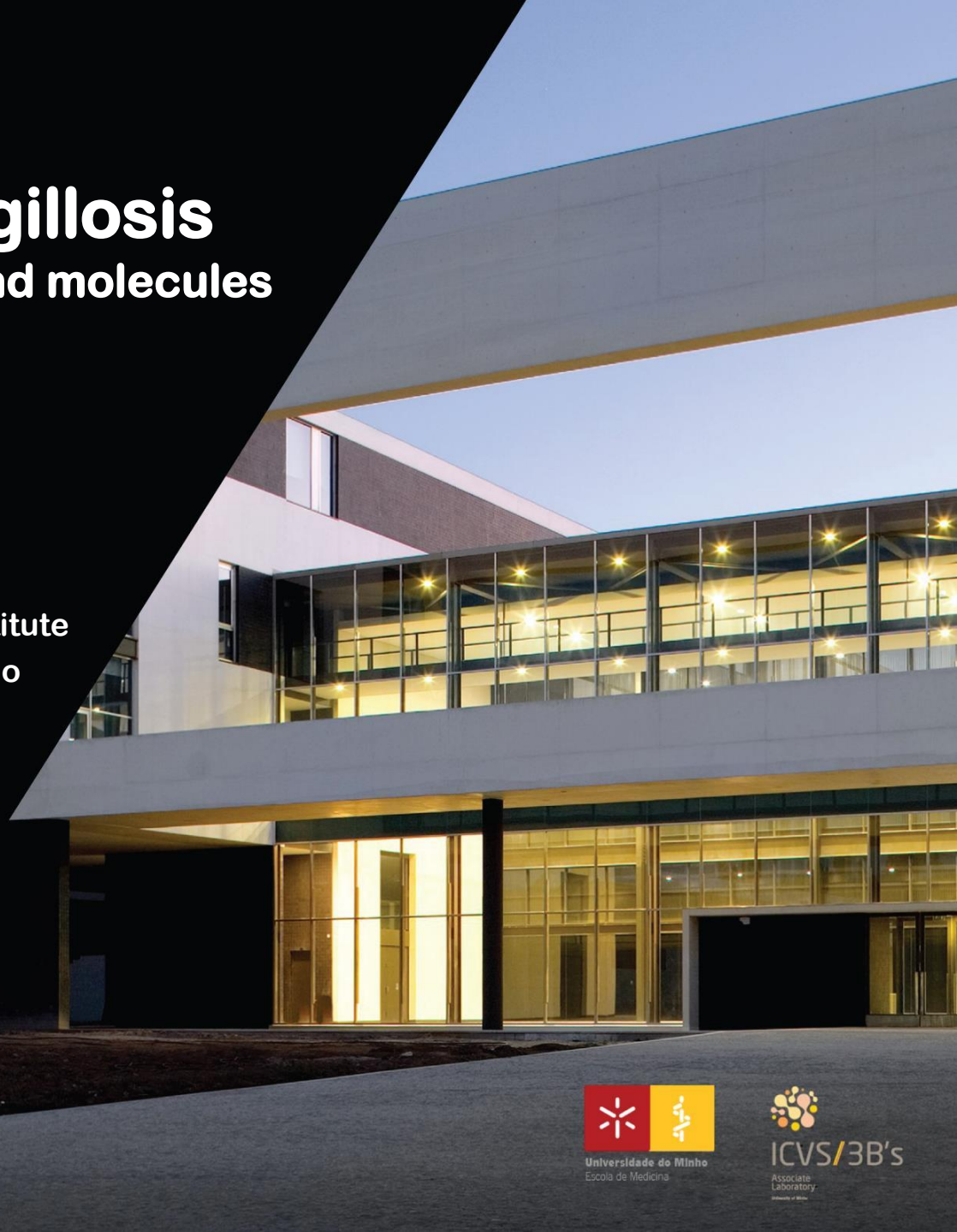
Genetics of aspergillosis

Innate immune receptors and molecules

Agostinho Carvalho

Life and Health Sciences Research Institute
School of Medicine – University of Minho
Braga – PORTUGAL

agostinhocarvalho@med.uminho.pt

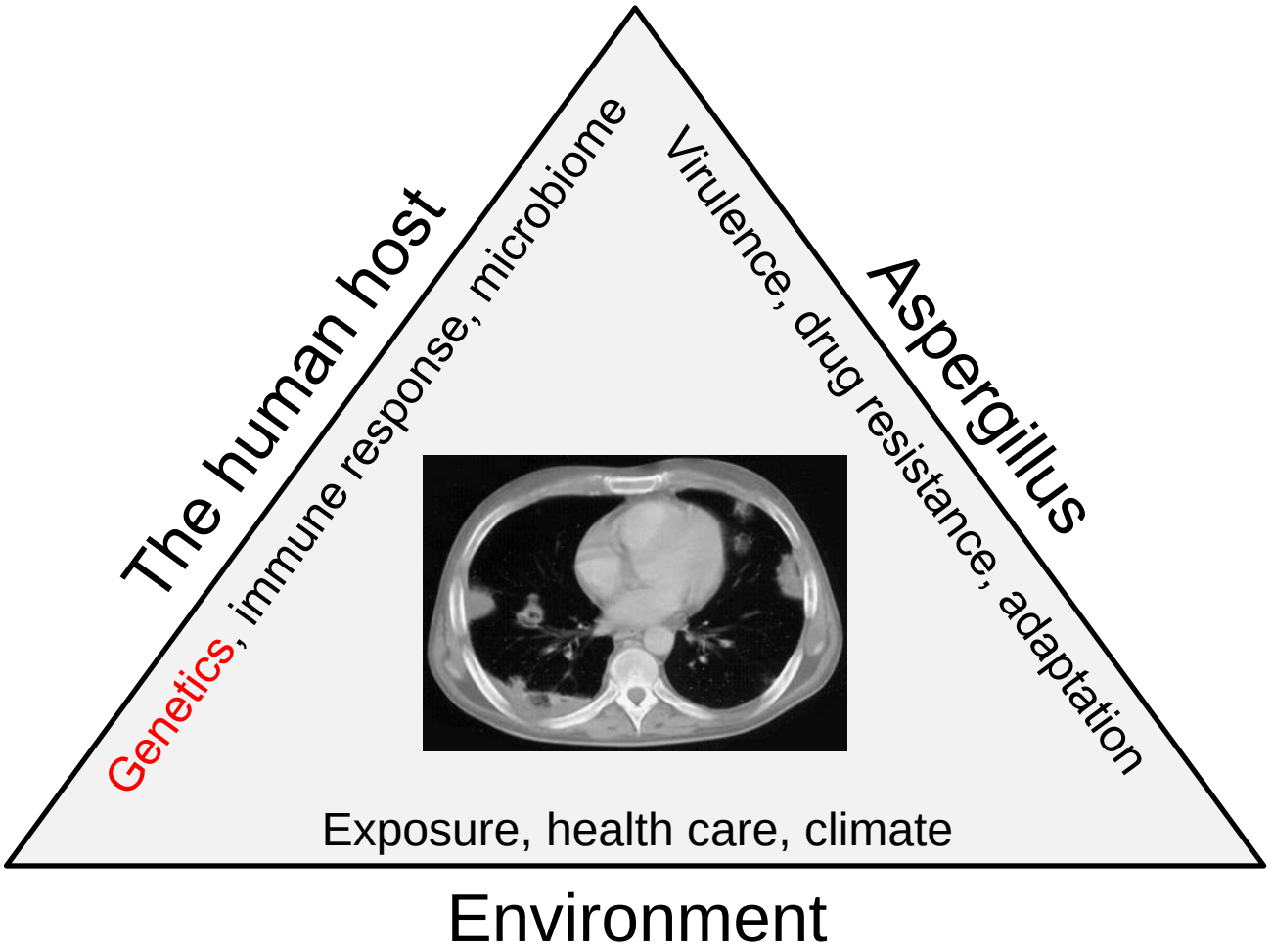


ICVS Life and Health Sciences Research Institute
Instituto de Investigação em Ciências da Vida e Saúde

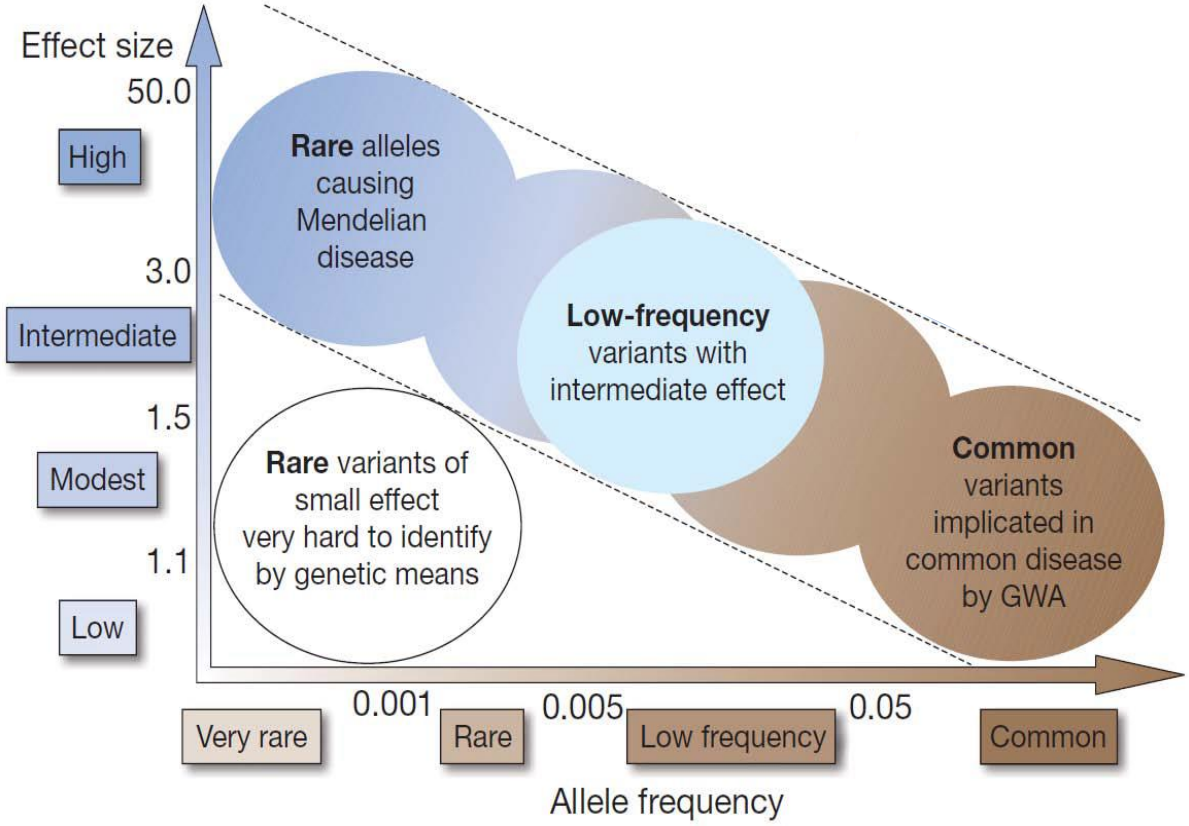
Universidade do Minho
Escola de Medicina

ICVS/3B's
Associate Laboratory

Susceptibility to aspergillosis

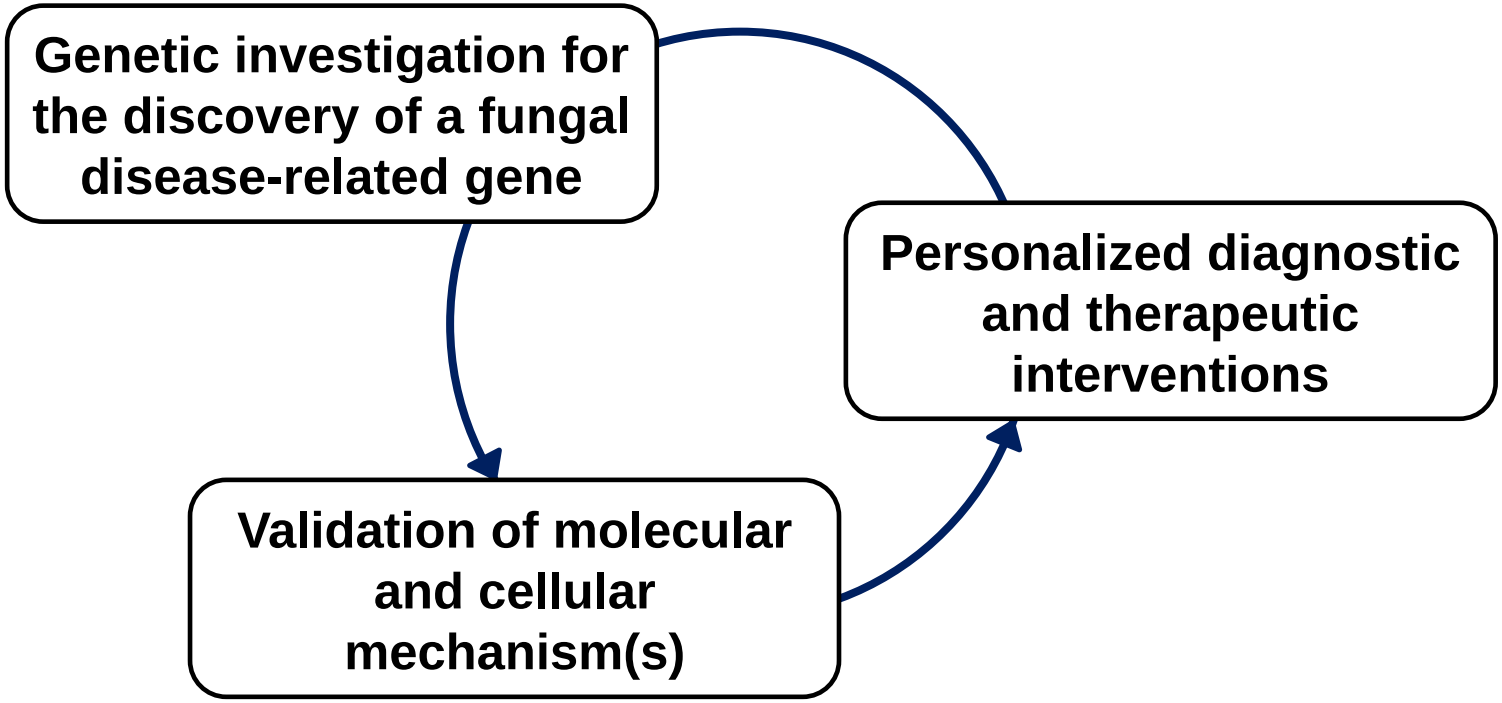


Genetics of susceptibility to infection



Manolio TA et al. Nature. 2009

The study of gene - fungal disease associations

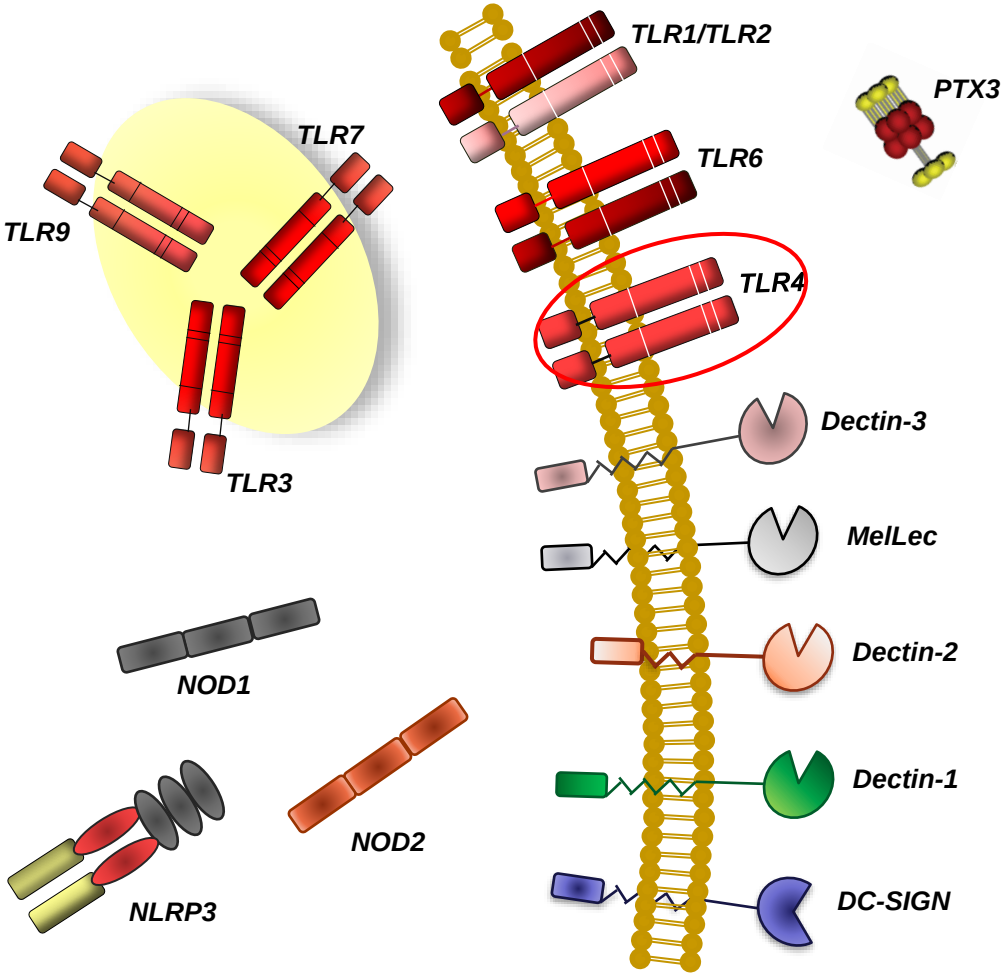


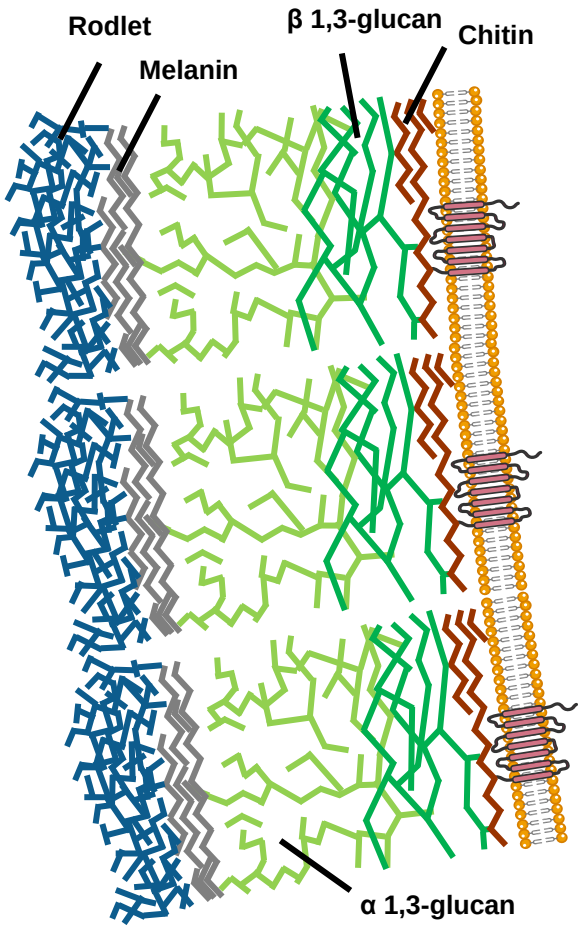
Immunogenetics of IA

Gene(s)	SNP(s)	Amino acid change	Type of patients[1]	Cases (total patients)	Association [OR (95% CI), P value]	Probable mechanism(s)
AGER	rs1800624	-	HSCT (D/R)	41 (223)	2.0 (1.0–3.8), P = 0.04 (D) 2.0 (1.0–4.1), P = 0.05 (R)	Enhanced expression of RAGE
CLEC7A (Dectin-1)	rs16910526	Y238X	HSCT (D/R) Hematological	39 (205) 21 (138)[2]	2.5 (1.0–6.5), P = 0.05 (D) 3.9 (1.5–10.0), P = 0.005 (D+R) n.a., P = 0.02	Defective cell surface expression of dectin-1 and cytokine production
	rs7309123	-	Hematological	57 (182)	5.5 (1.9–16.4), P = 0.001	Impaired expression of dectin-1 mRNA
CXCL10	rs1554013 rs3921 rs4257674	- - -	HSCT (D)	81 (139)	2.2 (1.2–3.8), P = 0.007 2.6 (1.4–5.0), P = 0.003 2.8 (1.6–5.2), P = 0.001	Impaired expression of CXCL10
IL1A *IL1B* *IL1RN*	rs1800587 rs16944 VNTR 86-bp(n)	- - -	Hematological[3]	59 (110)	15.4 (1.4–171.2), P = 0.02	Unknown
IL10	rs1800896 rs1800871 rs1800872	- - -	HSCT (R)[4]	9 (105)	9.3 (1.6–52.8), P = 0.01	Unknown
MBL2	rs1800896	-	Hematological	59 (120)	4.5 (1.6–12.9), P = 0.001	Unknown
MASP2	'MBL-low genotypes'[5]	-	HSCT (D)	15 (106)	7.3 (1.9–27.3), P = 0.003	Unknown
	rs72550870	D120G	HSCT (R)		6.4 (2.0–20.6), P = 0.002	
PLG	rs4252125	D472N	HSCT (R)	59 (194)	3.0 (1.5–6.1), P<0.001 5.6 (1.9–16.5), P<0.001[6]	Unknown
S100B	rs9722	-	HSCT (D)	41 (223)	3.15 (1.61–6.15), P<0.001	Enhanced secretion of S100B
TLR1	rs5743611 rs4833095 rs5743810	R80T N248S S249P	HSCT (R)	22 (127)	1.2 (1.0–1.5), P = 0.04 1.2 (1.0–1.5), P = 0.02 1.3 (1.1–1.5), P<0.001[7]	Unknown
TLR3	rs3775296	-	HSCT (D)	42 (223)	2.4 (1.3–4.6), P = 0.007	Defective antigen presentation and activation of CD8(+) T-cell responses
TLR4 **TLR6**	rs4986790 rs4986791	D299G T399I	HSCT (D)[8]	33 (336) 103 (366)	6.2 (2.0–19.3), P = 0.002 (discovery study) 2.5 (1.2–5.4), P = 0.02 (validation study)	Unknown
TNFR1	rs4149570	-	Hematological	77 (144)	n.a., P = 0.02	Impaired expression of TNFR1 mRNA
TNFR2	rs5745946	-	Hematological	54 (102)	2.5 (1.1–5.0), P = 0.03	Unknown

Cunha et al. PLoS Pathog. 2013

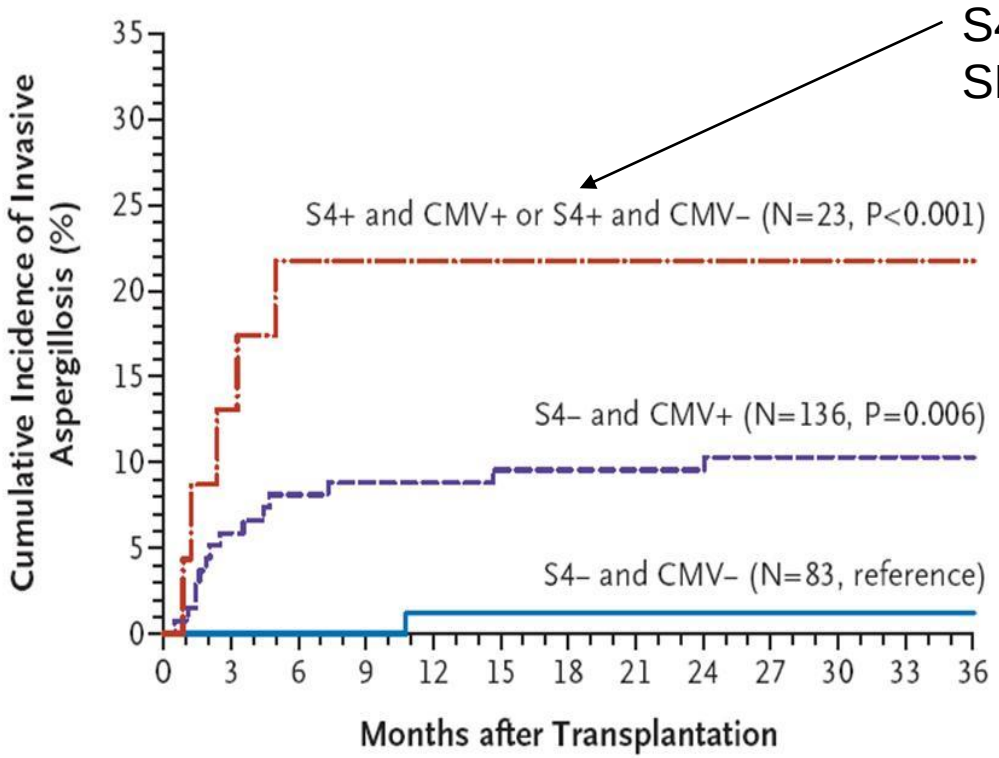
The host-fungus interaction





Intracellular PRRs | **Extracellular PRRs** | ***Aspergillus* conidium**

Immunogenetics of IA: TLR4



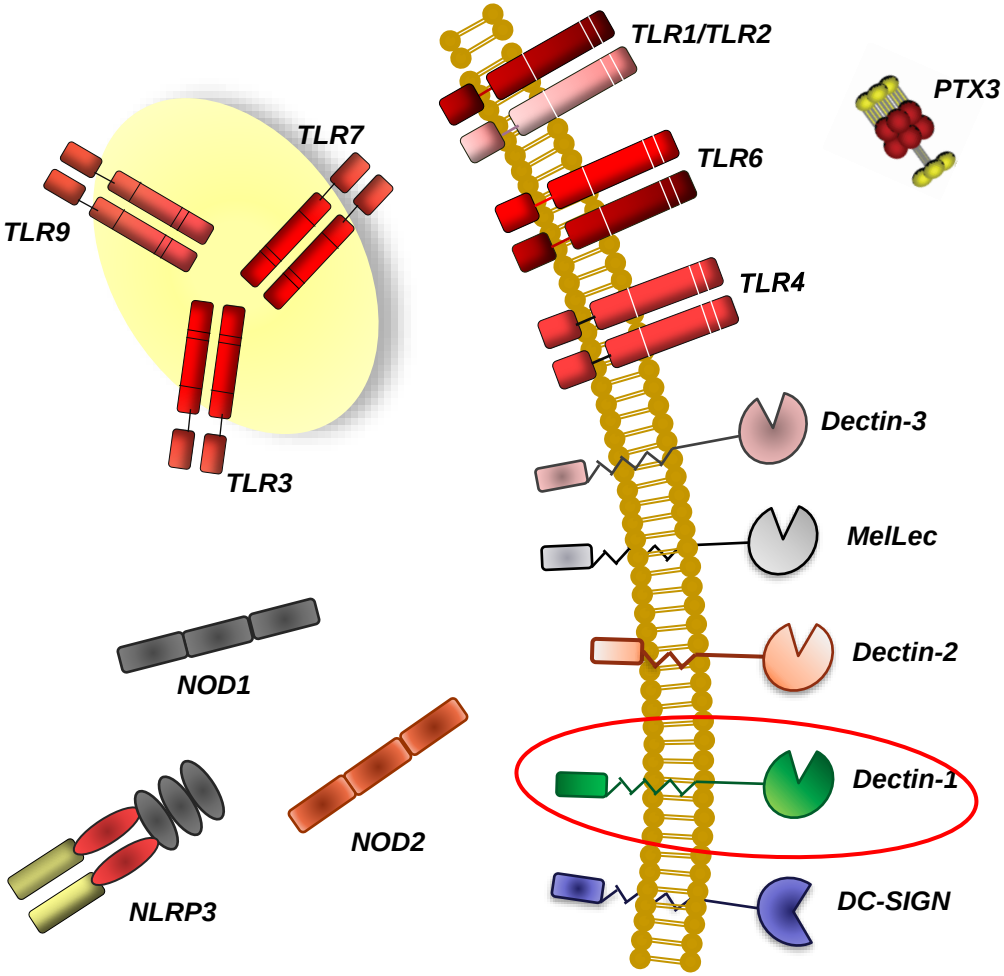
S4 – haplotype of TLR4
SNPs in LD

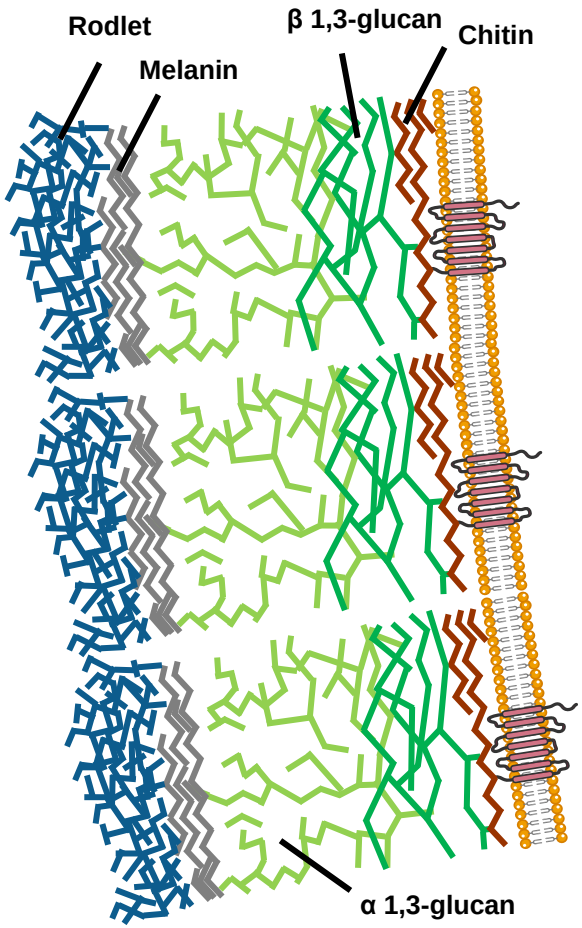
Adjusted hazard ratio:

discovery study, 6.16
validation study, 2.49

Bochud PY et al. N Engl J Med. 2008

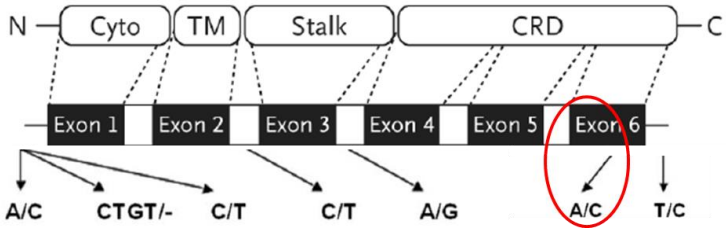
The host-fungus interaction



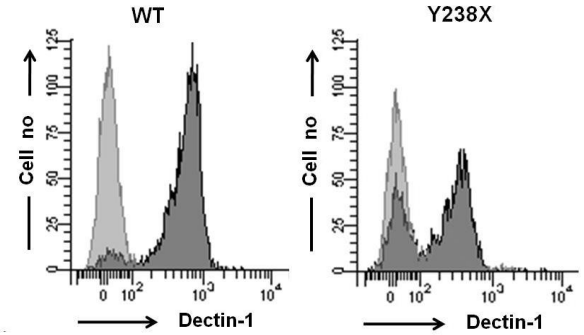


Intracellular PRRs | **Extracellular PRRs** | ***Aspergillus* conidium**

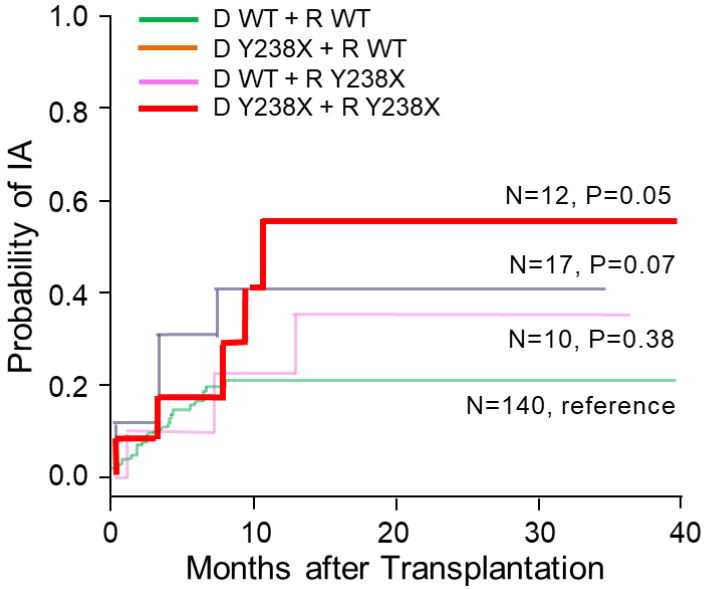
Immunogenetics of IA: Dectin-1

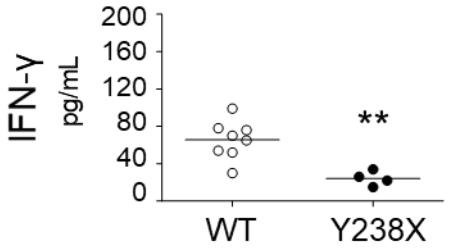


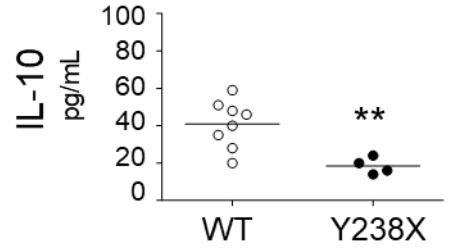
Y238X



Ferwerda B et al. N Engl J Med. 2009

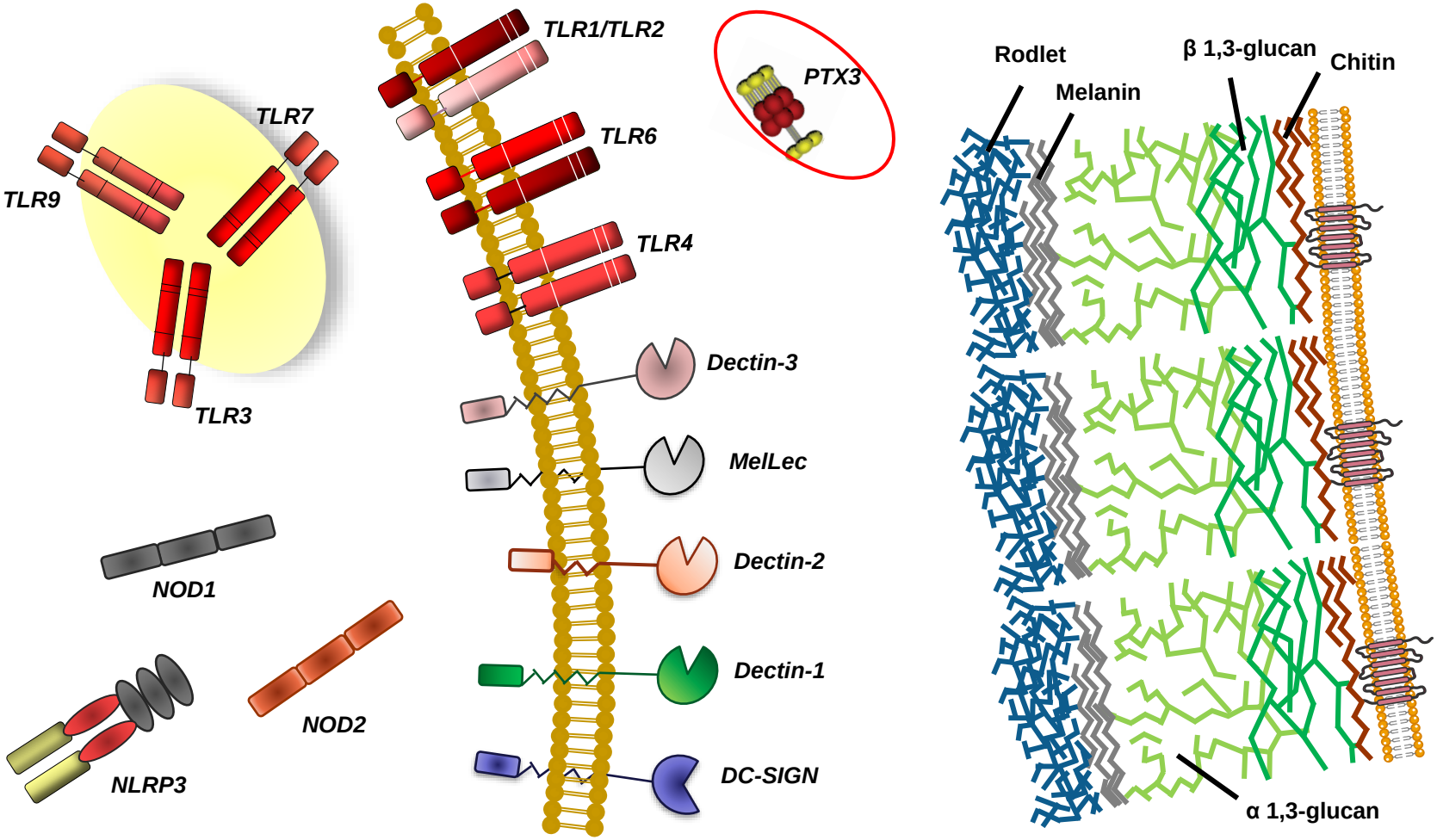






Cunha C et al. Blood . 2010

The host-fungus interaction



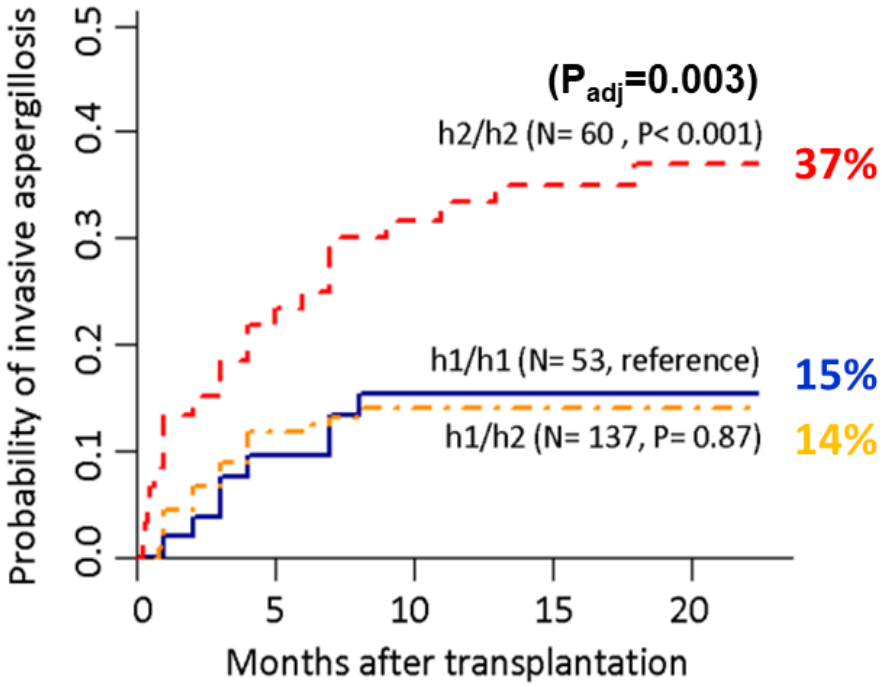
Intracellular PRRs **Extracellular PRRs** ***Aspergillus* conidium**

Immunogenetics of IA: PTX3

Donor PTX3 SNPs are associated with the development of IA after HSCT

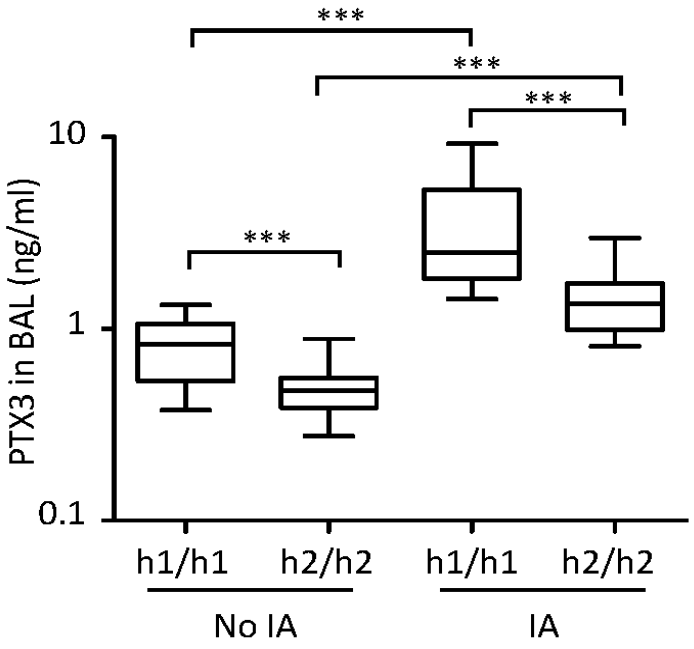
rs2305619
rs3816527 (D48A)
rs1840680

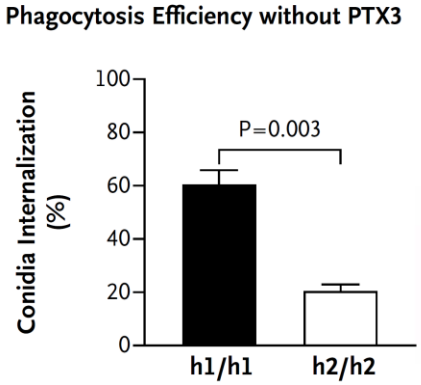
- A-C-A/A-C-A (h1/h1)
- G-A-G/G-A-G (h2/h2)
- A-C-A/G-A-G (h1/h2)

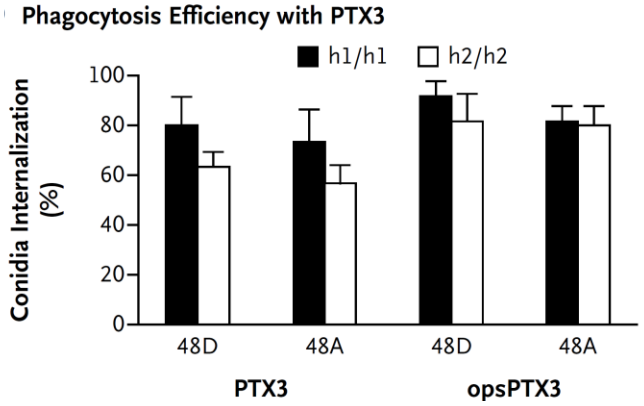


Cunha C et al. N Engl J Med. 2014

Functional impact of PTX3 SNPs

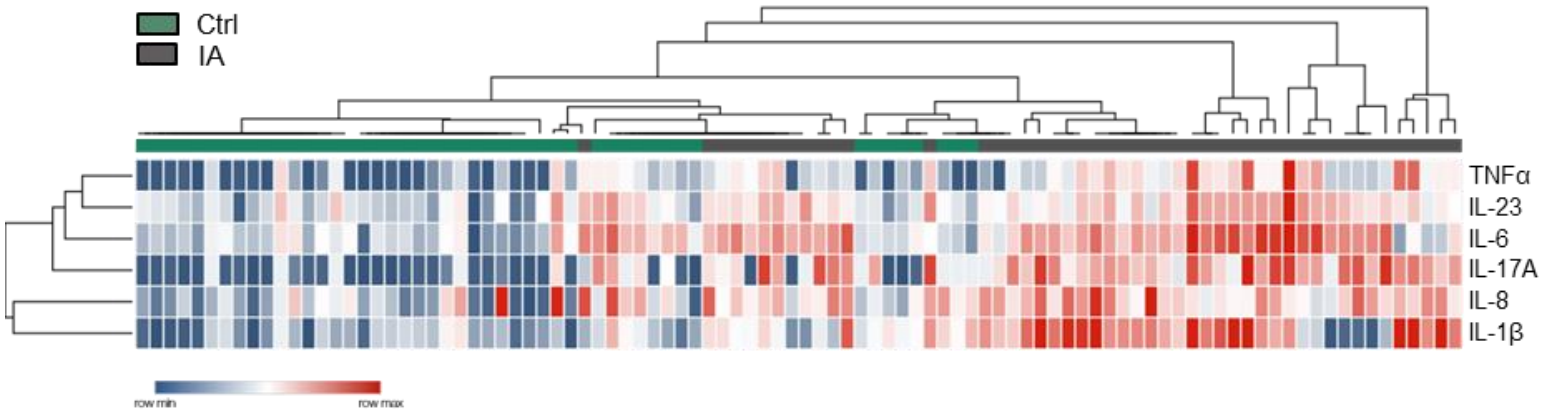




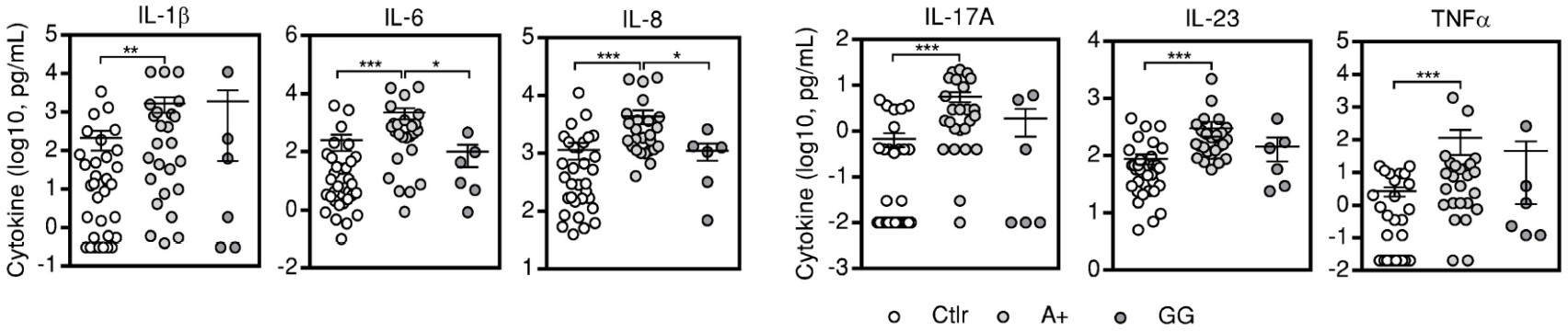


Cunha C et al. N Engl J Med. 2014

Functional impact of PTX3 SNPs



***PTX3* rs2305619**



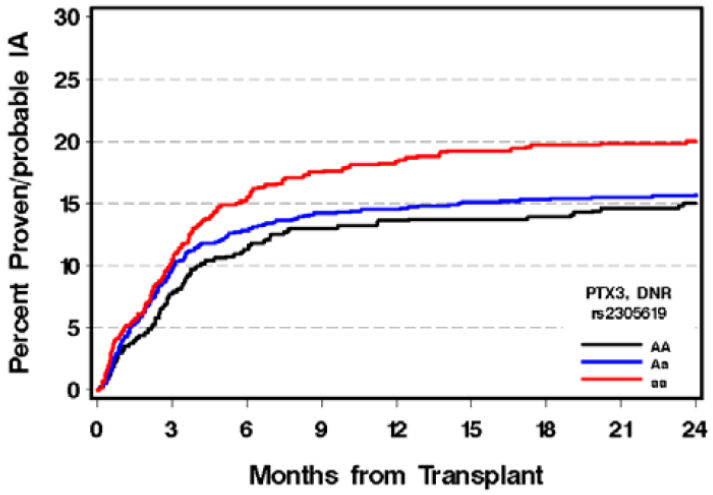
Gonçalves SM et al. Front Microbiol. 2017

Validation of SNPs in IA after HSCT

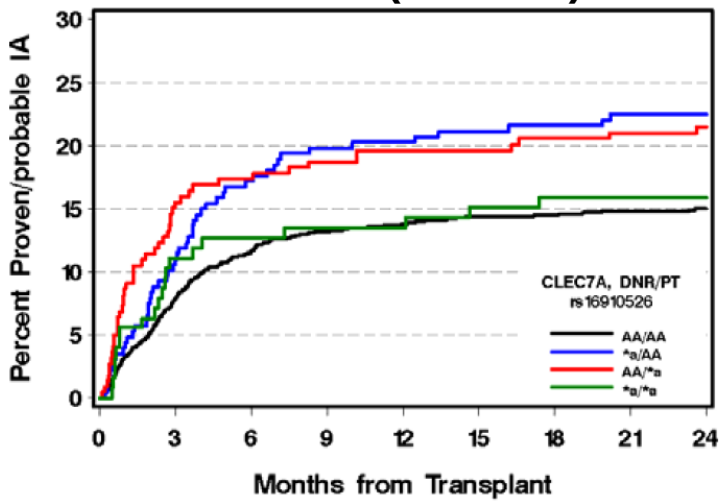
2,609 donor-recipient pairs; 483 patients with proven/probable IA
20 SNPs in 14 genes

Gene	SNP	Genome	Alleles	Model	HR	P value
PTX3	rs2305619	Donor	A/G	Recessive	1.33	0.005
CLEC7A (Dectin-1)	rs16910526 (Y238X)	Donor + Recipient	G/T	Dominant	1.49	0.009

PTX3



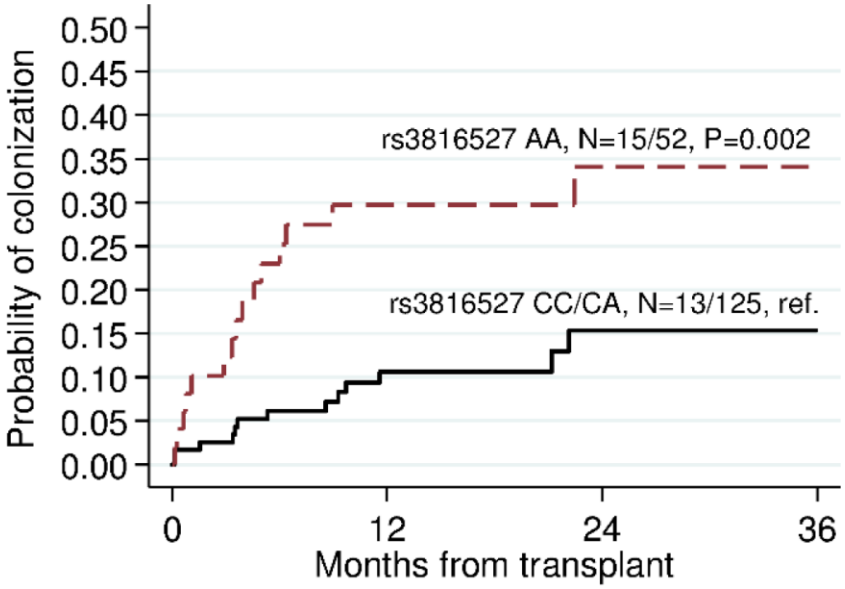
CLEC7A (Dectin-1)

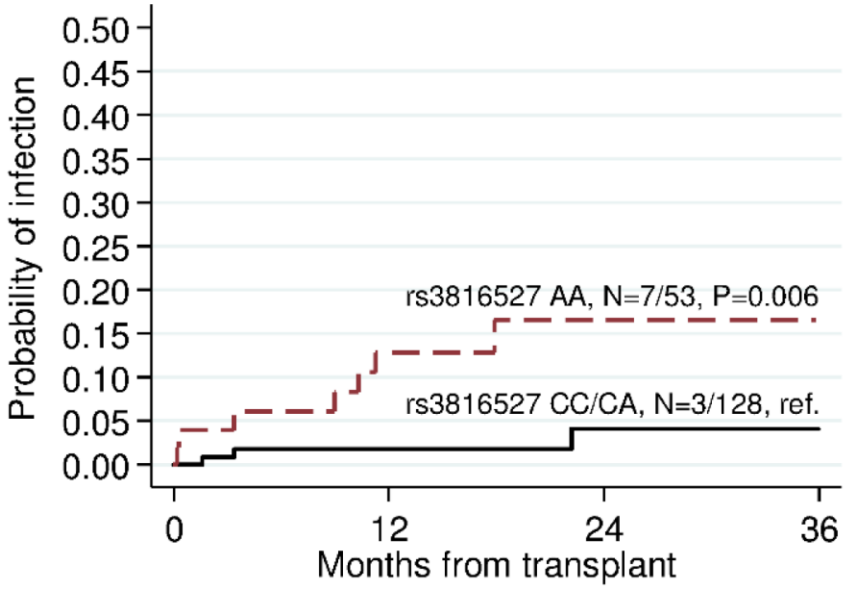


Fisher CE et al. Blood. 2017

PTX3 and mold infection in SOT

Swiss Transplant Cohort Study
1,101 SOT recipients (45 patients with mold colonization and 26 patients with IMI)



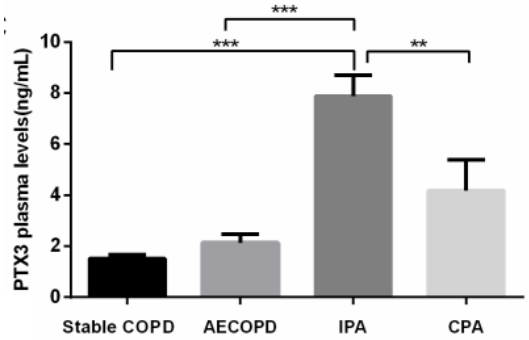


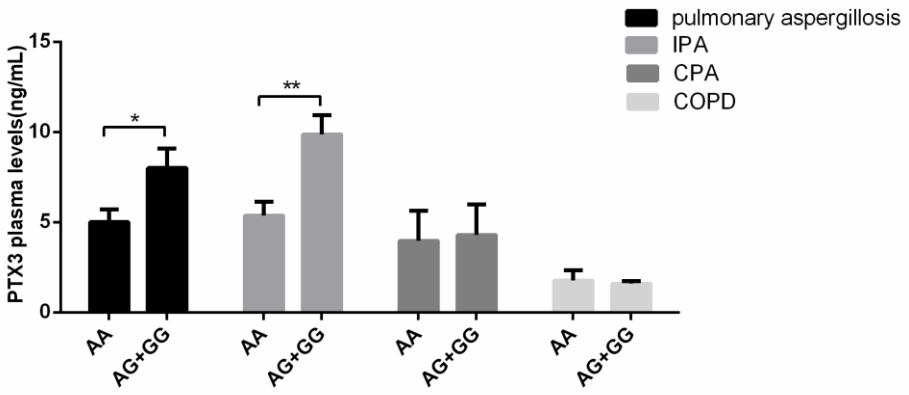
Wójtowicz A et al. Clin Infect Dis. 2015

PTX3 SNPs and IPA in COPD patients

COPD study (173 consecutive patients)

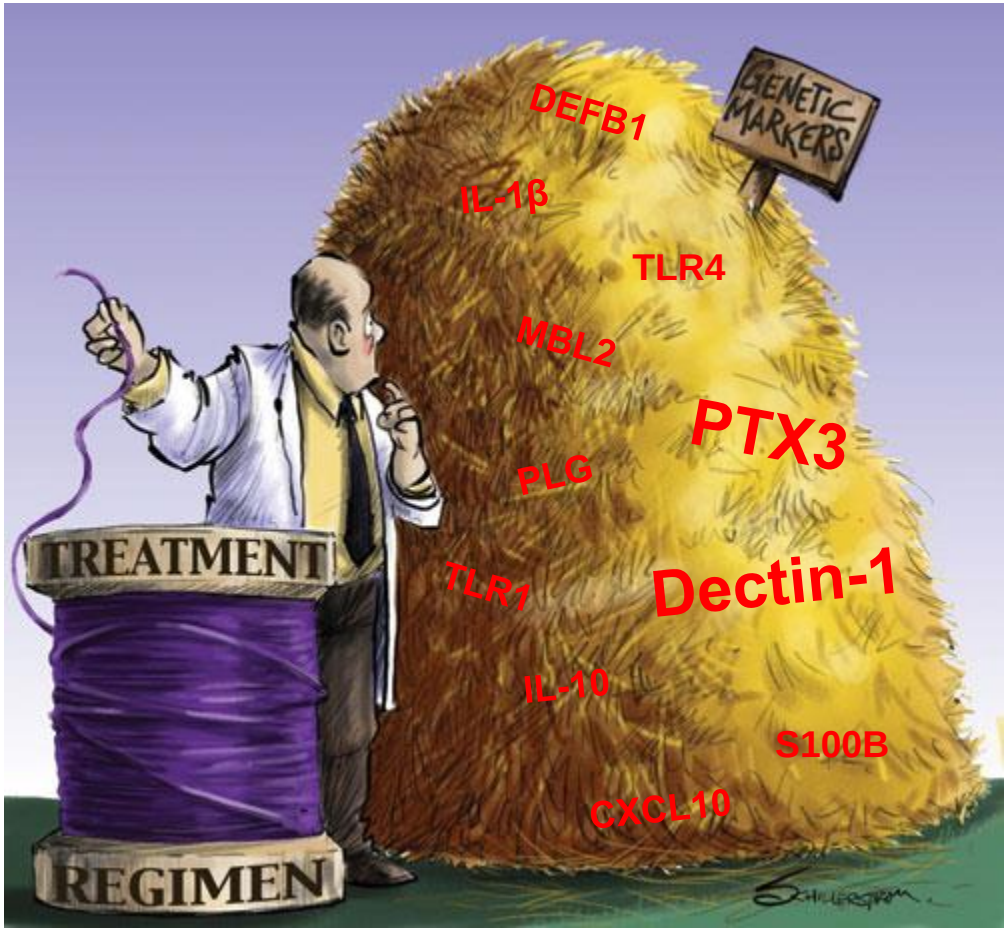
SNPs	Genotype	Pulmonary aspergillosis, n (%)		COPD (n=137)	OR	P value	OR	P value
		IPA (n=25)	CPA (n=11)					
rs1840680	GG+GA	14 (56)	7 (64)	121 (88)	Ref.			Ref.
	AA	11 (44)	4 (36)	16 (12)	5.94	0.0003	4.32	0.04



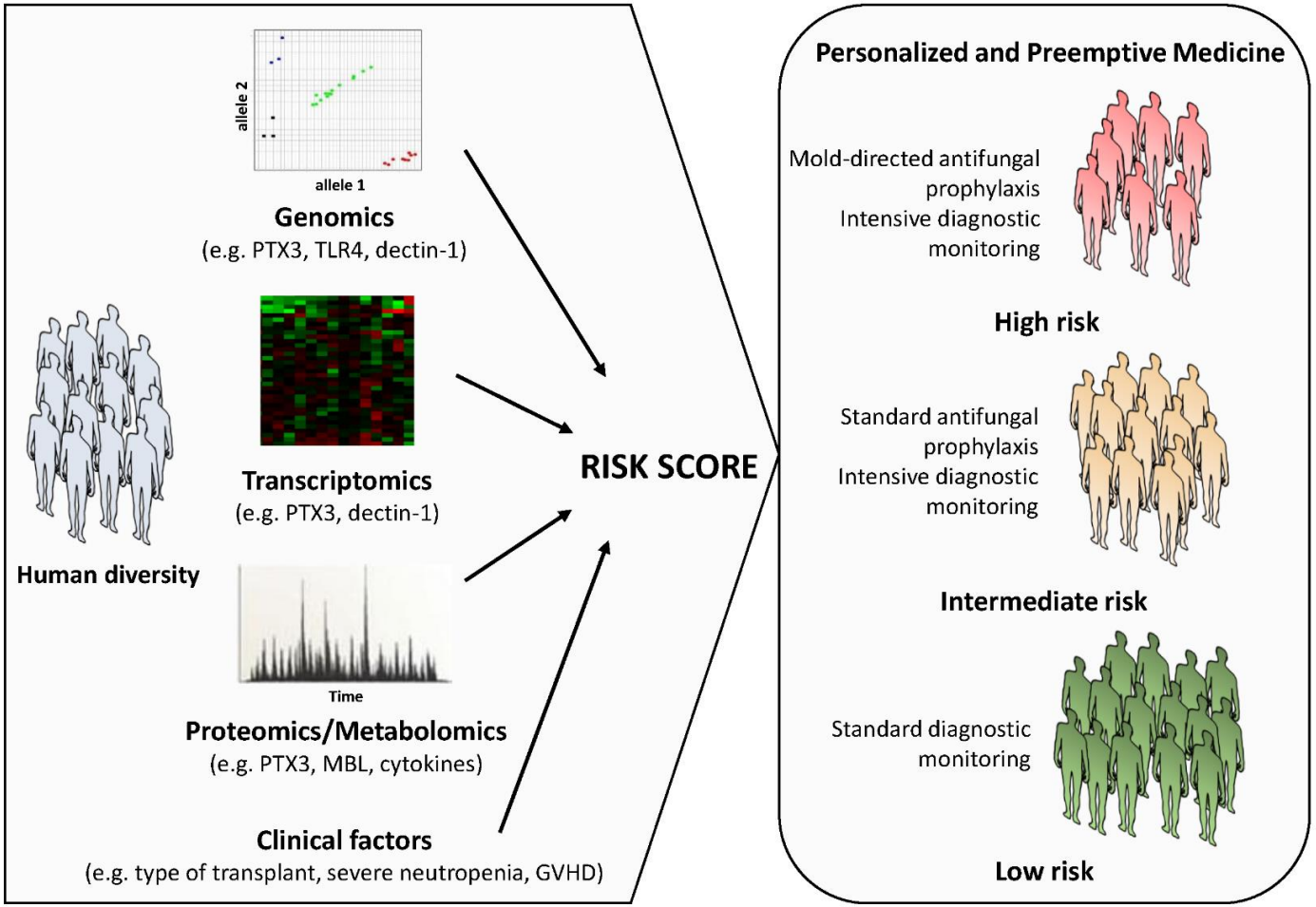


He Q et al. Clin Infect Dis. 2018

Which markers to use in clinics?



Antifungal theragnostics



Oliveira-Coelho A et al. Front Microbiol. 2015

Lab retreat, Frankfurt am Main (December 2017)

Cláudia Campos | Cláudio Oliveira | Cláudia Rodrigues | Samuel Gonçalves | Cristina Cunha

IFIGEN Working Party, Portugal
João F .Lacerda
António Campos Jr.
António Marques

UZ Leuven, Belgium
Toine Mercier
Katrien Lagrou
Johan Maertens

ICVS @ UMINHO
Fernando Rodrigues, Gil Castro, Ricardo Silvestre, Egídio Torrado

INSTITUT MERIEUX
ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
CRUP CONSELHO DE REITORES DAS UNIVERSIDADES PORTUGUESAS
2CABraga Centro Clínico Académico
FCT Fundação para a Ciência e a Tecnologia MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR
IF INVESTIGADOR FCT
POPH PROGRAMA OPERACIONAL POTENCIAL HUMANO
NORTE2020 PROGRAMA OPERACIONAL REGIONAL DO NORTE
PORTUGAL 2020
UNIÃO EUROPEIA Fundo Europeu de Desenvolvimento Regional