XXI CONGRESO SEIMC Málaga

SOCIEDAD ESPAÑOLA DE ENFERMEDADES INFECCIOSAS Y MICROBIOLOGÍA CLÍNICA

11 AL 13 DE MAYO 2017

PALACIO DE FERIAS Y CONGRESOS FYCMA

Instituto de Investigación Hospital 12 de Octubre

H12O UEI 25 años

ESCMID Collaborative Center

SaludMadrid Hospital Universitario 12 de Octubre

Impacto de la respuesta inmune y de la interacción huésped patógeno en el pronóstico de la candidemia

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Sesión Monográfica UEI

23 de Mayo de 2017

Declaración de conflictos de intereses

En los últimos 24 meses he recibido honorarios por impartir charlas científicas en nombre de

- **Astellas Pharma**
- **Gillead Sciences**
- **Roche**
- **Alere Healthcare**

Estudios de derivación de escalas predictivas de candidiasis invasiva en pacientes críticos

Table 2: Various developmental studies of risk prediction mo

Name of the study	Year	Study characte			Study results				
		Design	Centers	Cohort	Name of best performing risk prediction model/rule (see text for explanation)	PPV %	NPV %	Sensitivity	Specificity
Pittet *et al.*	1994	Prospective	Single	Surgical/ neonates	Colonization index	66	100	100	100
					Corrected colonization index	100	100	100	100
Dupont *et al.*	2003	Retrospective	Single	Surgical with peritonitis	Grade C	67	72	84	50
Michalopoulos *et al.*	2003	Prospective case control study	Single	Cardiothoracic surgery patients	Model had 4 risk factors	100	89	53.3	100
Paphitou *et al.*	2005	Retrospective	Single	Surgical	Paphitou rule 2	NA	NA	NA	NA
Leon *et al.*	2006	Prospective	Multicentre	Surgical/medical	Candida score	NA	NA	81	74
Ostrosky *et al.*	2007	Retrospective	Multicentre	Surgical/medical	Original	9	97	34	94
Ostrosky *et al.*	2009	Retrospective	Multicentre	Surgical/medical	Revised	10	97	50	83
Shorr *et al.*	2009	Retrospective	Multicentre	All patients at admission	Model had 6 risk factors. Score≥1	NA	99.6	90.7	28.9

Name of the study	PPV %
Pittet *et al.*	66
	100
Dupont *et al.*	67
Michalopoulos *et al.*	100
Paphitou *et al.*	NA
Leon *et al.*	NA
Ostrosky *et al.*	9
Ostrosky *et al.*	10
Shorr *et al.*	NA

Indian J Crit Care Med 2014;18:682-8

Estudios de validación de escalas predictivas de candidiasis invasiva en pacientes críticos

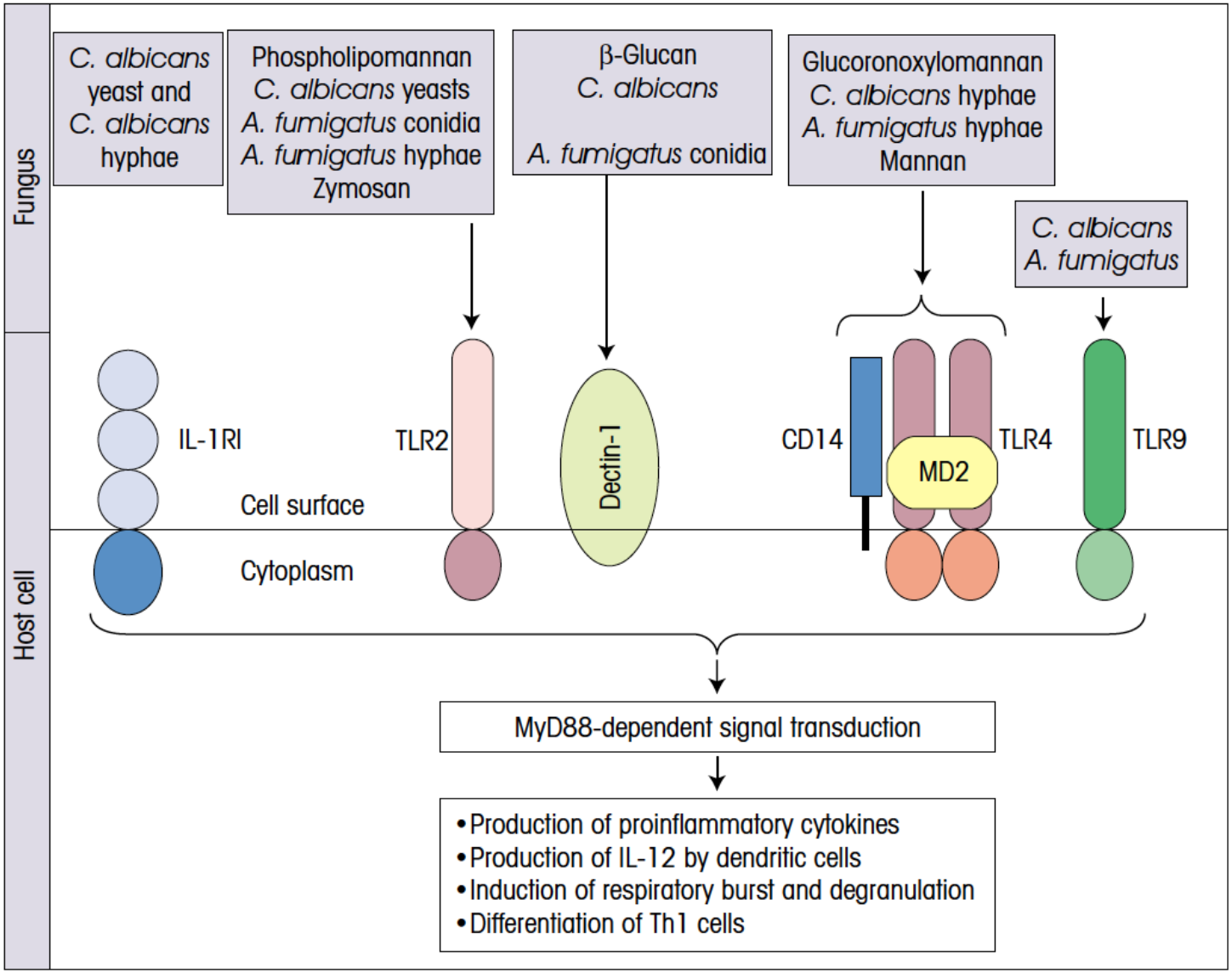
Table 3: Validation studies of various risk prediction r

Name of the study	Year	Study ch			Study results				
		Design	Center	Cohort	f risk prediction ule	PPV	NPV	Sensitivity	Specificity
León *et al.*	2009	Prospective	Multicenter	Surgical/ medical	score≥3	13.8	97.7	77.6	66.2
Leroy *et al.*	2011	Prospective	Multicenter	Surgical/ medical	score>3	23.8	100	NA	NA
Playford *et al.*	2009	Prospective	Multicenter	Surgical/ medical	original without CCI*	5.3	98	47	79
					original with CCI*	23.8	98	33	97
					revised without CCI*	4	99	80	51
					revised with CCI*	17	99	53	94
Hermsen *et al.* (NMC study)	2011	Prospective	Multicenter	Surgical/ medical	1	4.8	98	40	81
					2	5.4	98	45	81
					original	4.1	98	65	64
					revised	4.2	99	73	60
						4.7	99	84	60
Hall *et al.*	2013	Retrospective	Single	Severe a pancreat patients	core≥3	39	72	23	85
					original (modified)	21	85	61	49
						43	91	67	79

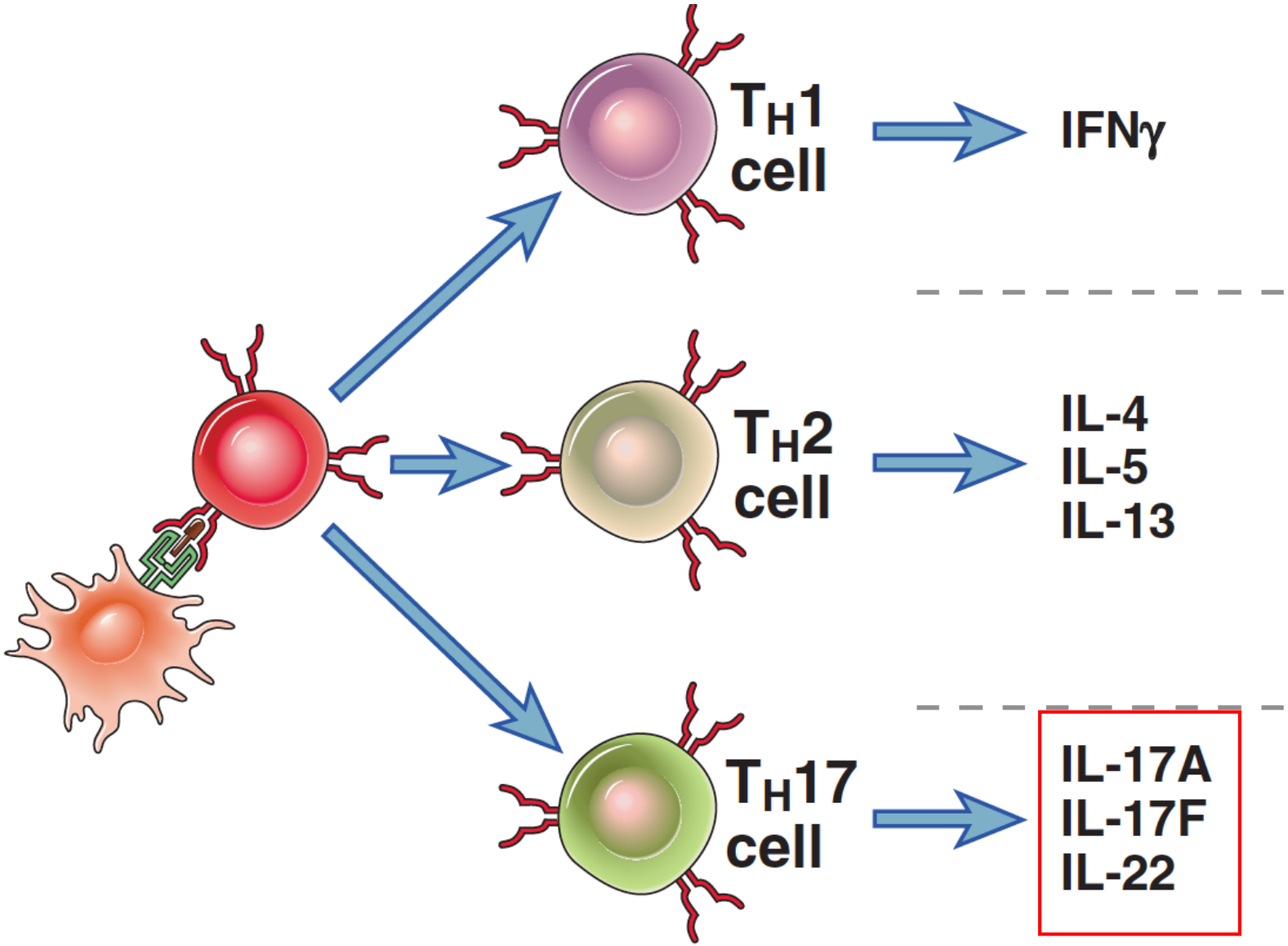
Name of risk prediction model/rule	PPV
Candida score≥3	13.8
Candida score>3	23.8
Ostrosky original without CCI*	5.3
Ostrosky original with CCI*	23.8
Ostrosky revised without CCI*	4
Ostrosky revised with CCI*	17
Paphitou 1	4.8
Paphitou 2	5.4
Ostrosky original	4.1
Ostrosky revised	4.2
NMC	4.7
Candia score≥3	39
Ostrosky original (modified)	21
CI>0.5	43

Indian J Crit Care Med 2014;18:682-8

A igualdad de factores de riesgo para candidiasis invasiva, ¿existe una base inmunológica en la susceptibilidad individual?

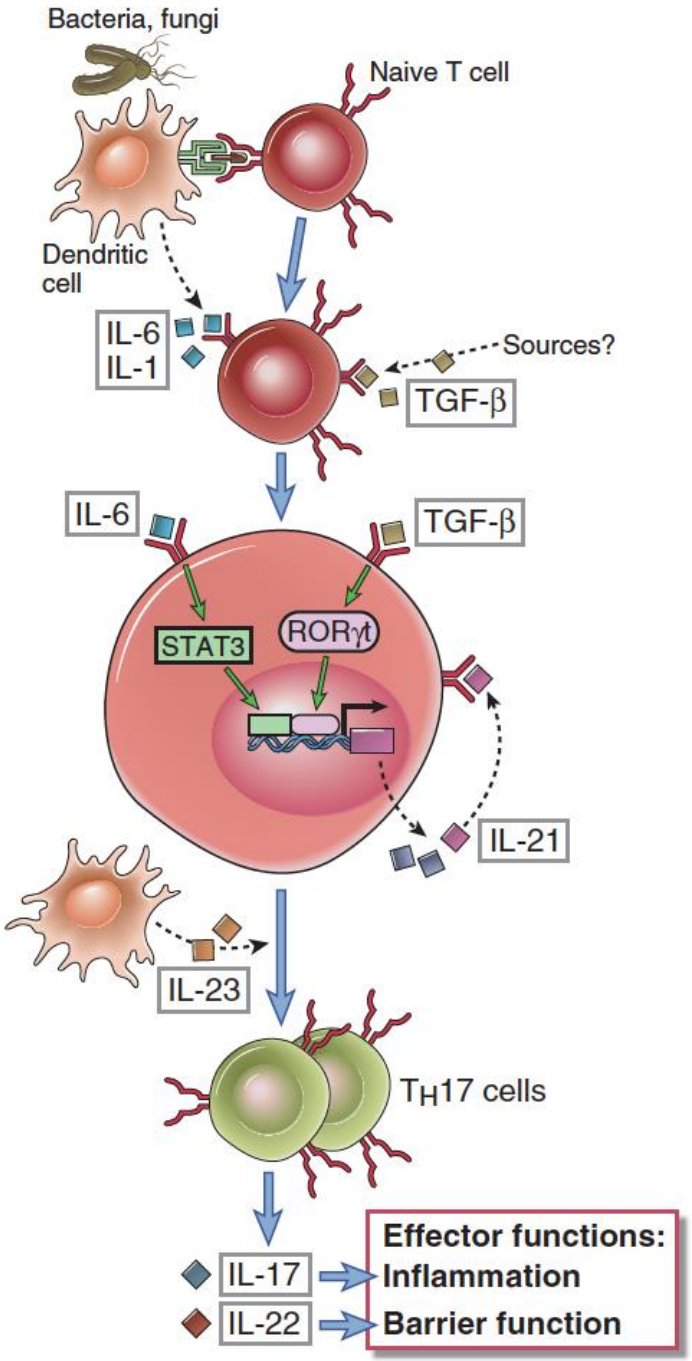


Roitt. 12ª edición



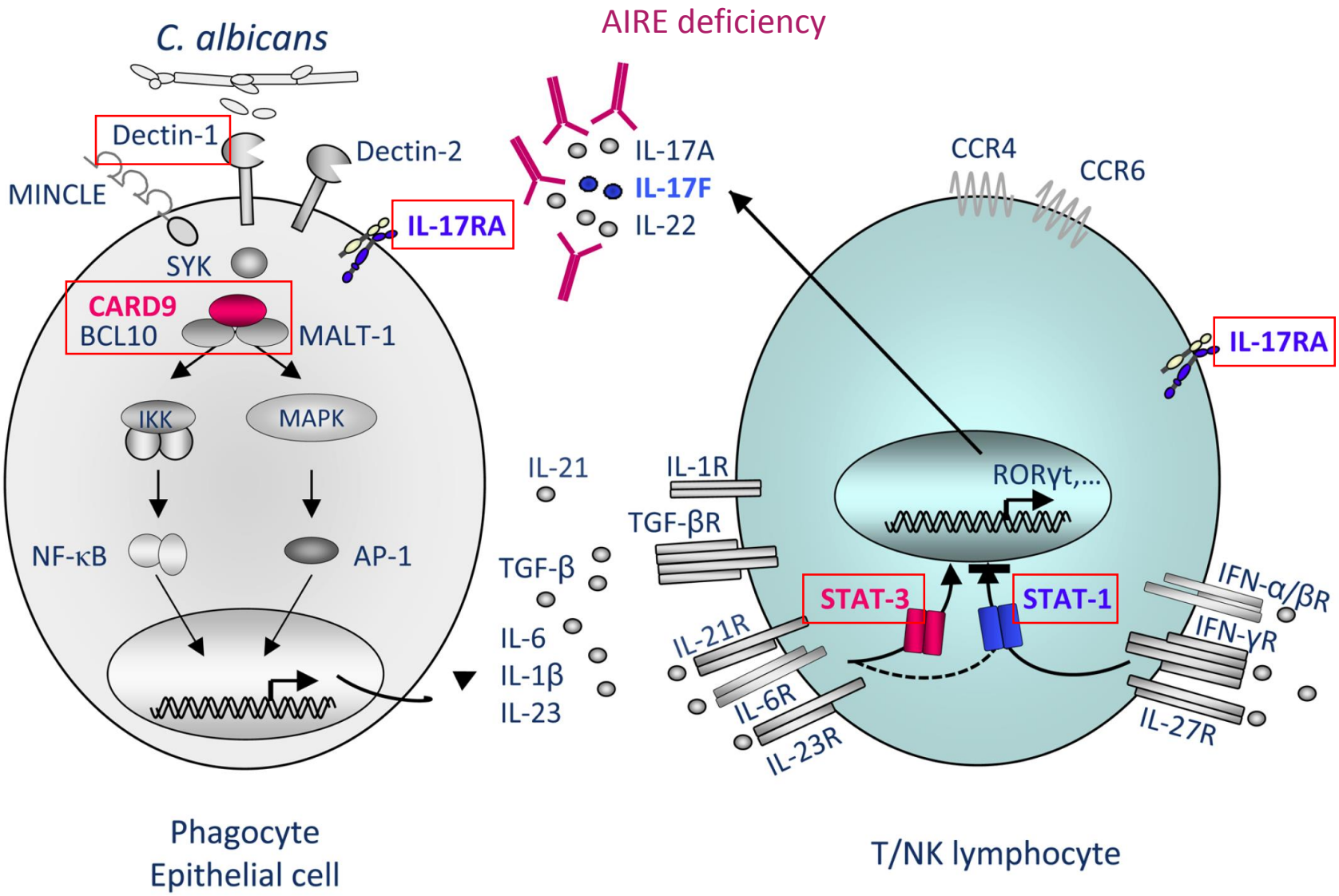
Abbas. 7ª edición

Linfocitos Th17



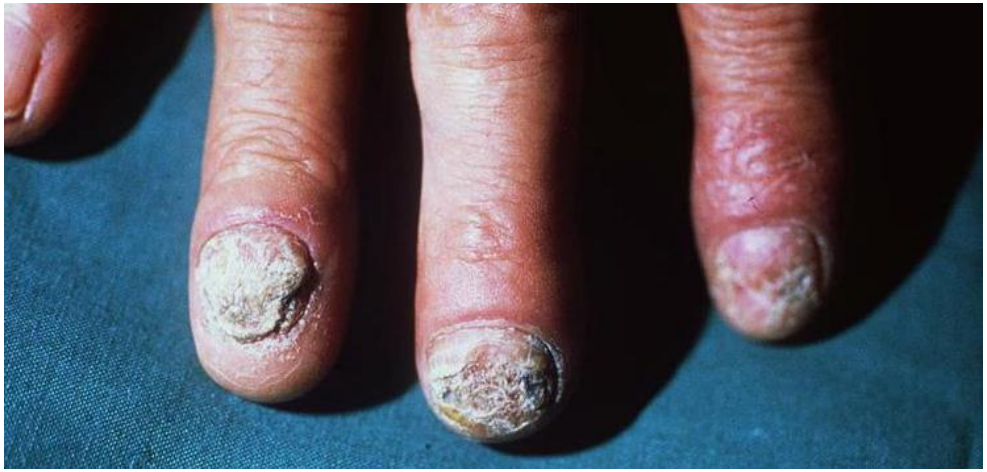
Abbas. 7ª edición

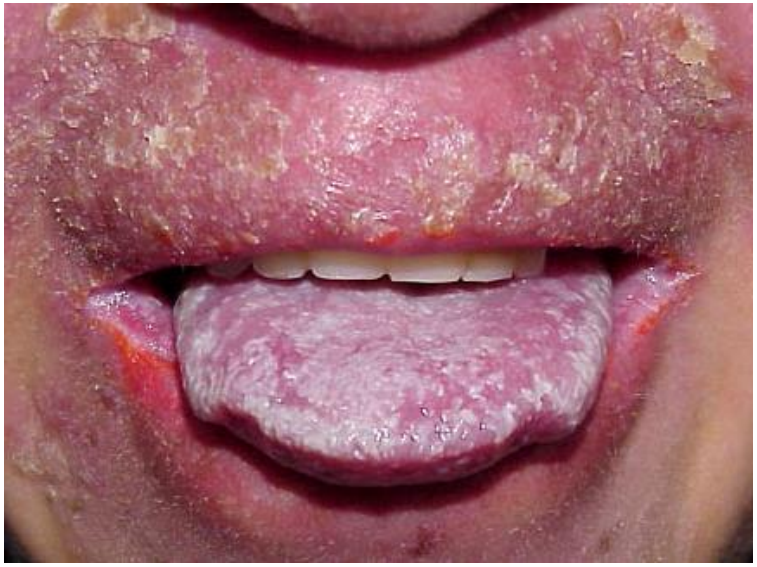
Candidiasis mucocutánea crónica

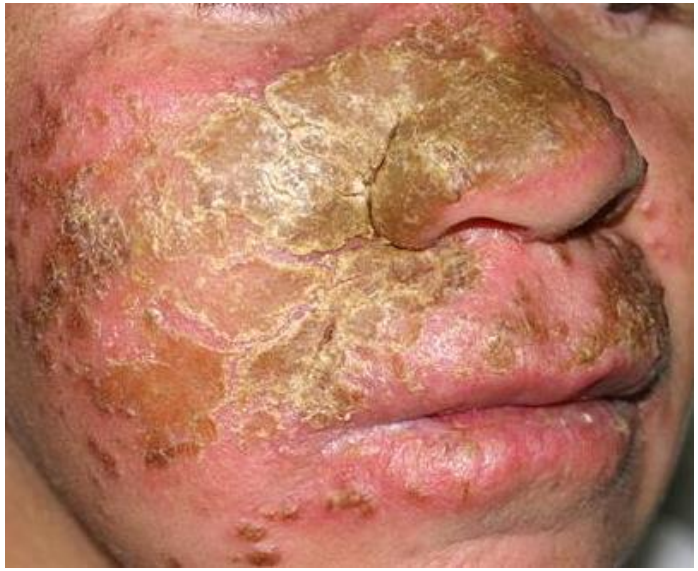


Curr Opin Allergy Clin Immunol 2012;12:616–22

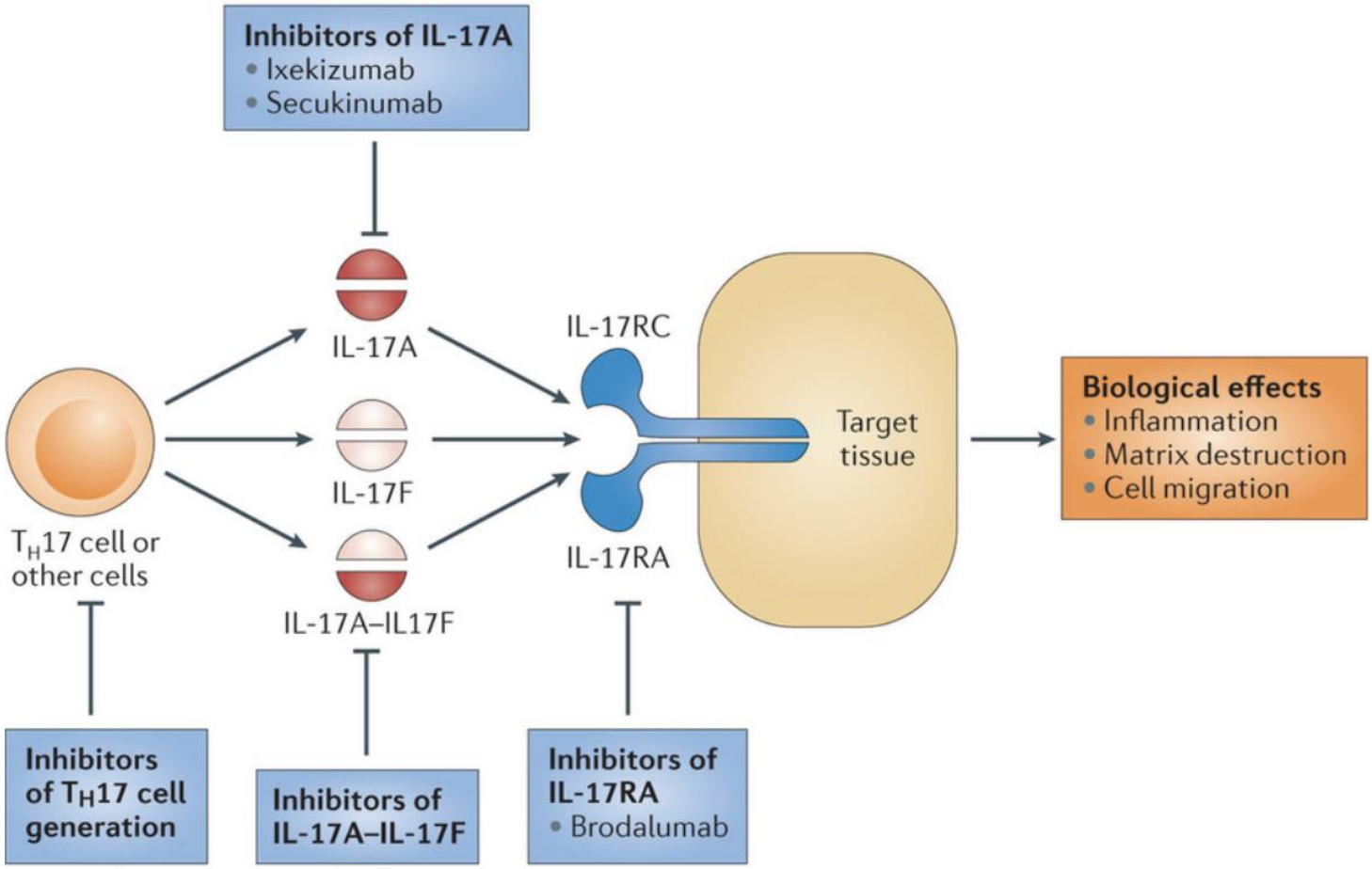
Candidiasis mucocutánea crónica







IL-17-axis-targeted agents



La mayor parte de las infecciones por Candida en pacientes que reciben fármacos dirigidos frente al eje IL-17 son superficiales

Treatment	Total no. patients included	Mild to moderate *Candida* infections (%)						Severe *Candida* infections (%)	Overall (%)
		Vulvovaginal /genital	Oral	Skin	Esophageal	Nail	Unknown infection site		Total
Secukinumab	4,277	7 (0.2%)	15 (0.4%)	2 (0.05%)	2 (0.05%)	0 (0%)	56 (1.3%)	1 (0.02%)	83 (2.1%)
Brodalumab	4,431	0 (0%)	7 (0.2%)	0 (0%)	1 (0.02%)	0 (0%)	169 (3.8%)	0 (0%)	177 (4.0%)
Ixekizumab	4,113	40 (1.0%)	63 (1.5%)	20 (0.5%)	2 (0.05%)	1 (0.025%)	9 (0.2%)	0 (0%)	135 (3.3%)
Etanercept	1,065	4 (0.4%)	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	4 (0.4%)	0 (0%)	9 (0.8%)
Ustekinumab	613	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	14 (2.3%)	0 (0%)	14 (2.3%)
Placebo	2,323	3 (0.1%)	2 (0.09%)	1 (0.04%)	0 (0%)	0 (0%)	1 (0.04%)	0 (0%)	7 (0.3%)

Br J Dermatol 2016 Aug 31 [epub ahead of print]

CARD9 (caspase recruitment domain-containing protein 9) deficiency

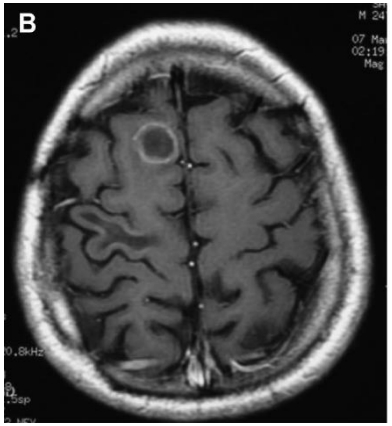
Immune deficiencies, infection, and systemic immune disorders

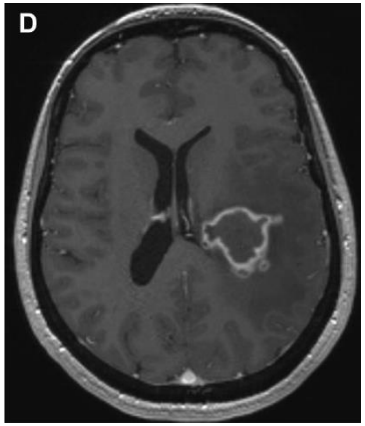
Inherited CARD9 deficiency in otherwise healthy children and adults with *Candida* species–induced meningoencephalitis, colitis, or both

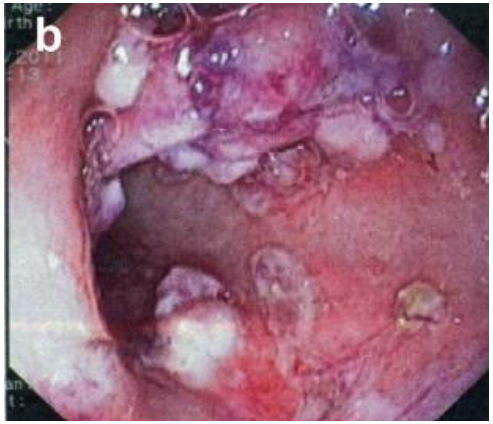
J Allergy Clin Immunol 2015;135:1558-68

TABLE I. Characteristics of the 5 patients with invasive fungal infection and homozygous *CARD9* mutations

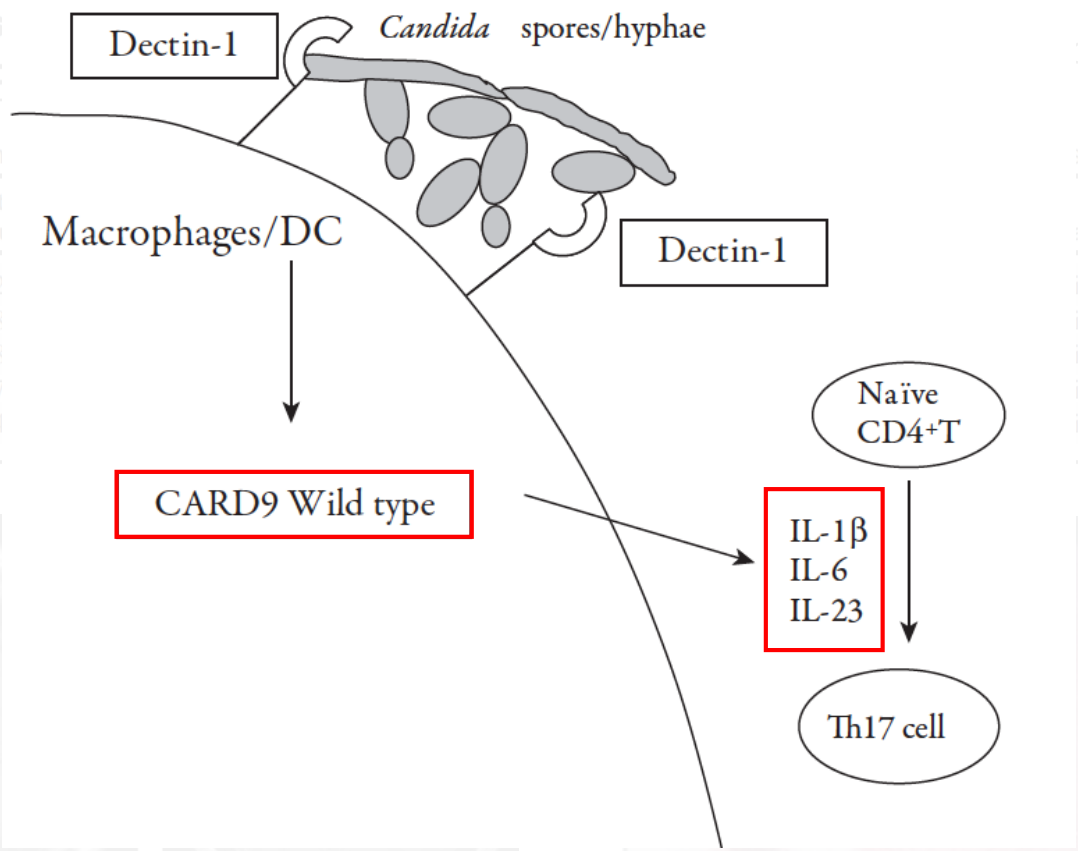
Patient ID	Age at onset (y)	Age at last follow-up (y)	Sex	Country of origin	Organ involvement	Associated CMC	Fungus	Status	*CARD9* mutation
P1	39	42	F	Turkey	CNS	Yes	*C albicans*	Alive	R70W/R70W
P2	7	8	F	Turkey	CNS	Yes	*C albicans*	Alive	R70W/R70W
P3	17	28	M	Iran	CNS, sinus, digestive tract	No	*C glabrata*	Alive	R35Q/R35Q
P4	37	37	F	Morocco	CNS	Yes	*C albicans*	Alive	Q289*/Q289*
P5	26	34	M	Pakistan	Digestive tract	No	*C albicans*	Alive	Q295*/Q295*







CARD9 (caspase recruitment domain-containing protein 9) deficiency

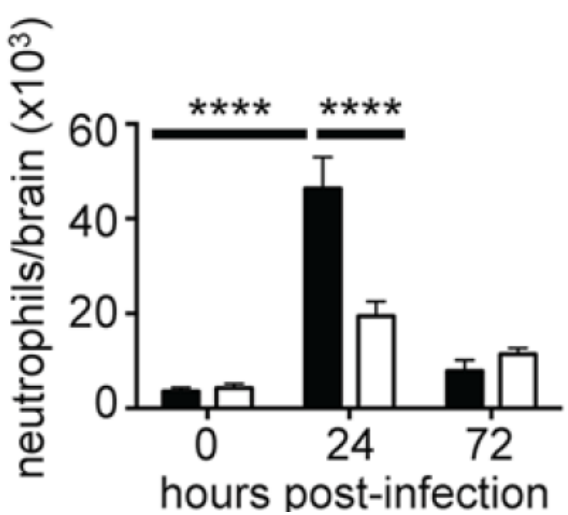


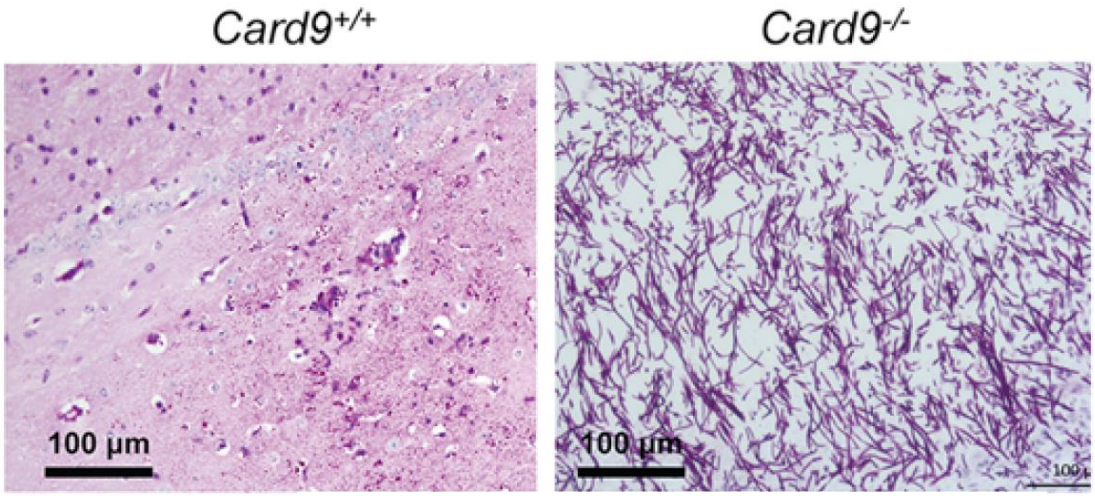
RESEARCH ARTICLE

CARD9-Dependent Neutrophil Recruitment Protects against Fungal Invasion of the Central Nervous System

PLoS Pathog 2015;11:e1005293

Rebecca A. Drummond[1☯], Amanda L. Collar[1☯], Muthulekha Swamydas[1], Carlos A. Rodriguez[2], Jean K. Lim[2], Laura M. Mendez[3], Danielle L. Fink[3], Amy P. Hsu[4], Bing Zhai[5], Hatice Karauzum[6], Constantinos M. Mikelis[7], Stacey R. Rose[1], Elise M. N. Ferre[1], Lynne Yockey[1], Kimberly Lemberg[8], Hye Sun Kuehn[8], Sergio D. Rosenzweig[8], Xin Lin[9], Prashant Chittiboina[10], Sandip K. Datta[6], Thomas H. Belhorn[11], Eric T. Weimer[12], Michelle L. Hernandez[13], Tobias M. Hohl[5], Douglas B. Kuhns[3], Michail S. Lionakis[1]*



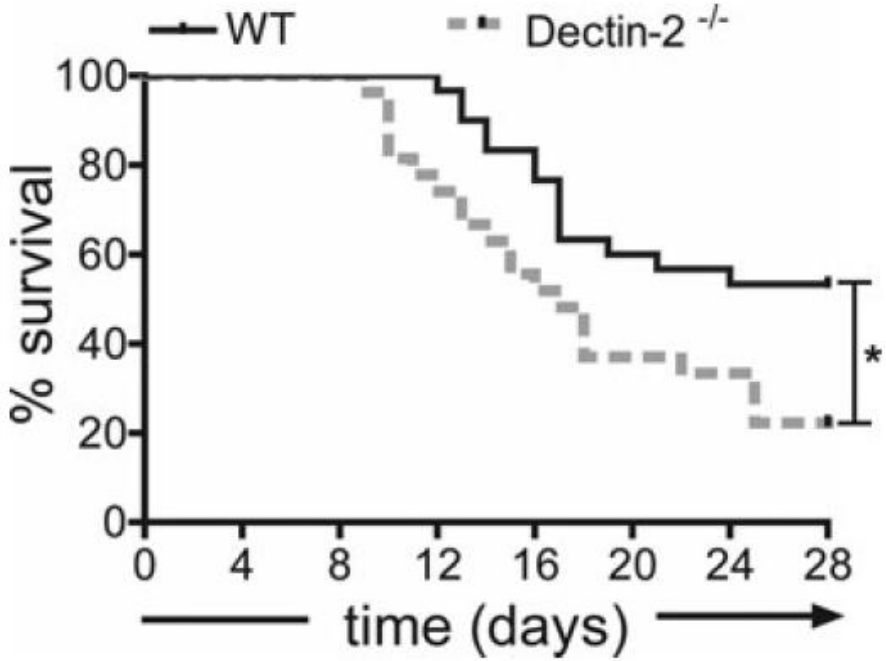


The Role of Dectin-2 for Host Defense Against Disseminated Candidiasis

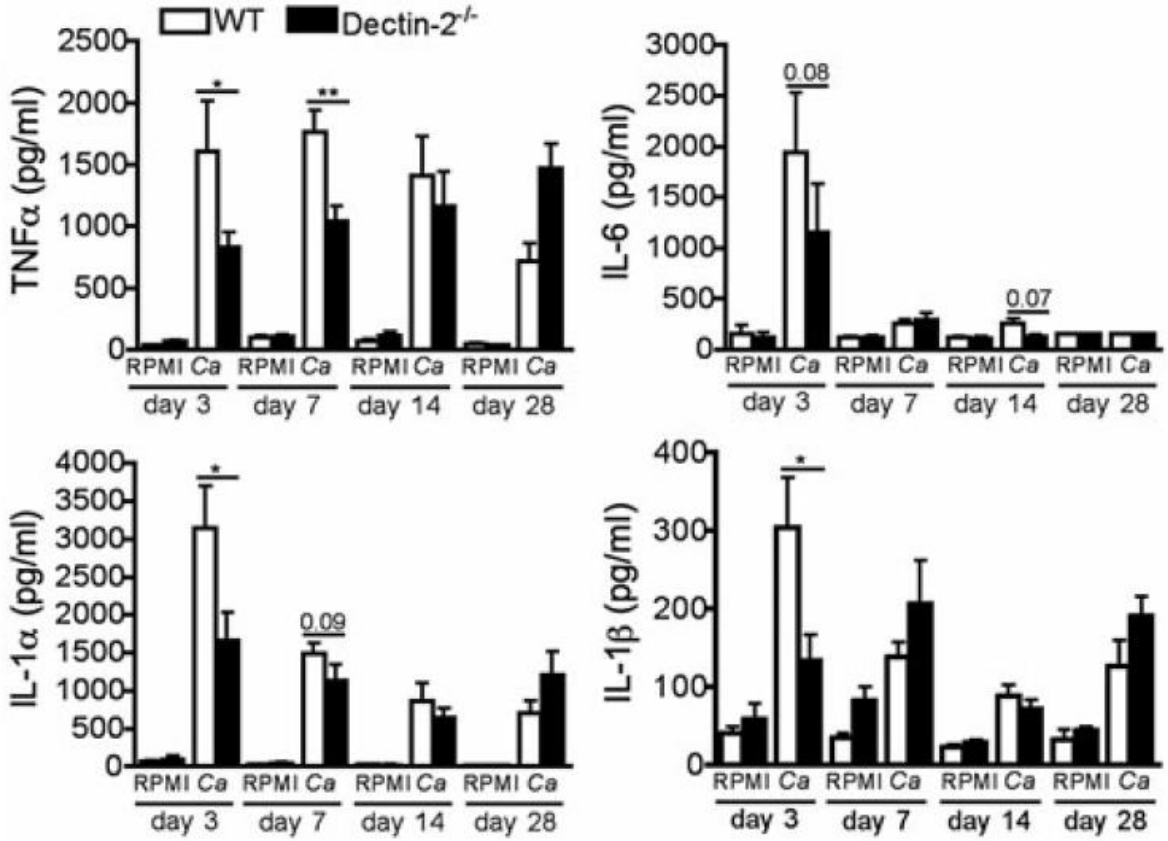
Daniela C. Ifrim,[1] Jessica Quintin,[1] Flavie Courjol,[2,3] Ineke Verschueren,[1] J. Han van Krieken,[4] Frank Koentgen,[5] Chantal Fradin,[2,3] Neil A.R. Gow,[6] Leo A.B. Joosten,[1] Jos W.M. van der Meer,[1] Frank van de Veerdonk,[1] and Mihai G. Netea[1]

J Interferon Cytokine Res. 2016;36:267-76

***Ratones K/O para dectina-2 y WT infectados con* C. albicans**

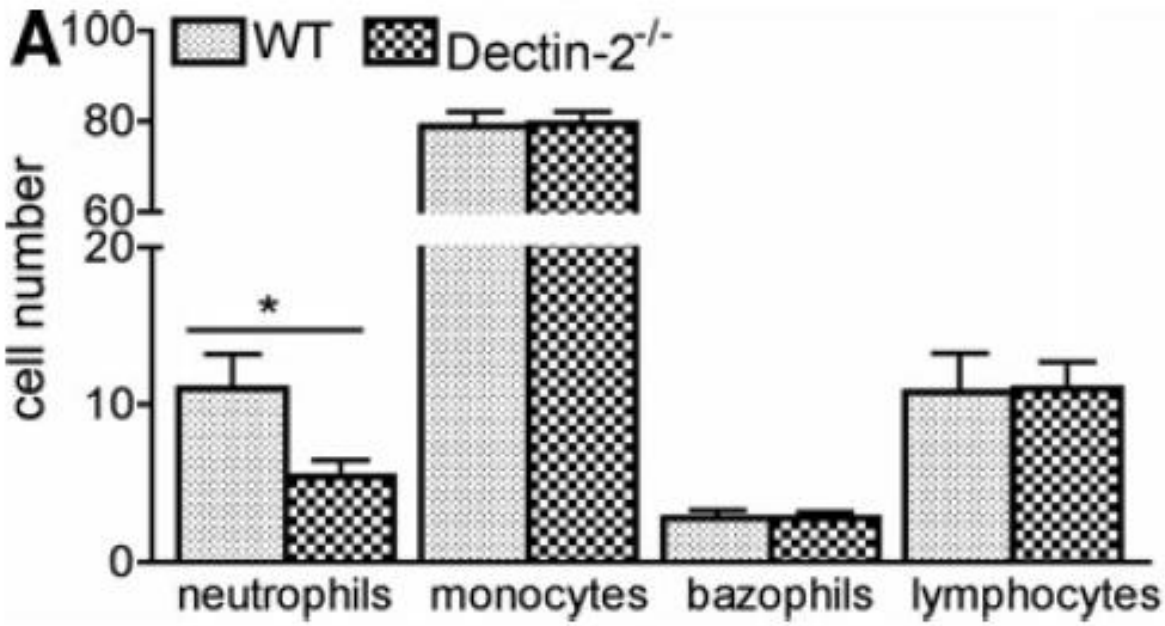


Producción de citoquinas pro-inflamatorias en macrófagos estimulados con C. albicans *en ratones K/O para dectina-2 y WT*



J Interferon Cytokine Res. 2016;36:267-76

Rdclutamiento de células inflamatorias en el peritoneo de ratones K/O para dectina-2 y WT infectados con C. albicans



J Interferon Cytokine Res. 2016;36:267-76

Respuesta Th17 en la infección por *Candida*

Elevated Levels of Interleukin 17A and Kynurenine in Candidemic Patients, Compared With Levels in Noncandidemic Patients in the Intensive Care Unit and Those in Healthy Controls

J Infect Dis 2015;211:445-51

Robert Krause,[1] Ines Zollner-Schwetz,[1] Helmut J. F. Salzer,[1,7] Thomas Valentin,[1] Jasmin Rabensteiner,[1] Florian Prüller,[2] Reinhard Raggam,[2] Andreas Meinitzer,[2] Jürgen Prattes,[1] Beate Rinner,[3] Heimo Strohmaier,[3] Franz Quehenberger,[4] Dirk Strunk,[6] Katharina Heidrich,[5] Walter Buzina,[5] and Martin Hoenigl[1]

- Grupo 1: controles sanos
- Grupo 2: pacientes en UCI
- Grupo 3: pacientes en UCI con neumonía
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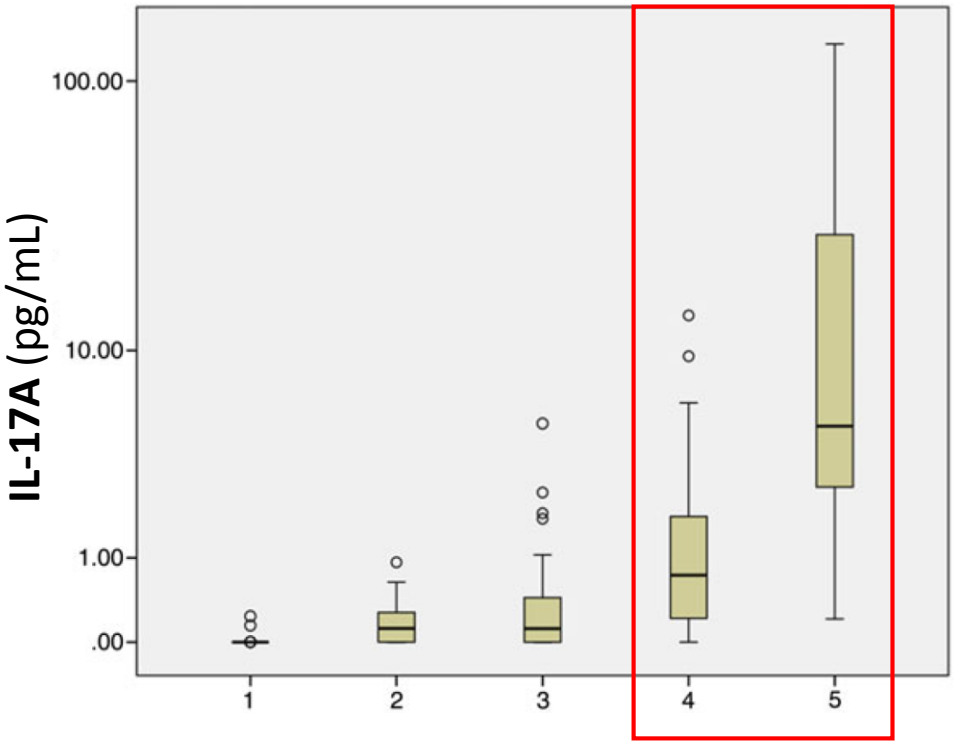
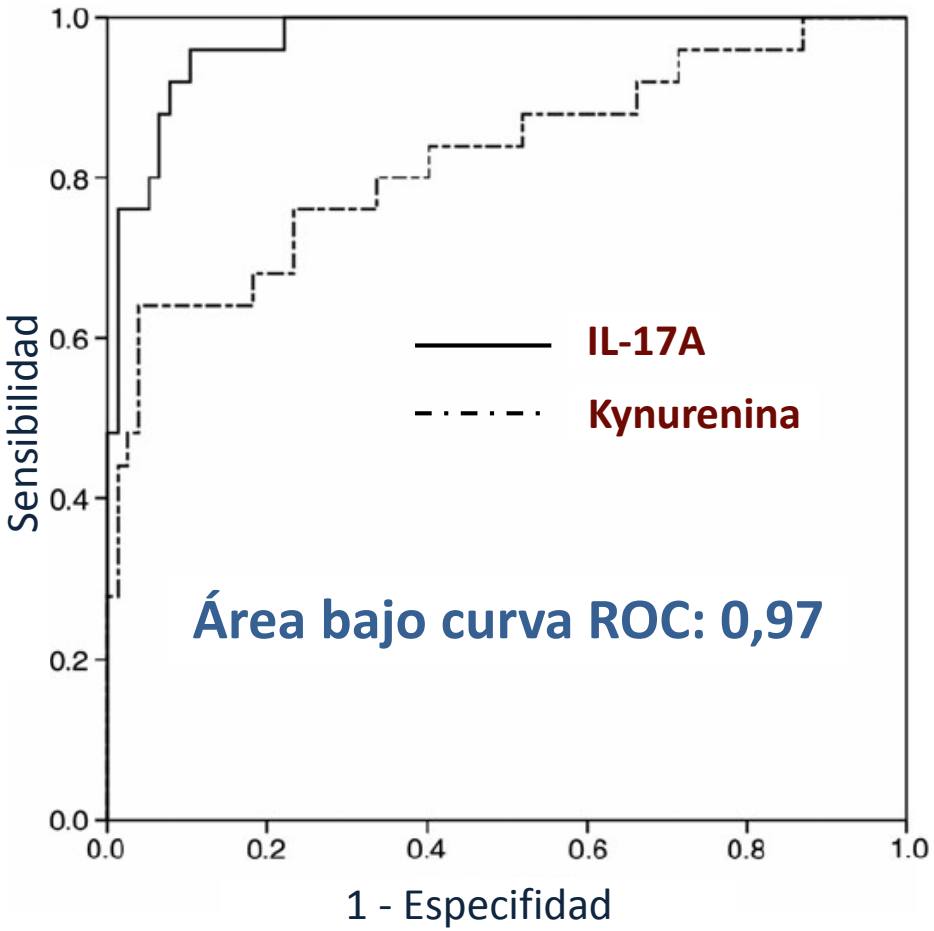
- Gr

Deter
citoquinas en suero

Los niveles de IL-17A están significativamente elevados en pacientes con candidemia



Los niveles de IL-17A permiten diferenciar entre pacientes con o sin candidemia



J Infect Dis 2015;211:445-51

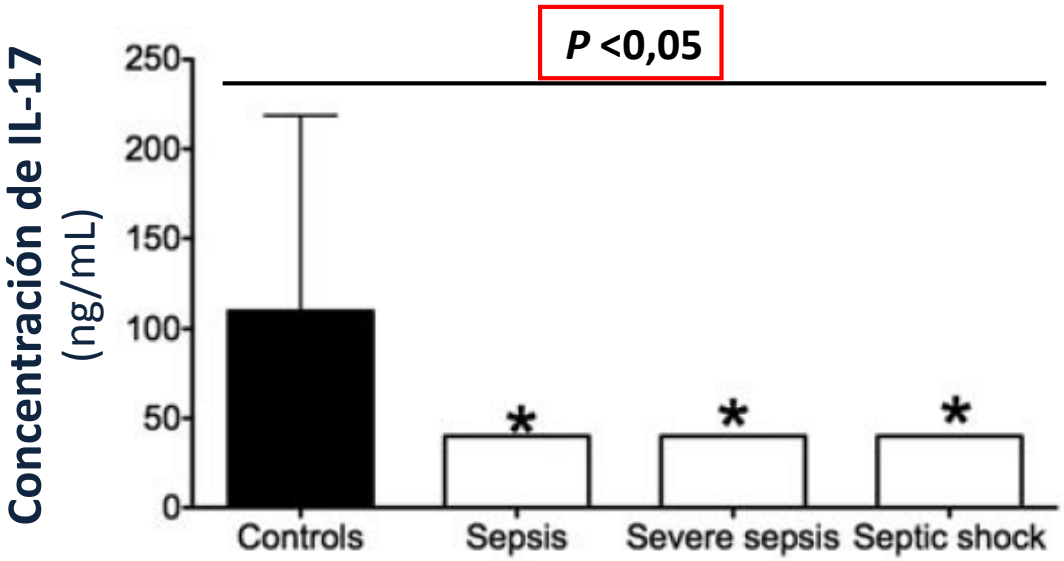
Deficient *Candida*-Specific T-Helper 17 Response During Sepsis

J Infect Dis 2012;206:1798-802

Frank L. van de Veerdonk,[1] Maria Mouktaroudi,[3] Bart P. Ramakers,[2] Aikaterini Pistiki,[3] Peter Pickkers,[2] Jos W. M. van der Meer,[1] Mihai G. Netea,[1] and Evangelos J. Giamarellos-Bourboulis[3]

- **Modelo experimental de endotoxinemia (inyección de LPS) en voluntarios sanos**
- **Pacientes ingresados en UCI con sepsis, sepsis grave o SS**
- **Estímulo de PBMCs con conidias o pseudohifas de *C. albicans* y medida de IL-17 e IL-1ß**

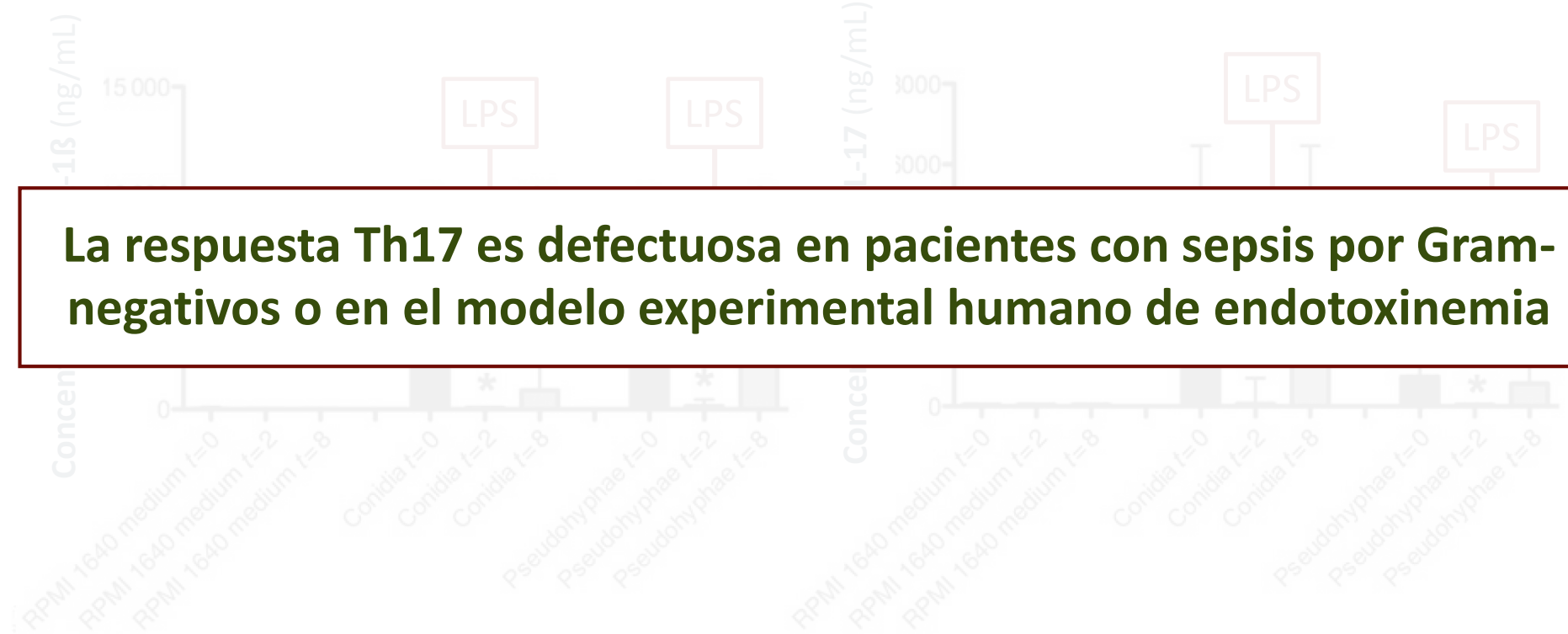
Expresión de IL-17 en PBMCs estimuladas en voluntarios sanos y pacientes con sepsis



Deficient *Candida*-Specific T-Helper 17 Response During Sepsis

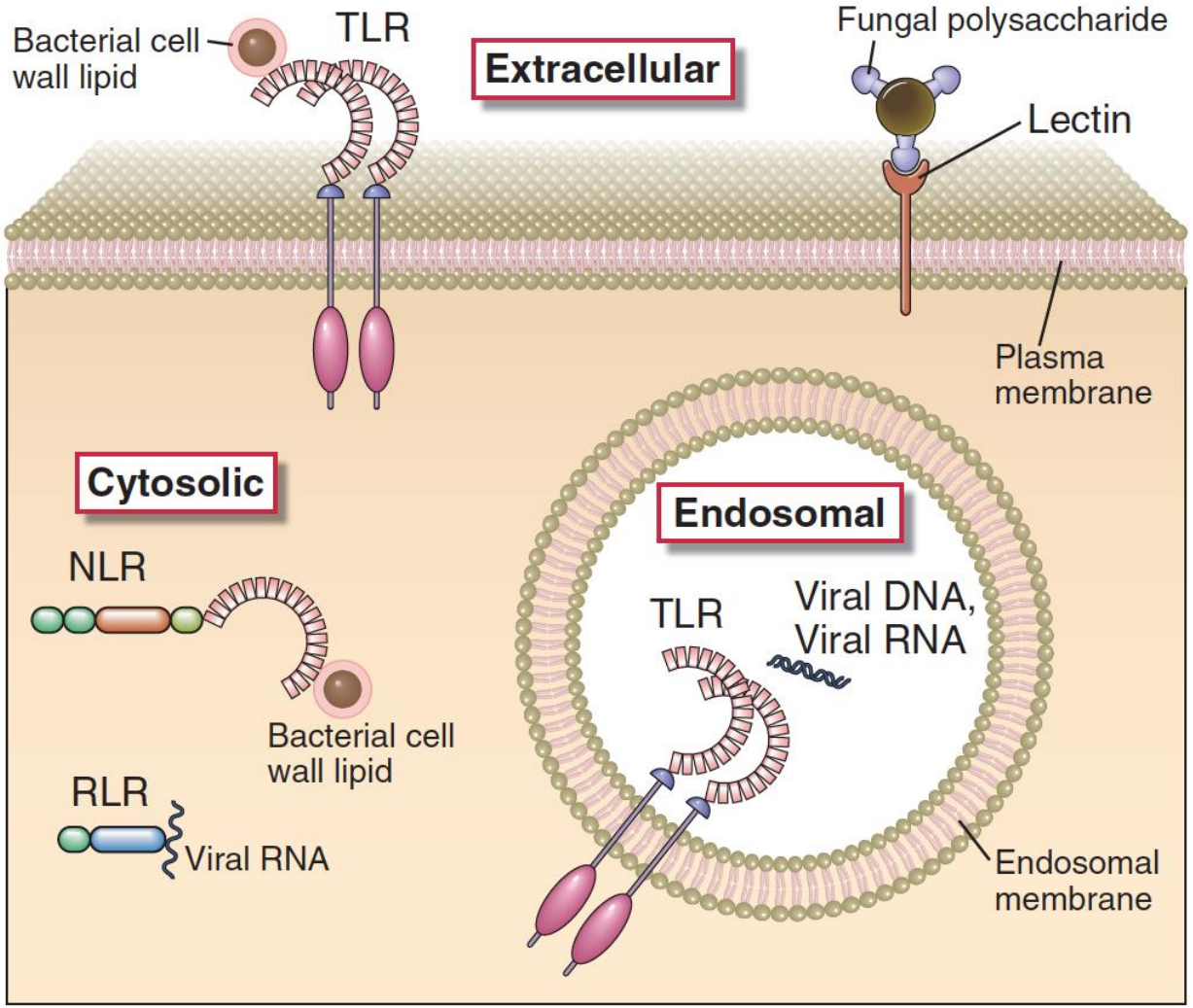
J Infect Dis 2012;206:1798-802

Expresión de IL-1ß e IL-17 en PBMCs estimuladas en voluntarios sanos tras la inyección de LPS



La respuesta Th17 es defectuosa en pacientes con sepsis por Gram-negativos o en el modelo experimental humano de endotoxinemia

Papel de los receptores de reconocimiento de patrones (PRPs)



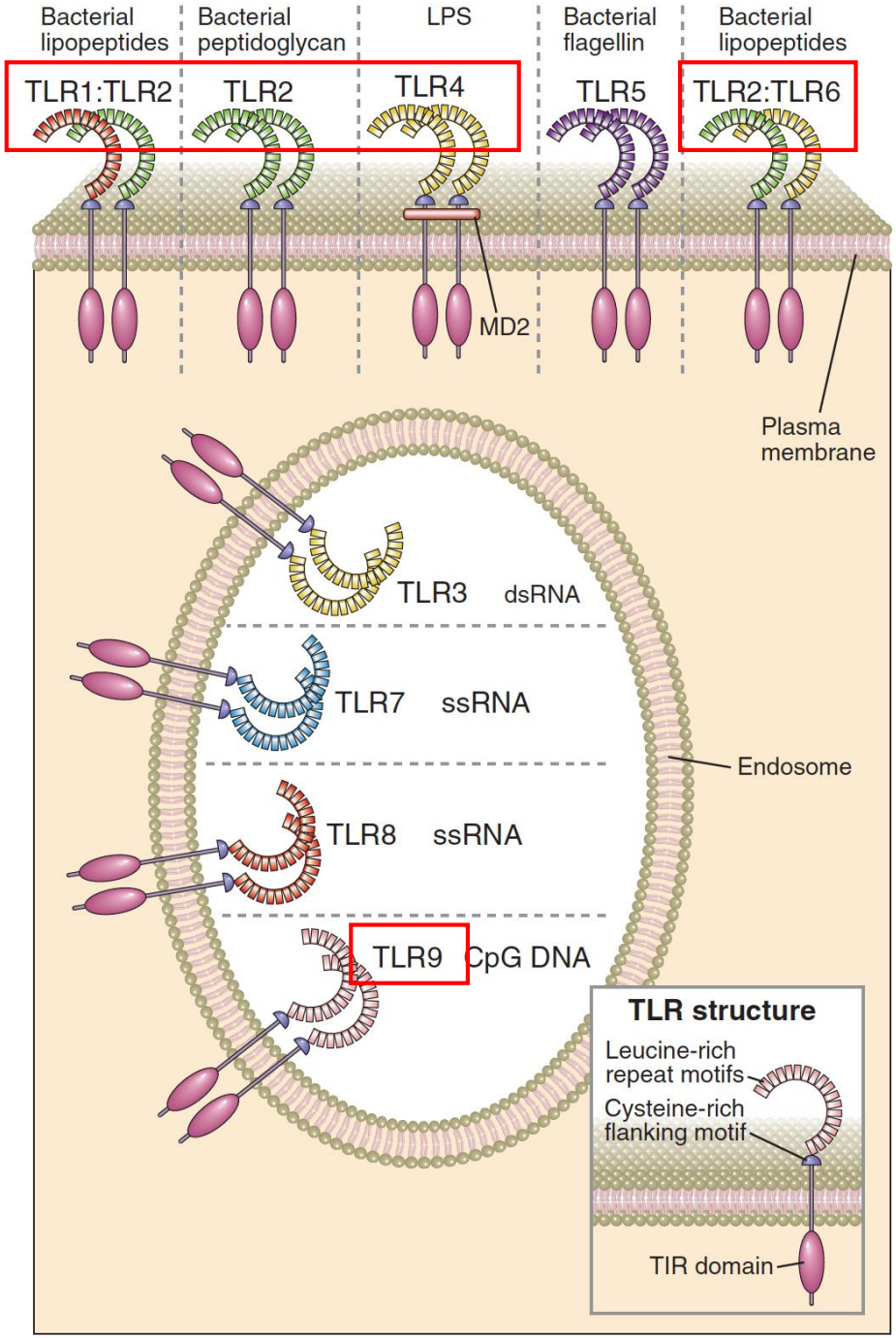
Abbas. 7ª edición

Toll-like Receptor 1 Polymorphisms Increase Susceptibility to Candidemia

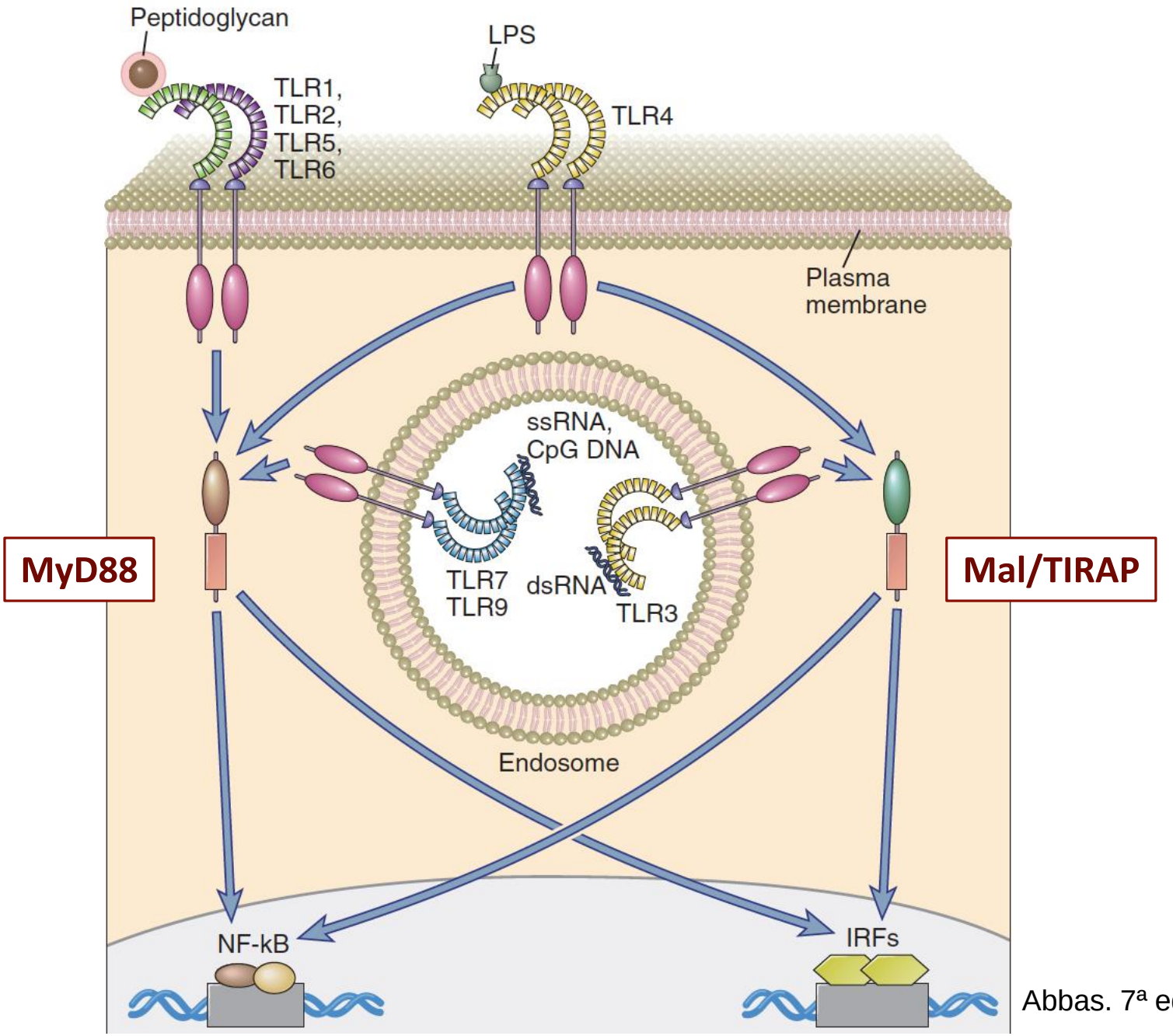
J Infect Dis 2012;205:934-43

Theo S. Plantinga,[1,2,a] Melissa D. Johnson,[5,6,a] William K. Scott,[7] Esther van de Vosse,[3] Digna R. Velez Edwards,[8] P. Brian Smith,[5] Barbara D. Alexander,[5] John C. Yang,[9] Dennis Kremer,[4] Gregory M. Laird,[5] Marije Oosting,[1,2] Leo A. B. Joosten,[1,2] Jos W. M. van der Meer,[1,2] Jaap T. van Dissel,[3] Thomas J. Walsh,[10] John R. Perfect,[5] Bart Jan Kullberg,[1,2] and Mihai G. Netea[1,2]

Gene	SNP ID	Gene Region	Amino Acid Change
MYD88	rs4988453	Promoter	…
	rs6853	3′ UTR	…
TIRAP	rs595022	Intron 1	…
	rs8177374	Exon 5	Nonsynonymous S180L
TLR1	rs4833095	Exon 4	Nonsynonymous S248N
	rs5743611	Exon 4	Nonsynonymous R80T
	rs5743618	Exon 4	Nonsynonymous I602S
TLR2	rs5743704	Exon 3	Nonsynonymous P631H
	rs5743708	Exon 3	Nonsynonymous R753Q
TLR4	rs4986790	Exon 3	Nonsynonymous D299G
	rs4986791	Exon 3	Nonsynonymous T399I
TLR6	rs5743810	Exon 1	Nonsynonymous S249P
TLR9	rs5743836	Promoter	…



Abbas. 7ª edición



Abbas. 7ª edición

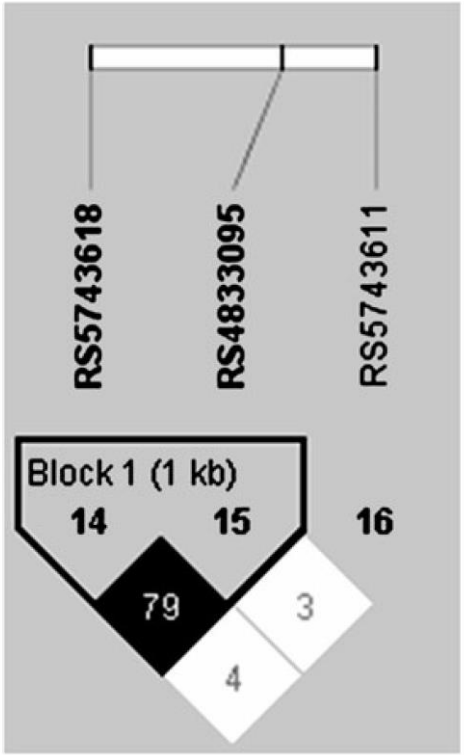
Tres SNPs en TLR1 *se asocian a mayor riesgo de candidemia en pacientes caucásicos*

Whites (245 Infected, 263 Noninfected) MAF					*P* Value	OR (95% CI)[b]
TLR1 R[a]80T	GG[a]	GC	CC		.02	1.82 (1.12–2.98)
Noninfected	88.2%	9.9%	1.91%	0.068		
Infected	80.2%	18.9%	0.86%	0.103		
TLR1 S248N[a]	GG	GA	AA[a]		.04	0.68 (.47–.96)
Noninfected	5.3%	41.8%	52.9%	0.262		
Infected	7.2%	30.1%	62.7%	0.223		
TLR1 I602S[a]	TT	TG	GG[a]		.02	0.69 (.49–.80)
Noninfected	7.6%	44.7%	47.7%	0.300		
Infected	10.2%	33.1%	56.8%	0.268		
African Americans (93 infected, 88 noninfected) MAF					*P* value	OR (95% CI)[c]
TLR1 R[a]80T	GG[a]	GC	CC		.62	2.92 (.23–155.70)
Noninfected	98.9%	1.1%	0%	0.006		
Infected	96.8%	3.2%	0%	0.016		
TLR1 S[a]248N	GG	GA	AA[a]		.09	3.86 (.71–39.15)
Noninfected	63.6%	28.4%	7.95%	0.222		
Infected	69.9%	27.9%	2.15%	0.161		
TLR1 I[a]602S	TT	TG	GG[a]		.60	3.12 (.25–166.70)
Noninfected	76.1%	20.5%	3.4%	0.137		
Infected	80.2%	18.7%	1.1%	0.105		

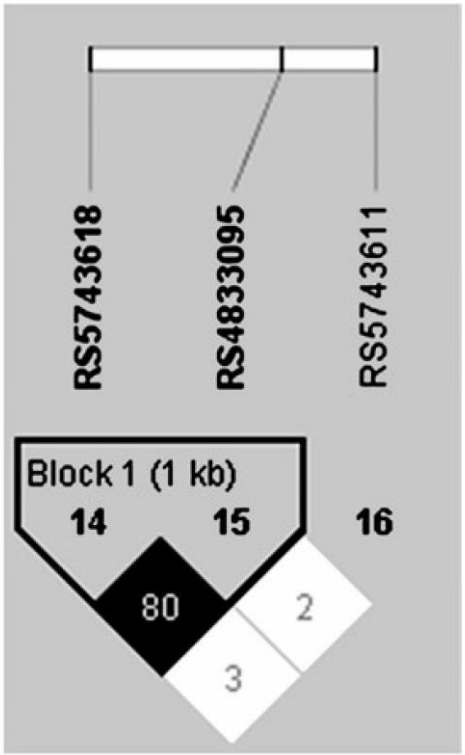
J Infect Dis 2012;205:934-43

***Desequilibrio de ligamiento en la tranmisión de esos tres SNPs en* TLR1**

Pacientes candidémicos

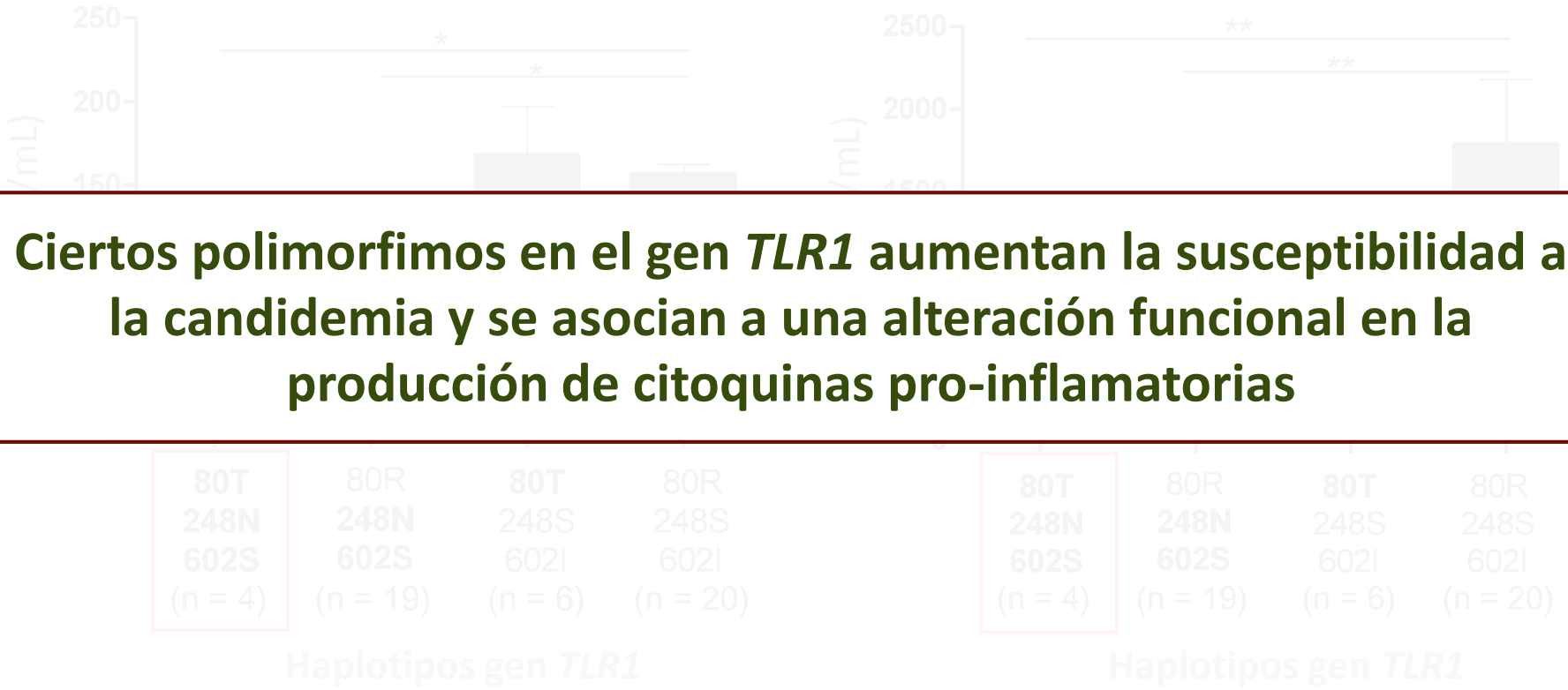


Controles no infectados



J Infect Dis 2012;205:934-43

Expresión de citoquinas proinflamatorias en PBMCs estimuladas en función de la presencia de distintos haplotipos en el gen TLR1



Ciertos polimorfimos en el gen *TLR1* aumentan la susceptibilidad a la candidemia y se asocian a una alteración funcional en la producción de citoquinas pro-inflamatorias

J Infect Dis 2012;205:934-43

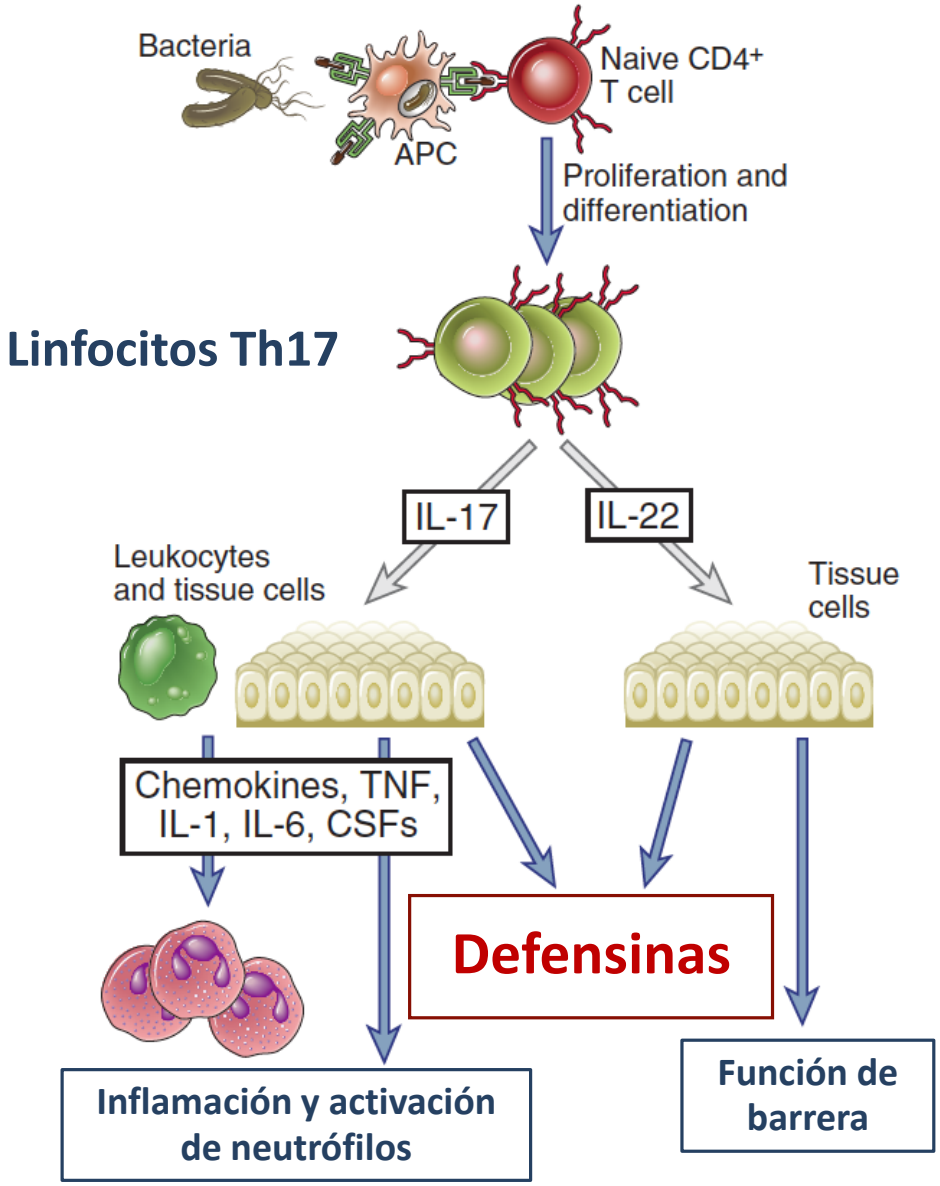
Citoquinas pro-inflamatorias y péptidos antimicrobianos

Polymorphisms in *Tumor Necrosis Factor-α* Increase Susceptibility to Intra-Abdominal *Candida* Infection in High-Risk Surgical ICU Patients*

Crit Care Med 2014;42:e304-8

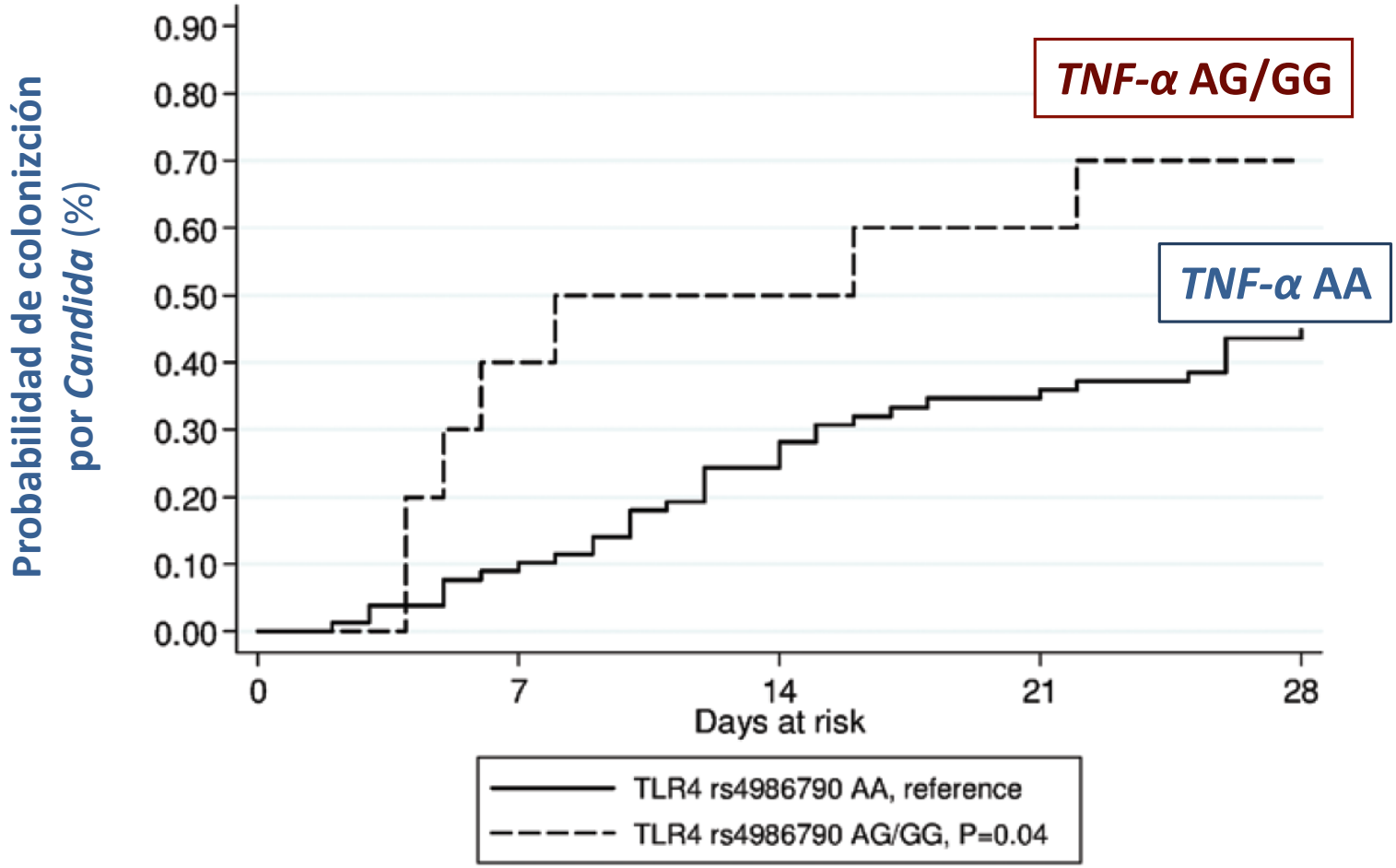
Agnieszka Wójtowicz, PhD[1]; Frederic Tissot, MD[1]; Frederic Lamoth, MD[1]; Christina Orasch, MD[1,2]; Philippe Eggimann, MD[3]; Martin Siegemund, MD[4]; Stephan Zimmerli, MD[5]; Ursula Maria Flueckiger, MD[2,6]; Jacques Bille, MD[7]; Thierry Calandra, MD, PhD[1]; Oscar Marchetti, MD[1]; Pierre-Yves Bochud, MD[1]; and the Fungal Infection Network of Switzerland (FUNGINOS)

	Multivariate Analysis	
Gene rs Number	**Hazard Ratio (95% CI)**	**Cox *p*[a]**
Candida colonization[b] ($n = 89$)		
Toll-like receptor 4 *rs4986790*, AA/AG vs GG	3.39 (1.45–7.93)	0.005
Surfactant protein A2 *rs17886395*, CC/GC vs GG	1.87 (0.93–3.74)	0.08
Male sex	1.27 (0.67–2.43)	0.5
Age (yr)	0.99 (0.97–1.01)	0.4
Intra-abdominal candidiasis[c] ($n = 69$)		
Model 1		
TNF-α *rs1800629*, GA/AA vs GG	4.31 (1.85–10.1)	0.0007
DEFB1 *rs1800972*, GG/CG vs CC	3.21 (1.36–7.59)	0.008
SAPS II score[d]	2.41 (1.01–5.75)	0.05



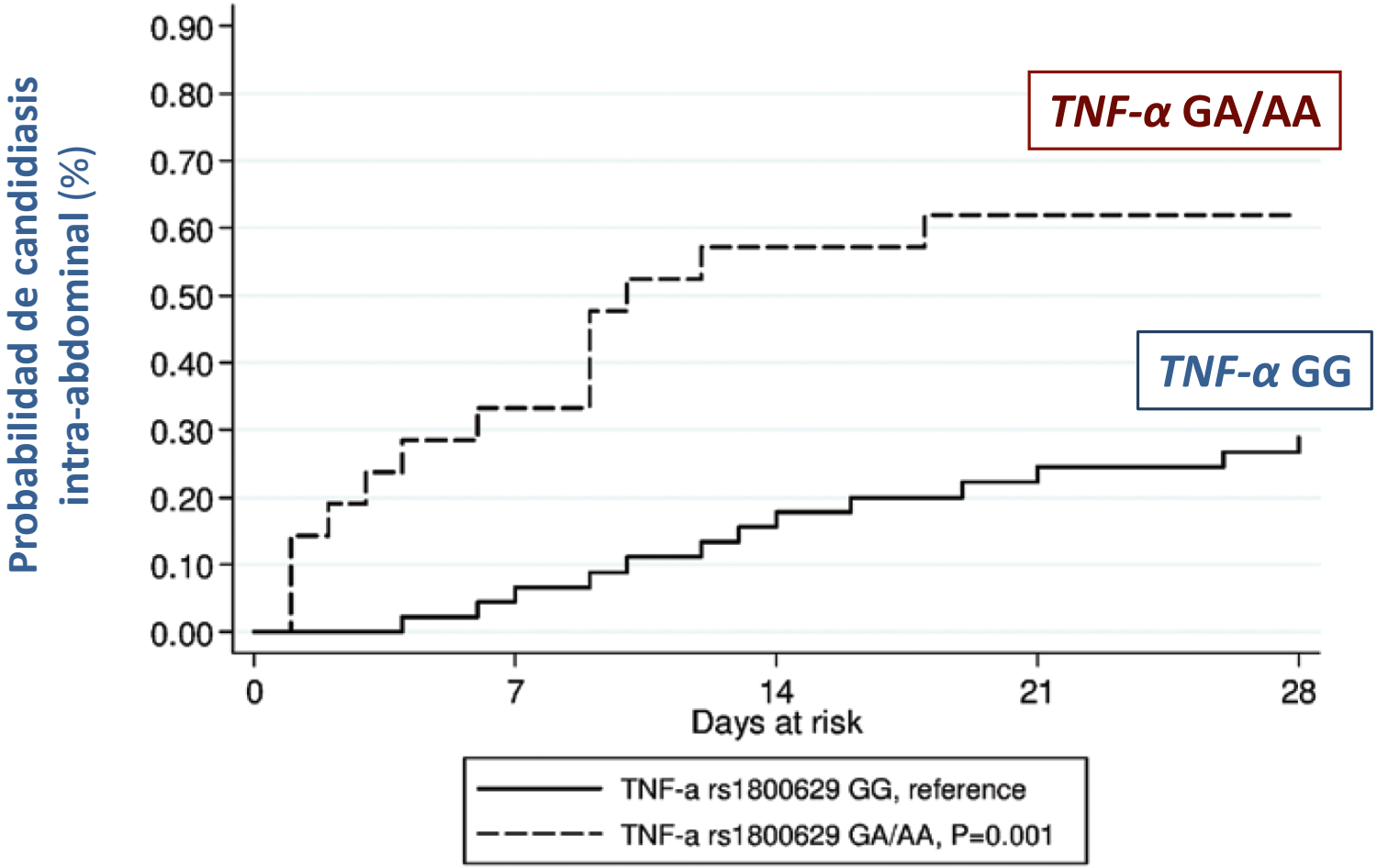
Abbas. 7ª edición

El SNP rs49866790 en TNF-α *se asocia a mayor riesgo de colonización "pesada" por* Candida *spp.* *(índice de Pittet corregido >0,4)*



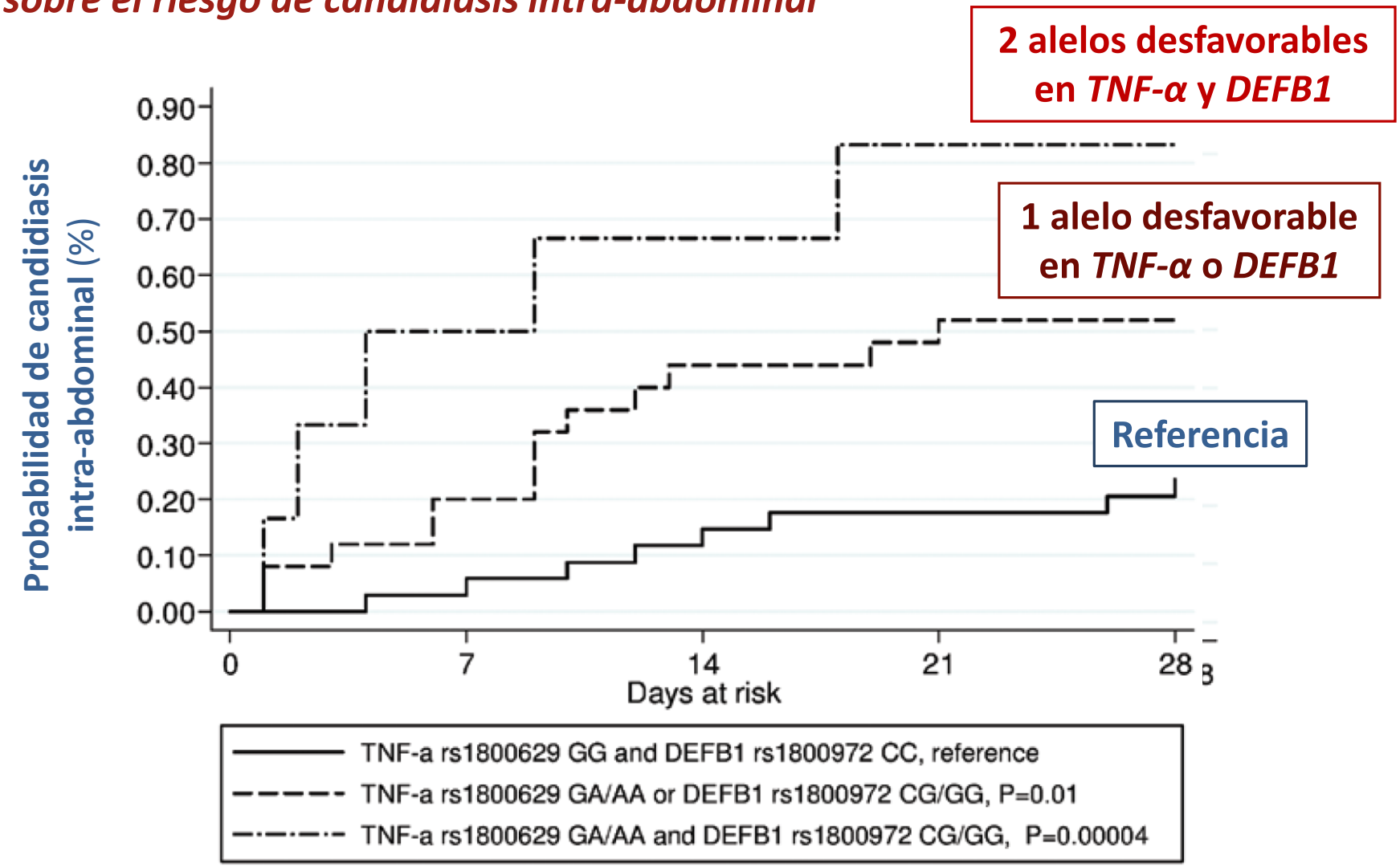
Crit Care Med 2014;42:e304-8

El SNP rs1800629 en TNF-α *se asocia a mayor riesgo de candidiasis intra-abdominal*



Crit Care Med 2014;42:e304-8

Efecto de la combinación de SNP en TNF-α *y* DEFB1 *sobre el riesgo de candidiasis intra-abdominal*



Respuesta celular T CD4 y CD8

RESEARCH Open Access

T cells from patients with *Candida* sepsis display a suppressive immunophenotype

Crit Care 2016;20:15.

Andrej Spec[1†], Yuichiro Shindo[2†], Carey-Ann D. Burnham[3], Strother Wilson[2], Enyo A. Ablordeppey[2], Evan R. Beiter[2], Katherine Chang[2], Anne M. Drewry[2] and Richard S. Hotchkiss[1,2,4*]

- **27 pacientes con candidemia y 16 controles ingresados en UCI**
- **Citometría de flujo en PBMCs** (muestra obtenida al cabo de 24-48 horas desde el primer HC)

Table 1 Baseline characteristics of patients with *Candida* bloodstream infections and critically ill control patients

	CBSI N = 27 (%)	Critically ill, non-septic patients N = 16 (%)	*p* value
Mean age (±SD), years	56.9 (23.4)	58.9 (18.1)	0.19
Male gender (%)	14 (51.9)	10 (62.5)	0.46
APACHE II score (±SD)*	11.61 (6.7)	8.69 (4.0)	0.11
SOFA score (±SD)*	4.7 (4.2)	2.6 (1.8)	0.06
White blood cell count (±SD), thousand/mm^3	11.7 (5.8)	9.9 (3.5)	0.25
Absolute lymphocyte count (±SD), thousand/mm^3	1.13 (0.99)	0.61 (0.49)	0.02
Absolute neutrophil count (±SD), thousand/mm^3	7.23 (5.76)	6.43 (5.32)	0.77
Heart rate (±SD), beats/min	102.2 (19.9)	109.5 (17.0)	0.23
Respiratory rate (±SD), breaths/min	23.19 (5.6)	24.4 (4.1)	0.46
Baseline creatinine (±SD), mg/dl	1.46 (1.62)	1.1 (0.85)	0.4
90-day mortality (%)	6 (22.2)	3 (18.8)	0.79

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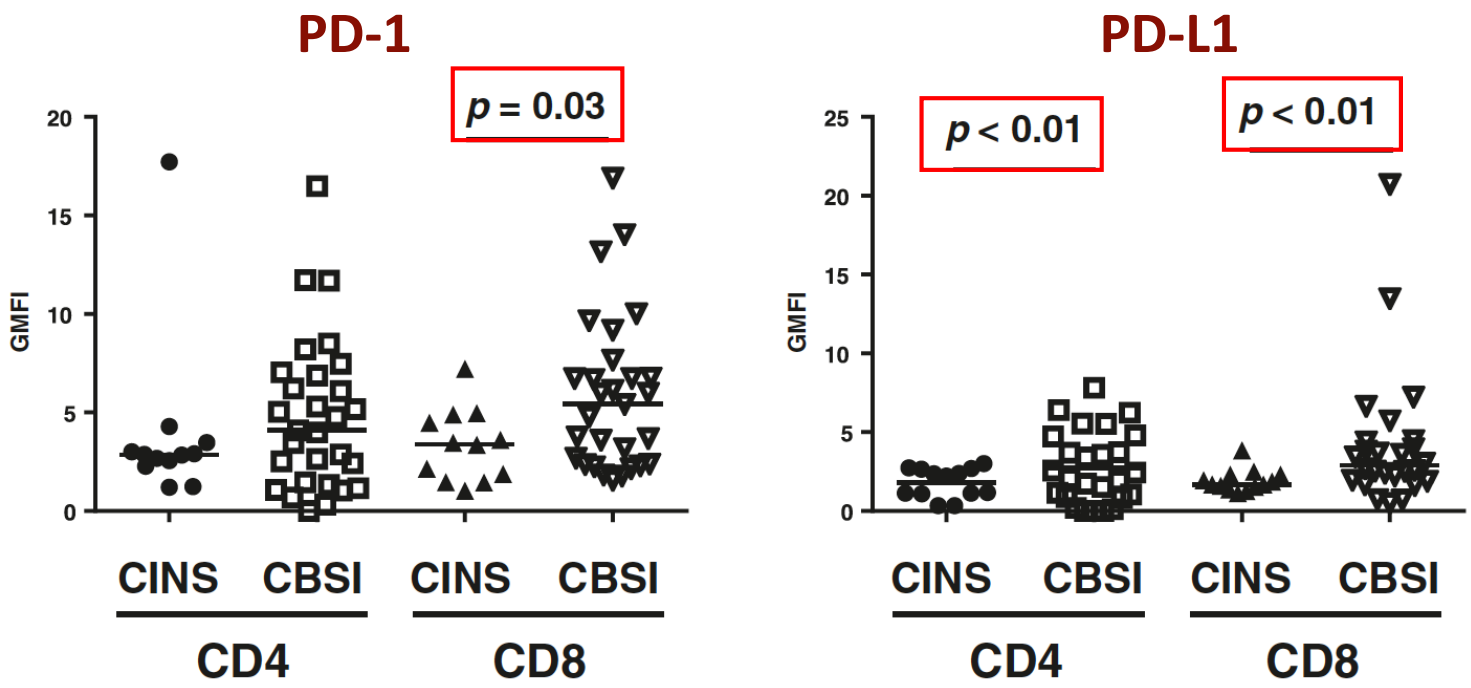

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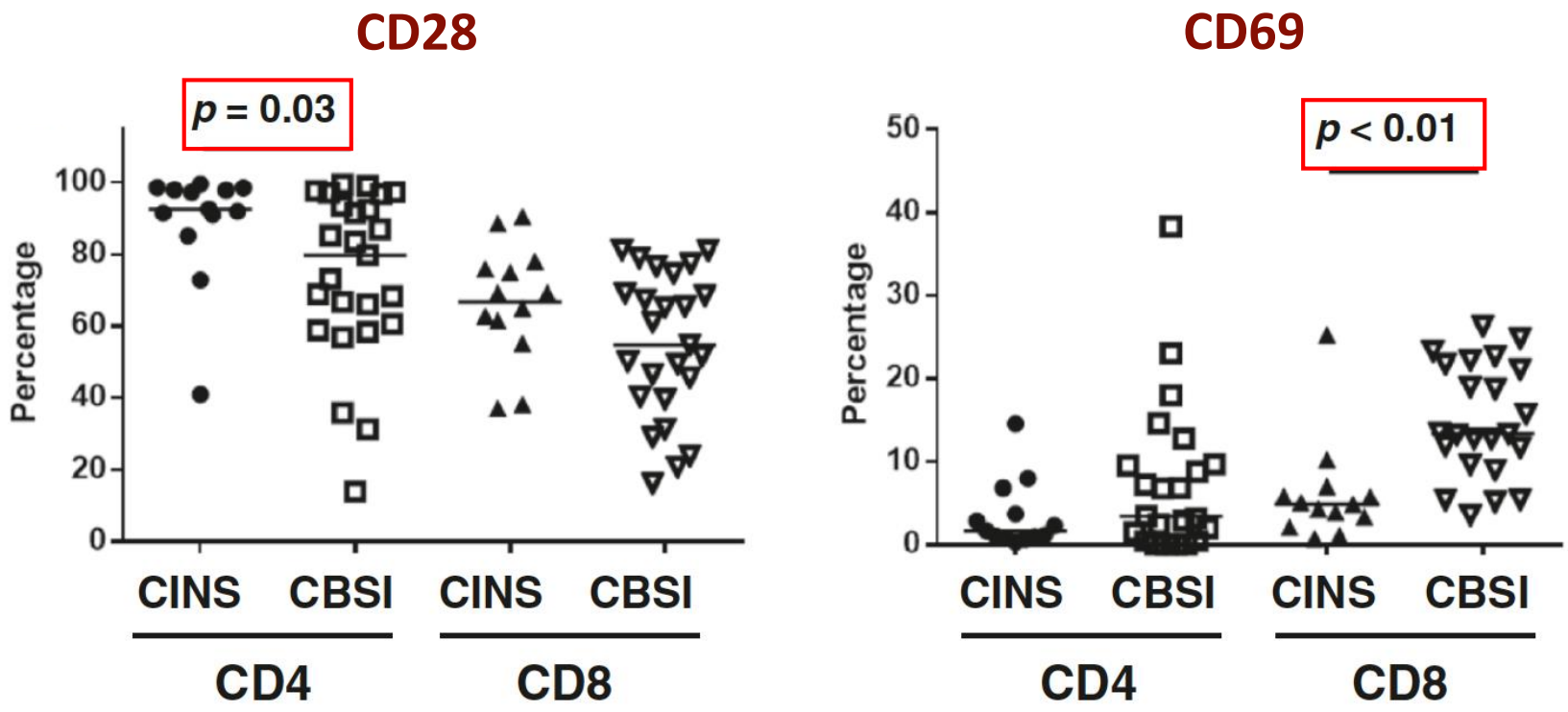
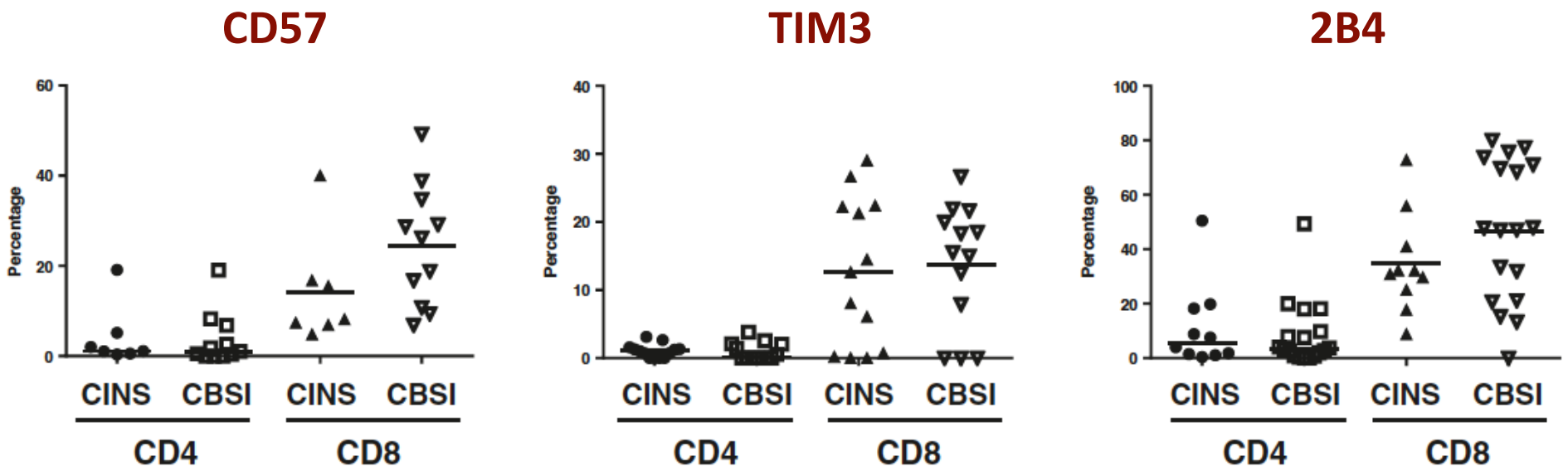




En comparación con otros pacientes críticos, los pacientes con candidemia presentan un inmunofenotipo T CD4 y CD8 ”exhausto”

(disminución de receptores de co-estimulación positiva [CD28], aumento de receptores de co-estimulación negativa [PD-1 y PD-L1] y de moléculas de activación [CD69])

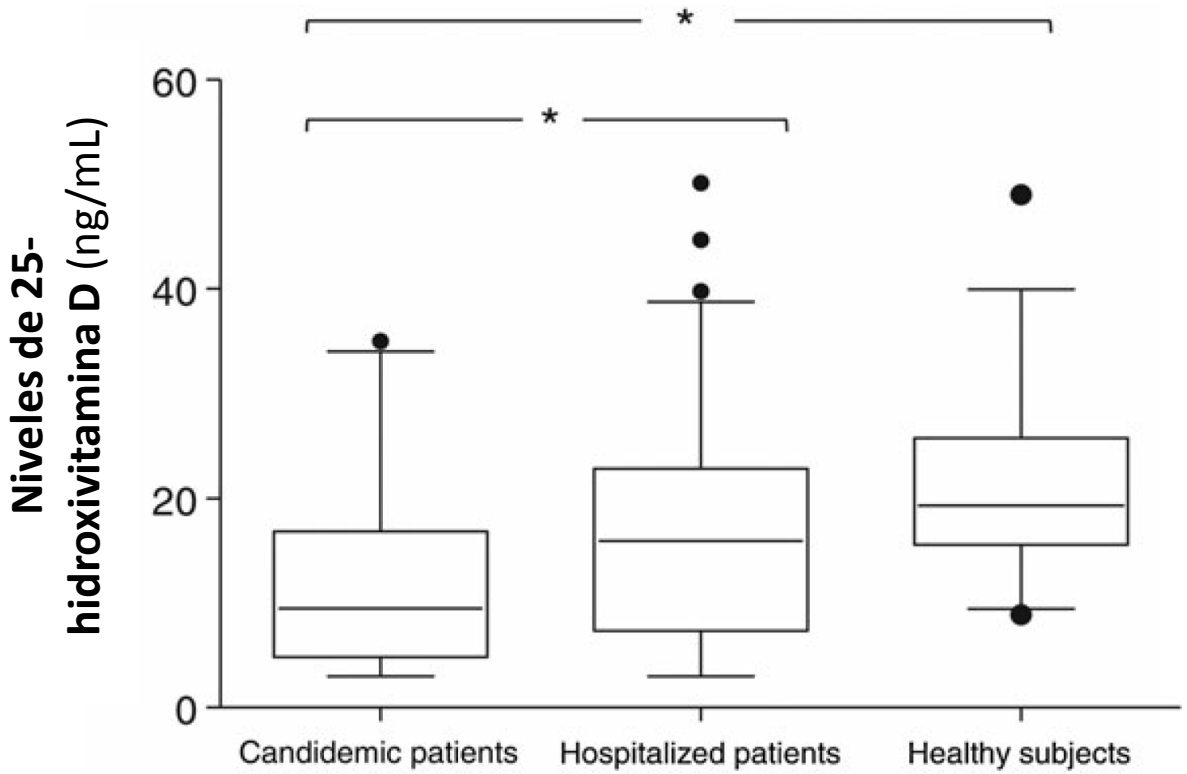
Papel inmunomodulador de la vitamina D

Bimodal Influence of Vitamin D in Host Response to Systemic *Candida* Infection—Vitamin D Dose Matters

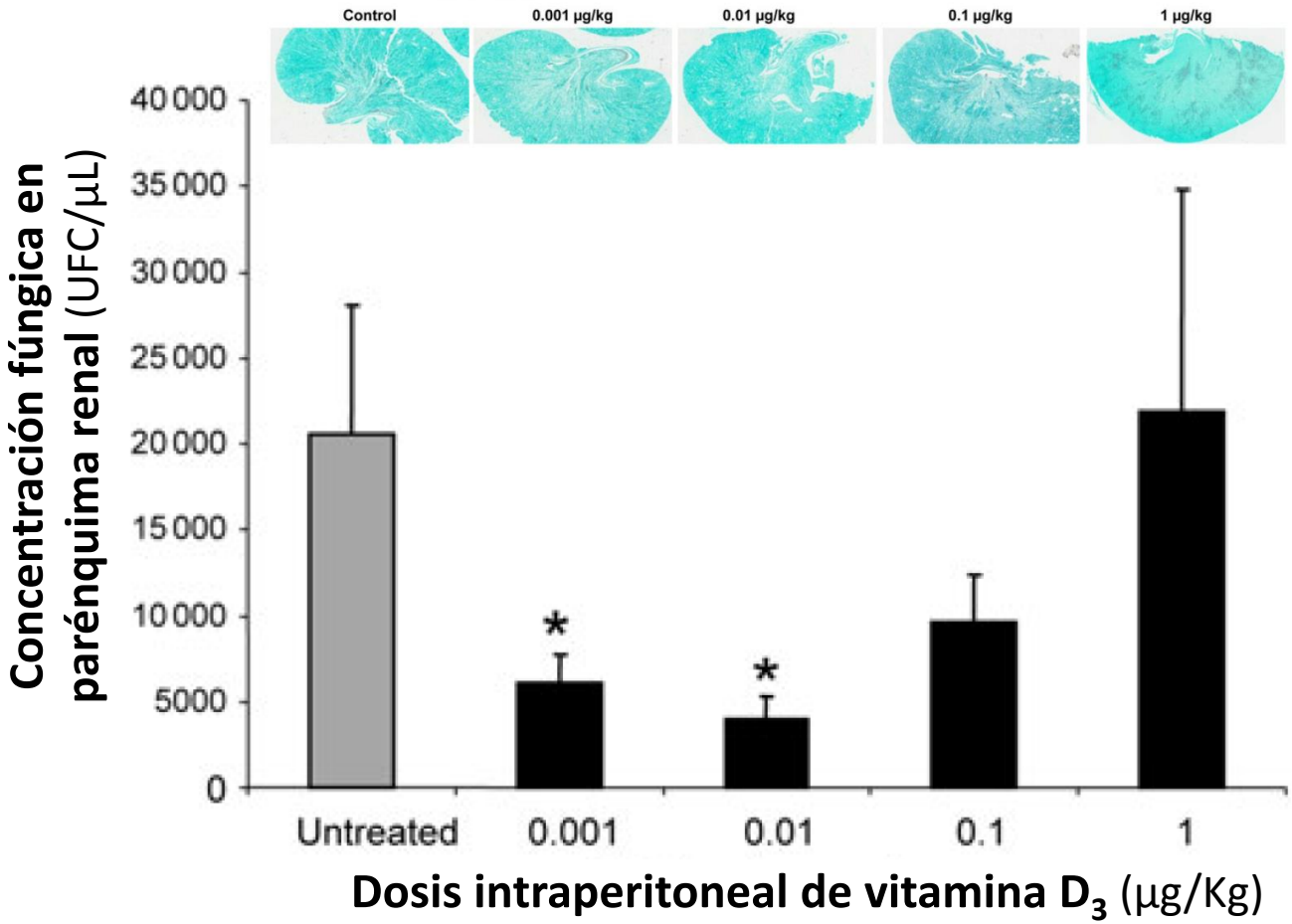
J Infect Dis 2015;212:635-44

Joan Hui Juan Lim,[1,a] Sharada Ravikumar,[1,a] Yan-Ming Wang,[7] Thomas Paulraj Thamboo,[4] Lizhen Ong,[5] Jinmiao Chen,[8] Jessamine Geraldine Goh,[1] Sen Hee Tay,[2] Lufei Chengchen,[9] Mar Soe Win,[1,9] Winnie Leong,[1] Titus Lau,[3] Roger Foo,[10] Haris Mirza,[11] Kevin Shyong Wei Tan,[11] Sunil Sethi,[5] Ai Leng Khoo,[13] Wee Joo Chng,[6,9,12] Motomi Osato,[9] Mihai G. Netea,[14] Yue Wang,[7] and Louis Yi Ann Chai[1]

- Pacientes con candidemia
- Controles hospitalizados
- Controles sanos

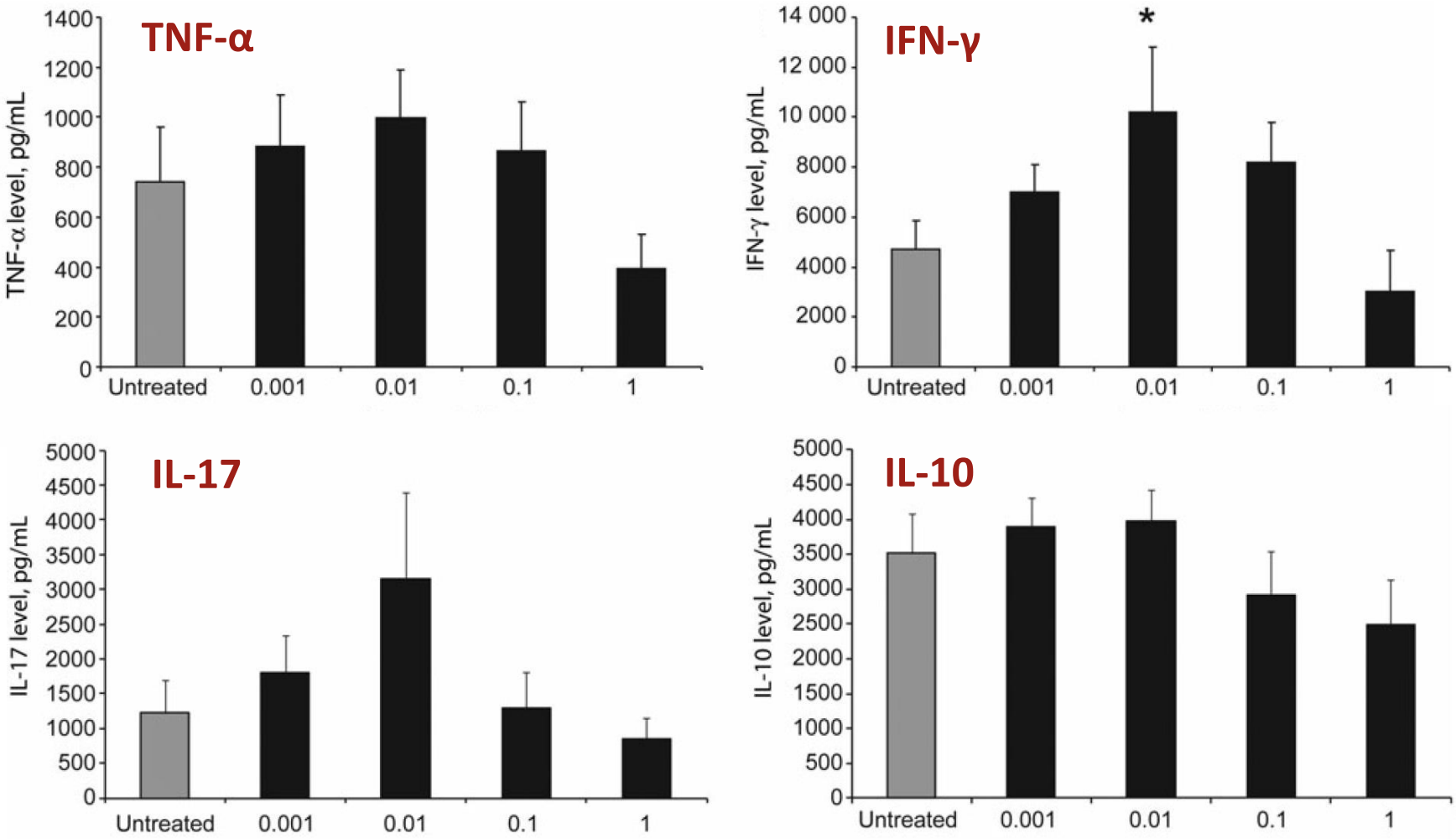


- ***Modelo murino tratado con vitamina D_3***



J Infect Dis 2015;212:635-44

- ***Expresión de citoquinas en esplenocitos estimulados con* Candida *spp.***



J Infect Dis 2015;212:635-44

- *Niveles de mRNA de STAT1 y STAT3 en función de la dosis de vitamina D_3*

Esplenocitos de ratón

La vitamina D ejerce un papel bimodal sobre la respuesta frente a *Candida* (polarización Th17, expresión de *STAT3*, respuesta de citoquinas pro-inflamatorias): **dosis bajas son beneficiosas, dosis elevadas son deletéreas**

PBMCs humanas

J Infect Dis 2015;212:635-44

Conclusiones

- Los modelos clínicos de predicción de candidiasis son imperfectos: ¿papel de la respuesta inmune del huésped?
- Ejemplos de la relevancia del eje Th17-IL-17: candidiasis mucocutánea crónica, nuevos fármacos biológicos
- Deficiencia de CARD9 y riesgo de candidiasis invasiva (SNC)
- Polimorfimos en los genes que codifican TLRs, citoquinas proinflamatorias y péptidos antimicrobianos
- Fenotipo exhausto CD4 y CD8 durante la candidemia
- Papel bimodal de la vitamina D según su concentración

Propuesta de investigación...

incluir parámetros de respuesta inmune e interacción huésped-patógeno en futuros estudios en candidemia

¿Estudio Inmuno-CANDIPOP 2?

Muchas gracias

mario_fdezruiz@yahoo.es