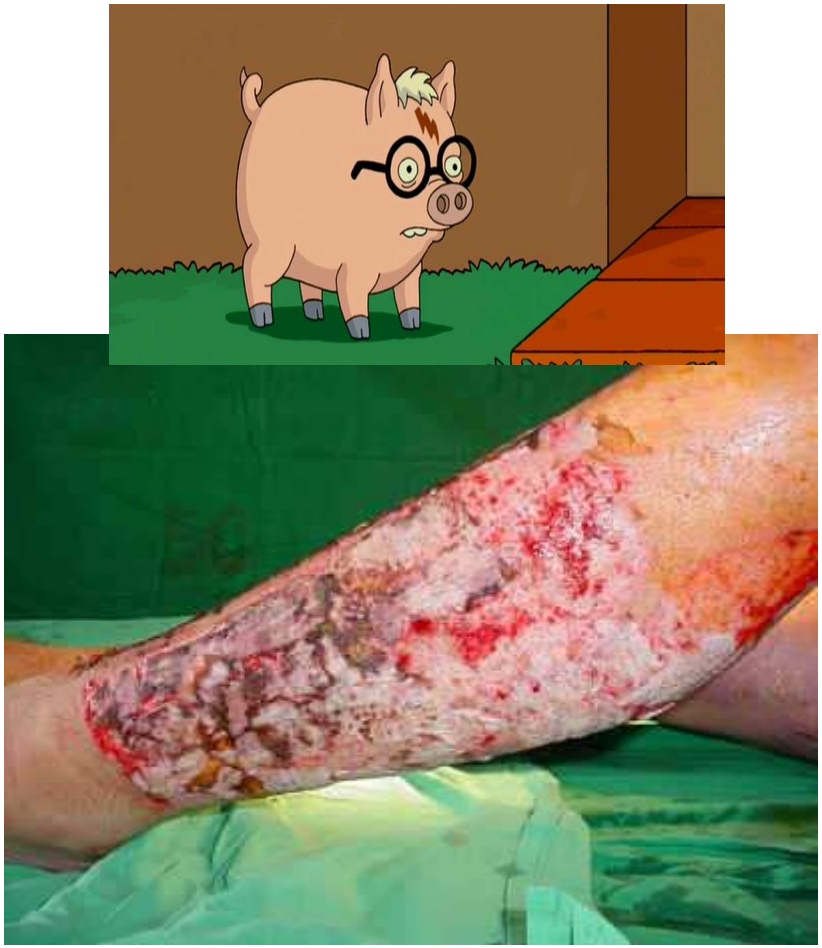
+

RBC

RBC

RBC

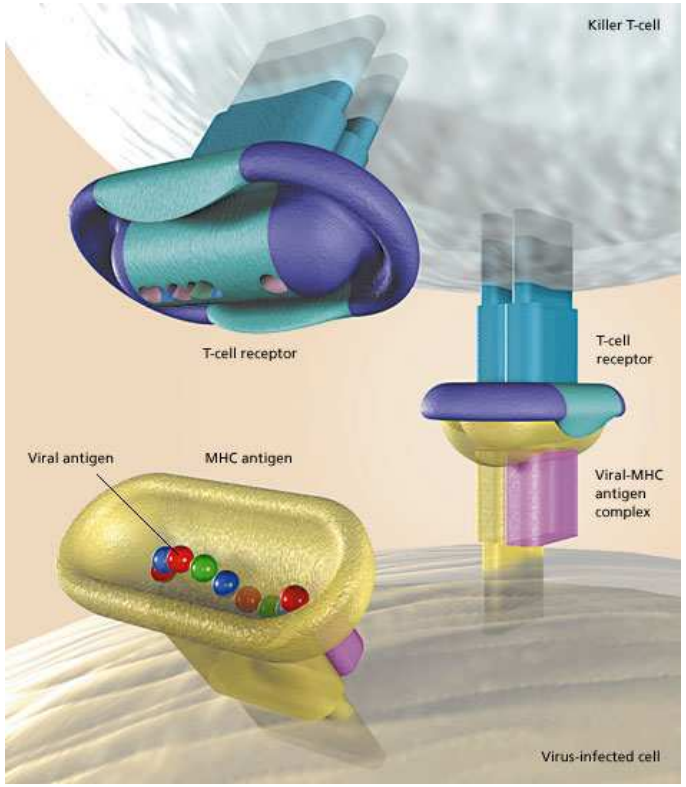
REACCIÓN TRANSFUSIONAL



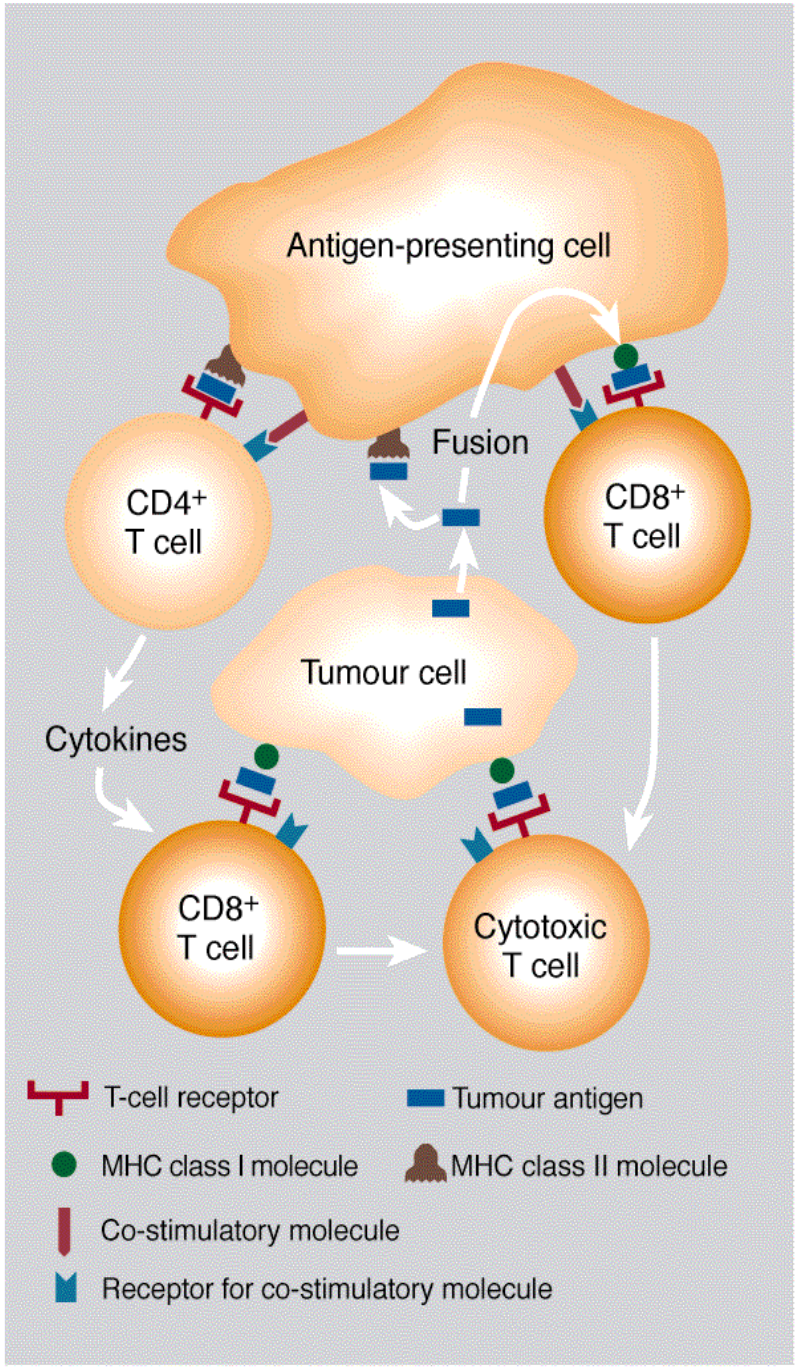
XENOINJERTO: Áreas Donantes cubiertas con xenoinjerto de piel de cerdo, en un paciente que ha sufrido quemaduras graves.

TRASPLANTES

ANTÍGENOS DE HISTOCOMPATIBILIDAD



TIENEN IMPORTANCIA EN LA INMUNORREACCIÓN A UN INJERTO o TUMOR Y EN LA PRESENTACIÓN ANTIGÉNICA

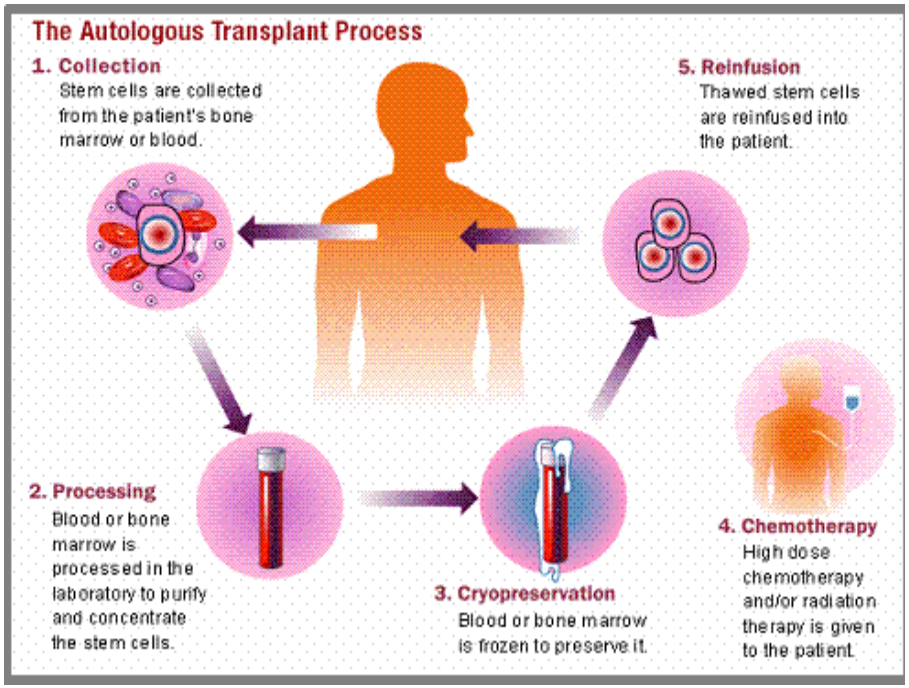


Types of Transplants

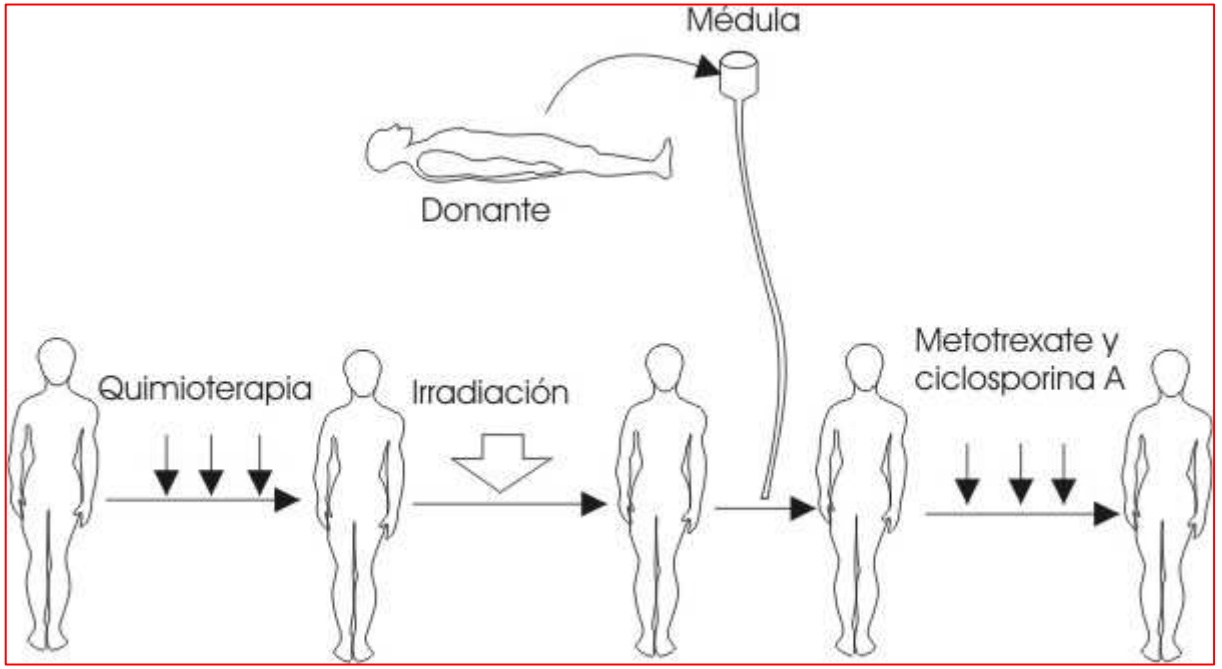
Allogeneic: Family/ Unrelated Donor

Autologous: Self-Donation

Syngeneic: Identical Twin

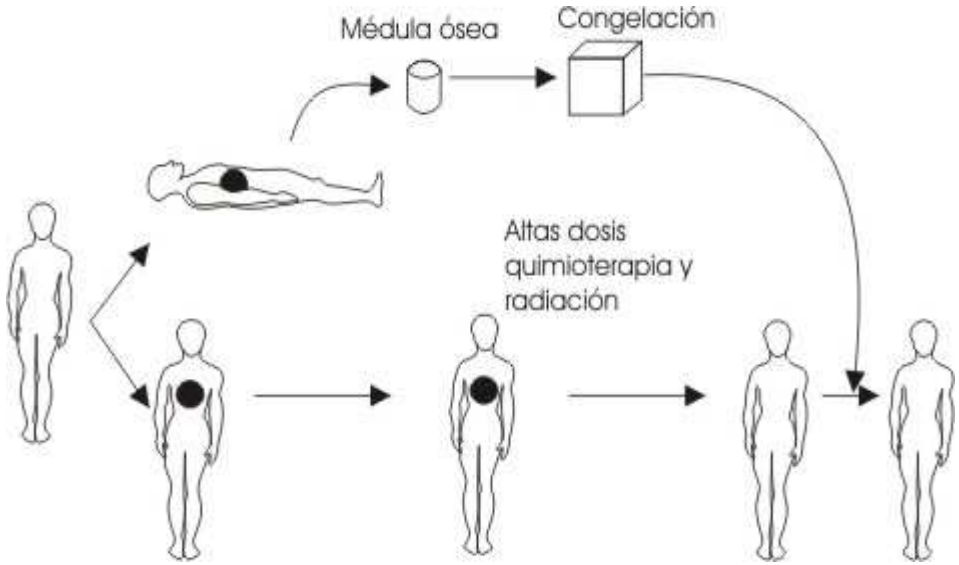


Trasplante AUTÓLOGO

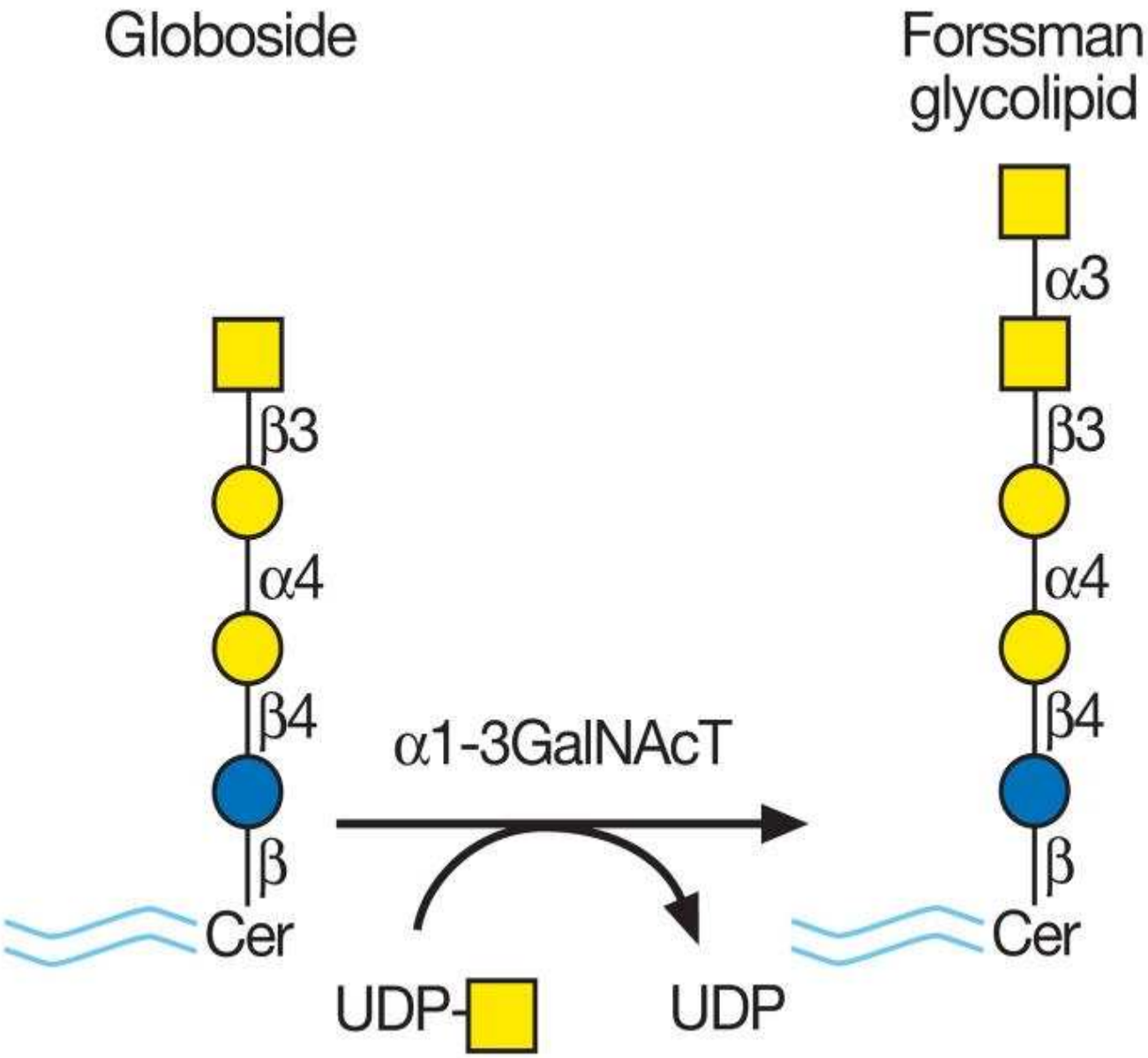


Sustitución del menisco (aloinjerto)

En algunos casos, el daño sostenido por el menisco puede ser tan severo que se necesita una meniscectomía total. En ese caso, se puede considerar un aloinjerto, es decir, un menisco extraído de un donante de tejido humano e implantado para reemplazar el menisco original. La técnica de sustitución del menisco se refiere al procedimiento de reemplazar el menisco por tejido meniscal obtenido de un donante humano.



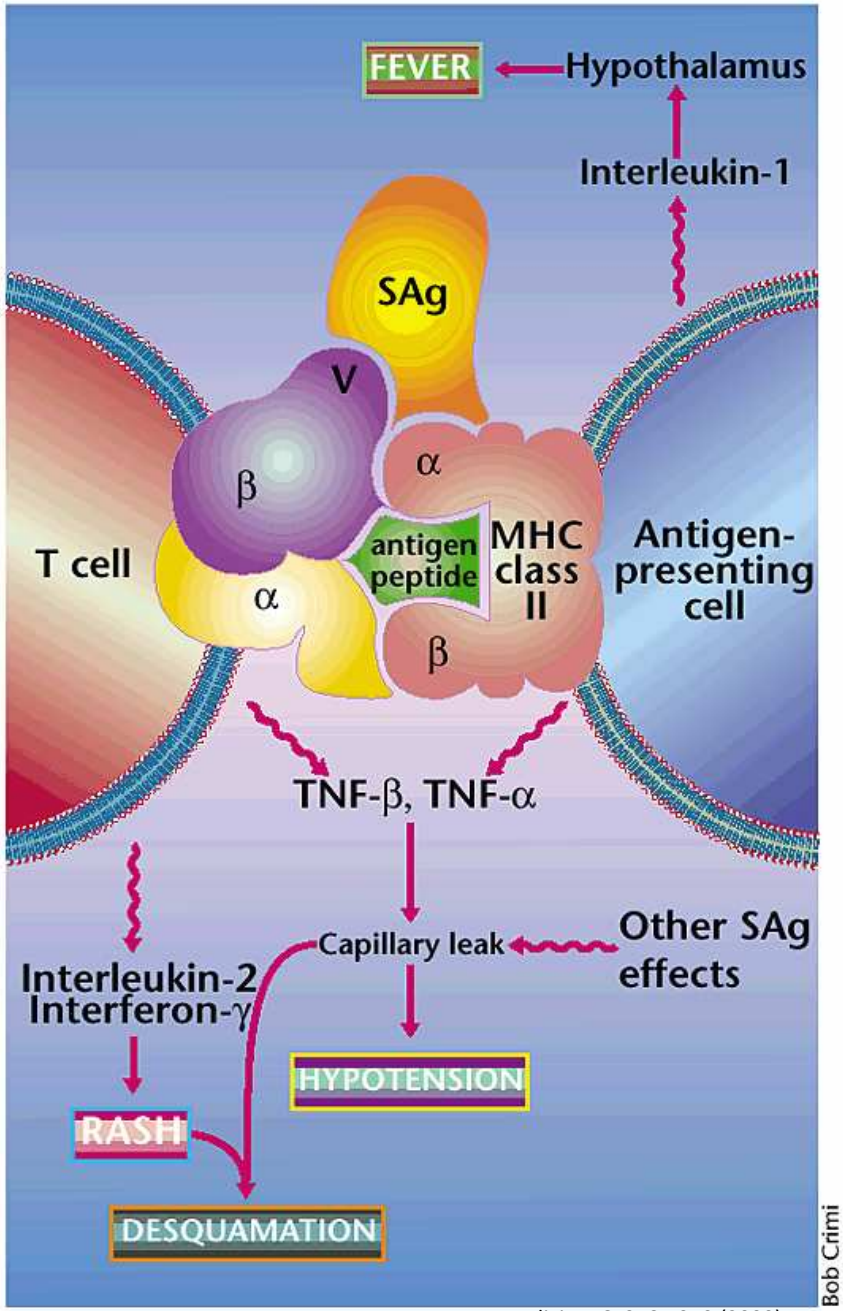
Trasplante ALOGÉNICO



ANTÍGENO FORSSMAN: antígeno heterófilo

- The **Forssman antigen** (also known as globopentosylceramide) is a glycolipid that contains terminal *N*-acetylgalactosamine (GalNAc) in α1–3 linkage to the terminal GlcNAc of globoside.
- **The Forssman antigen is expressed during embryonic and adult stages in many mammals. It was first described for sheep red cells and is not present on human, rabbit, rat, porcine or bovine cells.**
- **Humans carry anti-Forssman antibodies in their serum, suggesting that we do not synthesize the Forssman antigen.**
- Although such antibodies are not consistently present, they may contribute to the pathogenesis of Guillain–Barré syndrome by binding to glycolipid components of peripheral nerve myelin.
- Similarly, there is evidence that small amounts of Forssman antigen may be found on human gastrointestinal epithelium, in various human cultured cells, and in pulmonary and gastointestinal tract carcinomas.
- These conflicting observations may reflect different specificities of the anti-Forssman monoclonal antibodies and differences in epitope reactivities with respect to detection methods. The function of the Forssman antigen is not known. However, anti-Forssman antibodies can disrupt tight junction formation, apical-basal polarization, and cell adhesion, suggesting that this molecule may participate in cell–cell adhesion and communication processes.

SUPERANTÍGENOS



Nature Medicine 6, 378 - 379 (2000)

Superantígenos

When the immune system encounters a conventional T-dependent antigen, **only a small fraction (1 in 10^4 -10^5) of the T cell population is able to recognize the antigen and become activated (monoclonal/oligoclonal response).** However, there are **some antigens which polyclonally activate a large fraction of the T cells (up to 25%). These antigens are called superantigens.**

Nominal antigens & superantigens

Nominal antigens

Require processing to peptides

TcRα and β chains are involved in peptide

Recognition restricted by an MHC class I or II molecule

Almost all proteins can be nominal antigens

Superantigens

Not processed

Only TcR β chain involved in recognition

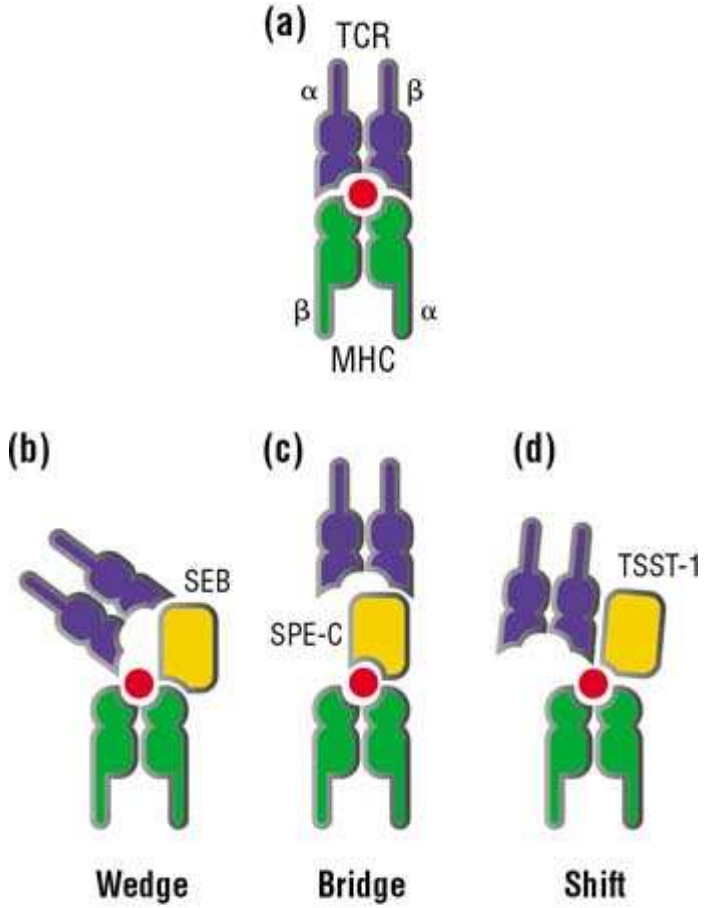
Sugiere mecanismos diferentes de reconocimiento y presentación……

Presented by almost any MHC class II molecule

Very few antigens are superantigens

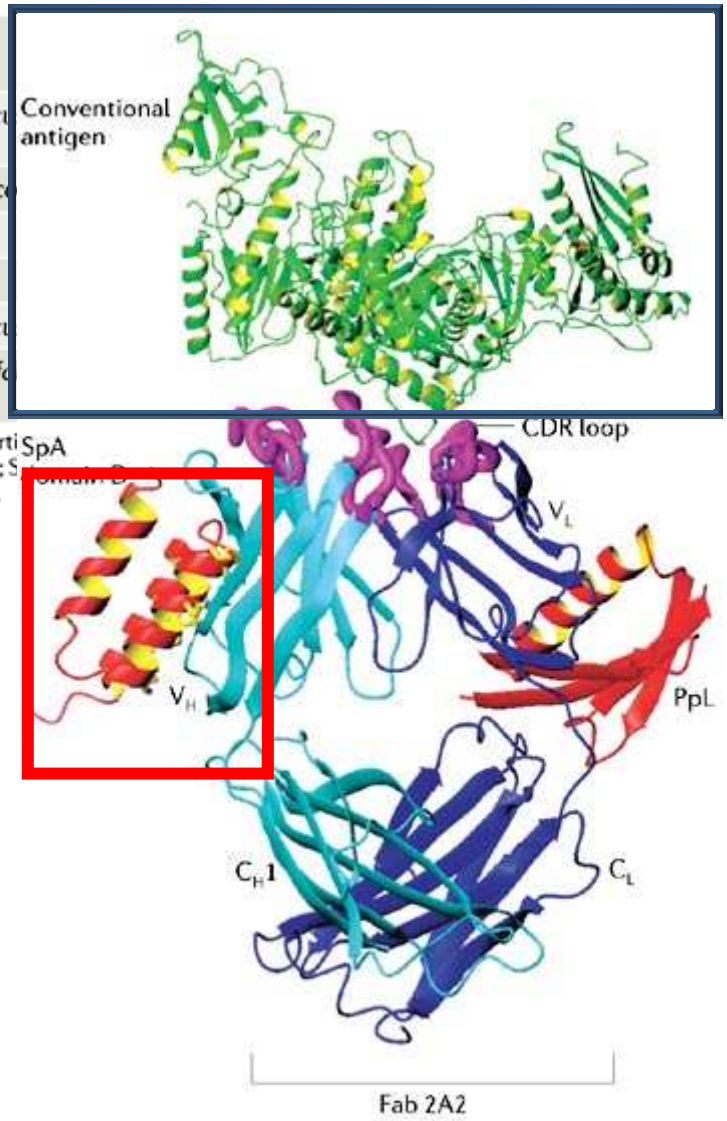
Microbial Superantigens and the Diseases in which they are Implicated

Superantigen	Disease
Staphylococcal exotoxins	
SEA enterotoxin	food poisoning
SEB enterotoxin	food poisoning; TSS
SEC1 enterotoxin	food poisoning; TSS
SEC2 enterotoxin	food poisoning
SEC3 enterotoxin	food poisoning
SED enterotoxin	food poisoning
SEE enterotoxin	food poisoning
SEA G-L	food poisoning
Toxic-shock-syndrome toxin (TSST-1)	toxic shock syndrome (TSS)
Exfoliative toxins A and B (ETA and ETB)	scalded-skin syndrome
Mycoplasma arthritidis superantigen (MAS)	arthritis, shock
Streptococcal erythrogenic exotoxins	
SPE-A, -B, -C	scarlet fever, strep toxic shock
Streptococcal mitogenic exotoxins	
SPEF, SSA, SPM, SPM-2, SMEZ, SPEG, SPEH, SPEJ, SMEZ-2	unknown
Clostridium perfringens enterotoxin	food poisoning
Yersinia pseudotuberculosis mitogen (YPM)	enteritis, mesenteric adenopathy



Immunoglobulin-binding protein	Source		References
SpA	*Staphylococcu*	ssociated e	2,6–12,30–35,45,51,57,58, 66,67,70,79,80,84–86,92,99
PpL	*Peptostreptoc*		3,13–16,57,81,102
gp120	HIV-1	protein	17–20,71–75
pFv	Gut or liver		7,21,82
SED	*Staphylococcu*		22
EMP1	*Plasmodium f*	on infected es	23

Fab, antigen-binding fragment; Fcγ, Fc porti velope; EMP1, erythrocyte membrane protein 1; PpL, *Peptostreptococcus magnus* protein L; S tein A; V_H, heavy chain antibody variable region; Vκ, light chain κ antibody variable region.



Silverman *et al. Nature Reviews*

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Nature Reviews | Immunology

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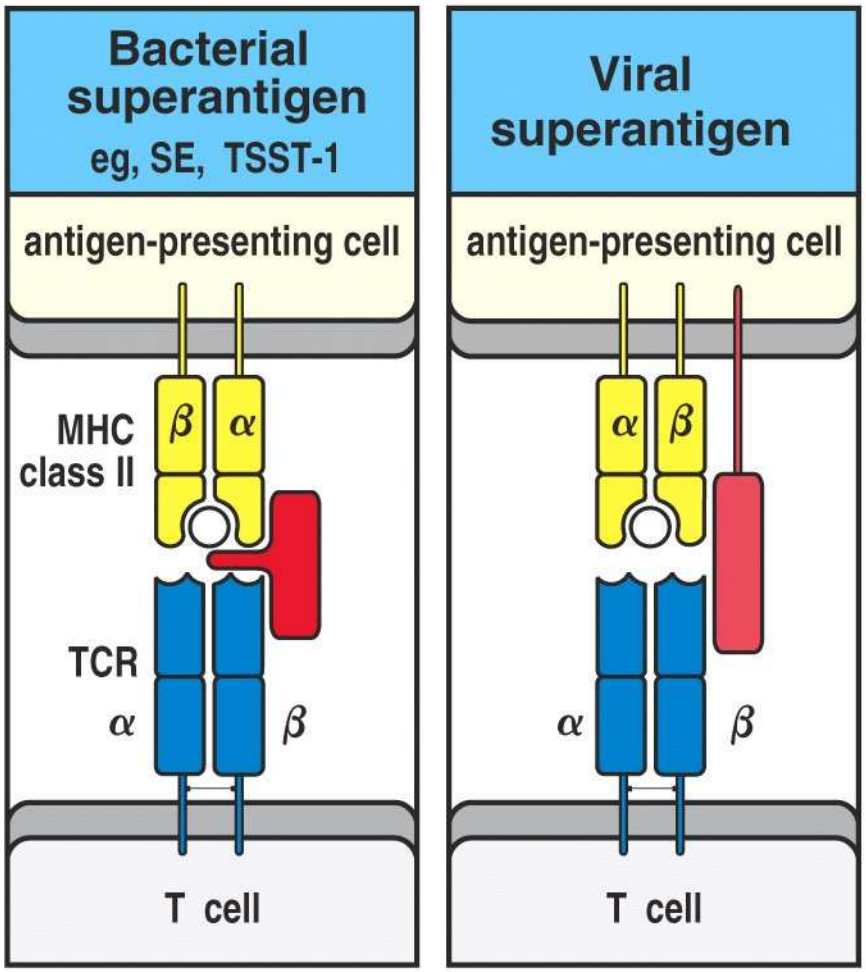


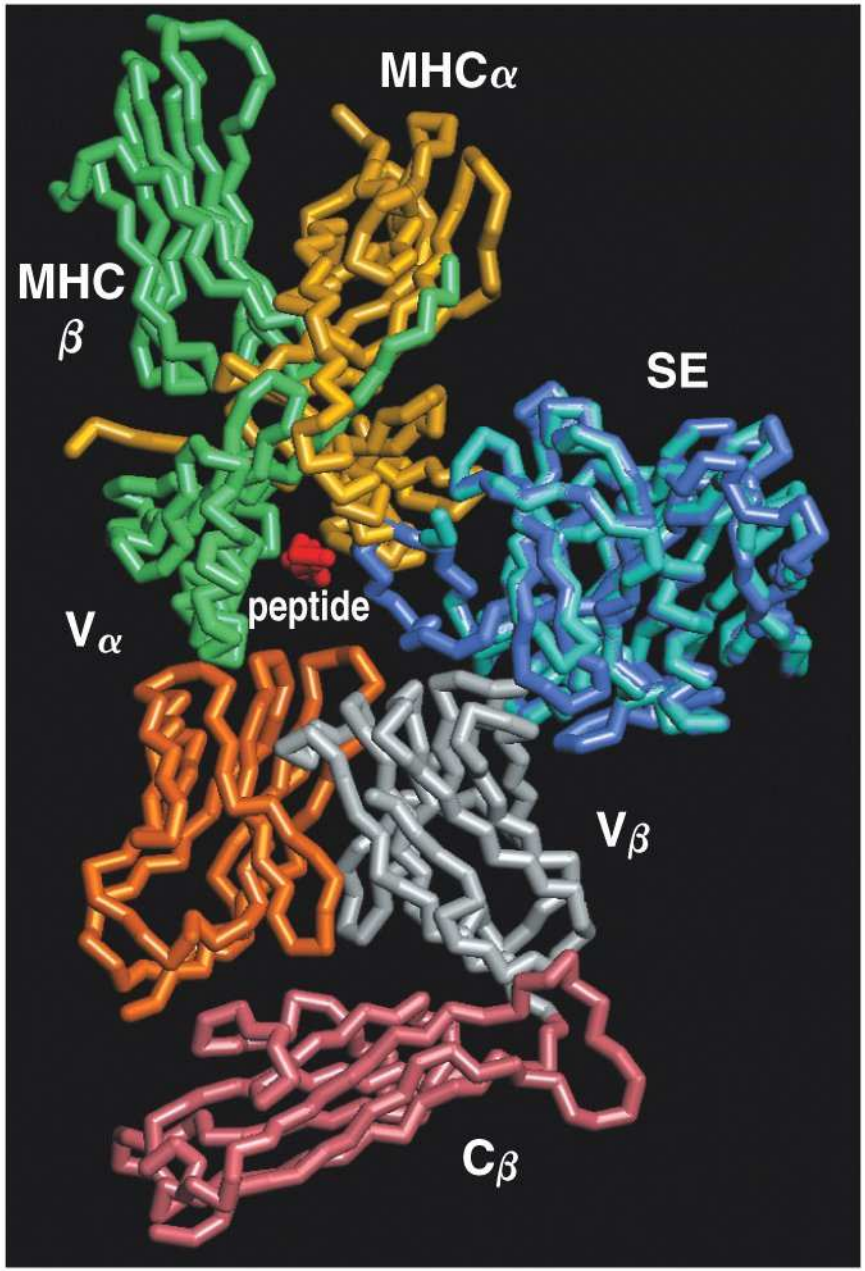
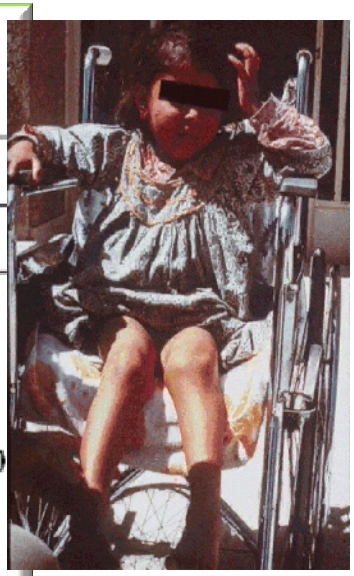


Figure 5-19 Immunobiology, 6/e. (© Garland Science 2005)

TABLE 10-4 EXOGENOUS SUPERANTIGENS AND THEIR V_β SPECIFICITY

Superantigen	Disease*	V_β specificity	
		Mouse	Human
Staphylococcal enterotoxins			
SEA	Food poisoning	1, 3, 10, 11, 12, 17	nd
SEB	Food poisoning	3, 8.1, 8.2, 8.3	3, 12, 14, 15, 17, 20
SEC1	Food poisoning	7, 8.2, 8.3, 11	12
SEC2	Food poisoning	8.2, 10	12, 13, 14, 15, 17, 20
SEC3	Food poisoning	7, 8.2	5, 12
SED	Food poisoning	3, 7, 8.3, 11, 17	5, 12
SEE	Food poisoning	11, 15, 17	5.1, 6.1–6.3, 8, 18
Toxic-shock-syndrome toxin (TSST1)	Toxic-shock syndrome	15, 16	2
Exfoliative-dermatitis toxin (ExFT)	Scalded-skin syndrome	10, 11, 15	2
Mycoplasma-arthritidis supernatant (MAS)	Arthritis, shock	6, 8.1–8.3	nd
Streptococcal pyrogenic exotoxins (SPE-A, B, C, D)	Rheumatic fever, shock	nd	nd

*Disease results from infection by bacteria that produce the indicated superantigens.



Superantígenos de Streptococcus pyogenes

Toxina	Nombre	Especificidad Vß
SPE A	Exotoxina pirogénica A Toxina eritrogénica A. Toxina encarlatiniforme	2, 12, 14, 15
SPE A	Exotoxina pirogénica B Proteinasa Streptopapaína Activador de IL - 1ß	8
SPE C	Exotoxina pirogénica C	1, 2, 5, 1, 10
Fragmentos	Péptidos de M5, M6, M18	1, 2, 4, 5, 2, 8
de Proteína M	Péptidos de M19, M24, M2	
SSA	Superantígeno streptocócico	1, 3, 5.2, 15
SPE F	Exotoxina pirogénica F	2, 4, 8, 15,19

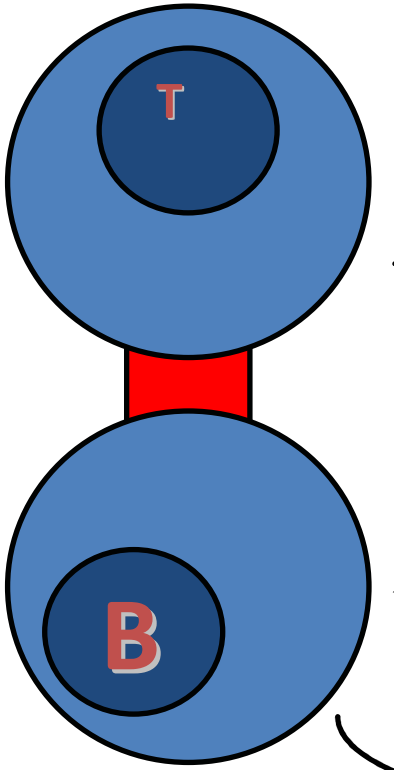
¿Cómo los microorganismos utilizan los SA??

Una respuesta inmune adaptativa NO FOCALIZADA es capaz de estimular células inespecíficas como específicas para el SA en cuestión.....

- **Reduce la posibilidad de que una efectiva selección clonal de células T elimine el patógeno....**
- **En lugar de resolver la situación, las células estimuladas por el SA mueren....**

Transmisión de la infección.....

Transmisión de la infección



2. Massive T cell response to MMTV superantigen

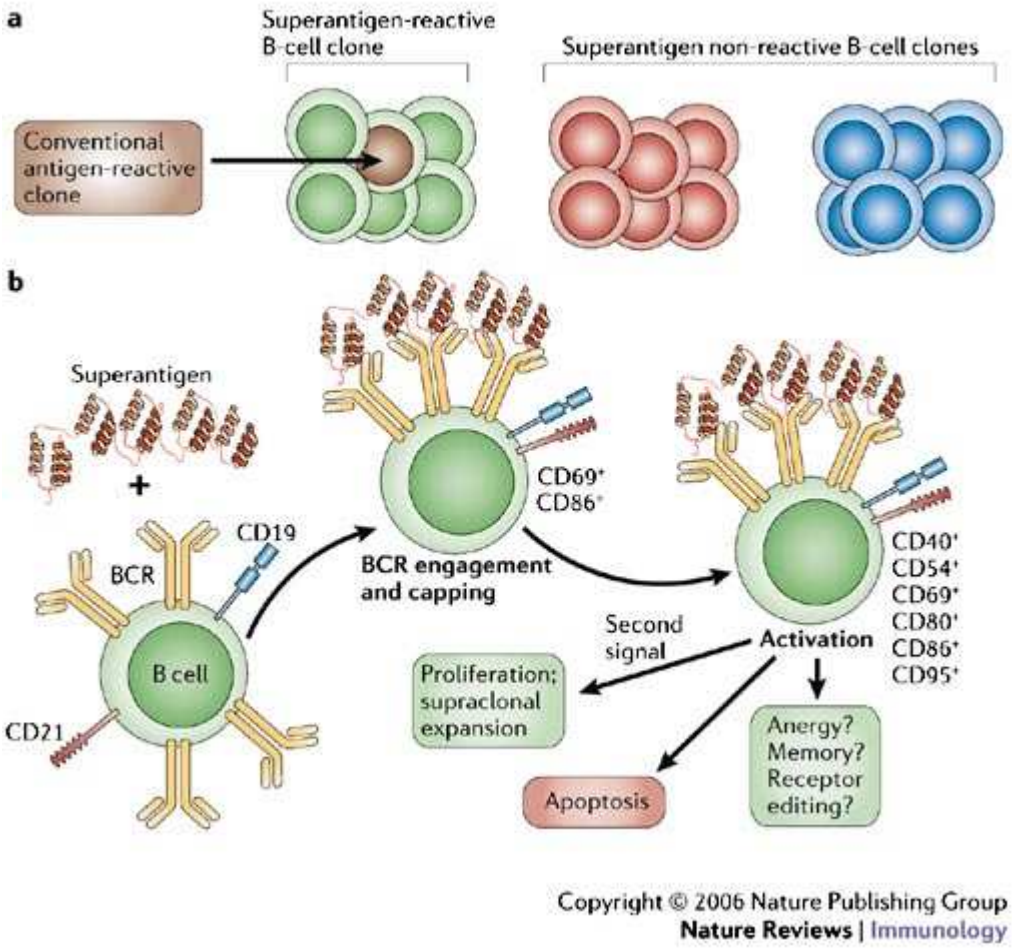
3. Vigorous T cell help leads to B cell proliferation and differentiation to long-lived B cells

1. MMTV infected, MHC class II positive B cells

4. Infected cells traffic to mammary gland and infect young via milk

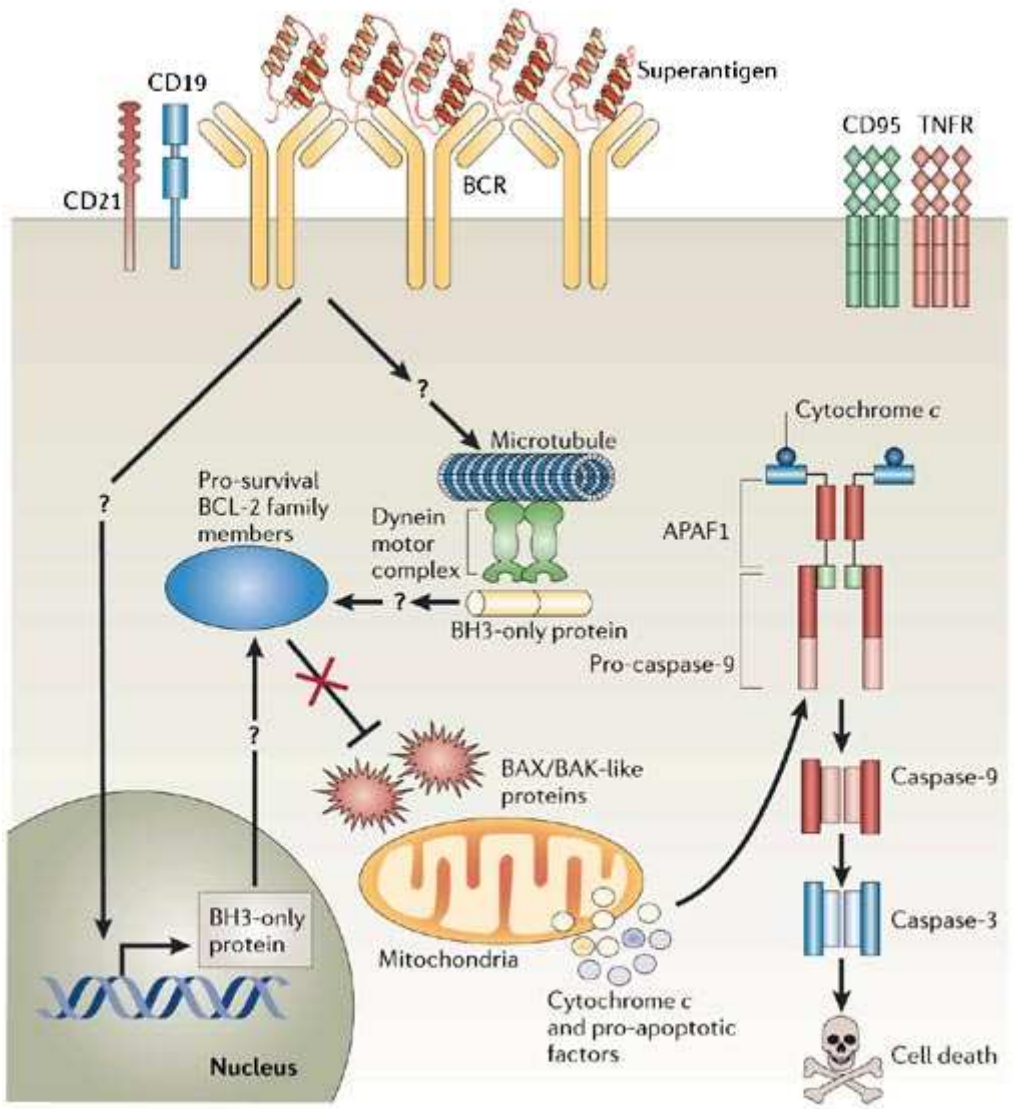
MMTV:Tumor virus mamario (ratón)

Superantígenos de células B

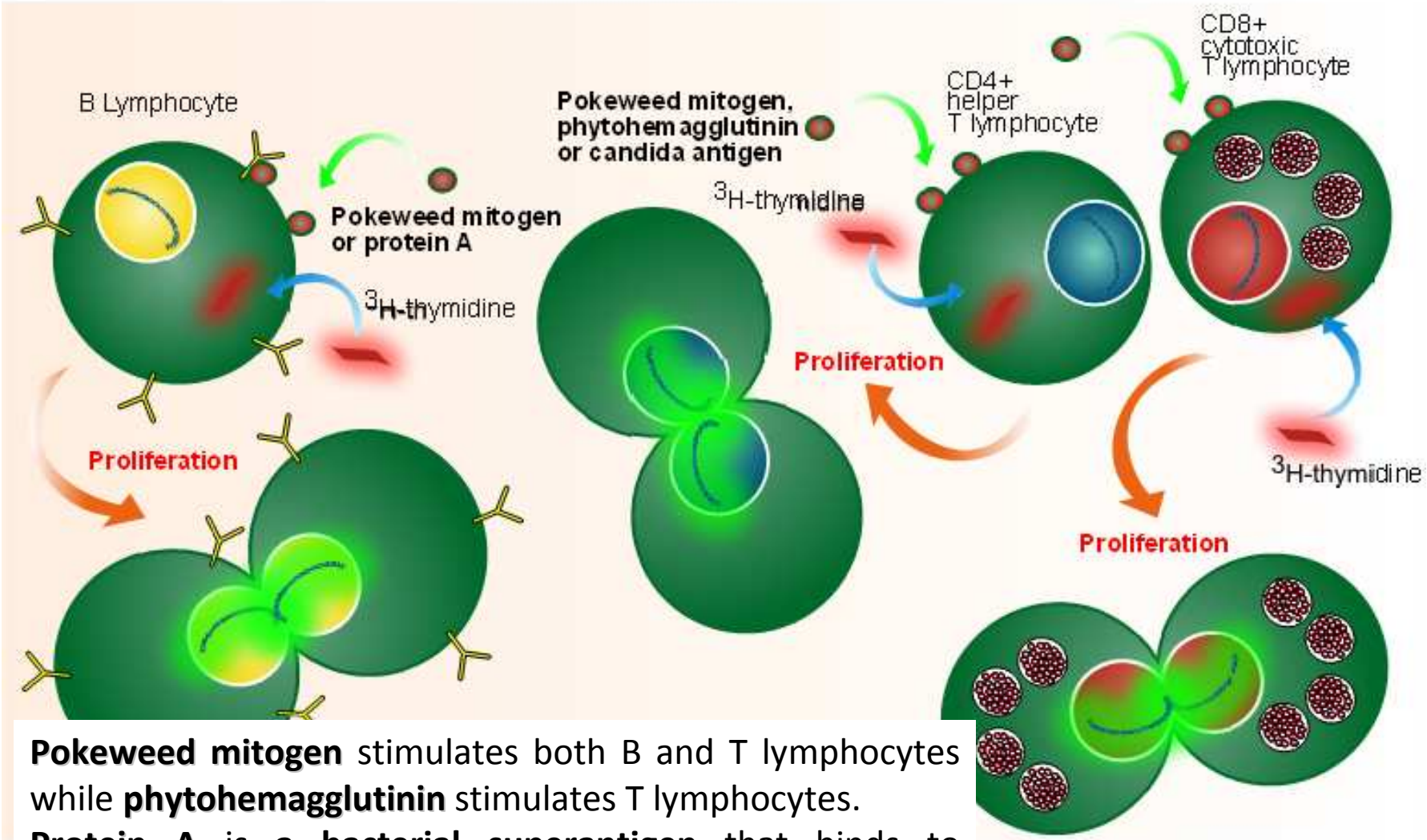


Nature Reviews Immunology 6, 465-475 (June 2006)

Superantigens can interact with a large proportion of the B-cell compartment. a | The superantigen can interact with all clones of a particular family (green) no matter what their conventional antigen specificity is. The conventional antigen, however, might be able to interact with only certain clones of a defined binding-specificity (brown) and of a particular family (green). b | On initial B-cell exposure to a superantigen, the B-cell receptor (BCR) of all susceptible clones are recruited into complexes that appear as membrane-associated caps. This is followed by the subsequent clustering of the CD21 and CD19 co-receptors and the resulting activation of the B cell, which is associated with early upregulation of CD69 and CD86 expression. Later activation events include the upregulation of CD40, CD54, CD80 and CD95. At early time points, migration of B cells to the spleen is observed**. Several outcomes have been shown to follow this exposure, the main one being apoptosis, which is first observed within 4 hours of superantigen exposure. Although some proliferation occurs following superantigen encounter, if an appropriate second signal, such as CD40 ligand or interleukin-4, is delivered, increased proliferation and survival of clones results. Alternative outcomes, such as the induced differentiation of clones into memory cells, functional inactivation (anergy) or receptor editing, have not yet been documented, but based on B-cell responses to conventional antigenic-ligands, these are also possible outcomes after superantigen exposure.**



MITÓGENOS



Pokeweed mitogen stimulates both B and T lymphocytes while **phytohemagglutinin** stimulates T lymphocytes.

Protein A is **a bacterial superantigen** that binds to particular variable region of the B cell receptor and induces polyclonal activation and antibody secretion.

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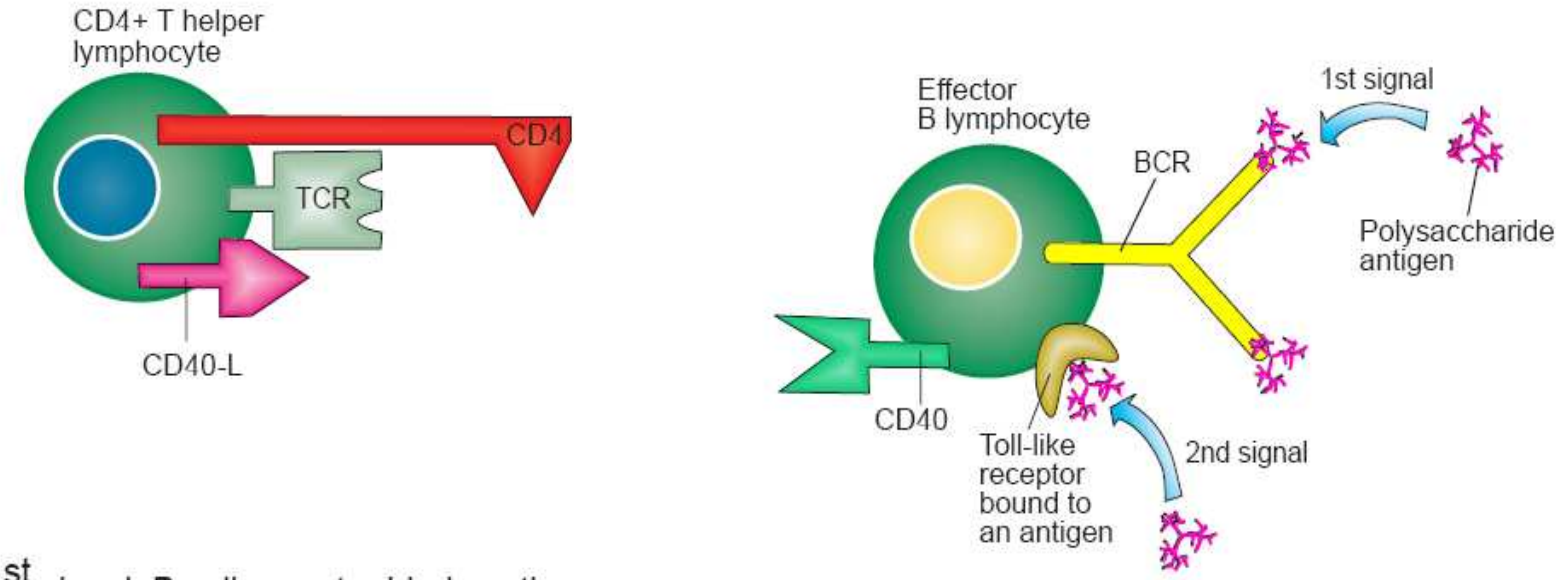
LOS ANTÍGENOS PUEDEN INDUCIR UNA RESPUESTA INMUNE ….

T-INDEPENDIENTE

Figure 3: B cell activation by a polysaccharide antigen: Thymic Independent Type-1 (TI-1)



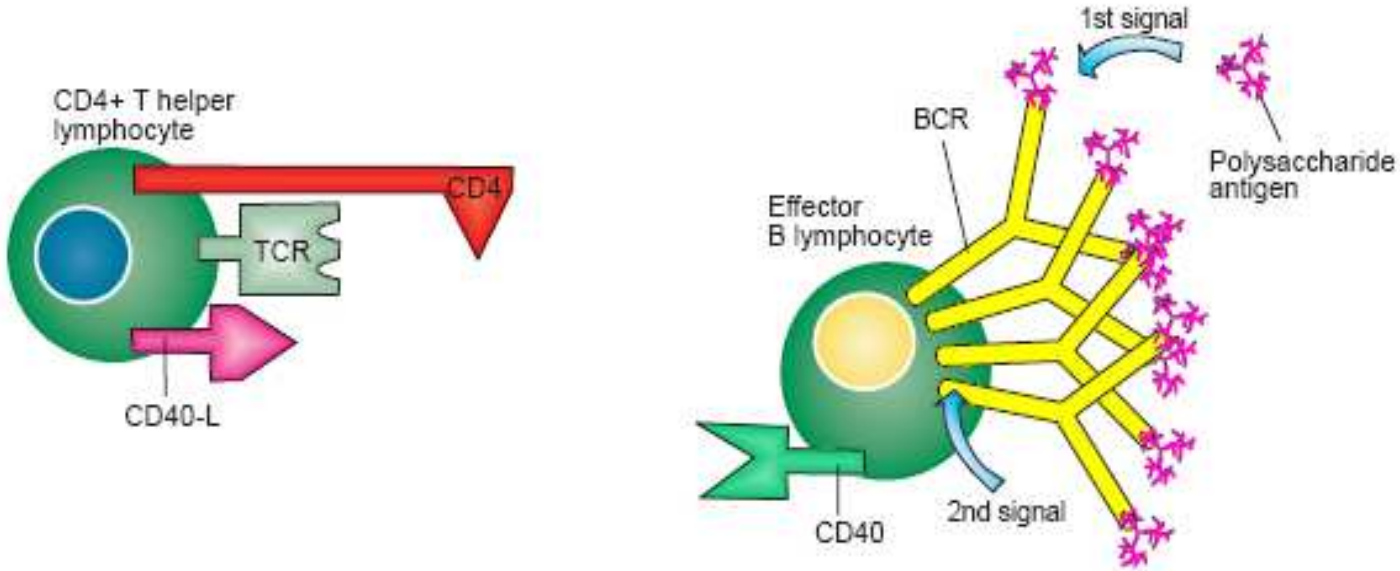
1st signal: B cell receptor binds antigen.

Note: This may be in a NON-SPECIFIC way eg. via a mitogen such as lipopolysaccharide – can bind to many different B cell receptors!

2nd signal provided by Toll-like receptor.

No CD4 cell help

Figure 4: B cell activation by a polysaccharide antigen: Thymic Independent Type-2 (TI-2)



1st signal: B cell receptor binds antigen.

2nd signal provided by clustering of B cell receptors.

No CD4 cell help.

Mature B cell only, if B cell immature – anergy!
Also if density of antigens too high – anergy!

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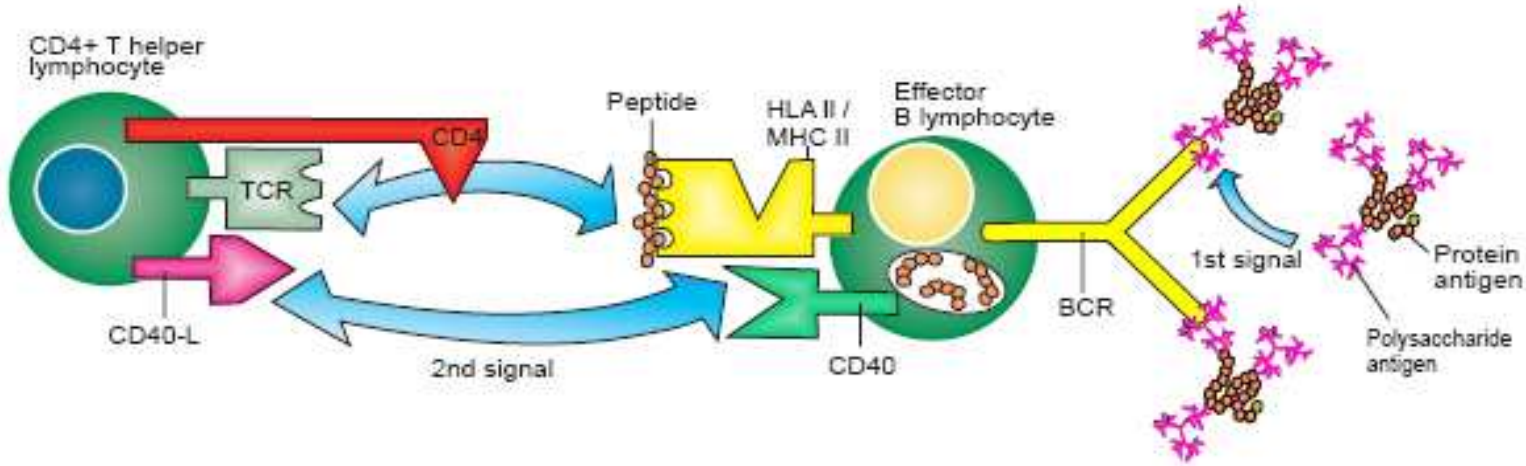
- The reason that newborns cannot adequately make antibodies to repeating polysaccharide epitopes is only partially elucidated. The reasons may be due to immaturity of receptors in the innate immune system. It may also be due to most of their B cells being immature and unable to respond to B cell receptor crosslinking (Janeway et.al, 2005).
- **The ability to respond to polysaccharide antigens is developed by 18months – 2years of age.**

Figure 5: B cell activation by a polysaccharide antigen conjugated to a protein



The B cell receptor is specific for the polysaccharide antigen.

The polysaccharide antigen **does not** get presented on the B cell surface.

The protein gets processed and presented to the T cell.

The T cell provides help to the B cell via CD40L binding to CD40.

The B cell makes antibodies against the polysaccharide antigen.

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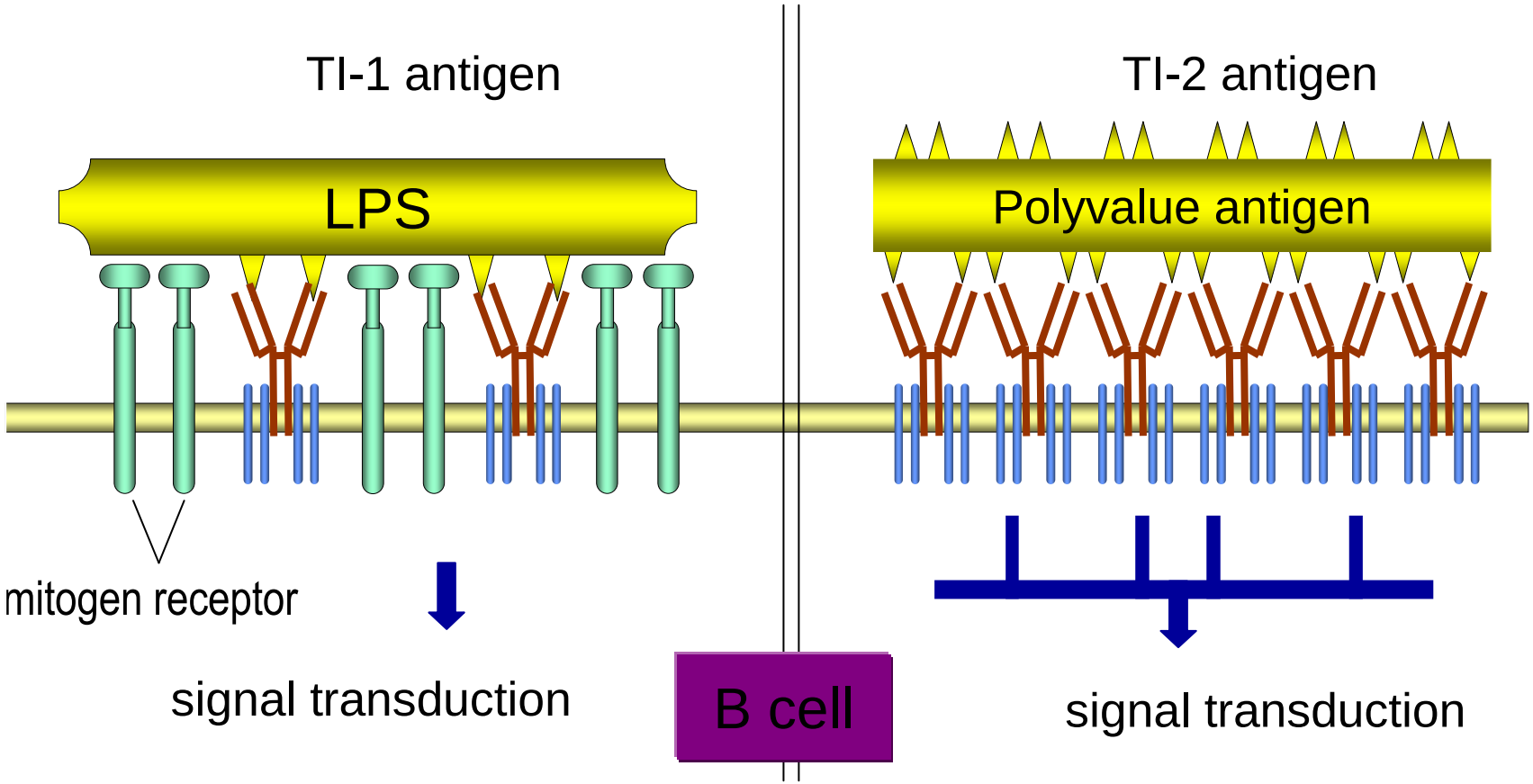
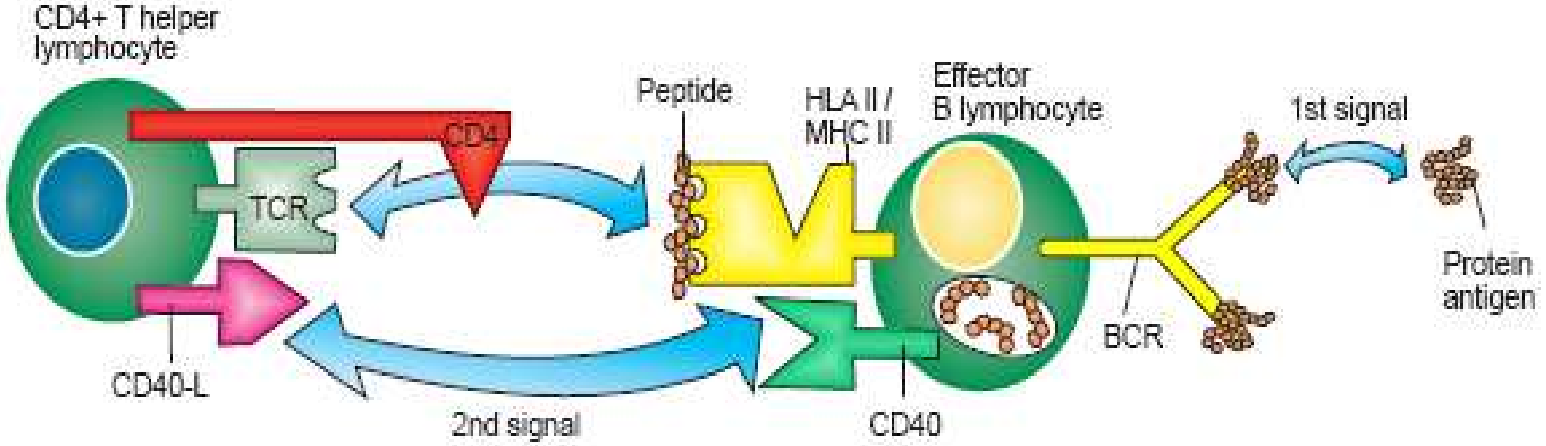
Antígenos TI-1 y TI-2



T-DEPENDIENTES

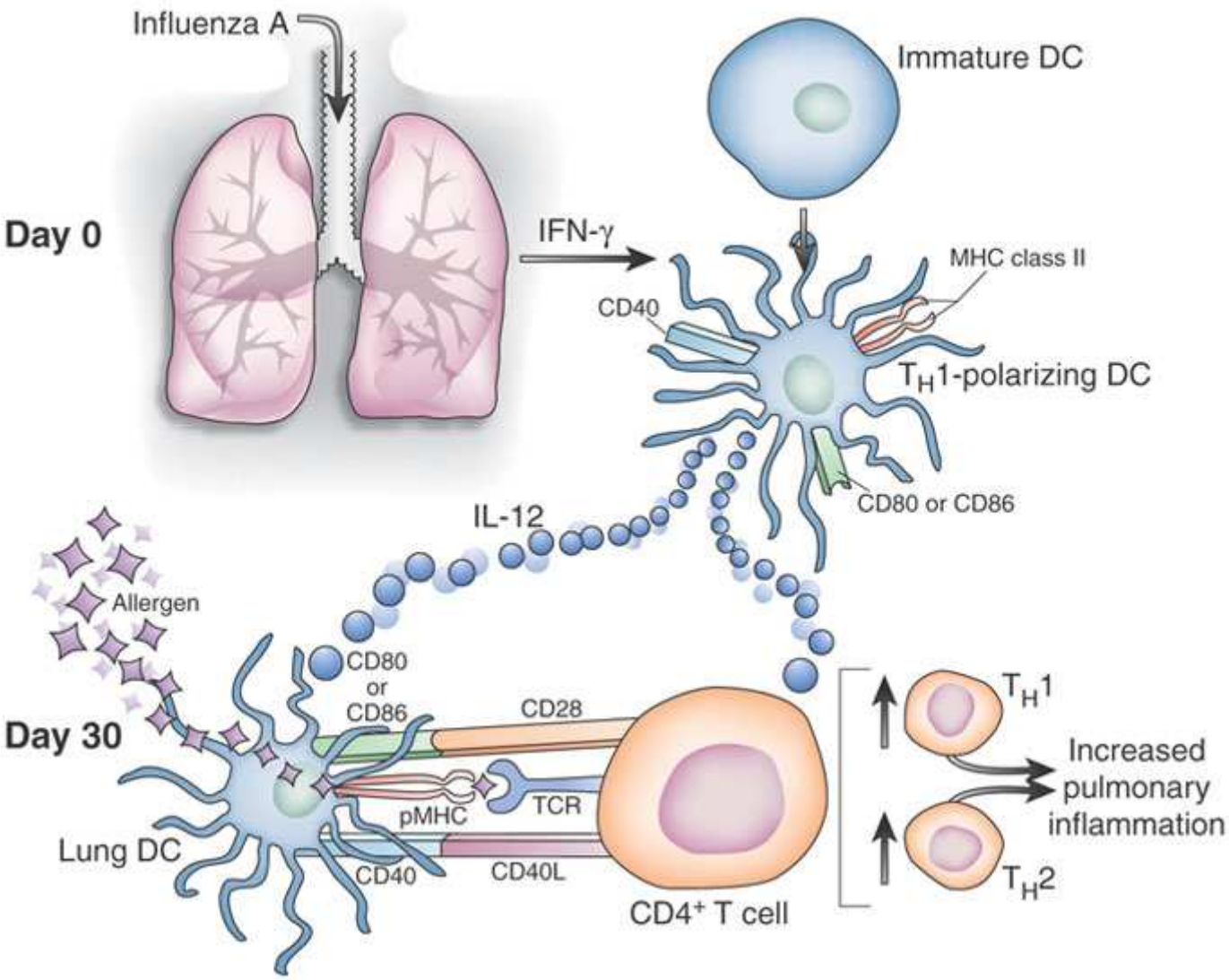
Figure 2: B cell activation by a protein antigen (Thymus dependent)

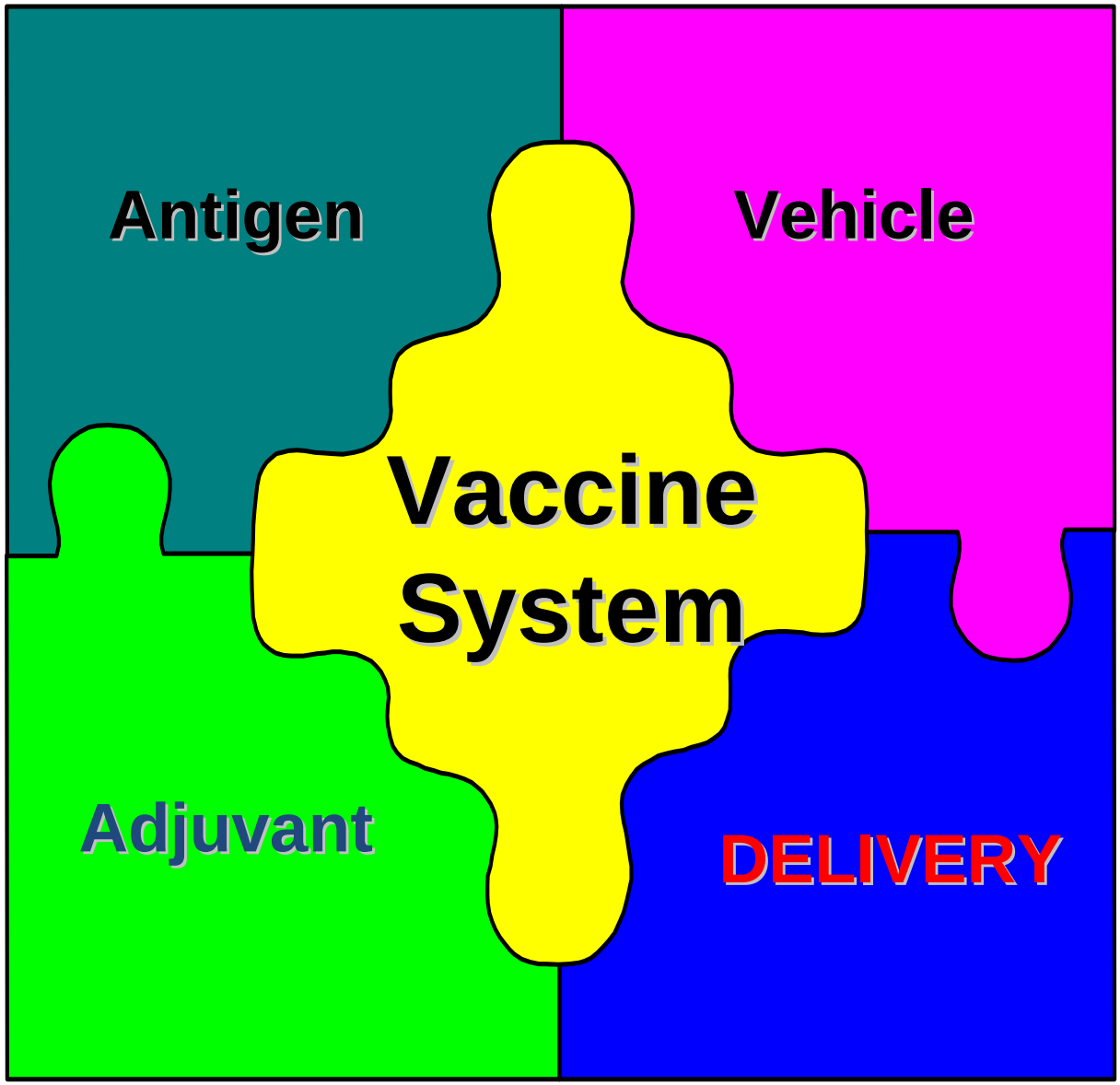


1st signal is B cell receptor binding to peptide antigen.

2nd signal is CD40-L binding to CD40.

Note: The peptide to which the T cell receptor binds is not necessarily identical to the protein to which the B cell receptor binds.


Influenza A
Immature DC
Day 0
IFN-γ
MHC class II
CD40
T_H1-polarizing DC
CD80 or CD86
IL-12
Allergen
CD80
or
CD86
CD28
Day 30
pMHC
TCR
Lung DC
CD40
CD40L
CD4+ T cell
T_H1
Increased
pulmonary
inflammation
T_H2


Antigen
Vehicle
Vaccine System
Adjuvant
DELIVERY

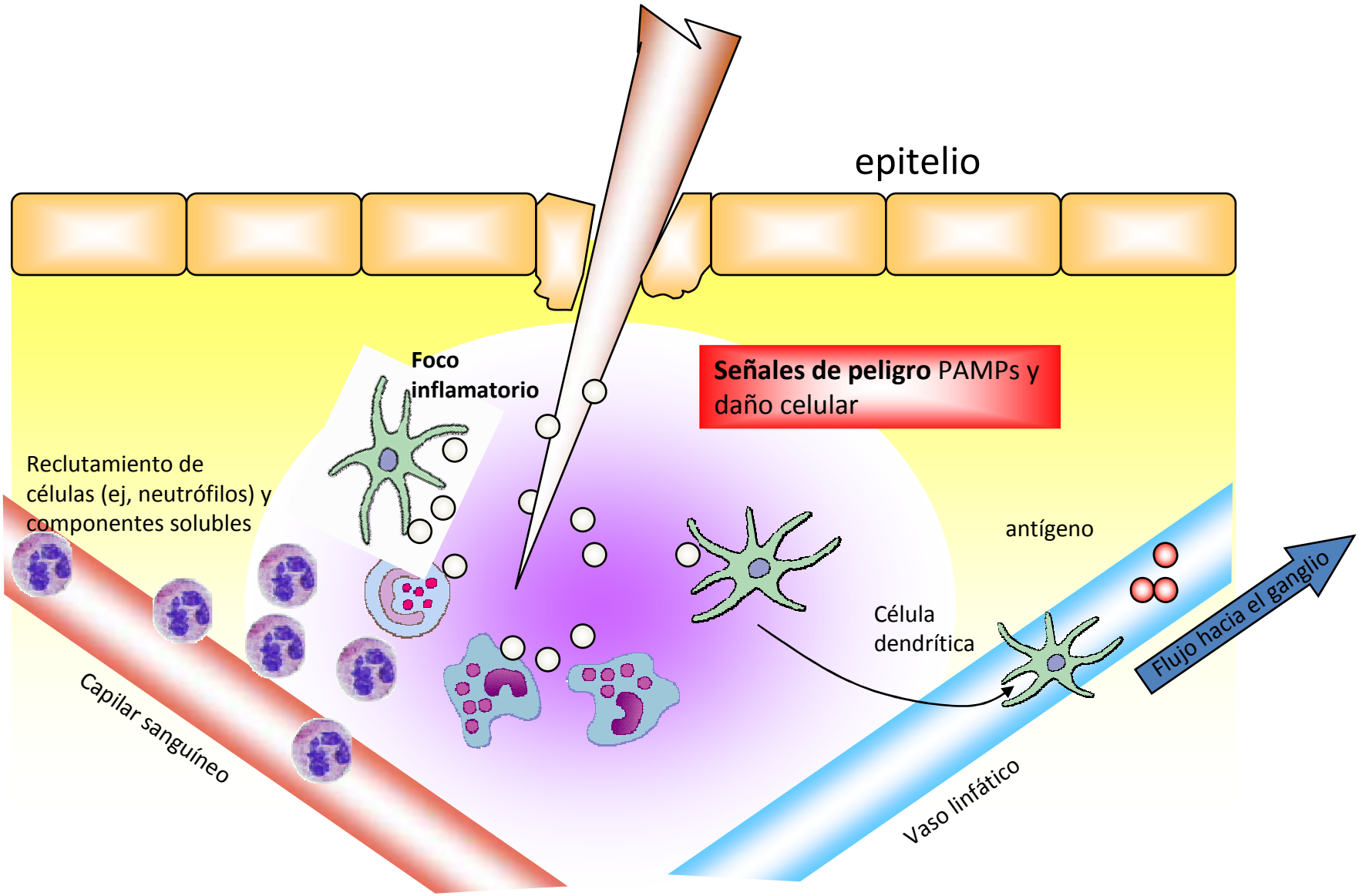
INMUNÓGENOS Y VACUNAS

Vacuna: preparación diseñada para inducir una respuesta inmune de larga duración (años) que sea capaz de evitar el desarrollo de la enfermedad.

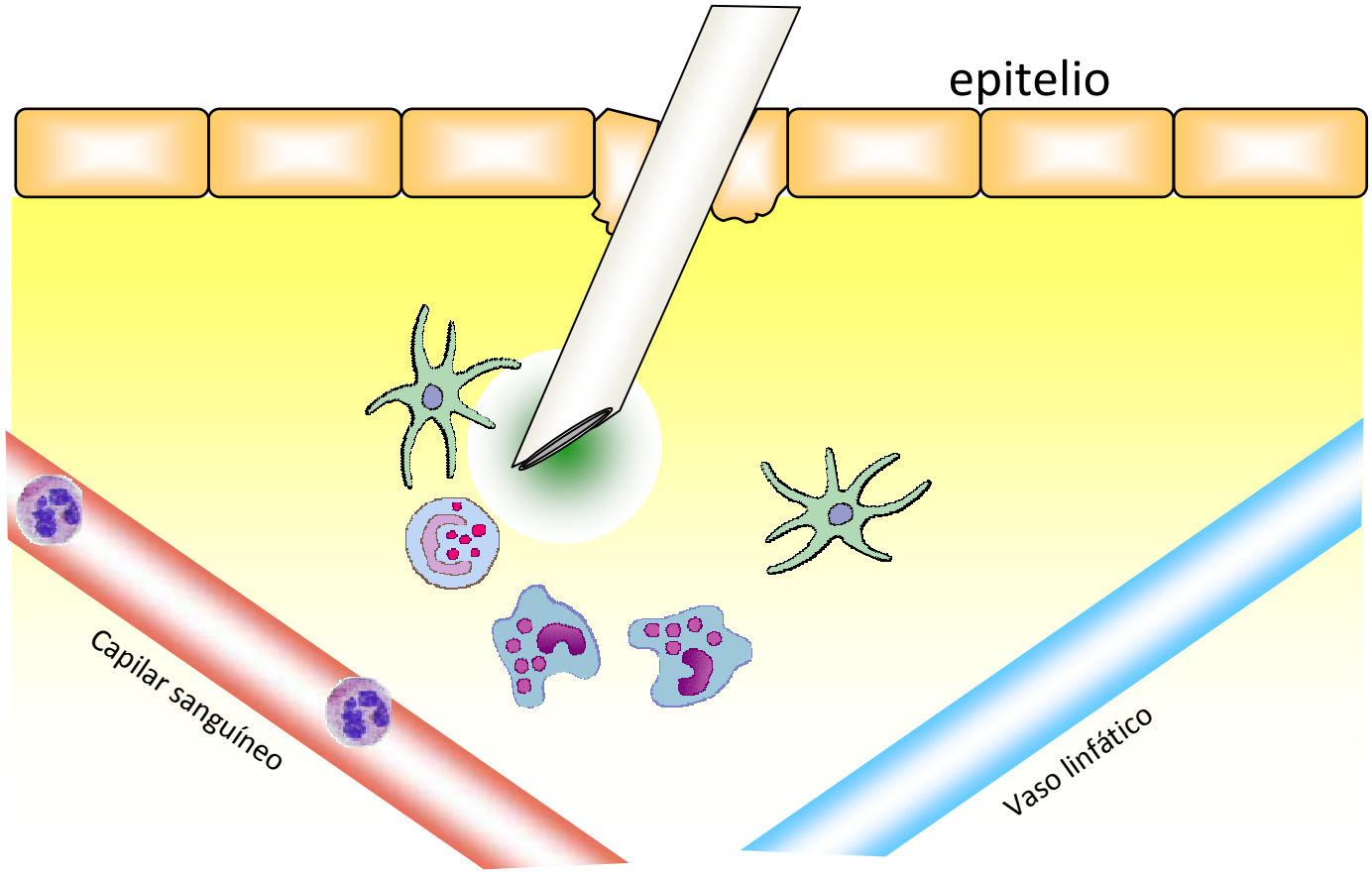
Tipos de vacunas

Microorganismos vivos (respuesta B y T)	Patógenos similares o atenuados
Microorganismos inactivados químico etc.	Calor, radiaciones, tratamiento
Componentes individuales conjugadas	Componentes sintéticos o recombinantes, se incluyen en esta categoría las vacunas
DNA (experimentales) contiene el B y T)	Plásmido con fuerte promotor viral que gen del antígeno de interés (respuesta

Las vacunas deben activar la inmunidad innata y la adaptativa



Las vacunas a subunidades son más seguras pero deben incluir un adyuvante para activar la respuesta inmune



Adyuvante: Compuesto que aumenta la immunogenicidad de los antígenos con los cuales se mezclan.

Modo de acción: formación de partículas, persistencia en el tejido, generación de señales de peligro

Distintos tipos de adjuvantes han sido desarrollados para aumentar la inmunogenicidad de las vacunas

Adjuvants that enhance immune responses

Adjuvant name	Composition	Mechanism of action
Incomplete Freund's adjuvant	Oil-in-water emulsion	Delayed release of antigen; enhanced uptake by macrophages
Complete Freunds adjuvant	Oil-in-water emulsion with dead mycobacteria	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators in macrophages
Freunds adjuvant with MDP	Oil-in-water emulsion with muramyldipeptide (MDP), a constituent of mycobacteria	Similar to complete Freund's adjuvant
Alum (aluminum hydroxide)	Aluminum hydroxide gel	Delayed release of antigen; enhanced macrophage uptake
Alum plus *Bordetella pertussis*	Aluminum hydroxide gel with killed *B. pertussis*	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators
Immune stimulatory complexes (ISCOMs)	Matrix of Quil A containing viral proteins	Delivers antigen to cytosol; allows induction of cytotoxic T cells

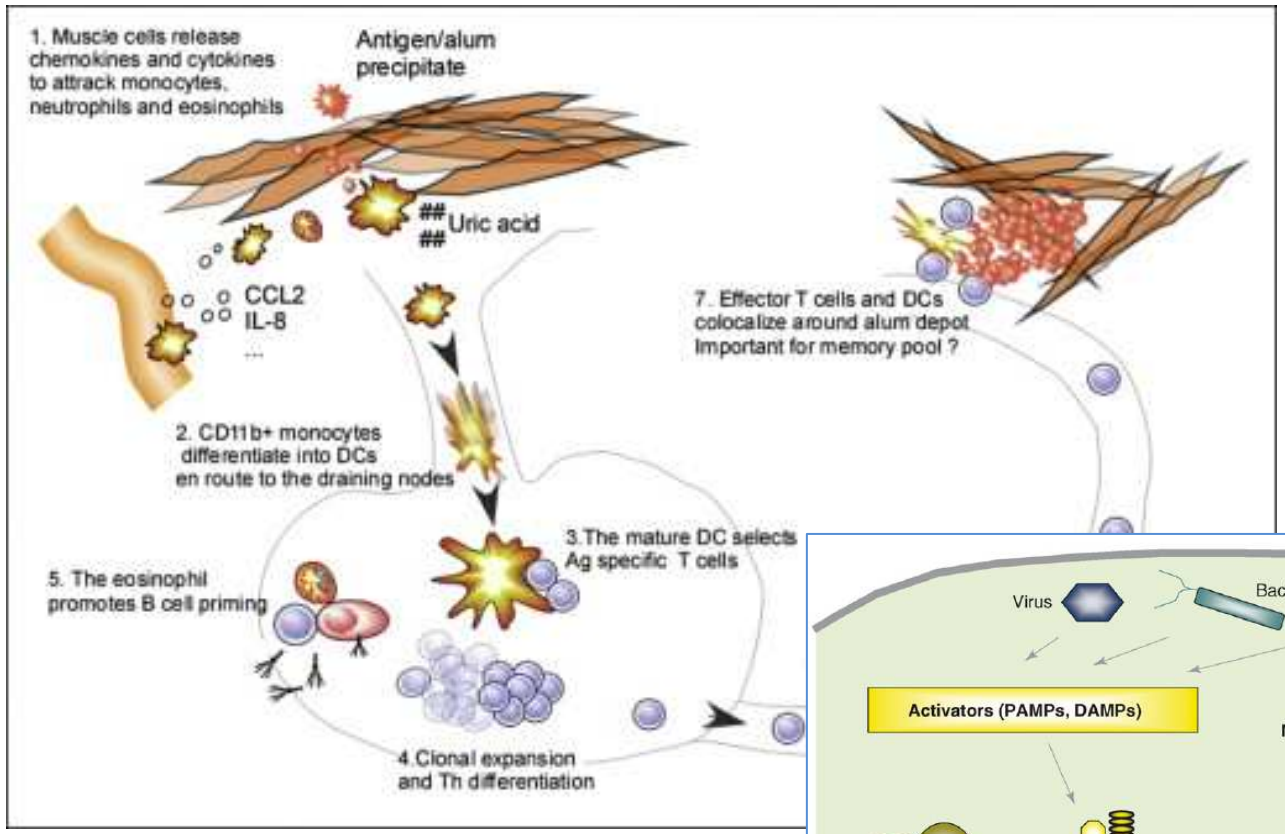
Figure A-4 Immunobiology, 6/e. (© Garland Science 2005)

Los adyuvantes que tienen PAMPs, tienen una clara forma de acción, principalmente a través de la estimulación de los receptores TLR

La respuesta a **adyuvantes sin PAMPs** (alúmina, incompleto de Freund) es prácticamente normal en ratones MyD88-/- o TRIF-/- (que tienen bloqueada la señalización por TLRs)

Exceptuando la alúmina (fosfato o hidróxido de aluminio) para otros adyuvantes, la FDA aprueba individualmente la combinación antígeno-adyuvante de las nuevas vacunas

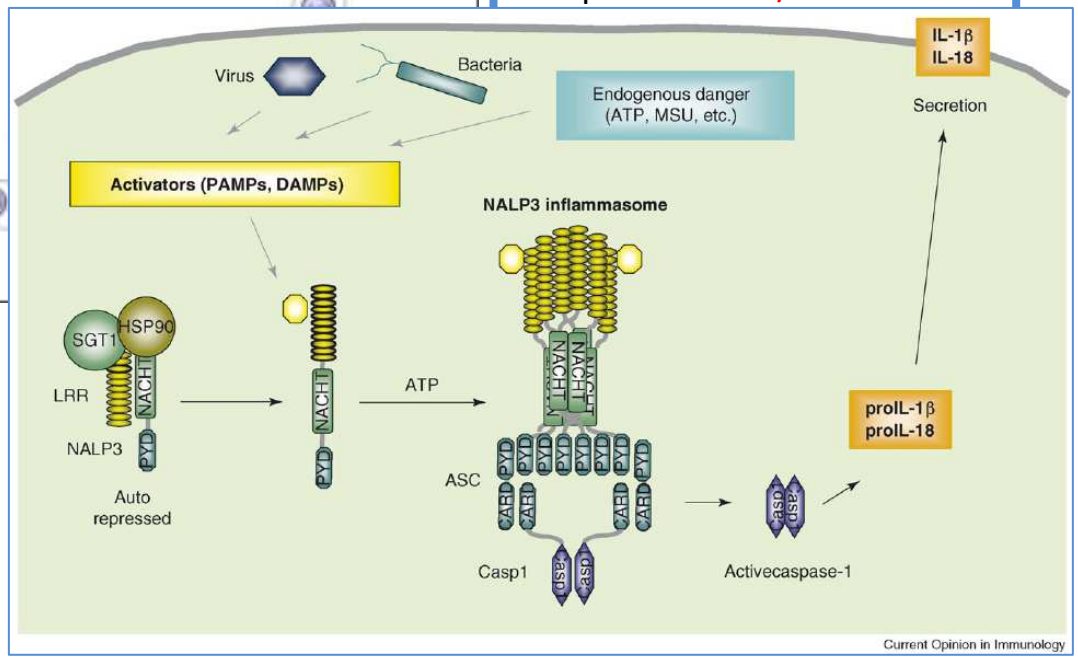
El poder de los adyuvantes depende de la activación del adyuvante fisiológico, la célula dendrítica



Ejemplos de PAMPs que vienen siendo estudiados experimentalmente como componentes de adyuvantes

Monofosforil lípido A (LPS) TLR4
CpG dimetilado TLR9
Pam3Cys y BCG PGs TLR2
Flagelina TLR5
Resquimod TLR 7/8

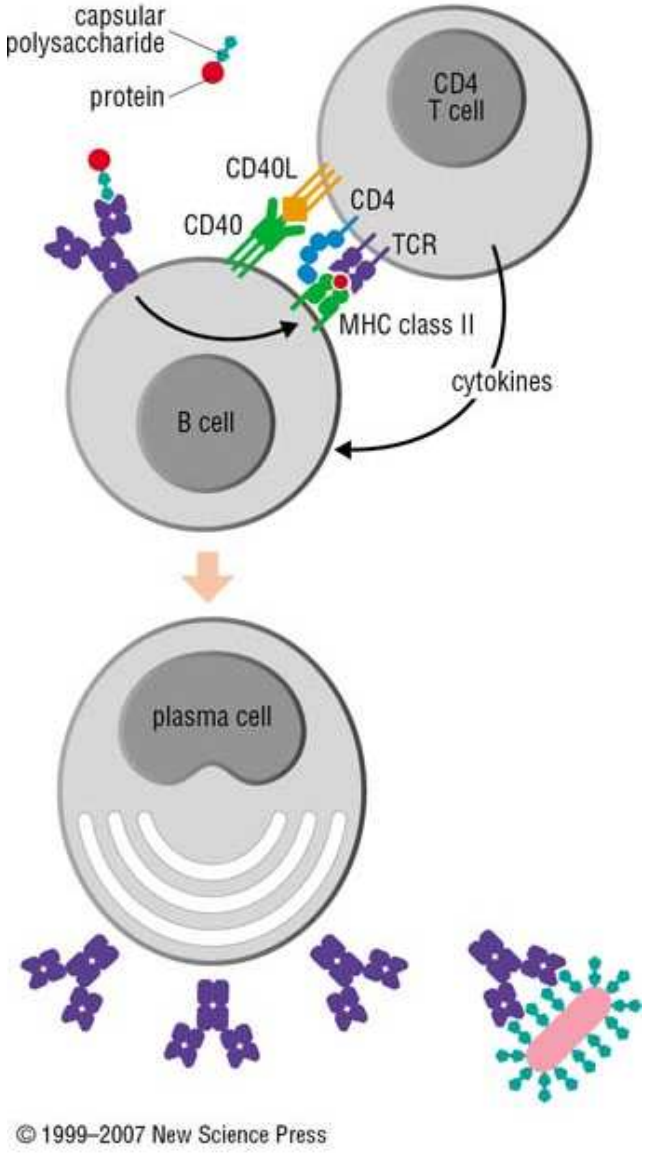
Mecanismo de acción de adyuvantes que carecen de PAMPs



- **Recientemente se ha mostrado que una importante vía de activación de la inflamación por células necróticas es a través la liberación de cristales de ác. úrico (no del ác. en solución). Estos activan una vía adicional de detección de patógenos, a través de receptores intracelulares llamados NOD-like receptors (NLRs), siendo el más estudiado el NALP3, los cuales además de detectar PAMPs (como peptidoglicanos) reaccionan también con ligandos endógenos que tienen carácter de señales de peligro, como cristales de ác. úrico, altas concentraciones de ATP, o especies reactivas del oxígeno (ROS).**

- Al ser inyectadas, las partículas de hidróxido de aluminio, y quizás también las microgotas de las emulsiones de aceite minerales, resultan necróticas para las células del tejido donde han sido inyectados, las cuales responden inmediatamente secretando citoquinas que atraen células del sistema inmune innato. Además, en este proceso hay una liberación de crístales de ác. úrico (al menos en algunos modelos) por las células dañadas. Los monocitos reclutados fagocitan la alúmina y los cristales de ác. úrico que han sido liberados. Estos probablemente a través de la desestabilizan de la vesícula fagocítica entran en contacto con el componente NALP3 del denominado inflamasoma, favoreciendo la polimerización de varios de los mismos que recluta nuevos factores resultando en un complejo con capacidad de activar caspasas, como la caspasa 1, que procesa el precursor de la IL-1beta y la IL-18 disparando el proceso inflamatorio local. A través de este estímulo los monocitos se diferencian dando lugar a céluals dendríticas maduras que presentan el antígeno en los ganglios, activando células T específicas para ese antígeno. Particularmente en ratones, esta respuesta es del tipo Th2. En el baso y probablemente también en los ganglios se da el reclutamiento de eosinófilos Gr1+, IL-4+ que estimulan la respuesta de linfocitos B.

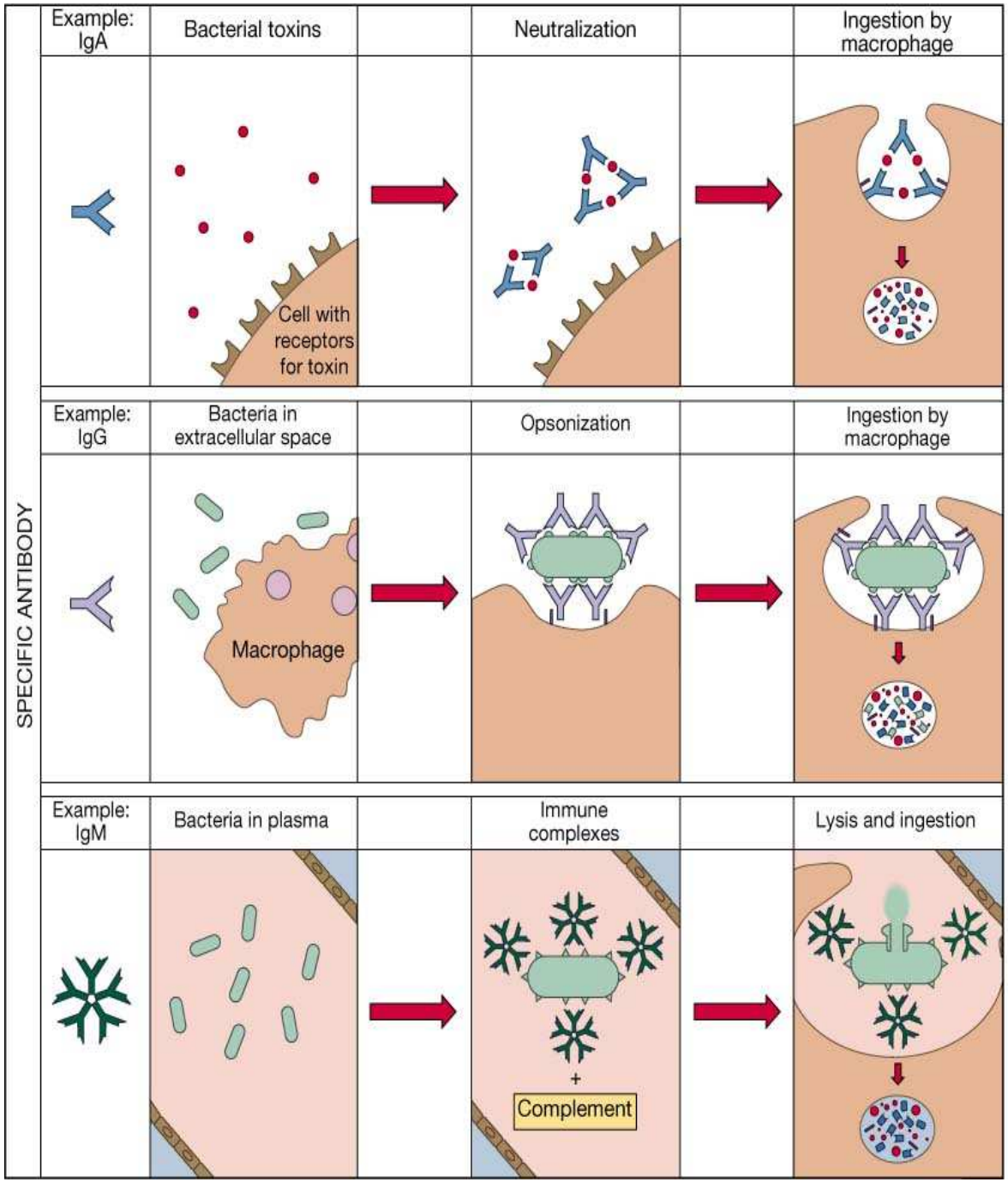
Las vacunas conjugadas activan las células T y permiten la vacunación contra polisacáridos



Los ejemplos más destacados de estas vacunas son la vacuna contra *Haemophilus influenzae* tipo b, y contra *Streptococcus pneumoniae*

Los polisacáridos de las cápsulas bacterianas son altamente inmunogénicos en el curso de la infección, sin embargo el polisacárido purificado no da lugar a respuestas T dependientes, y por lo tanto es necesario conjugarlo (generalmente al toxoide tetánico o diftérico, ya aprobados para vacunas)

La aplicación de esta vacuna es un buen ejemplo de la 'inmunidad de rebaño' que se logra con la vacunación. La aplicación en infantes redujo dramáticamente la incidencia en los mismos pero también en los adultos



INMUNÓGENOS Y ANTICUERPOS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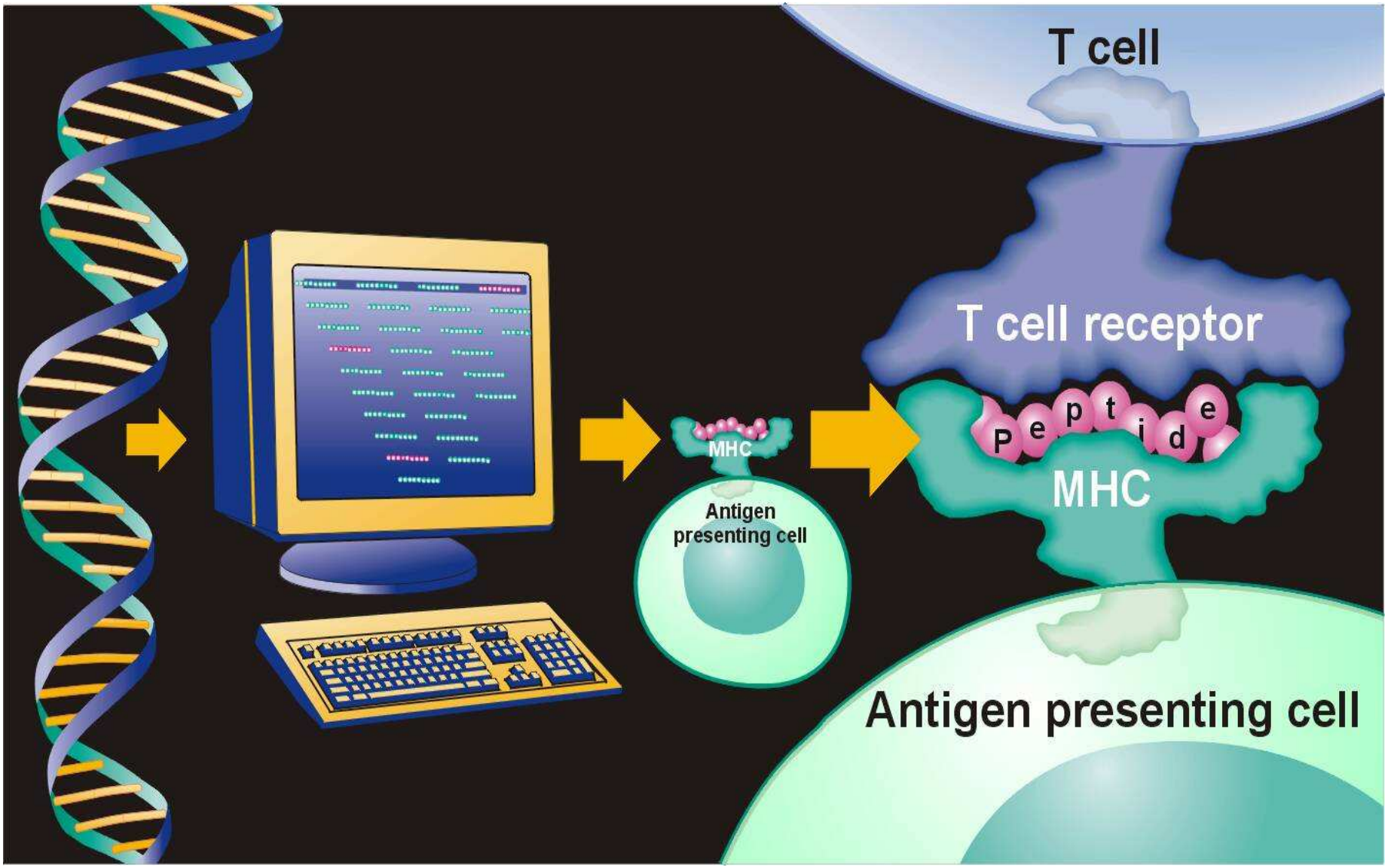
DO YOU WANT TO PLAY DOCTOR?
I CAN'T. YOU'RE NOT INSURED.
PIERO TONIN

GRACIAS!!!!!!!!


T cell
T cell receptor
Peptide
MHC
MHC
Antigen presenting cell
Antigen presenting cell