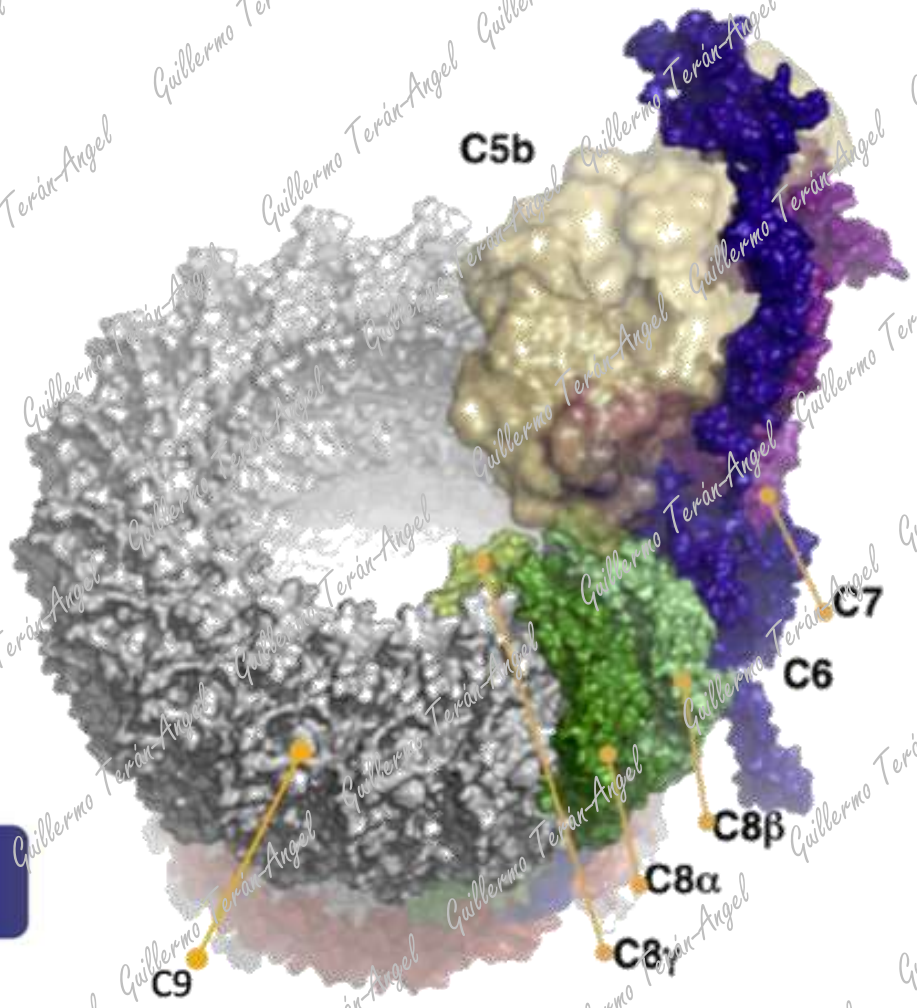
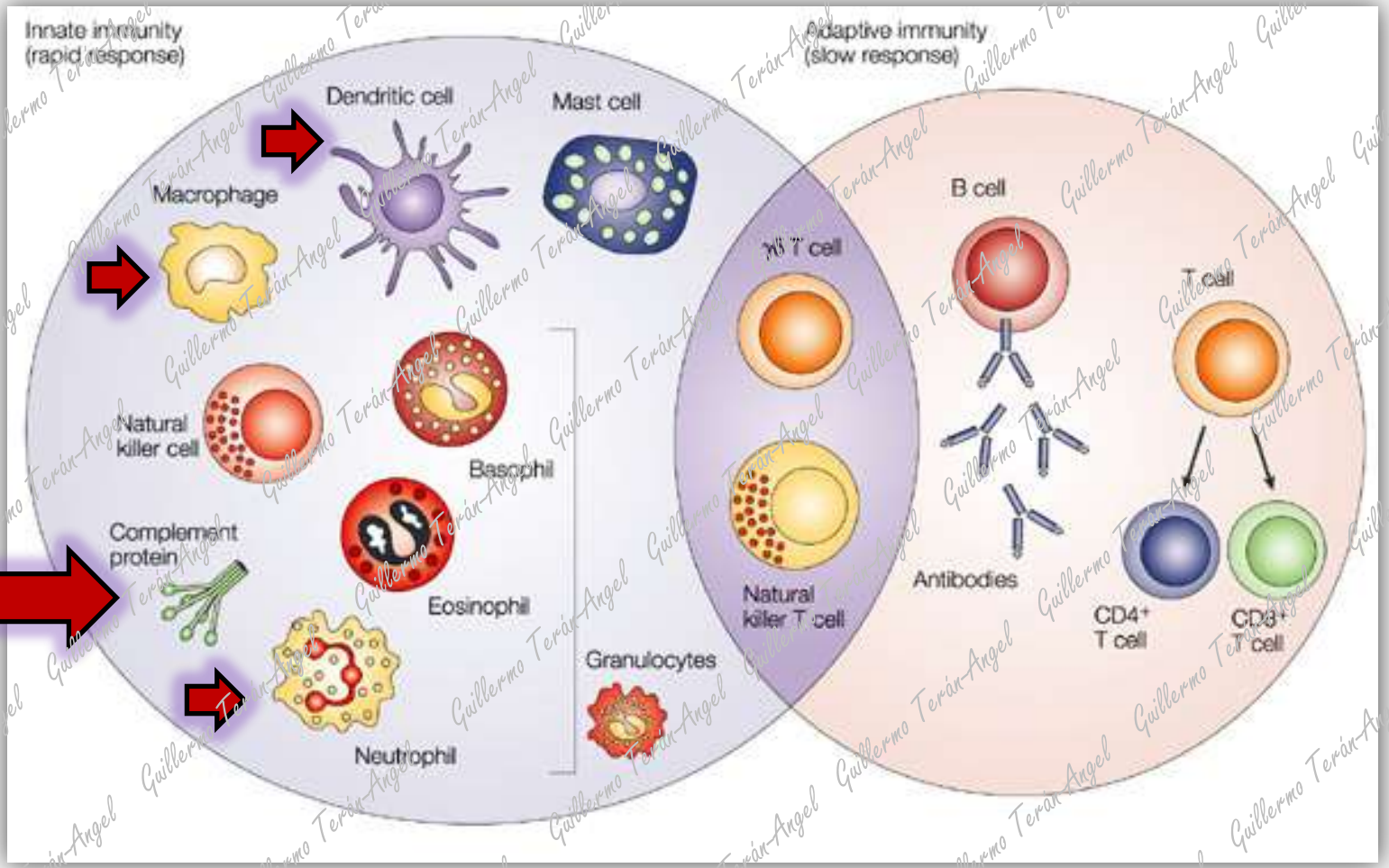


MECANISMOS DE AMPLIFICACIÓN DE LA RESPUESTA INMUNOLÓGICA: COMPLEMENTO Y FAGOCITOSIS

Guillermo Terán-Angel
IDIC-ULA

Temario

Ubicándonos



Nature Reviews Cancer 4, 11-22 (January 2004)

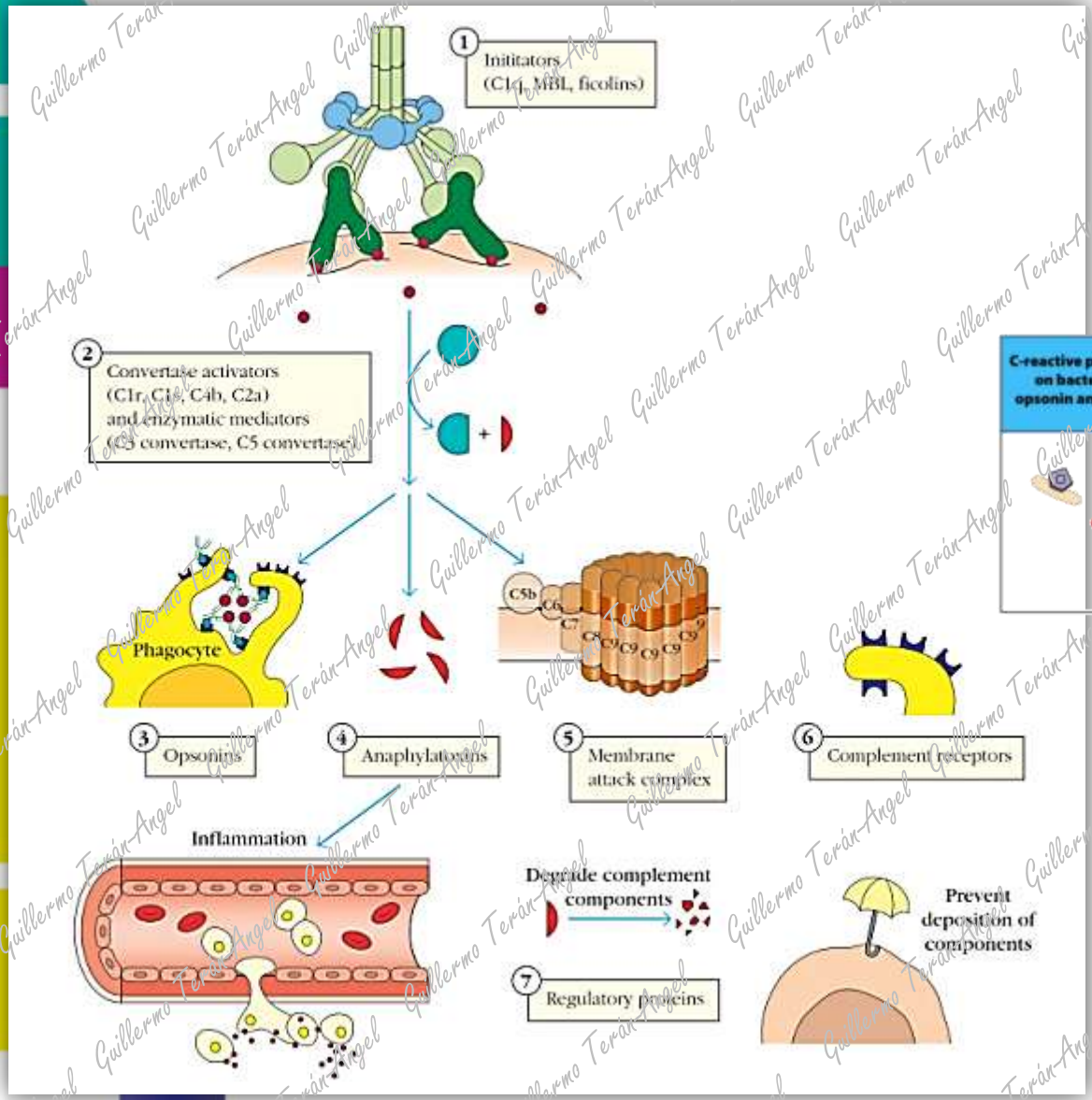
Interconsulta

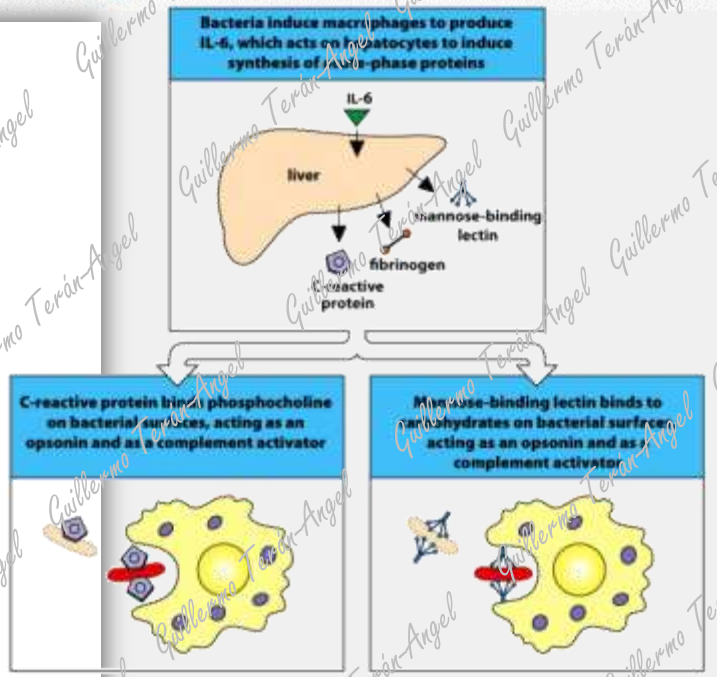
Paciente con valores:

CH50=0 & AH50=0

Próximo paso: evaluar C4????????

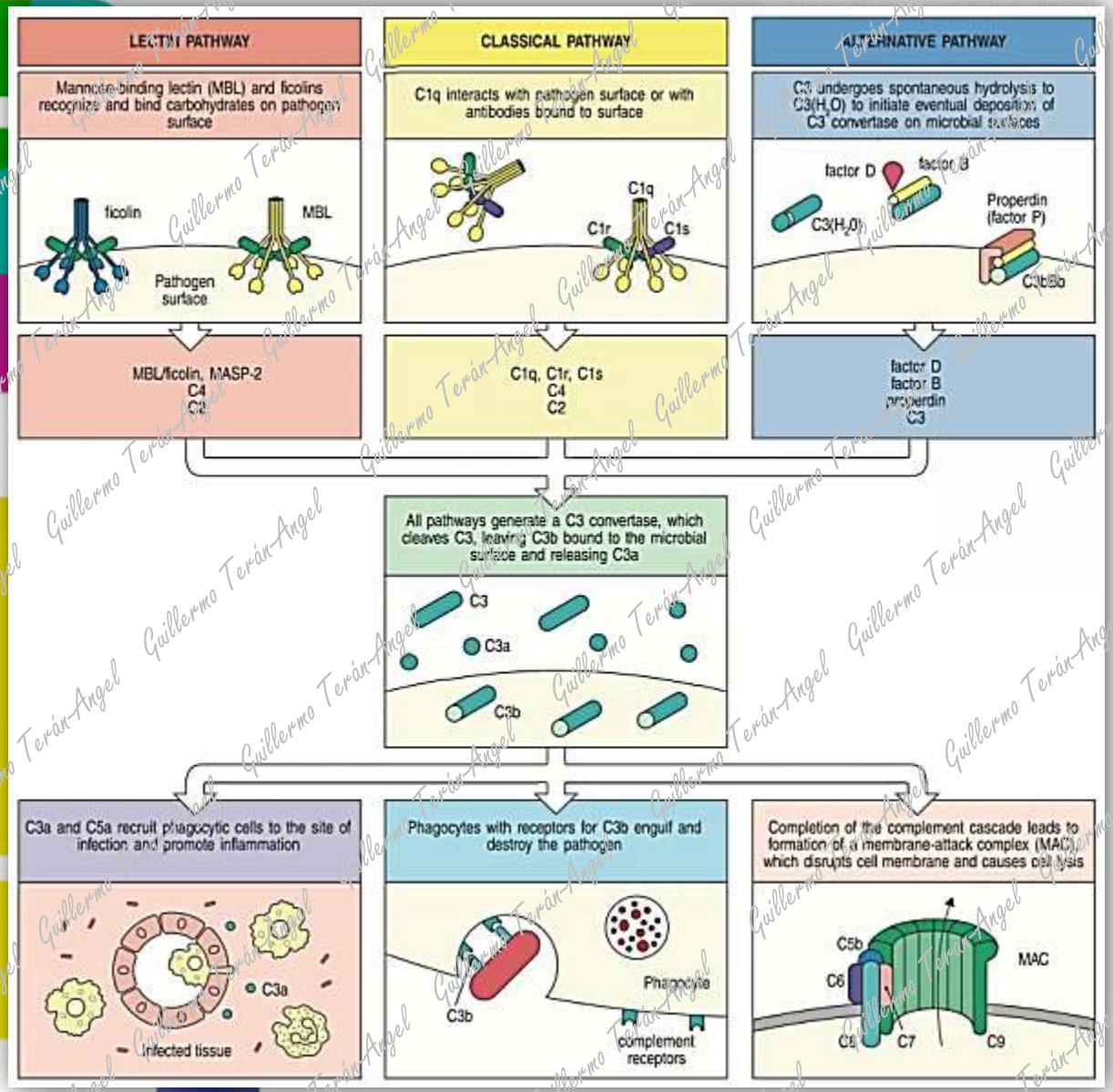
Complemento





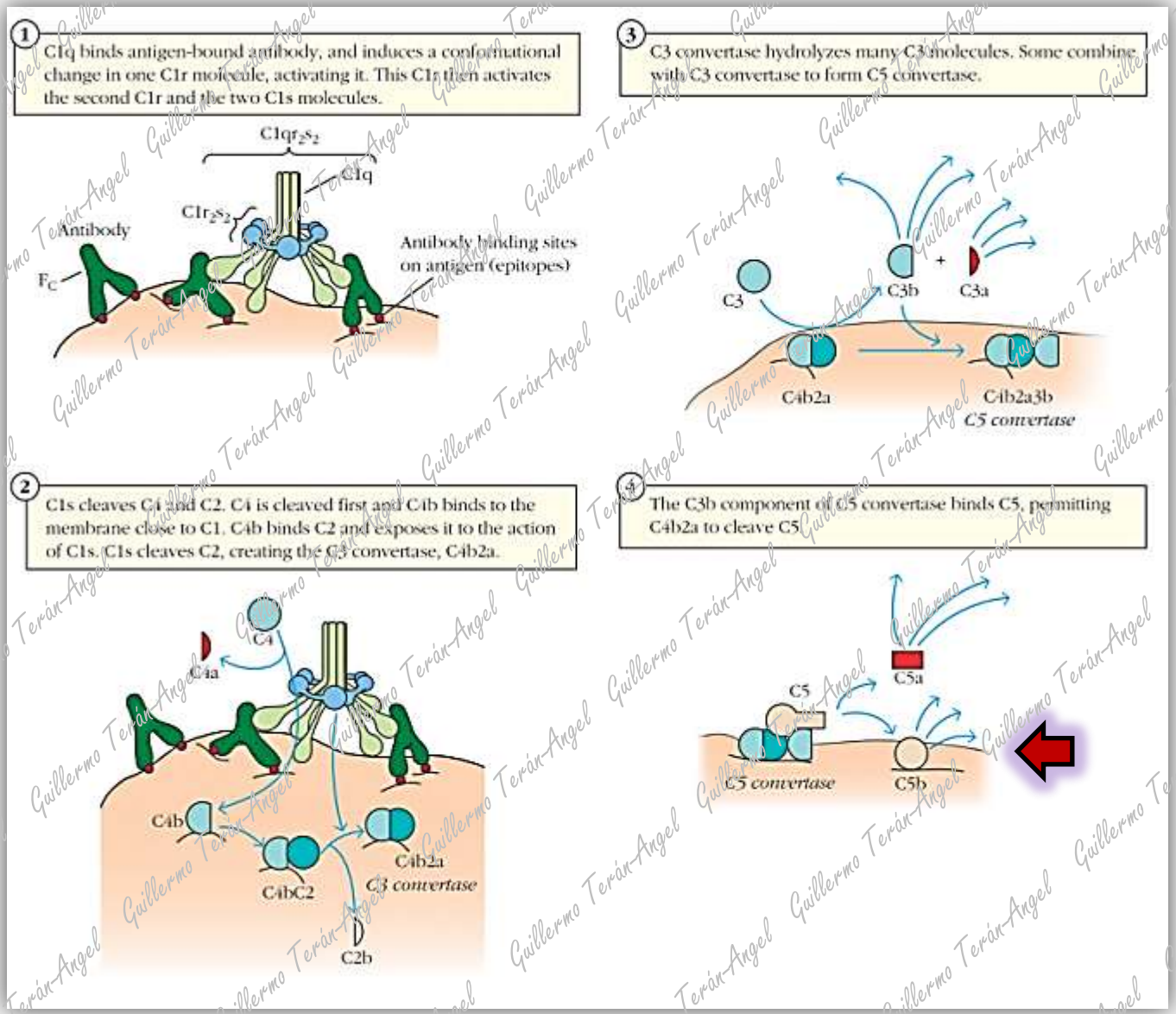
- Cromosoma 6:
  - ✓ C2, C4, B
- Cromosoma 1:
  - ✓ C1q, C4BP, CR1
- Cromosoma 5:
  - ✓ C6,C7,C9

Globalmente



Functional protein classes in the complement system	
Binding to antigen:antibody complexes and pathogen surfaces	C1q
Binding to carbohydrate structures such as mannose or GlcNAc on microbial surfaces	MBL Ficolins C1q Properdin (factor P)
Activating enzymes	C1r C1s C2a Bb D MASP-2
Membrane-binding proteins and opsonins	C4b C3b
Peptide mediators of inflammation	C5a C3a C4a
Membrane-attack proteins	C5b C6 C7 C8 C9
Complement receptors	CR1 CR2 CR3 CR4 CRIg
Complement-regulatory proteins	C1INH C4BP CR1 MCP DAF H I P CD59

Una a una: Vía clásica

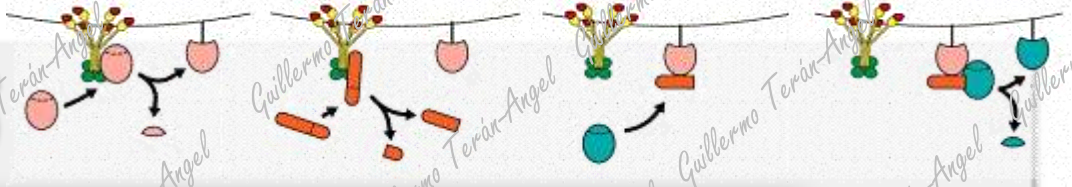


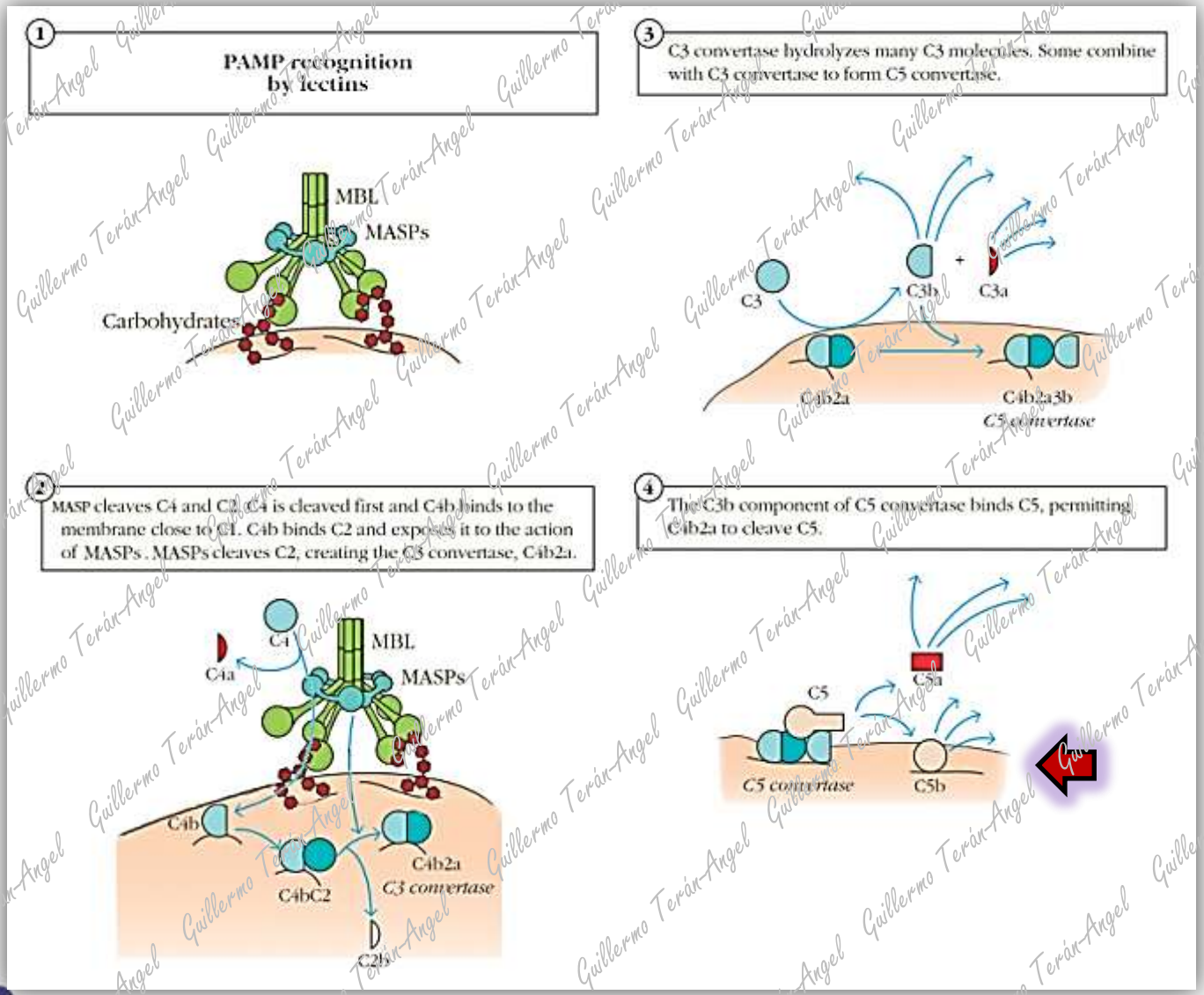
Vía clásica

Proteins of the classical pathway of complement activation

Native component	Active form	Function of the active form
C1 ($C1q:C1r_2:C1s_2$)	C1q	Binds directly to pathogen surfaces or indirectly to antibody bound to pathogens, thus allowing autoactivation of C1r
	C1r	Cleaves C1s to active protease
	C1s	Cleaves C4 and C2
C4	C4b	Covalently binds to pathogen and opsonizes it. Binds C2 for cleavage by C1s
	C4a	Peptide mediator of inflammation (weak activity)
C2	C2a	Active enzyme of classical pathway C3/C5 convertase: cleaves C3 and C5
	C2b	Precursor of vasoactive C2 kinin
C3	C3b	Many molecules of C3b bind to pathogen surface and act as opsonins. Initiates amplification via the alternative pathway. Binds C5 for cleavage by C2a
	C3a	Peptide mediator of inflammation (intermediate activity)

Vía de las lectinas



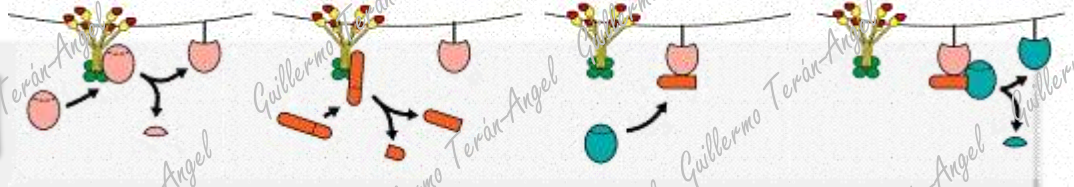


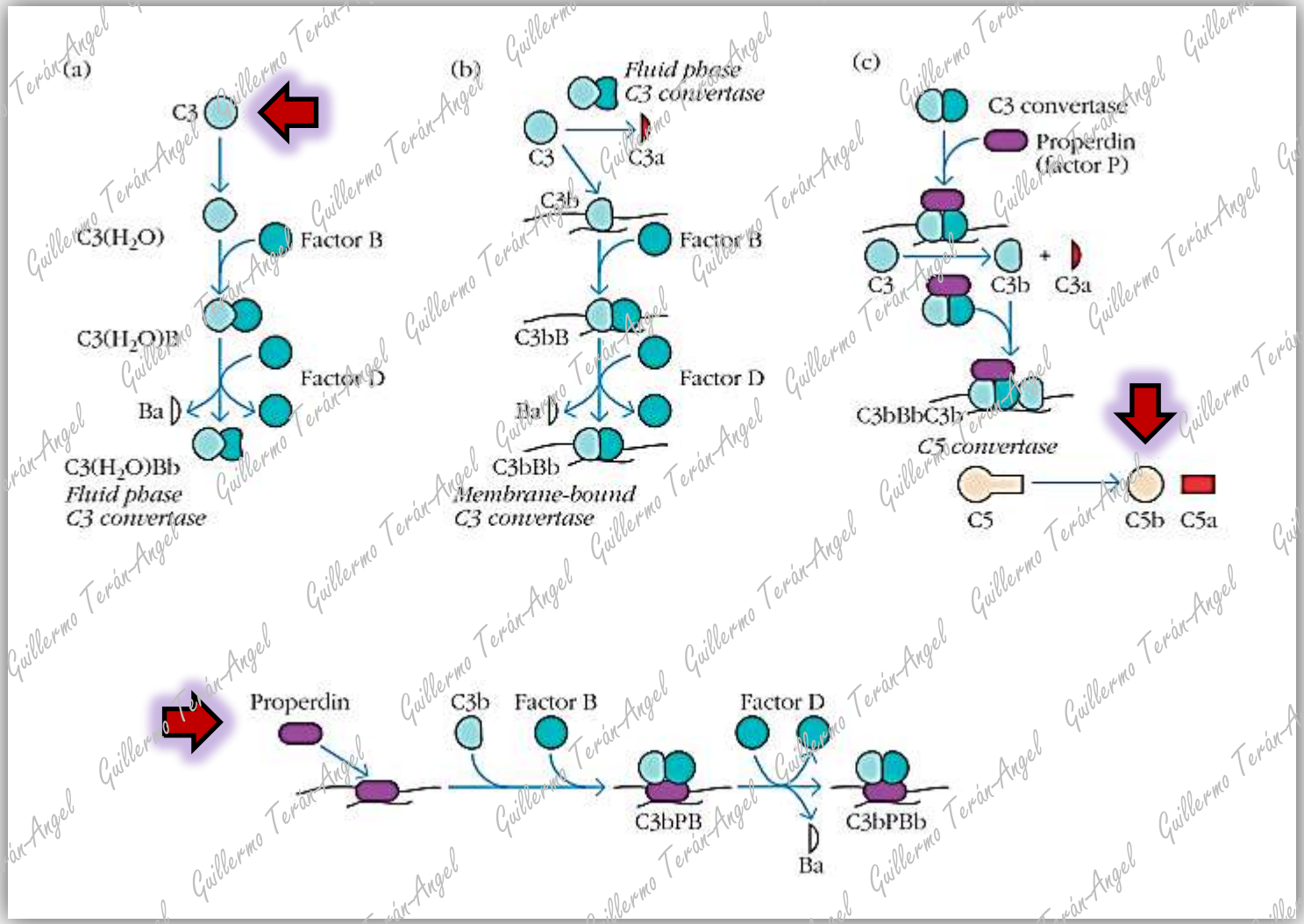
Vía de las lectinas

Proteins of the classical pathway of complement activation

Native component	Active form	Function of the active form
	MBL/ficolin	Binds directly to pathogen surfaces
	MASP-2	Cleaves C4 and C2
C4	C4b	Covalently binds to pathogen and opsonizes it. Binds C2 for cleavage by C1s
	C4a	Peptide mediator of inflammation (weak activity)
C2	C2a	Active enzyme of classical pathway C3/C5 convertase: cleaves C3 and C5
	C2b	Precursor of vasoactive C2 kinin
C3	C3b	Many molecules of C3b bind to pathogen surface and act as opsonins. Initiates amplification via the alternative pathway. Binds C5 for cleavage by C2a
	C3a	Peptide mediator of inflammation (intermediate activity)

Vía alterna

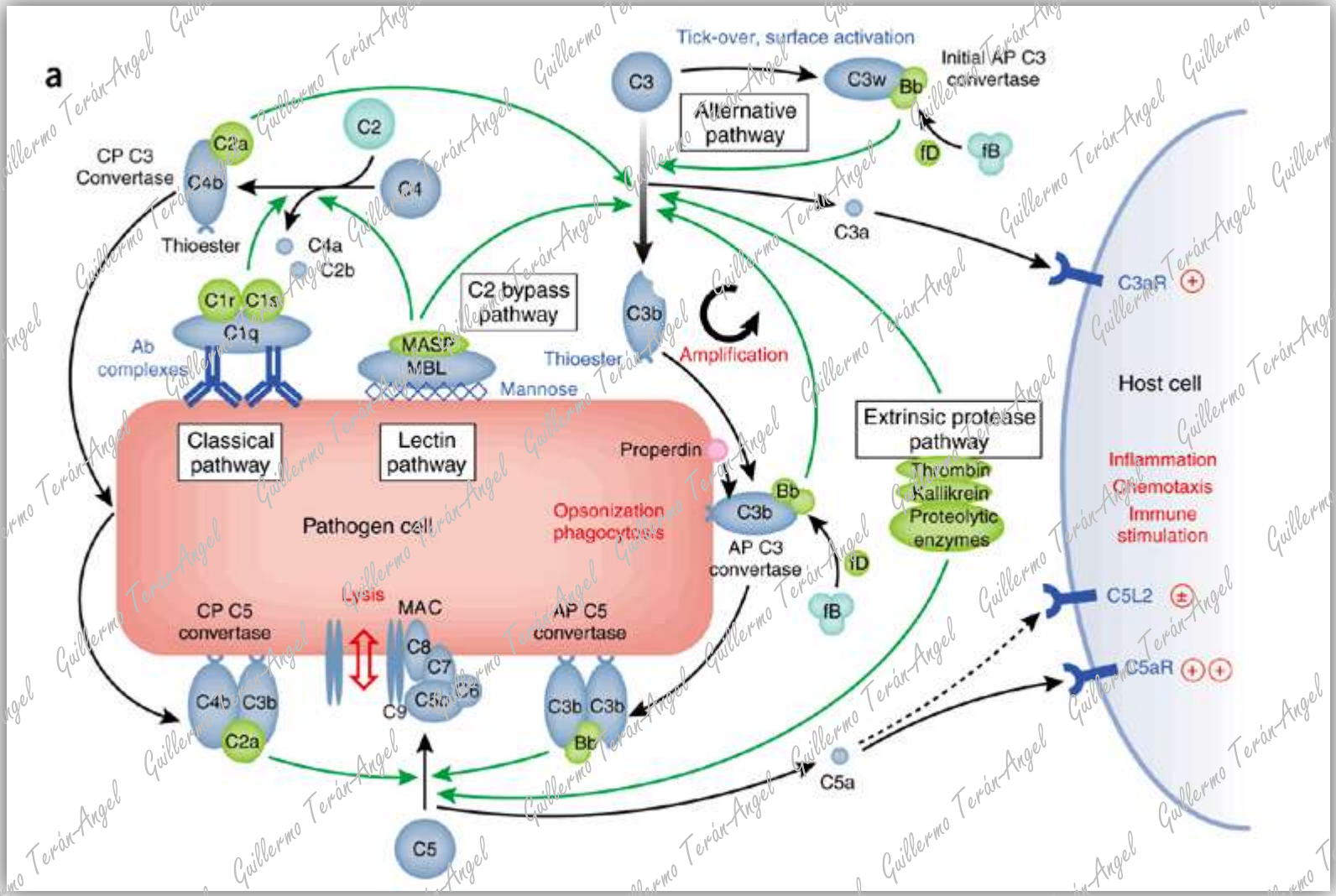



(a)
C3
C3(H2O)
Factor B
C3(H2O)B
Factor D
Ba
C3(H2O)Bb
Fluid phase
C3 convertase
(b)
Fluid phase
C3 convertase
C3
C3a
C3b
Factor B
C3bB
Factor D
Ba
C3bBb
Membrane-bound
C3 convertase
(c)
C3 convertase
Properdin
(factor P)
C3
C3b
C3a
C3bBbC3b
C5 convertase
C5
C5b
C5a
Properdin
C3b
Factor B
Factor D
C3bPB
C3bPBb
Ba

Vía alterna

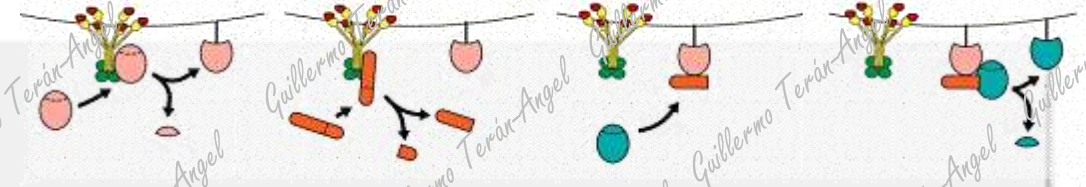
Proteins of the alternative pathway of complement activation		
Native component	**Active fragments**	**Function**
C3	C3b	Binds to pathogen surface, binds B for cleavage by D, C3bBb is C3 convertase and $C3b_2Bb$ is C5 convertase
Factor B (B)	Ba	Small fragment of B, unknown function
	Bb	Bb is active enzyme of the C3 convertase C3bBb and C5 convertase $C3b_2Bb$
Factor D (D)	D	Plasma serine protease, cleaves B when it is bound to C3b to Ba and Bb
Properdin (P)	P	Plasma protein that binds to bacterial surfaces and stabilizes the C3bBb convertase

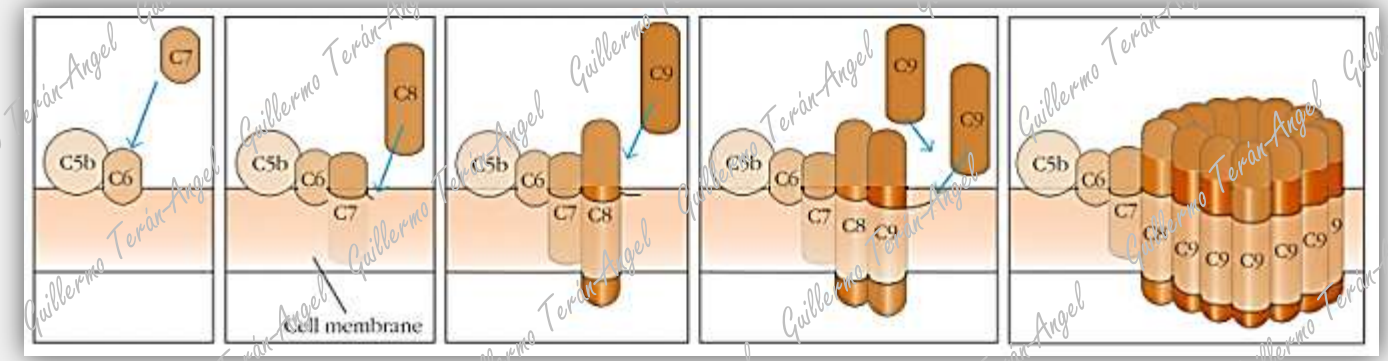
Y otras vías

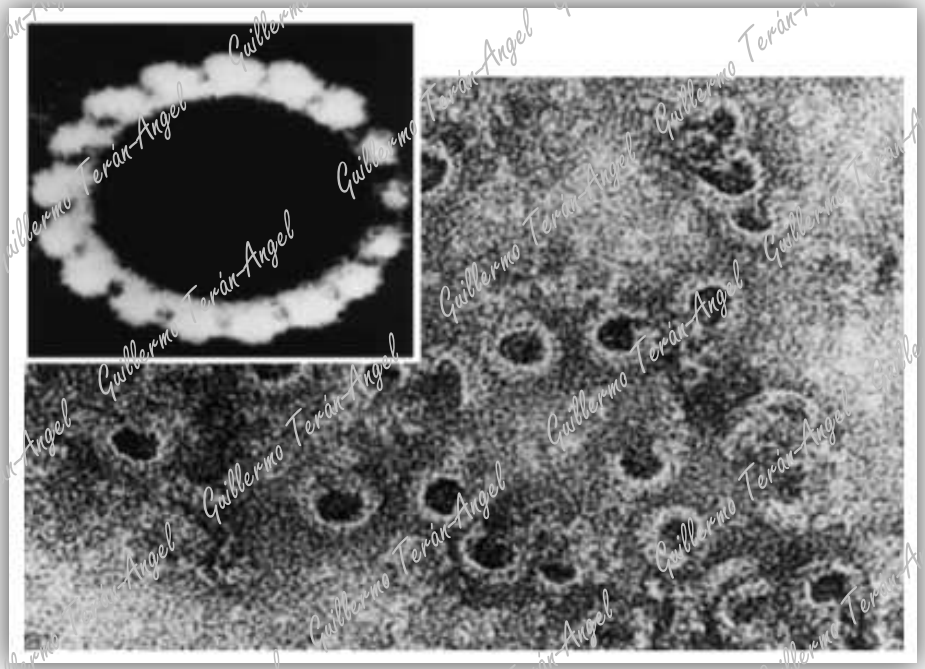


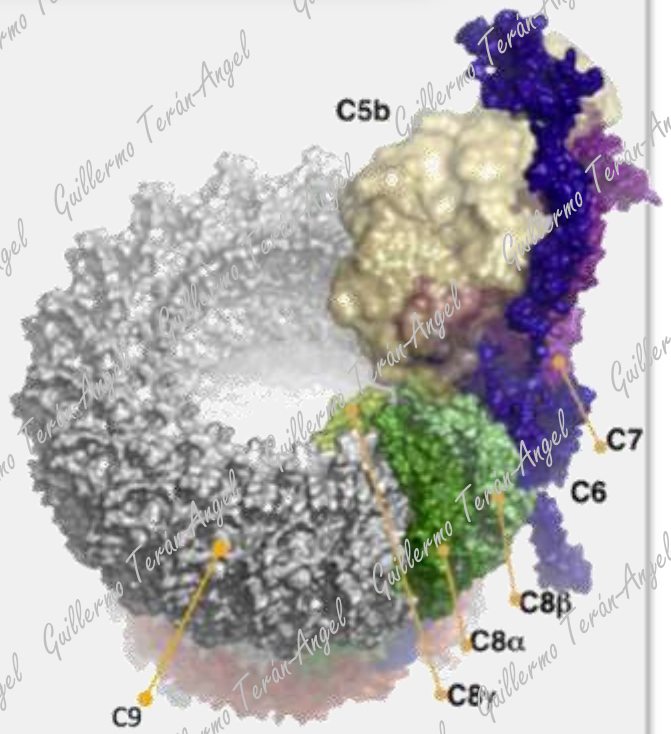
Nature Biotechnology 25, 1265 - 1275 (2007)

Y la vía común

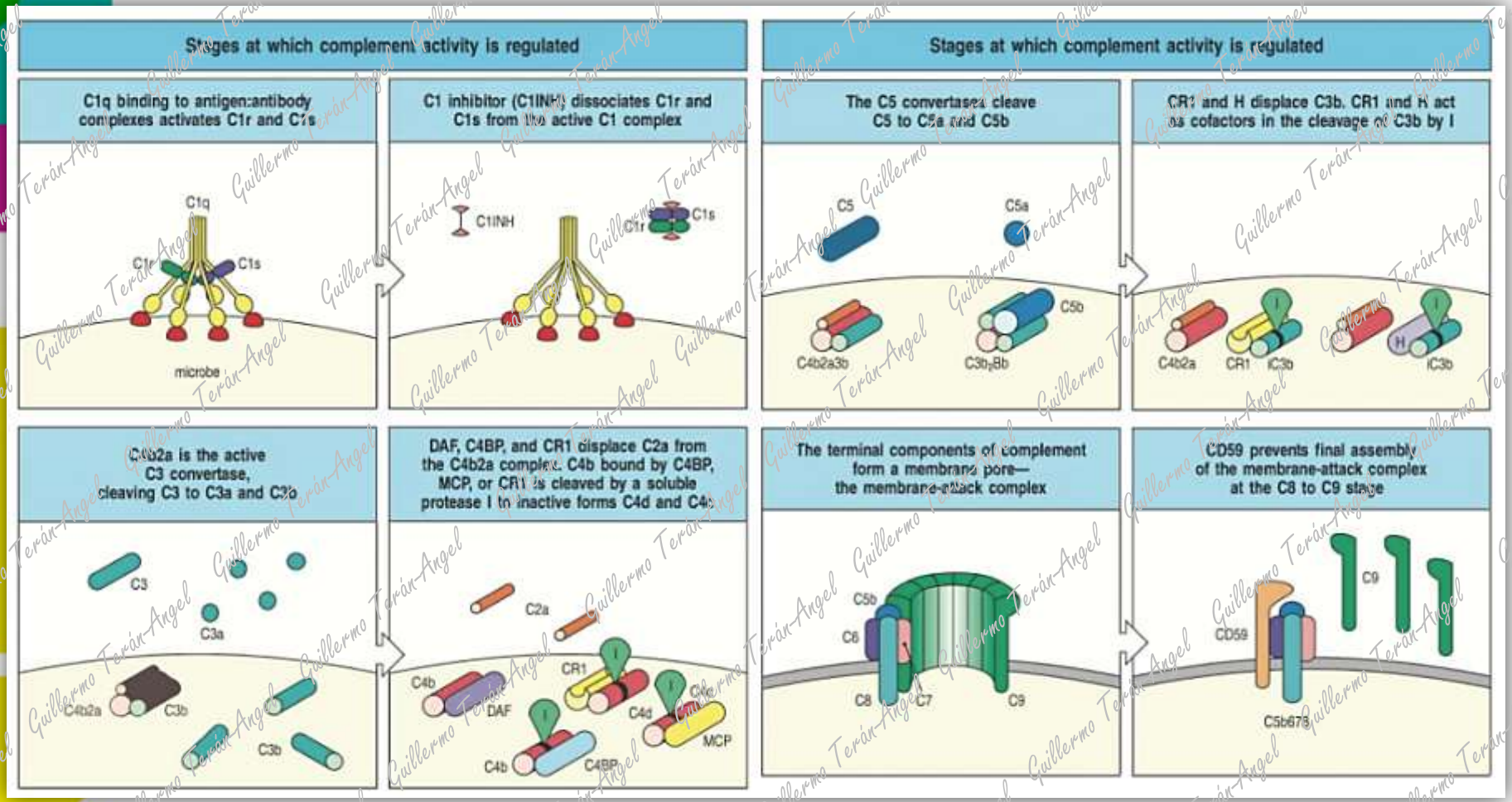








Aja! Y por que no se lisan todas nuestras células?

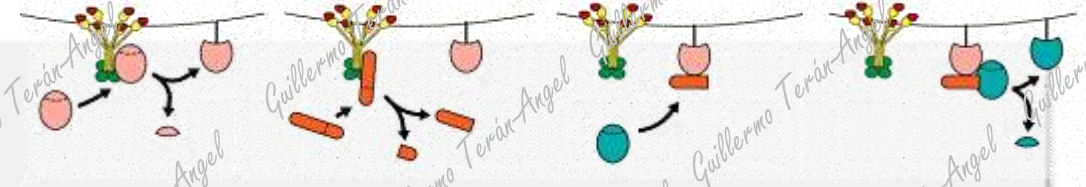


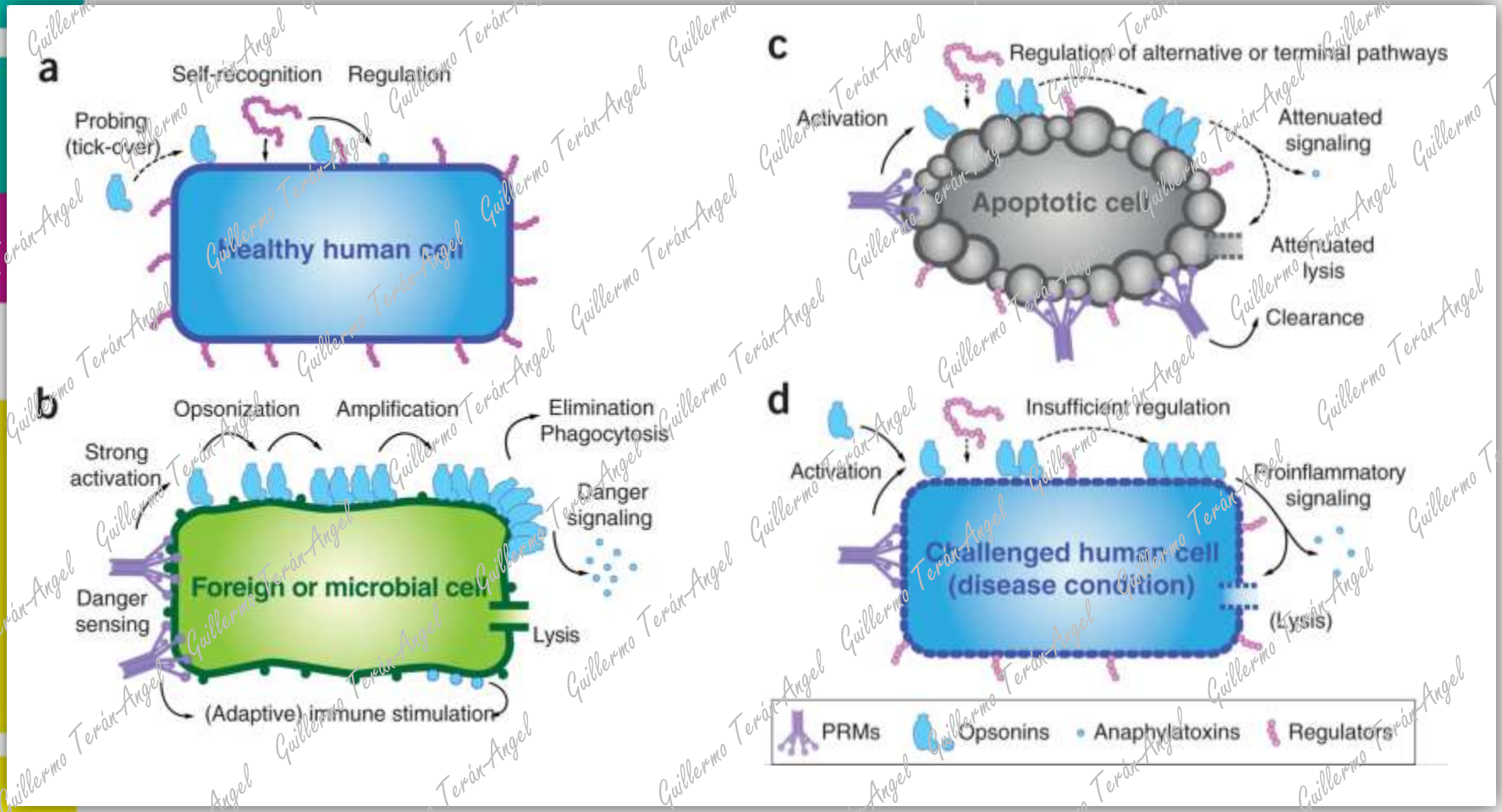
Proteinas reguladoras

TABLE 6-4 Proteins involved in the regulation of complement activity

Protein	Fluid phase or membrane	Pathway affected	Function
C1 inhibitor (C1INH)	Fluid phase	Classical and lectin	Induces dissociation and inhibition of $C1r_2s_2$ from C1q; serine protease inhibitor
Decay Accelerating Factor (DAF) CD55	Membrane bound	Classical, alternative, and lectin	Accelerates dissociation of C4b2a and C3bBb C3 convertases
CR1 (CD35)	Membrane bound	Classical, alternative, and lectin	Blocks formation of, or accelerates dissociation of, the C3 convertases C4b2a and C3bBb by binding C4b or C3b Cofactor for factor I in C3b and C4b degradation on host cell surface
C4BP	Soluble	Classical and lectin	Blocks formation of, or accelerates dissociation of, C4b2a C3 convertase Cofactor for factor I in C4b degradation
Factor H	Soluble	Alternative	Blocks formation of, or accelerates dissociation of, C3bBb C3 convertase Cofactor for factor I in C3b degradation
Factor I	Soluble	Classical, alternative, and lectin	Serine protease: cleaves C4b and C3b using cofactors shown in Figure 6-16
Membrane cofactor of proteolysis, MCP (CD46)	Membrane bound	Classical, alternative, and lectin	Cofactor for factor I in degradation of C3b and C4b
S protein or Vitronectin	Soluble	All pathways	Binds soluble C5b67 and prevents insertion into host cell membrane
Protectin (CD59)	Membrane bound	All pathways	Binds C5b678 on host cells, blocking binding of C9 and the formation of the MAC complex
Carboxypeptidases N, B, and R	Soluble	Anaphylatoxins produced by all pathways	Cleave and inactivate the anaphylatoxins C3a and C5a

Homeostasis





Nature Immunology 11, 785–797 (2010)

Patogenia

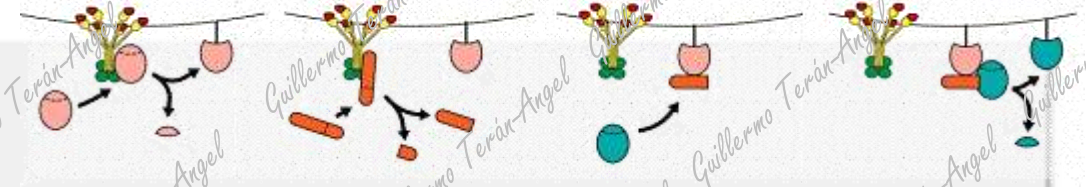


Table 1. Conventional Complement Deficiencies

Protein	Disease Associations
Recognition	
MBL	infections in immunocompromised individuals
H-ficolin	immune deficiency, necrotizing enterocolitis
C1q	SLE-like syndrome, recurrent bacterial infections
Enzymes	
MASP-2	immune deficiency
C1r/s	SLE-like syndrome, recurrent bacterial infections
C2	autoimmune disease
Factor D	meningococcal and encapsulated bacterial infections
Factor I	encapsulated bacterial infections

Protein	Disease Associations
Structural	
C3	bacterial infections, SLE-like syndrome
C4	SLE-like syndrome, encapsulated bacterial infections
C5	meningococcal infection
C6	meningococcal infection
C7	meningococcal infection
C8	meningococcal infection
C9	meningococcal infection

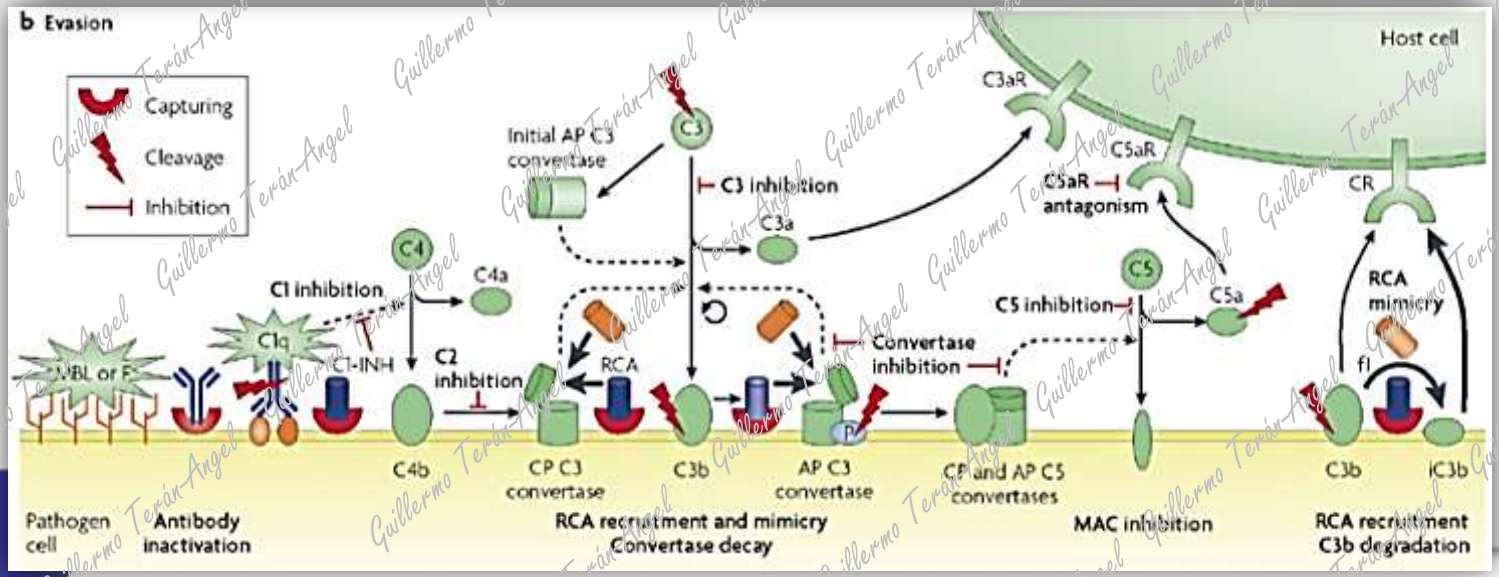
Protein	Disease Associations
Control	
Properdin	meningococcal infection
Factor H	hemolytic uremic syndrome (HUS), dense deposit disease
C1-INH	hereditary angioedema (HAE)
CD11a (LFA-1), CD11b (CR3), CD11c (CR4) /CD18[1]	leukocyte adhesion deficiency type I (LAD I)
CD46 (MCP)	atypical hemolytic uremic syndrome (aHUS)
CD55, CD59 (PIGA)[2]	paroxysmal nocturnal hemoglobinuria (PNH)

Am J Hum Genet. 2011 Jun 10; 88(6): 689–705

Mecanismos de evasión

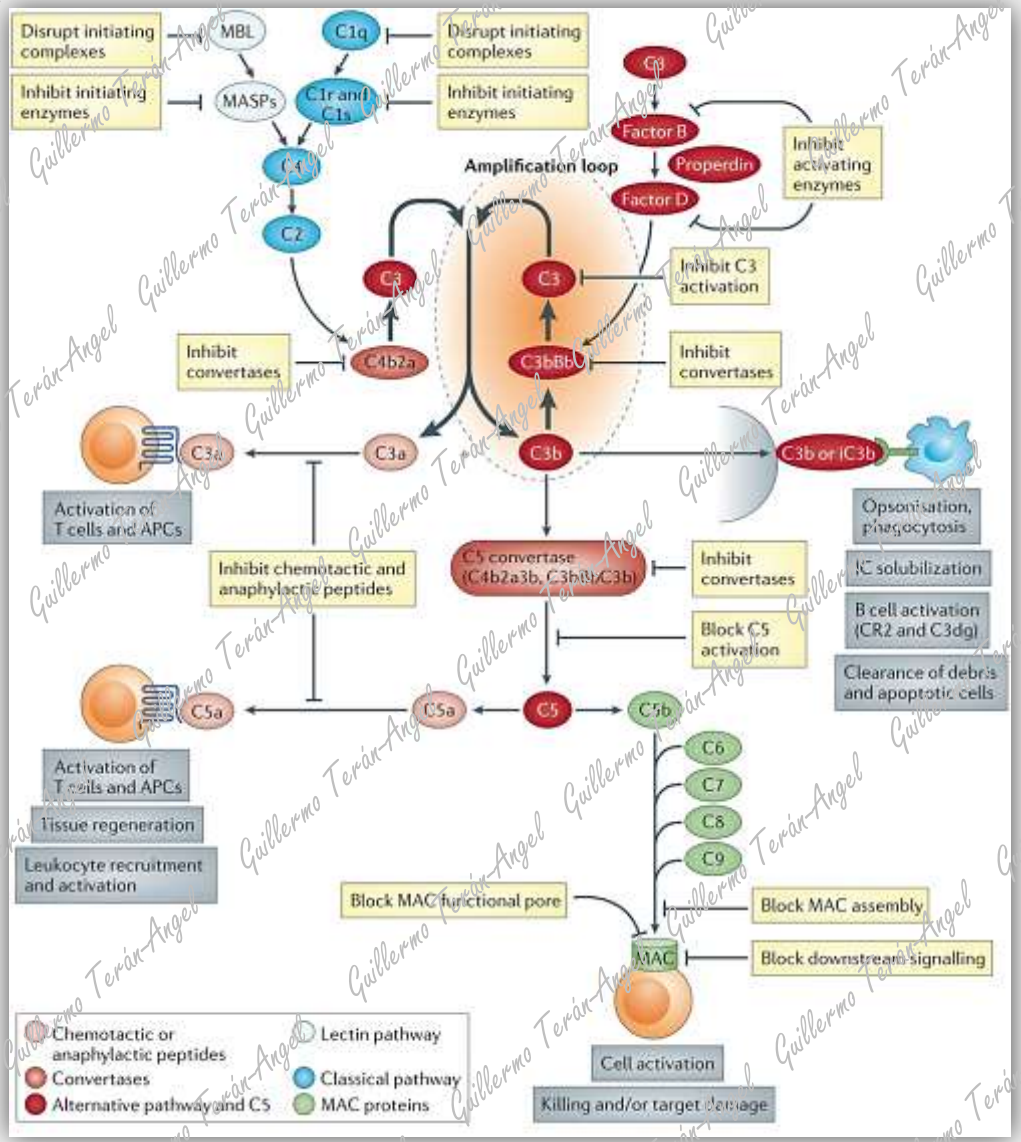
TABLE 6-5 Some microbial complement evasion strategies

Complement evasion strategy	Example
Interference with antibody–complement interaction	Antibody depletion by Staphylococcal protein A
	Removal of IgG by Staphylokinase
Binding and inactivation of complement proteins	*S. aureus* protein SCIN binds and inactivates the C3bBb C3 convertase
	Parasite protein C2 receptor trispanning protein disrupts the binding between C2 and C4
Protease-mediated destruction of complement component	Elastase and alkaline phosphatase from *Pseudomonas* degrade C1q and C3/C3b
	ScpA and ScpB from *Streptococcus* degrade C5a
Microbial mimicry of complement regulatory components	*Streptococcus pyogenes* M proteins bind C4BP and factor H to the cell surface, accelerating the decay of C3 convertases bound to the bacterial surface
	Variola and *Vaccinia* viruses express proteins that act as cofactors for factor I in degrading C3b and C4b



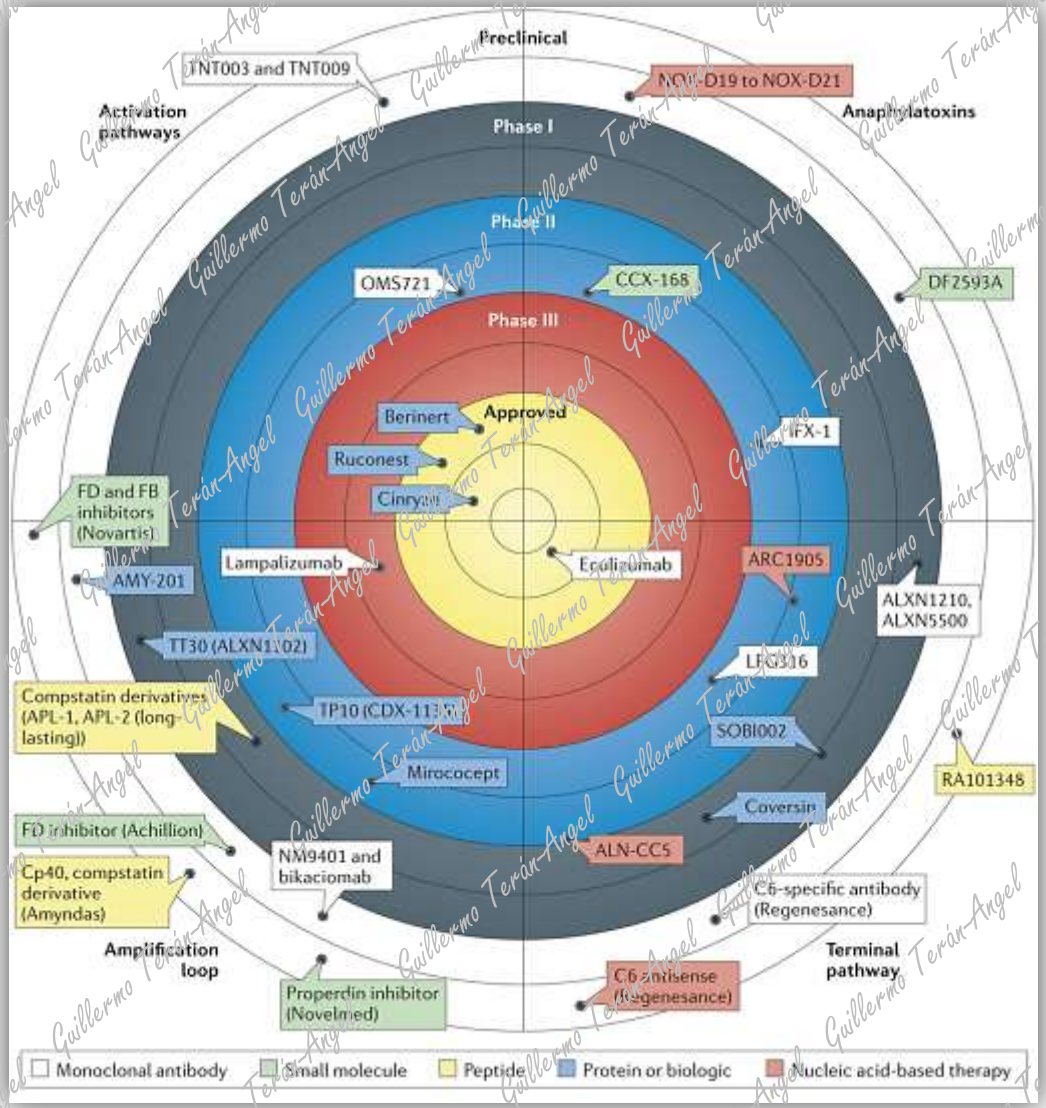
Nature Reviews Microbiology 6, 132-142 (February 2008)

Terapéutica



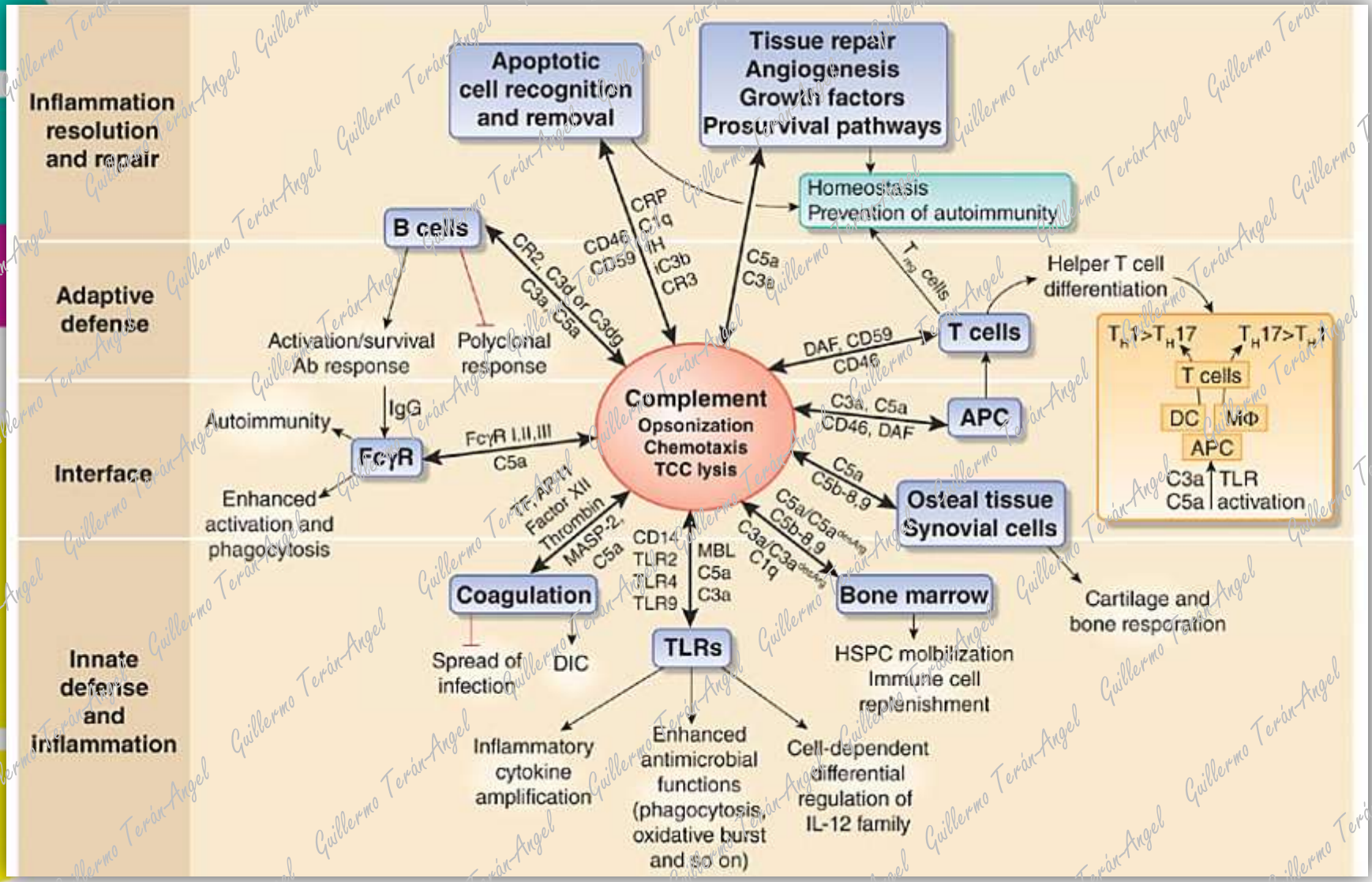
Nature Reviews Drug Discovery 14, 857–877 (2015)

Terapéutica



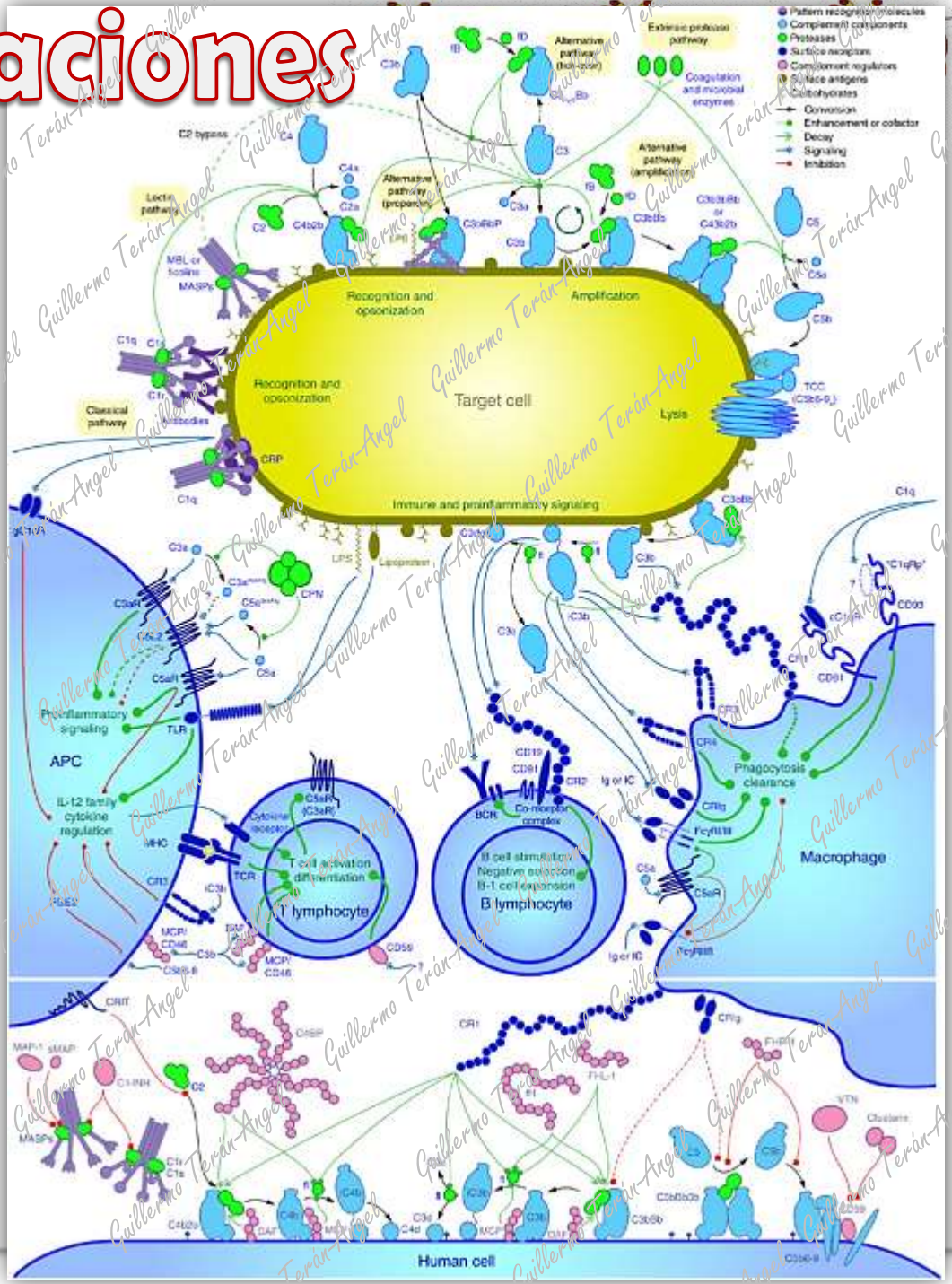
Nature Reviews Drug Discovery 14, 857–877 (2015)

Mas que complementar



Nature Immunology 11, 785–797 (2010)

Interrelaciones



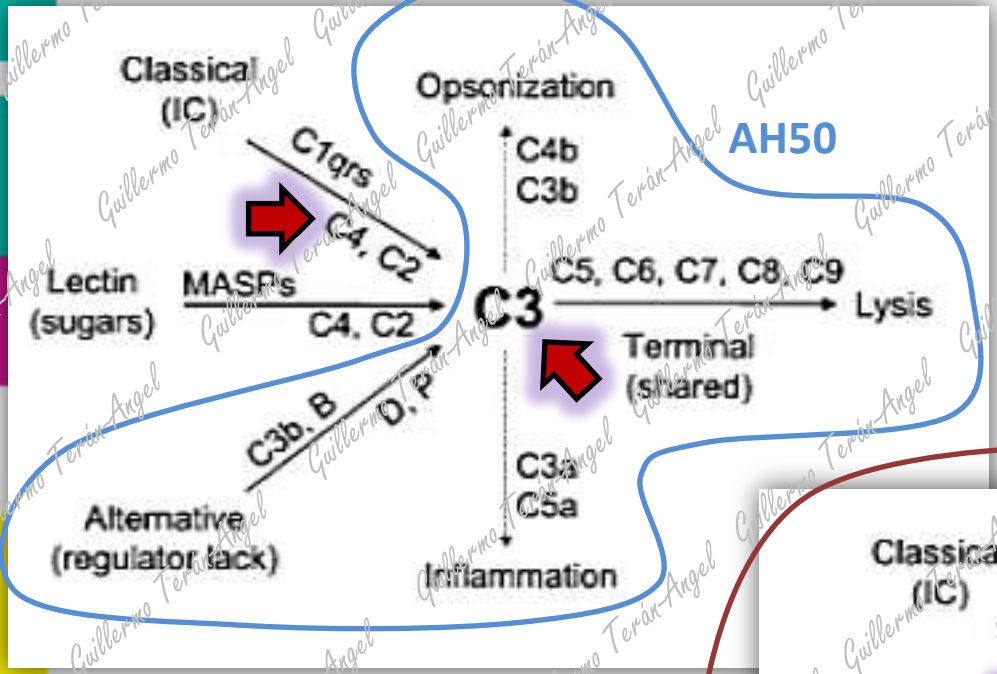
Nature Immunology 11, 785–797 (2010)

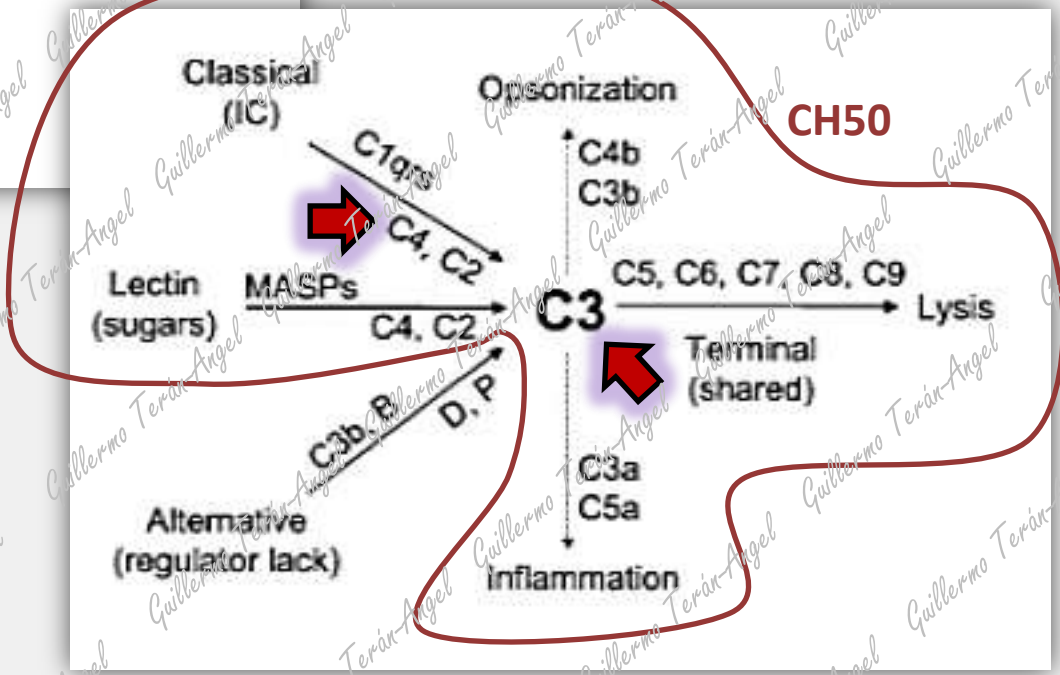
Receptores

TABLE 6-3 Receptors that bind complement components and their breakdown products

Receptor	Alternative name(s)	Ligand	Cell surface binding or expression	Function
CR1	CD35	C3b, C4b, C1q, iC3b	Erythrocytes, neutrophils, monocytes, macrophages, eosinophils, FDCs, B cells, and some T cells	Clearance of immune complexes, enhancement of phagocytosis, regulation of C3 breakdown
CR2	CD21, Epstein-Barr virus receptor	C3d, C3dg (human), C3d (mouse) iC3b	B cells and FDCs	Enhancement of B-cell activation, B-cell coreceptor, and retention of C3d-tagged immune complexes
CR3	CD11b/CD18, Mac-1	iC3b and factor H	Monocytes, macrophages, neutrophils, NK cells, eosinophils, FDCs, T cells	Binding to adhesion molecules on leukocytes, facilitates extravasation; iC3b binding enhances opsonization of immune complexes
CR4	CD11c/CD18	iC3b	Monocytes, macrophages, neutrophils, dendritic cells, NK cells, T cells	iC3b-mediated phagocytosis
CRIg	VSIG4	C3b, iC3b, and C3c	Fixed-tissue macrophages	iC3b-mediated phagocytosis and inhibition of alternative pathway
$C1qR_p$	CD93	C1q, MBL	Monocytes, neutrophils, endothelial cell, platelets, T cells	Induces T-cell activation; enhances phagocytosis
SIGN-R1	CD209	C1q	Marginal zone and lymph node macrophages	Enhances opsonization of bacteria by MZ macrophages
C3aR	None	C3a	Mast cells, basophils, granulocytes	Induces degranulation
C5aR	CD88	C5a	Mast cells, basophils, granulocytes, monocytes, macrophages, platelets, endothelial cells, T cells	Induces degranulation; chemoattraction; acts with IL-1β and/or TNF-α to induce acute phase response; induces respiratory burst in neutrophils
C5L2	None	C5a	Mast cells, basophils, immature dendritic cells	Uncertain, but most probably down-regulates proinflammatory effects of C5a

Evaluación

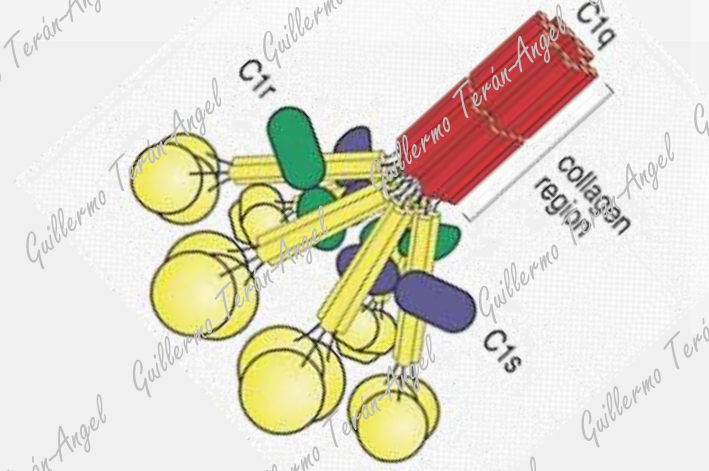

Classical
(IC)
C1qrs
C4, C2
Opsonization
C4b
C3b
AH50
Lectin
(sugars)
MASPs
C4, C2
C3
C5, C6, C7, C8, C9
Lysis
Terminal
(shared)
C3b, B
D, P
C3a
C5a
Alternative
(regulator lack)
Inflammation


Classical
(IC)
C1qrs
C4, C2
Opsonization
C4b
C3b
CH50
Lectin
(sugars)
MASPs
C4, C2
C3
C5, C6, C7, C8, C9
Lysis
Terminal
(shared)
C3b, B
D, P
C3a
C5a
Alternative
(regulator lack)
Inflammation

Evaluación

- A/CH50 75 a 160 U/ml
- C1 Inhibidor 16 a 33 mg/ dl
- C3 Hombres 88 a 252 mg/ dl
- C3 Mujeres 83 a 206 mg/ dl
- C4 Hombres 12 a 72 mg/ dl
- C4 Mujeres 13 a 75 mg/ dl

- CH50=0 & AH50=normal ▶ Clásica (upst)
- CH50=normal & AH50=0 ▶ Alterna (upst)
- CH50=0 & AH50=0 ▶ Común



- La actividad aumentada de complemento puede verse en:
  - ✓ Cáncer
  - ✓ Colitis ulcerosa
  - ✓ Infarto agudo de miocardio
- La actividad disminuida de complemento puede verse en:
  - ✓ Angioedema hereditario
  - ✓ Cirrosis hepática
  - ✓ Glomerulonefritis
  - ✓ Hepatitis infecciosa
  - ✓ Lupus Eritematoso Sistémico con afectación renal
  - ✓ Malnutrición
  - ✓ Rechazo de transplante de órganos

Interconsulta

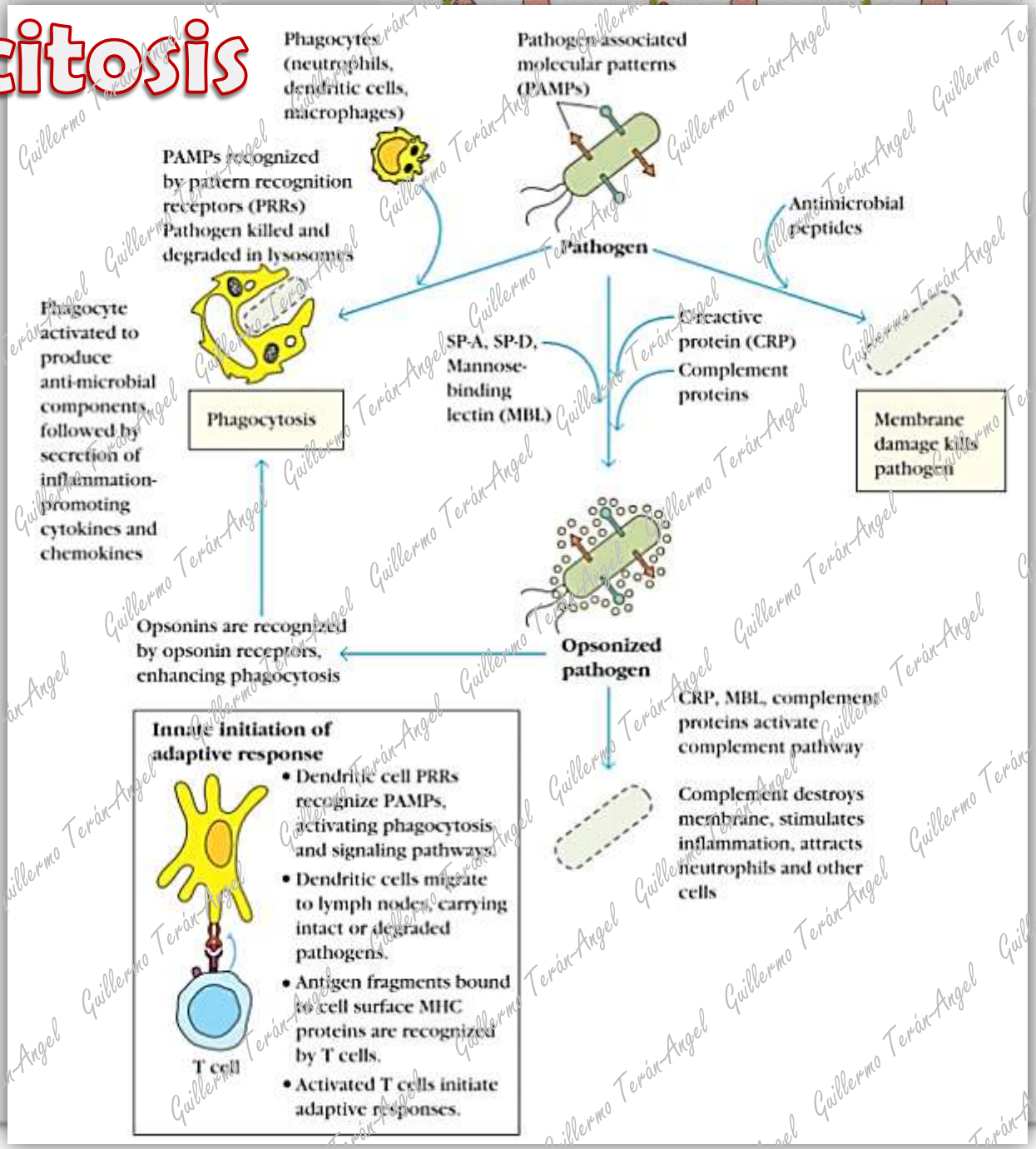
Paciente con valores:

CH50=0 & AH50=0

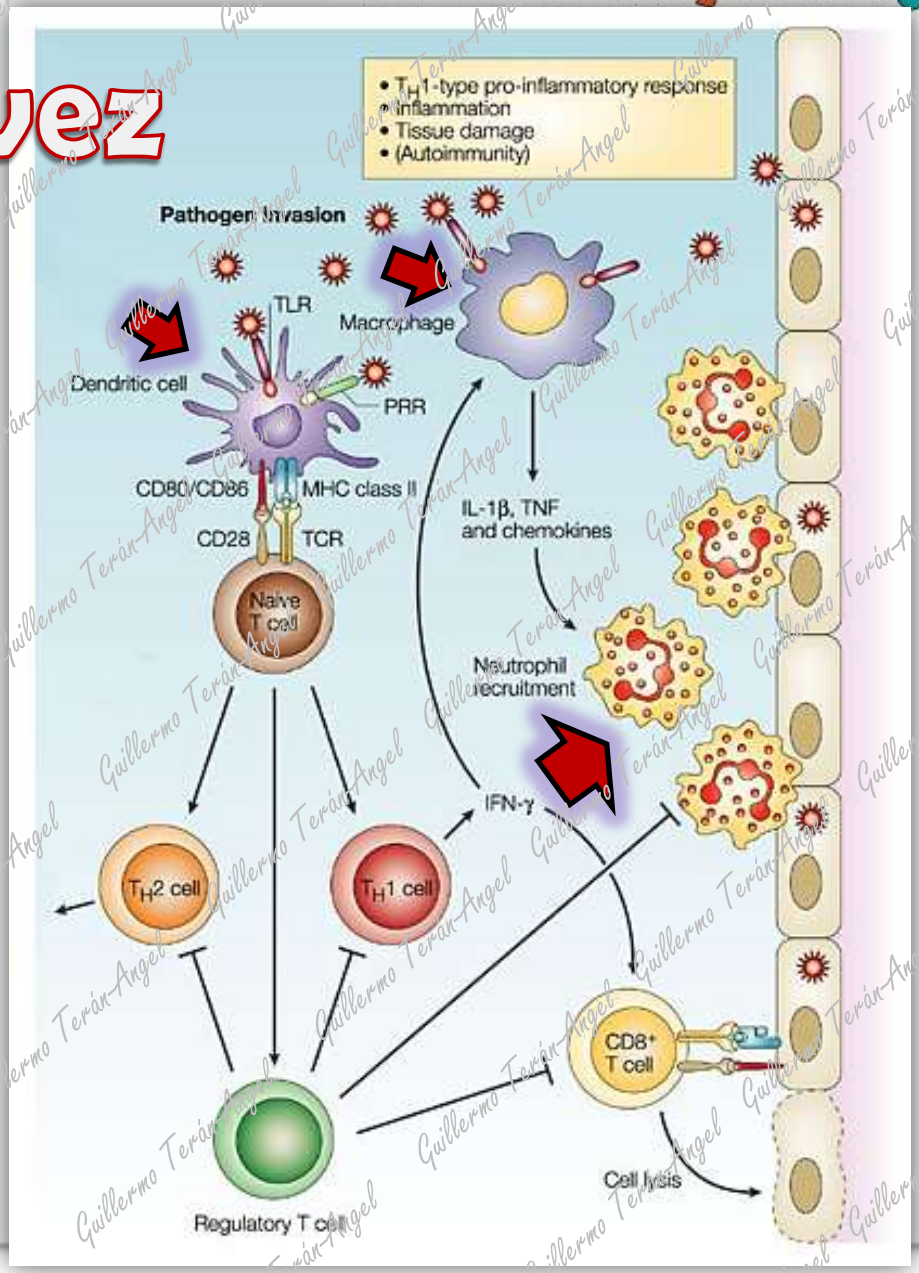
Próximo paso: evaluar C4????????

Fagocitosis

Fagocitosis

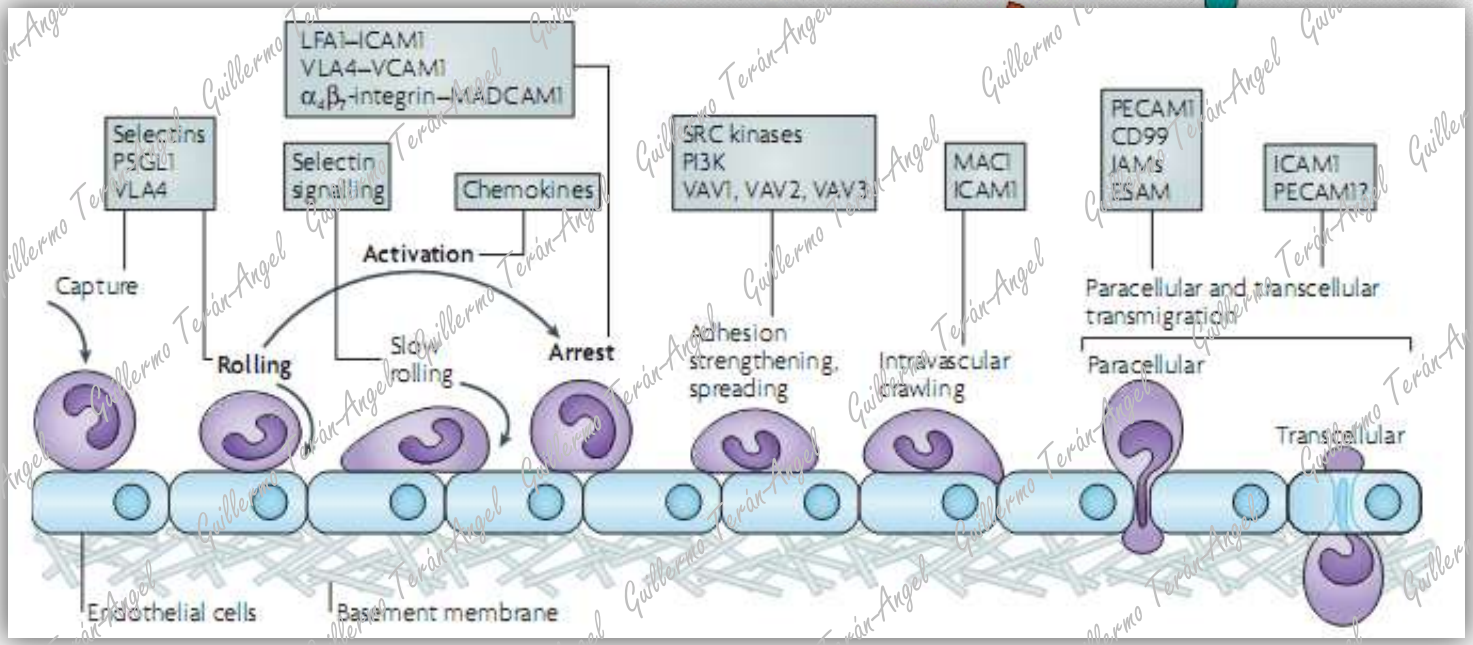


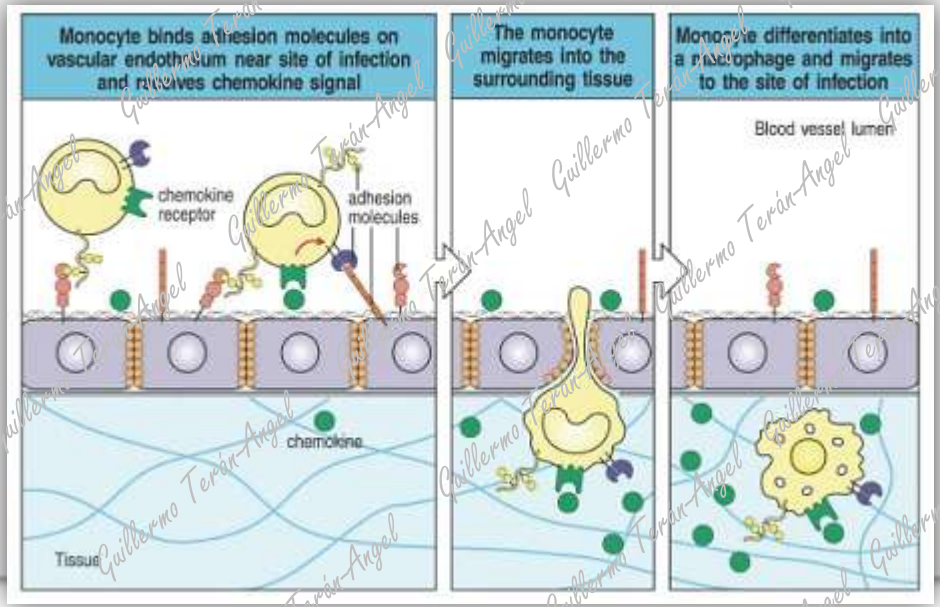
Ubicándonos otra vez



Nature Reviews Immunology 4, 841-855 (November 2004)

Como llegan?





Ley K, et al. Nat Rev Immunol. 2007 Sep;7(9):678-89.

Como reconocen?

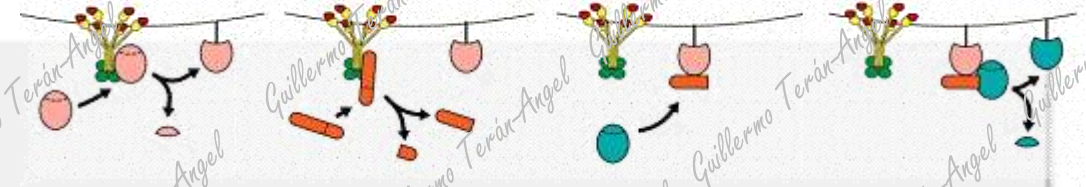
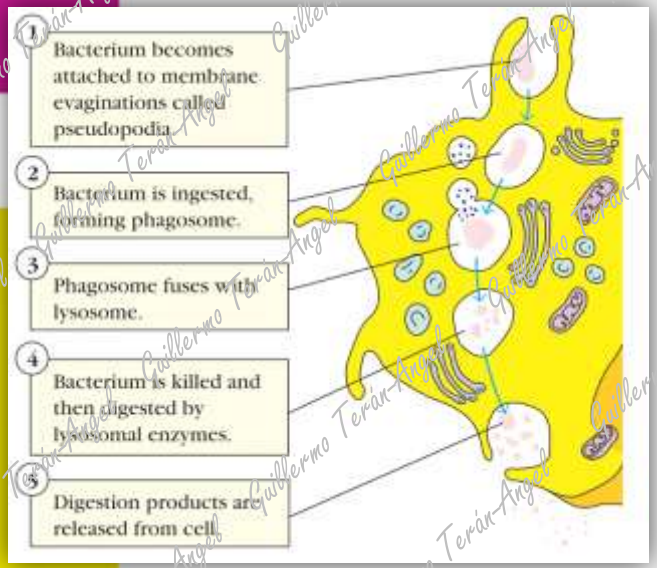


TABLE 5-3 Human receptors that trigger phagocytosis

Receptor type on phagocytes	Examples	Ligands
Pattern recognition receptors		**Microbial ligands (found on microbes)**
C-type lectin receptors (CLRs)	Mannose receptor	Mannans (bacteria, fungi, parasites)
	Dectin-1	β-glucans (fungi, some bacteria)
	DC-SIGN	Mannans (bacteria, fungi, parasites)
Scavenger receptors	SR-A	Lipopolysaccharide (LPS), lipoteichoic acid (LTA) (bacteria)
	SR-B	LTA, lipopeptides, diacylglycerides (bacteria), β-glucans (fungi)
Opsonin receptors		**Microbe-binding opsonins (soluble; bind to microbes)**
Collagen-domain receptor	CD91/calreticulin	Collectins SP-A, SP-D, MBL; L-ficolin; C1q
Complement receptors	CR1, CR3, CR4, CRIg, C1qRp	Complement components and fragments*
Immunoglobulin Fc receptors	FcαR	Specific IgA antibodies bound to antigen#
	FcγRs	Specific IgG antibodies bound to antigen;# C-reactive protein

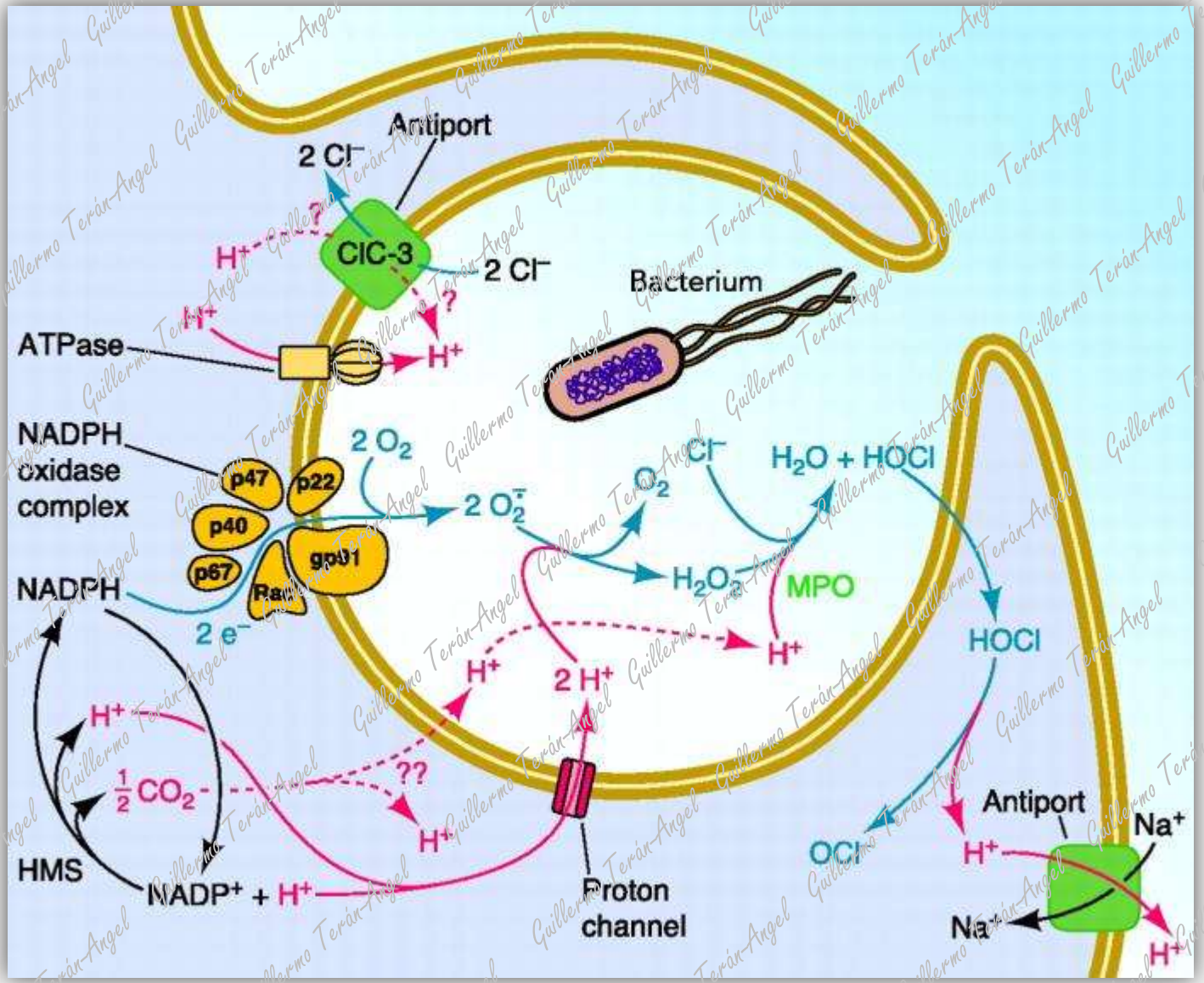
Mecanismos antimicrobianos



Antimicrobial mechanisms of phagocytes

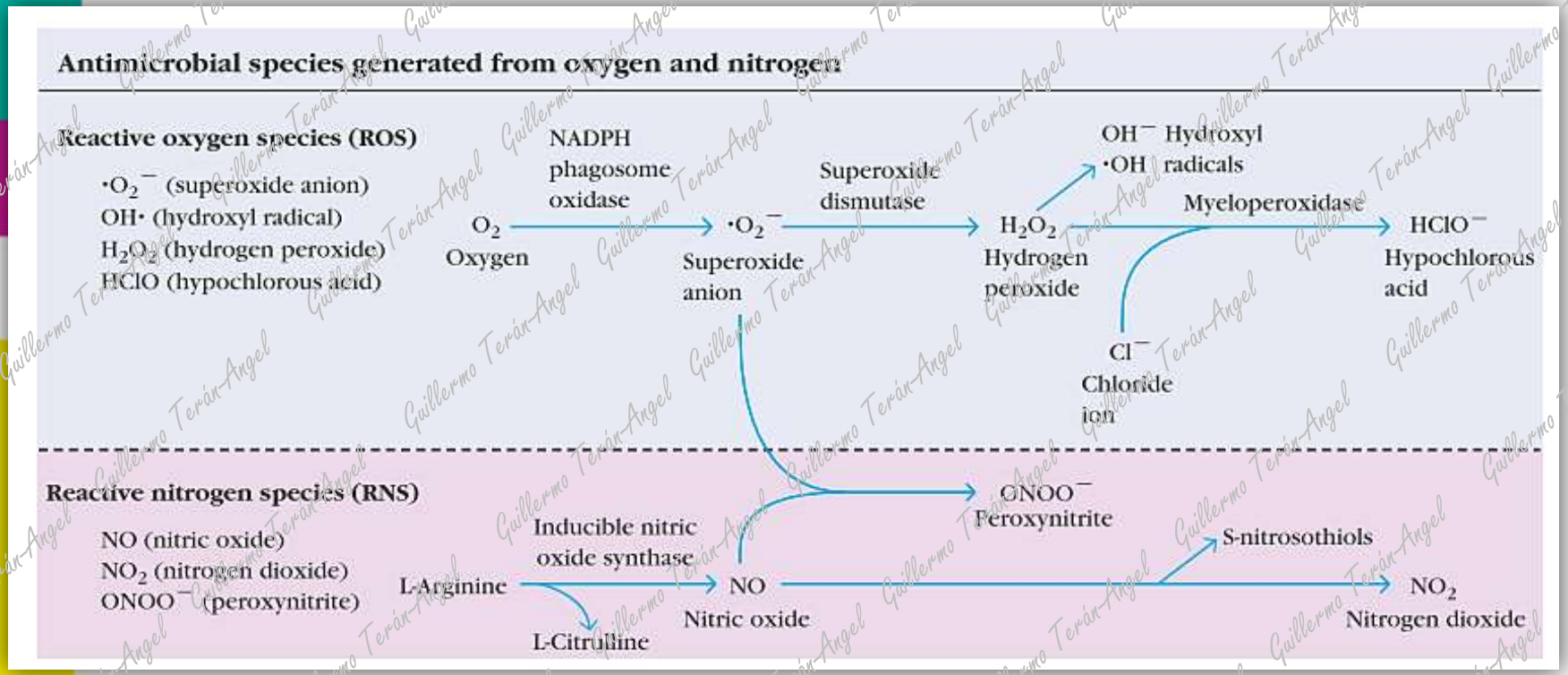
Class of mechanism	Macrophage products	Neutrophil products
Acidification	pH=~3.5–4.0, bacteriostatic or bactericidal	
Toxic oxygen-derived products	Superoxide O_2^-, hydrogen peroxide H_2O_2, singlet oxygen $^1O_2^*$, hydroxyl radical $^*OH$, hypohalite OCl^-	
Toxic nitrogen oxides	Nitric oxide NO	
Antimicrobial peptides	Cathelicidin, macrophage elastase-derived peptide	α-Defensins (HNP1–4), β-defensin HBD4, cathelicidin, azurocidin, bacterial permeability inducing protein (BPI), lactoferricin
Enzymes	Lysozyme: digests cell walls of some Gram-positive bacteria Acid hydrolases (e.g. elastase and other proteases): break down ingested microbes	
Competitors		Lactoferrin (sequesters Fe^{2+}), vitamin B_{12}-binding protein

Estallido respiratorio

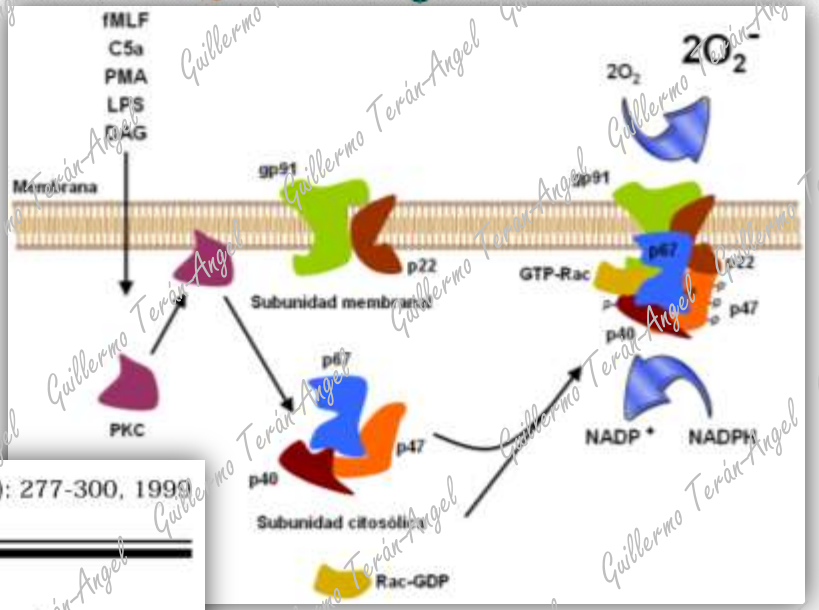


Front Biosci. 2003 Sep 1;8:s1266-79. Kidney Int Suppl. 2002 May;(80):109-14.

Radicales oxidativos



EGC



Invest Clin 40(4): 277-300, 1999

El complejo NADPH-oxidasa en la enfermedad granulomatosa crónica: Descripción preliminar de un foco en Mérida-Venezuela.

Siham Salmen[1], Lisbeth Berrueta[1], Paul Heyworth[2], Lérida Borges[1], Manuel Hernández[1] y José Muñoz[1].

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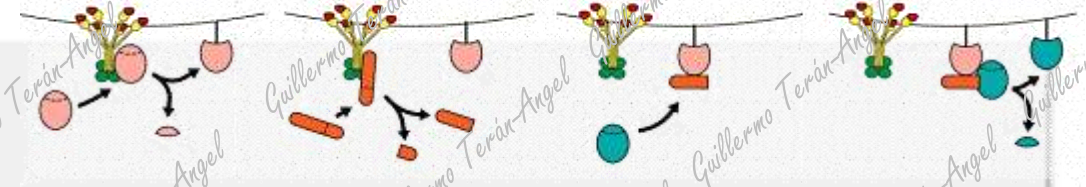
EGC

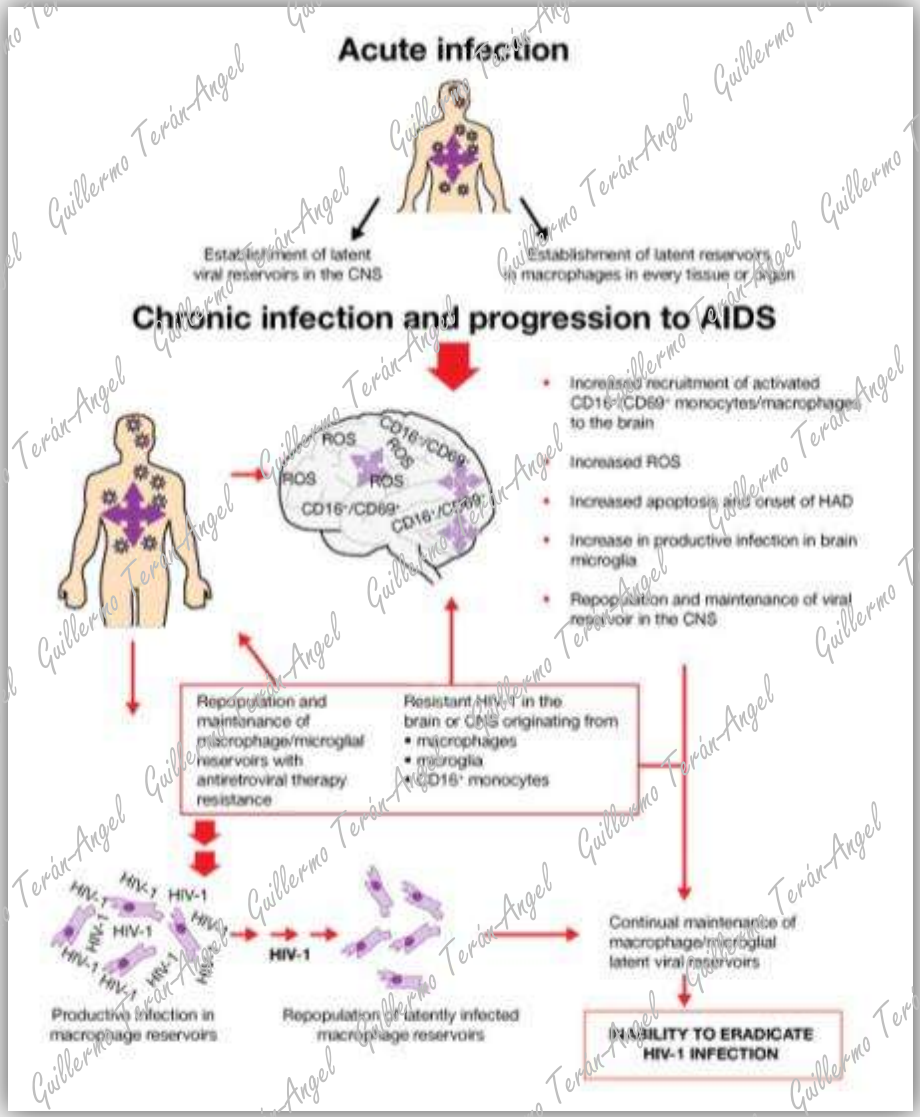
INFECCIONES Y CONDICIONES CRÓNICAS QUE SE PRESENTAN EN LA ENFERMEDAD GRANULOMATOSA CRÓNICA

INFECCIONES	% DE EPISODIOS	MICROORGANISMOS INVOLUCRADOS	% DE AISLADOS	CONDICIONES CRÓNICAS ASOCIADAS	% DE CASOS
Neumonía	70-80	*Staphylococcus aureus*	30-50	Linfadenopatía	98
Linfadenitis	60-80	*Aspergillus sp*	10-20	Hipergammaglobulinemia	60-90
Infecciones cutáneas/impétigo	60-70	*Escherichia coli*	5-10	Hepatomegalia	50-90
Hepatitis /absceso perihepático	30-40	*Klebsiella sp*	5-10	Esplenomegalia	60-80
Osteomielitis	20-30	*Salmonella sp*	5-10	Anemia crónica	Común
Abscesos perirectal/fístulas	15-30	*Pseudomona cepacia y aeruginosa*	5-10	Bajo peso	70
Septicemia	10-20	*Serratia marcescens*	5-10	Diarrea crónica	20-60
Otitis media	20	*Staphylococcus epidermidis*	5	Baja estatura	50
Conjuntivitis	15	*Streptococcus sp*	4	Gingivitis	50
Infecciones entéricas	10	*Enterobacter sp*	3	Dermatitis	35
Infección del tracto urinario/ pielonefritis	5-15	*Proteus sp*	3	Hidronefrosis	10-25
Sinusitis	<10	*Candida albicans*	3	Estomatitis ulcerativa	5-15
Renal/abscesos perifrénico	<10	*Nocardia sp*	2	Fibrosis pulmonar	<10
Absceso cerebral	<5	*Haemophilus influenzae*	1	Esofagitis	<10
Pericarditis	<5	*Pneumocystis carinii*	<1	Estrechez gástrica antral	<10
Meningitis	<5	*Mycobacterium fortuitum*	<1	Ileocolitis granulomatosa	<10
		Chromobacterium violaceum	<1	Corioretinitis	<10
		Francisella philomiragia	<1	Cistitis granulomatosa	<10
		Torulopsis glabrata	<1	Glomerulonefritis	<10
				Lupus eritematoso discoide	<10

ROS




Heart
Eyes
Skin
Multi-Organ
Kidney
Free Radical Oxidative Stress
Blood Vessels
Joints
Immune System
Lung
Brain


Acute infection
Establishment of latent viral reservoirs in the CNS
Establishment of latent reservoirs in macrophages in every tissue or organ
Chronic infection and progression to AIDS
ROS
CD16+/CD69+
Increased recruitment of activated CD16+/CD69+ monocytes/macrophages to the brain
Increased ROS
Increased apoptosis and onset of HAD
Increase in productive infection in brain microglia
Repopulation and maintenance of viral reservoir in the CNS
Repopulation and maintenance of macrophage/microglial reservoirs with antiretroviral therapy resistance
Resistant HIV-1 in the brain or CNS originating from
• macrophages
• microglia
• CD16+ monocytes
HIV-1
Productive infection in macrophage reservoirs
Repopulation of latently infected macrophage reservoirs
Continual maintenance of macrophage/microglial latent viral reservoirs
INABILITY TO ERADICATE HIV-1 INFECTION

¡Pregunten Ahora o Callen Para Siempre!

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