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Cytokine auto-antibodies: from regulation to disease

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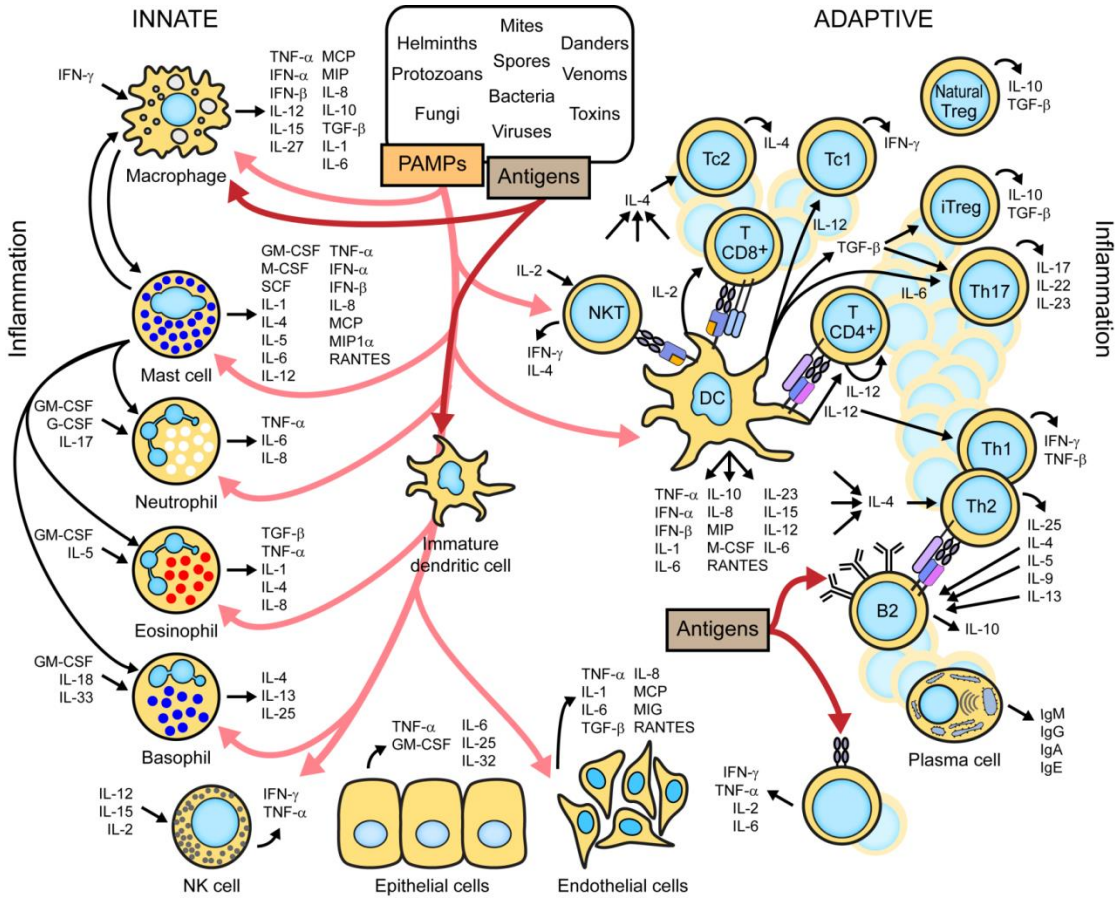
IPOPI 4 th Regional Asian PID Doctors and Patients' Meeting
Intercontinental Kuala Lumpur

The immune system and cytokines



Cytokines

Proteins that transmit signals between cells of the immune system but also between immune system and non-immune cells; the language of the immune system

Important in shaping host's immune response against pathogens

Mutations in a cytokine itself, its receptor or downstream (intracellular) signaling molecule may interrupt its biological function with subsequent impaired immune response that can cause susceptibility to infection and/or immune dysregulation

Anticytokine autoantibodies transiently increase after infection

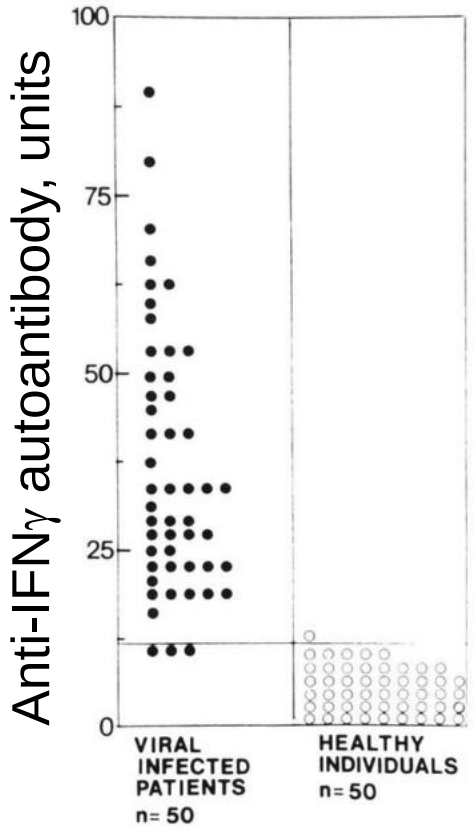


Figure 3. Reactivity of sera collected from healthy individuals and viral infected patients with a rIFN-γ protein preparation. Patients with viral diseases were suffering from: Herpes infections (n = 5), infectious mononucleosis (n = 7), CMV infections (n = 6), varicella (n = 6), measles (n = 5), mumps (n = 4), rubella (n = 3), adenovirus infections (n = 4), and AIDS (n = 10). The upper limit taken as a normal value (expressed as arbitrary AU) is calculated on the mean figure obtained for 180 healthy individuals plus twice the SD (*solid lane*). Data are the average of three independent experiments and three to five replicates per assay.

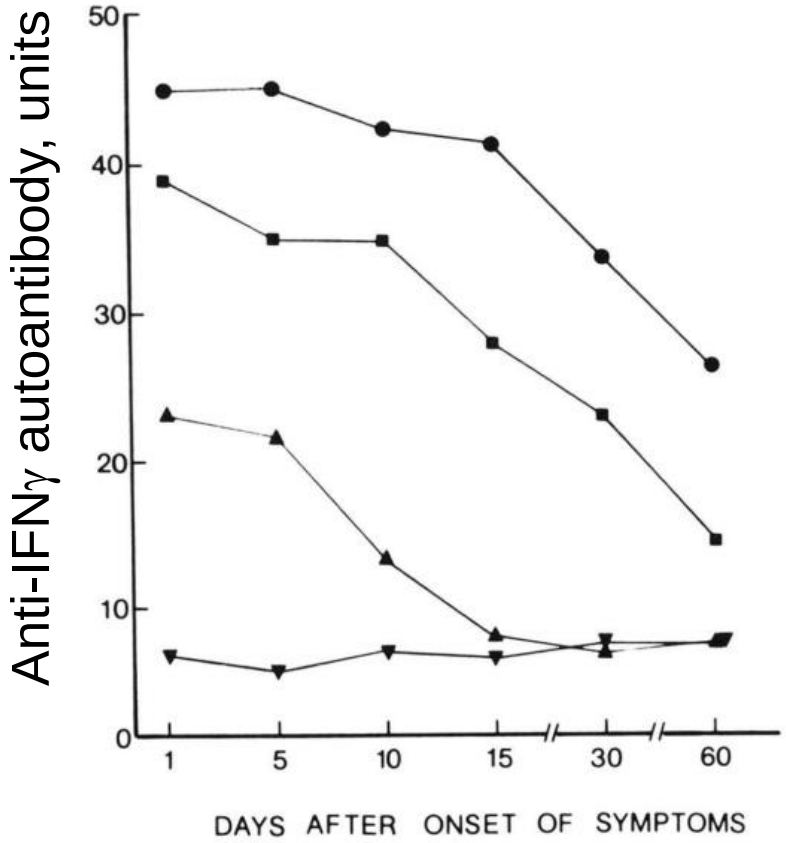


Figure 4. Variations in the titer of anti-IFN-γ antibodies during a viral infection. The titer of antibodies to IFN-γ was determined by a solid-phase RIA on sera taken on days 1, 5, 10, 15, 30, and 60 from the onset of symptoms from three patients suffering from infectious mononucleosis (●), varicella (■), and measles (▲). The titer of antibodies to IFN-γ was also determined, at the same intervals of time, in serum collected from a healthy individual (▼).

ACAA
may represent a normal manifestation of the immunoregulatory process, serving to limit the intensity and/or duration of immune response

What if ACAA are produced excessively/uncontrolled?
impairment of the immune response?

These anti-IFNγ autoantibodies exhibit immunoregulatory properties

Caruso A et al, J Immunol 1990;144:685-690, Turano A et al, Proc Natl Acad Sci 1992;89:4447-4451

Anti-cytokine auto-antibodies (ACAA): association with increased susceptibility to infection

Persitent and high concentration/titer

Functionally neutralizing: blocking cytokine function

Directed against a single cytokine or multiple cytokines

Clinical phenotype similar as the related inborn genetic disorders that impair specific pathways

Autoimmune phenocopies of primary immunodeficiencies/“inborn errors of immunity”

Genetic defects impairing IFN-γ production or impairing the response to IFN-γ (IL-12/IFN-γ pathway:mendelian susceptibility to mycobacterial disease (MSMD)

1. Mendelian Susceptibility to mycobacterial disease (MSMD)						
Disease	**Genetic defect**	**Inheritance**	**OMIM**	**Affected cells**	**Affected function**	**Associated features**
IL-12 and IL-23 receptor β1 chain deficiency	*IL12RB1*	AR	601604	L + NK	IFN-γ secretion	Susceptibility to mycobacteria and *Salmonella*
IL-12p40 (IL-12 and IL-23) deficiency	*IL12B*	AR	161561	M		
IL-12Rβ2 deficiency	*IL12RB2*	AR	601642	L + NK		
IL-23R deficiency	*IL23R*	AR	607562	L +NK		
IFN-γ receptor 1 deficiency	*IFNGR1*	AR	209950	M + L	IFN-γ binding and signaling	
		AD	615978	M + L		
IFN-γ receptor 2 deficiency	*IFNGR2*	AR	147569	M + L	IFN-γ signaling	
STAT1 deficiency	*STAT1*	AD LOF	614892	M + L		
Macrophage gp91 phox deficiency	*CYBB*	XL	300645	Macrophage only	Killing (faulty O_2^- production)	Isolated susceptibility to mycobacteria
IRF8 deficiency	*IRF8*	AD	614893	M + L	Impaired development of cDCs and Th1* cells	Susceptibility to mycobacteria
		AR	226990	M	Lack of circulating monocytes and DCs, reduced NK cell numbers and function reported in some patients	Susceptibility to mycobacteria and multiple other infectious agents including EBV
SPPL2a deficiency	*SPPL2A*	AR	608238	M + L	Impaired development of cDCs and Th1* cells	Susceptibility to mycobacteria and *Salmonella*
Tyk2 deficiency	*TYK2*	AR	611521	M + L	Impaired cellular responses to IL-10, IL-12, IL-23, and type I IFNs	Susceptibility to intracellular bacteria (mycobacteria, Salmonella), and viruses
P1104A TYK2 homozygosity	*TYK2*	AR	176941	L	Impaired cellular responses to IL-23	MSMD or tuberculosis
ISG15 deficiency	*ISG15*	AR	147571		IFNγ production defect	Susceptibility to mycobacteria (BCG), brain calcification
RORγt deficiency	*RORC*	AR	602943	L + NK	Lack of functional RORγT protein, IFNγ production defect, complete absence of IL-17A/F-producing T cells	Susceptibility to mycobacteria and candida
JAK1 deficiency	*JAK1*	AR LOF	147795	N + L	Reduced JAK1 activation to cytokines, Reduced IFNγ production	Susceptibility to mycobacteria and viruses, urothelial carcinoma
T-bet deficiency (1 patient)	***TBX21***	**AR**	**619630**	**L**	**↓ IFN-γ and TNF-α production by γδ T cells, MAIT cells, iNKT cells, NK cells, and CD4+ T cells**	**Susceptibility to mycobacteria**
IFNγ deficiency (2 patients)	***IFNG***	**AR**	**618963**	**L**	**No IFN-γ production by patient T and NK cells**	**Susceptibility to mycobacteria**

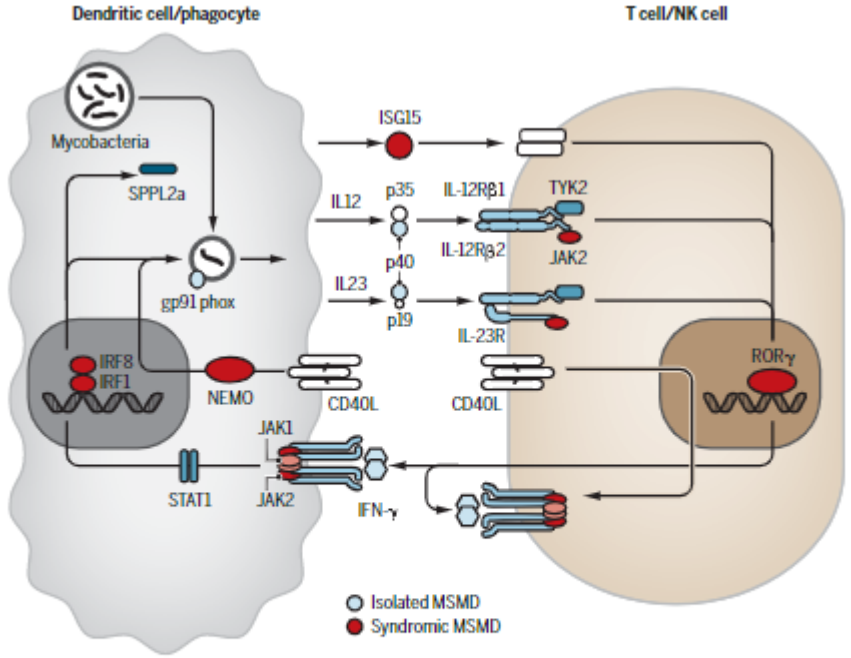


Fig. 3. Genetic etiologies of MSMD. Interactions between cells involved in the production of (T cells/NK cells) and in the response to IFN-γ (dendritic cells and phagocytes). Proteins whose mutations in the corresponding gene cause isolated MSMD are depicted in blue, whereas those responsible for syndromic MSMD are depicted in red.

Notarangelo LD et al, Sci Immunol 2020;5:eabb 1622

Tangye SG et al, J Clin Immunolol 2022; doi: 10.1007/s10875-022-01289-3:PMID: 35748970

Infectious agents in mendelian susceptibility to mycobacterial disease (MSMD)

Bacteria
Nontuberculous mycobacteria (NTM)
BCG
Mycobacterium tuberculosis (Mtb; occasionally)
Non-typhoidal *Salmonella*
Burkholderia
Listeria

Fungi
Histoplasma
Blastomyces
Coccidiodes

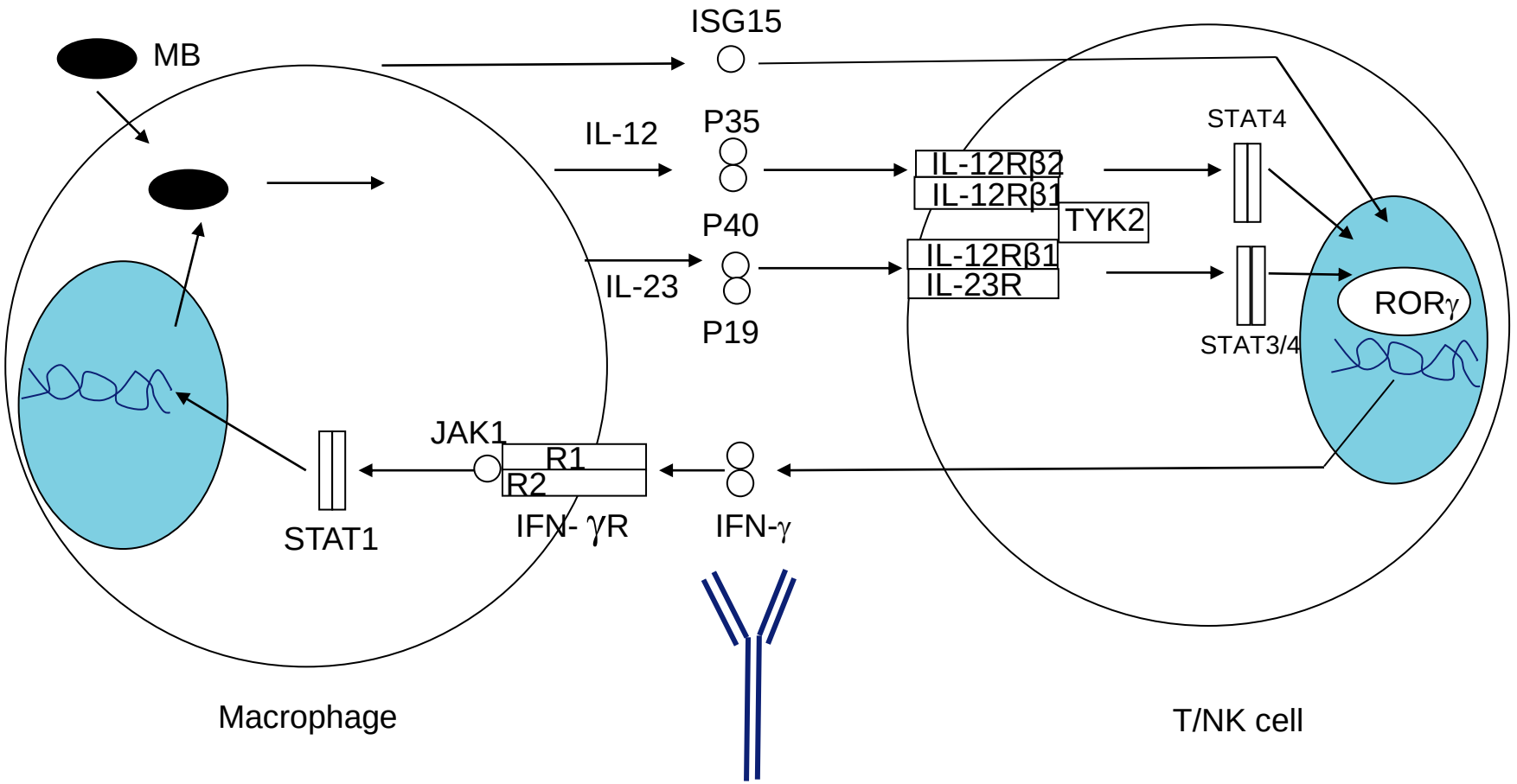
Parasites
Leishmania

Viruses
HSV
VSV
CMV
EBV

MSMD usually develops in childhood

Freeman AF and Holland SM, www.uptodate.com 2022; Mendelian susceptibility to mycobacterial diseases: An overview

Neutralizing anti-interferon-γ autoantibodies (nAIGA): auto-immune phenocopy of MSMD



High titer neutralizing anti-IFNγ auto-antibodies (nAIGA): AOI

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adult-Onset Immunodeficiency in Thailand and Taiwan

Group 1: disseminated nontuberculous mycobacterial (NTM) infection
Group 2: other opportunistic infections with (n=41) or without (n=4) nontuberculous mycobacterial infection
Group 3: disseminated tuberculososis (*Mtb*)
Group 4: pulmonary tuberculosis (*Mtb*)
Group 5: healthy controls

Table 1. Clinical Characteristics of the 203 Participants.*

Characteristic	Group 1 (N=52)	Group 2 (N=45)	Group 3 (N=9)	Group 4 (N=49)	Group 5 (N=48)	P Value†
Age — yr						<0.001
Median	50	49	38	43	38	
Range	18–78	22–69	21–74	18–77	21–62	
Male sex — no. (%)	21 (40)	17 (38)	3 (33)	28 (57)	22 (46)	0.32
Anti–interferon-γ autoantibody–positive — no. (%)	42 (81)	43 (96)	1 (11)	1 (2)	1 (2)	<0.001
Associated conditions — no.						
Lymphatic obstruction	3	9	0	0	—	0.002
Pain or neuropathy	4	3	0	2	—	0.86
Hypercalcemia	4	3	1	1	—	0.37
Erythema nodosum	3	3	0	1	—	0.76
Exanthematous pustulosis	5	1	0	0	—	0.09
Pustular psoriasis	0	2	0	0	—	0.20
Neutrophilic dermatosis	21	19	0	0	—	<0.001

* Patients in group 1 had disseminated, rapidly growing or slowly growing, nontuberculous mycobacterial infection. Patients in group 2 had other opportunistic infections (e.g., *Cryptococcus neoformans, Histoplasma capsulatum, Penicillium marneffei,* disseminated salmonellosis, or severe varicella–zoster virus infection) with or without nontuberculous mycobacterial infection. Patients in group 3 had disseminated tuberculosis. Patients in group 4 had pulmonary tuberculosis. Group 5 was composed of healthy controls.
† P values were determined with the use of Fisher's exact test for categorical variables and analysis of variance (F-test) for continuous variables.

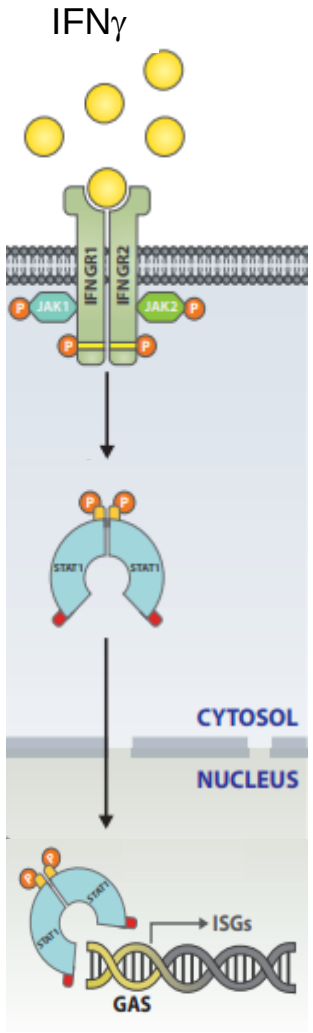
Table 2. Isolated Organisms in 97 Patients with Opportunistic Infections.

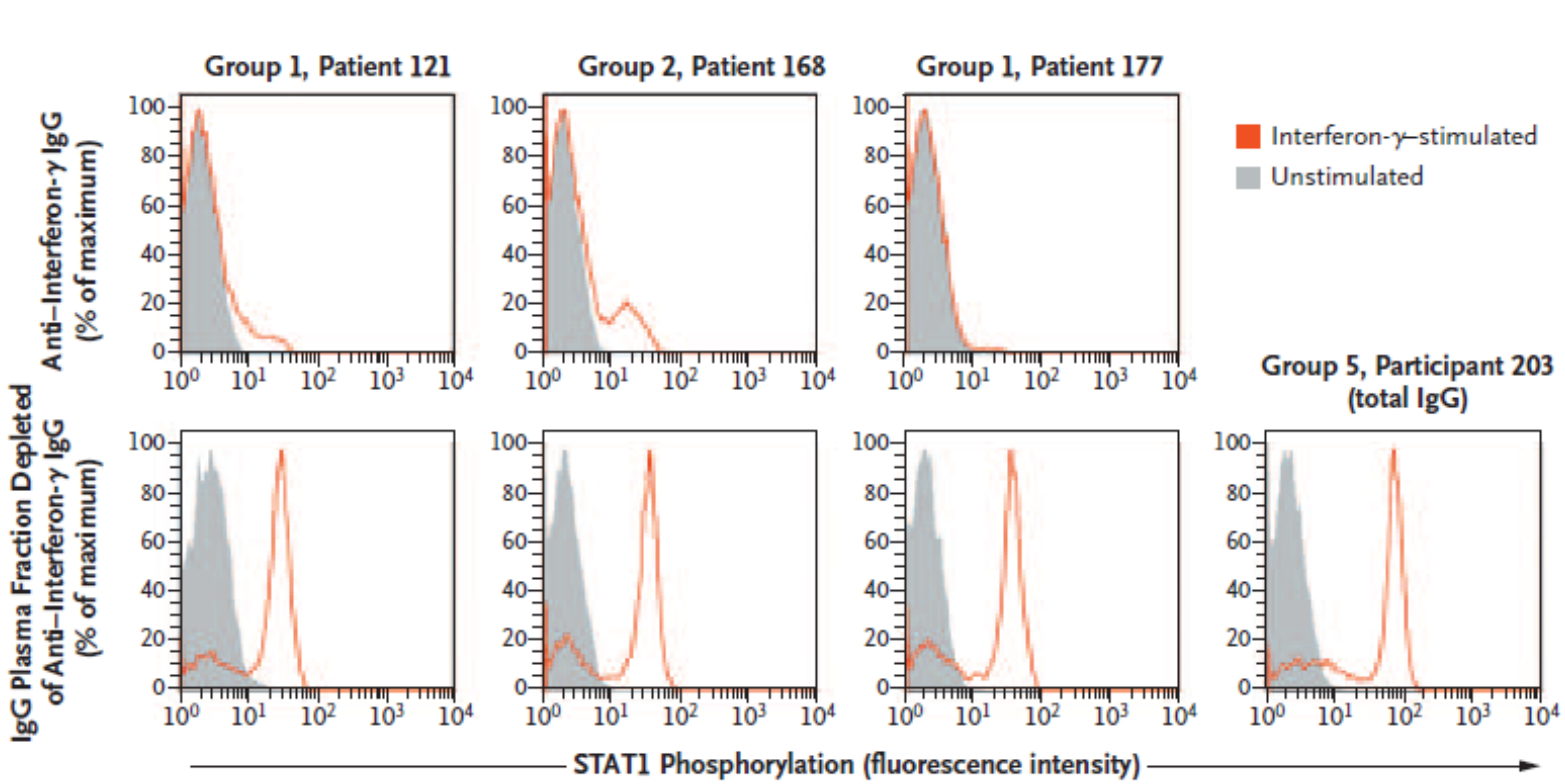
Variable	Group 1 (N=52)	Group 2 (N=45)
Organisms isolated (no./patient)		
Median	1	2
Range	1–4	1–5
Mycobacteria (no. of patients)		
Rapidly growing	36	39
Slowly growing	15	8
Nontuberculous mycobacteria, not specified	5	2
Mycobacterium tuberculosis	4*	10†
Total	60	59
Bacteria (no. of patients)		
Salmonella species		25
Burkholderia pseudomallei		4
Other		9
Fungi (no. of patients)		
Cryptococcus neoformans		10
Histoplasma capsulatum		7
Penicillium marneffei		7
Varicella–zoster virus (no. of patients)		
Disseminated		3
Local	5	10
Parasites (no. of patients)		
Strongyloides stercoralis		1

* Two patients had pulmonary tuberculosis, and two had disseminated tuberculosis.
† Three patients had pulmonary tuberculosis, and seven had disseminated tuberculosis.

Browne SK et al, N Engl J Med 2012;367:725-734

Neutralizing anti-IFNγ autoantibodies (nAIGA) inhibit IFN-γ induced STAT1 phosphorvlation



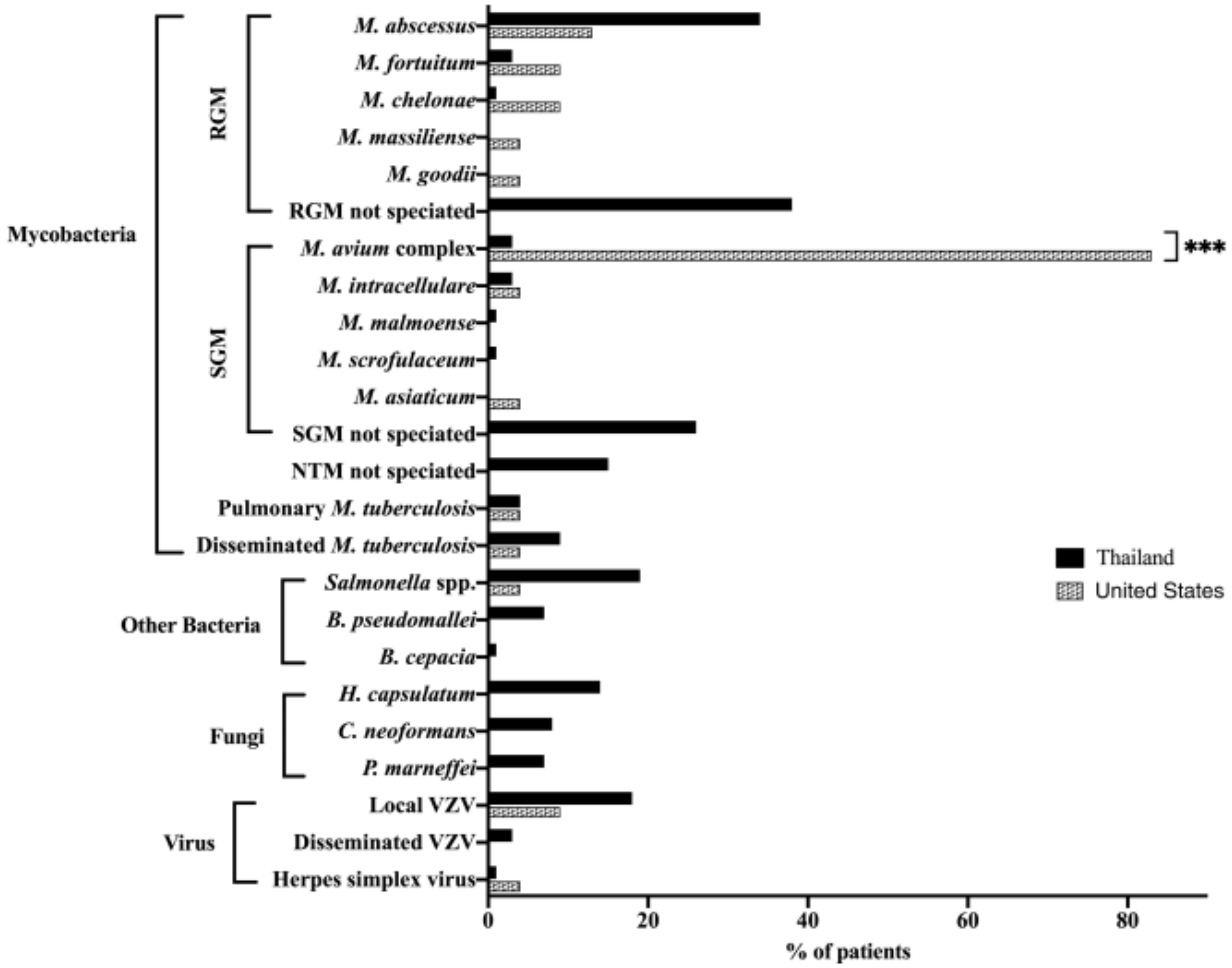


Kornvalee Meesilpavikkai, Erasmus MC Thesis 2019:
The State of STATs in primary immunodeficiencies

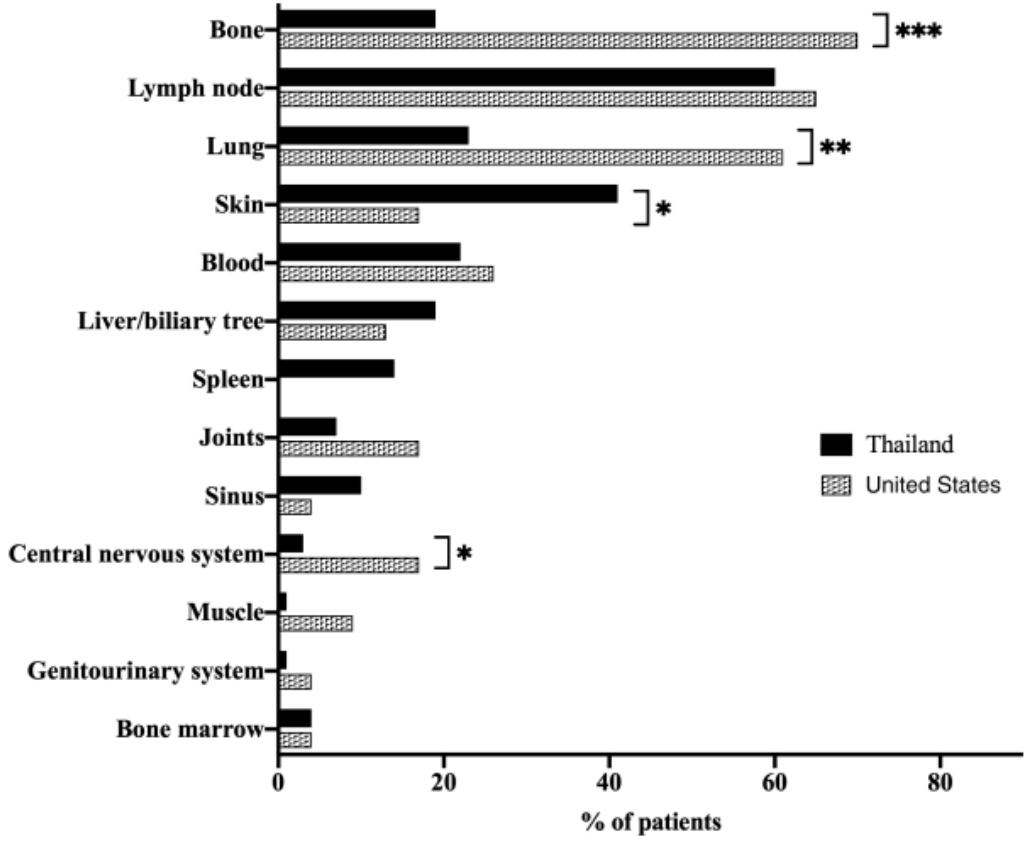
Browne SK et al, N Engl J Med 2012;367:725-734

Infections associated with high titer neutralizing anti-IFN-γ autoantibodies

Isolated organisms at presentation



Sites of infections at presentation



Hong GH et al, Clin Infect Dis 2020;71:53-62

High titer neutralizing anti-IFNγ auto-antibodies (nAIGA)

Adult-onset immunodeficiency (AOI)/Anti-IFN- γ autoantibody associated immunodeficieny syndrome)

Increased susceptibility to: non-tuberculous mycobacteria (NTM)
to lesser extent also tuberculosis (*Mycobacterium tuberculosis*)
other intracellular bacteria, viruses, fungi
(*Salmonella, Burkholderia, Cryptococcus, Talaromyces, Coccidioides, Histoplasma, VZV, HSV)*

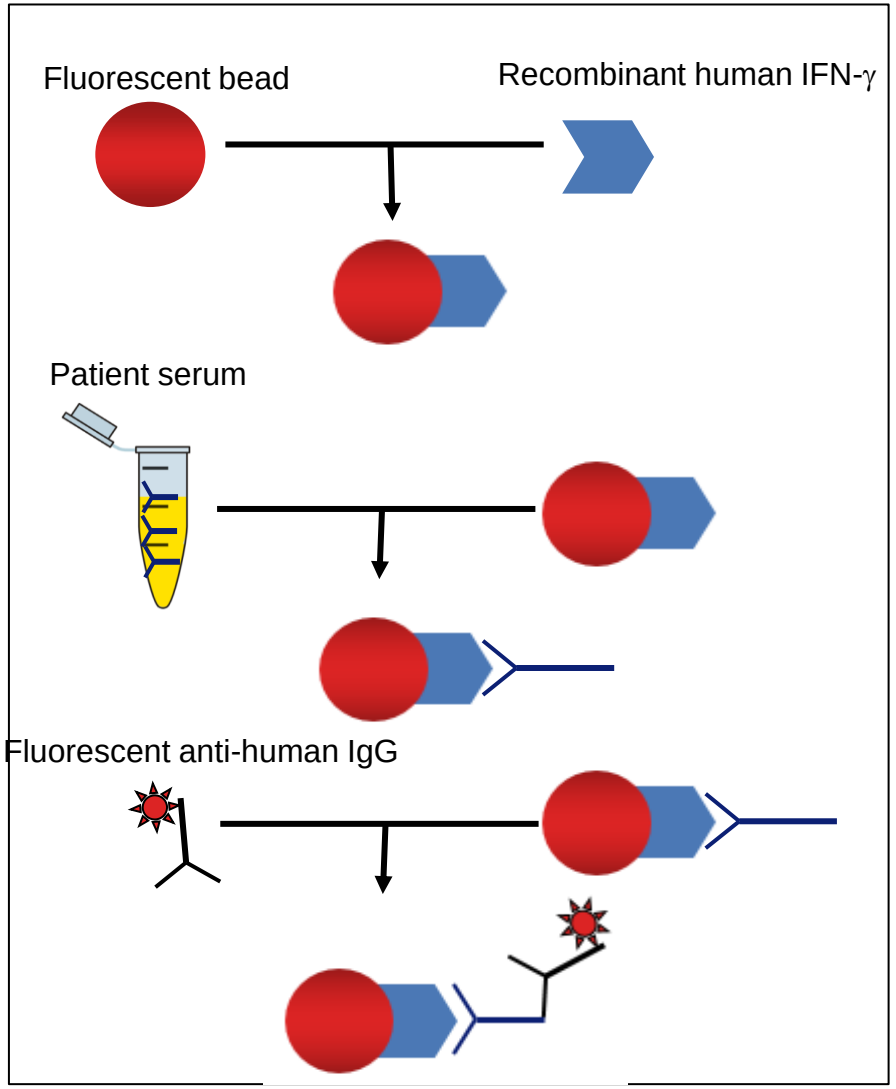
Adults Southeast-Asian descent (Thai, Taiwanese, Filipino, Laotian, Japanese..)

Only a few younger Asian patients (n = 2; 10 and 16 years)

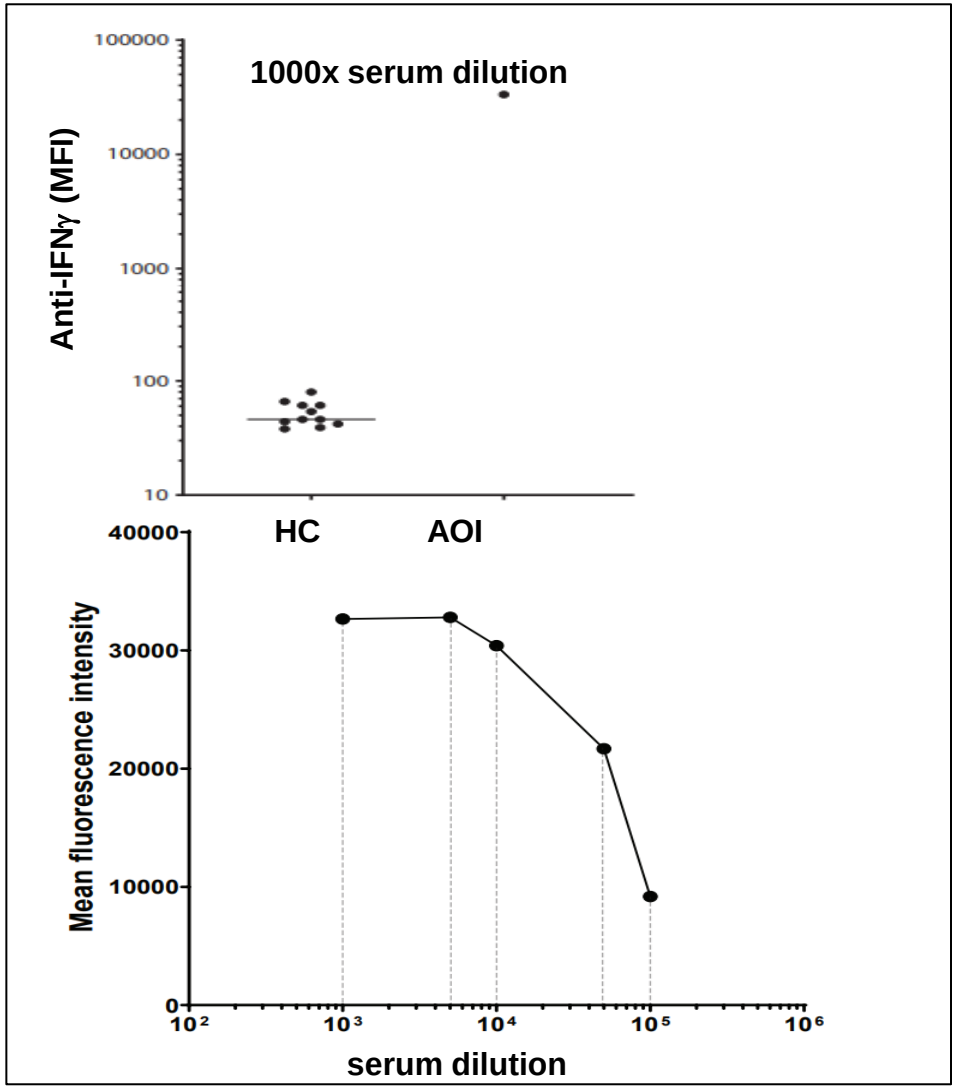
Only a few adult patients of non-Southeast Asian descent

nAIGA: an example from our Laboratory Medical Immunology in Rotterdam

In house bead-based assay to detect anti-IFNγ auto-Ab

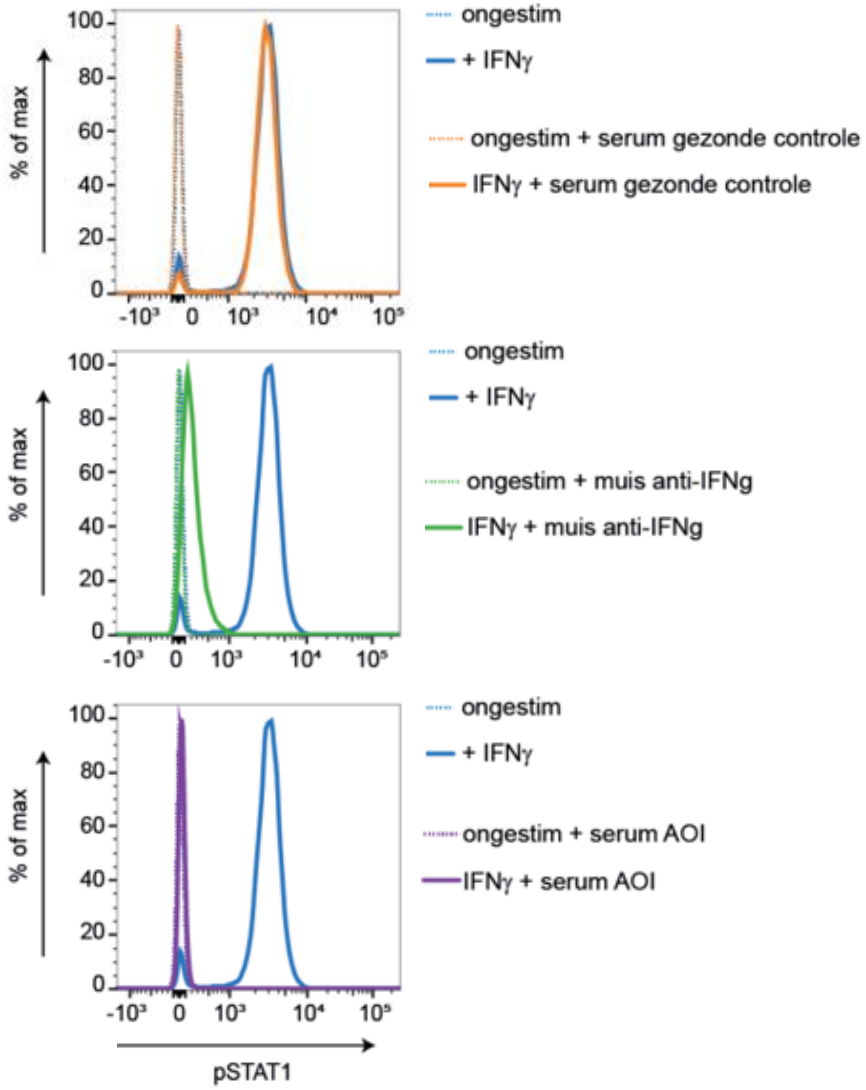


Detection of high titer auto-Ab that bind IFNγ

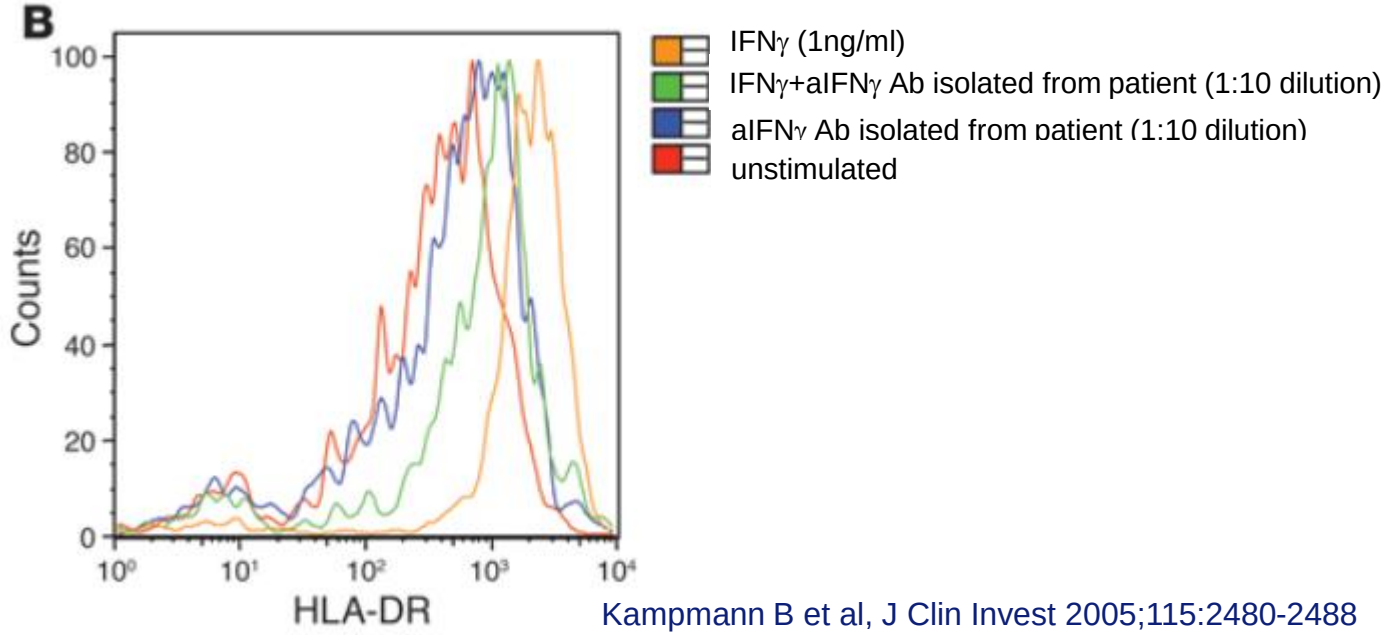


nAIGA: functional testing-blockade of IFNγ activity

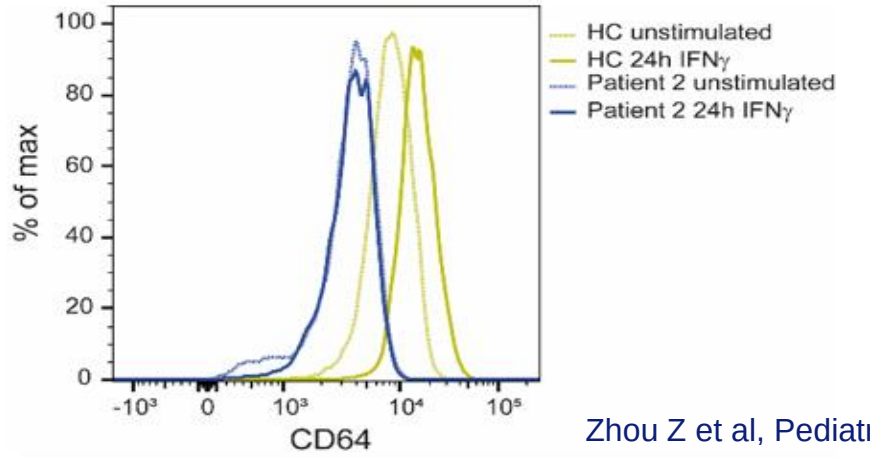
Functionallity of anti-IFNγ Ab



Flowcytometry-based alternatives for pSTAT1 induction



Kampmann B et al, J Clin Invest 2005;115:2480-2488



Zhou Z et al, Pediatr Allergy Immunol;33:e13768

Genetics: association between HLA-DR*15:02/16:02 and HLA-DQ*05:01/05:02 and nAIGA in Southeast Asia

TABLE I. The association of HLA-DRB1 and -DQB1 alleles with anti–IFN-γ autoantibodies in Thailand and Taiwan

	Control		Patient							
Allele type	**Count***	**%†**	**Count***	**%†**	χ^2	P_{χ}^2	**Fisher exact *P* value**	**OR (95% CI)**	$P_{logistic}$	P_{FDR}
Thailand	N = 101		N = 78							
DRB1*15:02	25	12.38	67	42.95	43.0875	5.23×10^{-11}	8.26×10^{-11}	5.33 (3.15-9.01)	4.26×10^{-10}	1.02×10^{-8}
DRB1*16:02	20	9.90	46	29.49	22.4560	2.15×10^{-6}	3.81×10^{-6}	3.80 (2.14-6.77)	5.41×10^{-6}	.0001
DQB1*05:01	21	10.40	51	32.69	27.2348	1.80×10^{-7}	2.57×10^{-7}	4.19 (2.39-7.34)	6.00×10^{-7}	9.61×10^{-6}
DQB1*05:02	44	21.78	65	41.67	16.4347	.0001	.0001	2.56 (1.62-4.07)	.0001	.0005
Taiwan	N = 102		N = 44							
DRB1*15:02	2	0.98	11	12.50	19.1789	1.19×10^{-5}	.0001	14.42 (3.13-66.53)	.0006	.0084
DRB1*16:02	17	8.33	38	43.18	48.8374	2.78×10^{-12}	2.53×10^{-11}	8.36 (4.36-16.04)	1.68×10^{-10}	4.53×10^{-9}
DQB1*05:01	7	3.43	10	11.36	7.0552	.0079	.0127	3.61 (1.33-9.82)	.0120	.1008
DQB1*05:02	25	12.25	42	47.73	43.7541	3.72×10^{-11}	2.21×10^{-10}	6.54 (3.62-11.81)	4.99×10^{-10}	1.05×10^{-8}

*Number of alleles observed.
†Allele frequencies found in cohort.

Ku CL et al, J Allergy Clin Immunol 2016;137:945-948

Chi CY et al, Blood 2013;121:1357-1366

Yet, only part of carriers of these risk alleles develop nAIGA

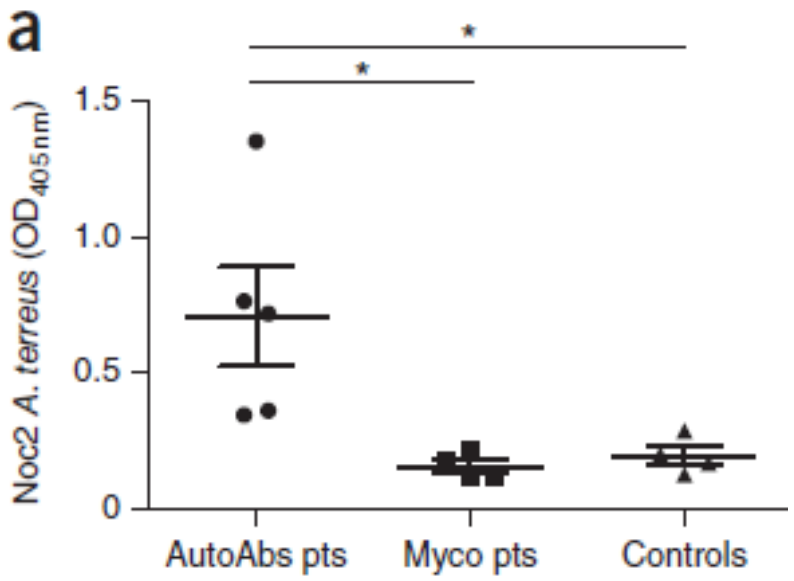
Other factors involved?

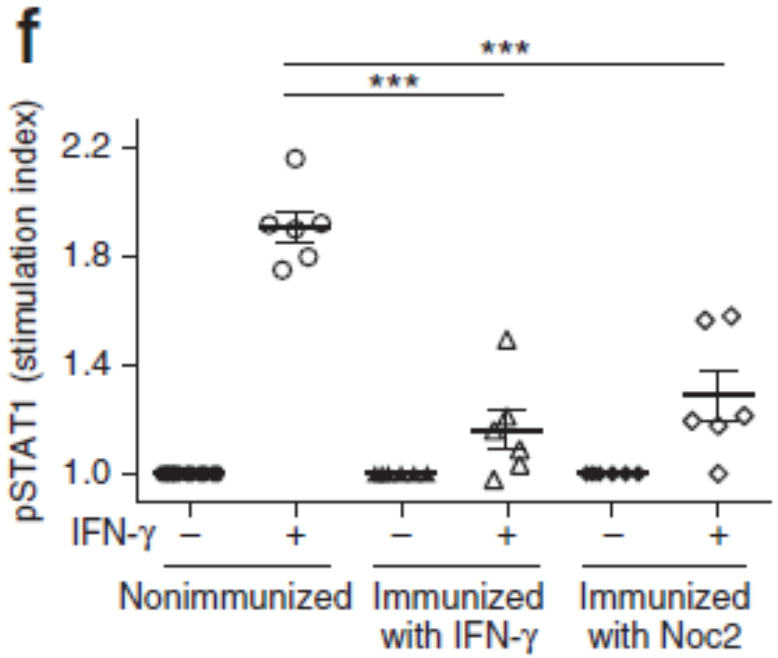
- Genetic
- Environmental (infections-molecular mimicry)

Neutralizing anti-IFNγ auto-autobodies (nAIGA): a role for molecular mimicry?

nAIGA bind the C-terminal part human IFN-γ (aa 121-131: SPAAKTGKRKR) that is required for optimal binding and activation of the IFN-γ receptor

Strong homology between human IFNγ125-133 and *Aspergillus Sp* ribosomal protein Noc2





Lin CH et al, Nat Med 2016;22:994-1001

Treatment of patients with nAIGA

Anti-mycobacterial therapy

Experimental treatment

Increase cytokine function

Exogenous IFN-γ

Döffinger R et al, Clin Infect Dis 2004;38:e10-e14
Kampmann B et al, J Clin Invest 2005;115:2480-2488
Brown SK et al, Blood 2012;119:3933-3939

Reduce antibody production/levels

Cyclophosphamide

Baerlecken N et al, Clin Infect Dis 2009;49:e76-e78
Chetchotisaskd P et al, J Immunol Res 2018;20:6473629
Laisuan W et al, Open Forum Infect Dis 2020;7:ofaa035
Hong GH et al, Clin Infect Dis 2020;71:53-62

Rituximab (anti-CD20)

Brown SK et al, Blood 2012;119:3933-3939
Czaja CA et al, Clin Infect Dis 2014;58:e115-118
Pruetpongpun et al, Open Forum Infect Dis 2016;10:ofw039
Naik R and Cortes JA Ann Allergy Asthma Immunol 2016;116:461-477
Koizumi Y et al, J Clin Immunol 2017;37:644-649
Hong GH et al, Clin Infect Dis 2020;71:53-62
Rocco JM et al, J Translational Autoimmunity 2021;4:100102
Zeitler K et al, BMJ Case Rep 2021;14:e237909

Bortezomib (proteosome inhibitor)

Rocco JM et al, J Translational Autoimmunity 2021;4:100102
Ochoa S et al, Clin Infect Dis 2021;72:2206-2208

Daratumumab (anti CD38)

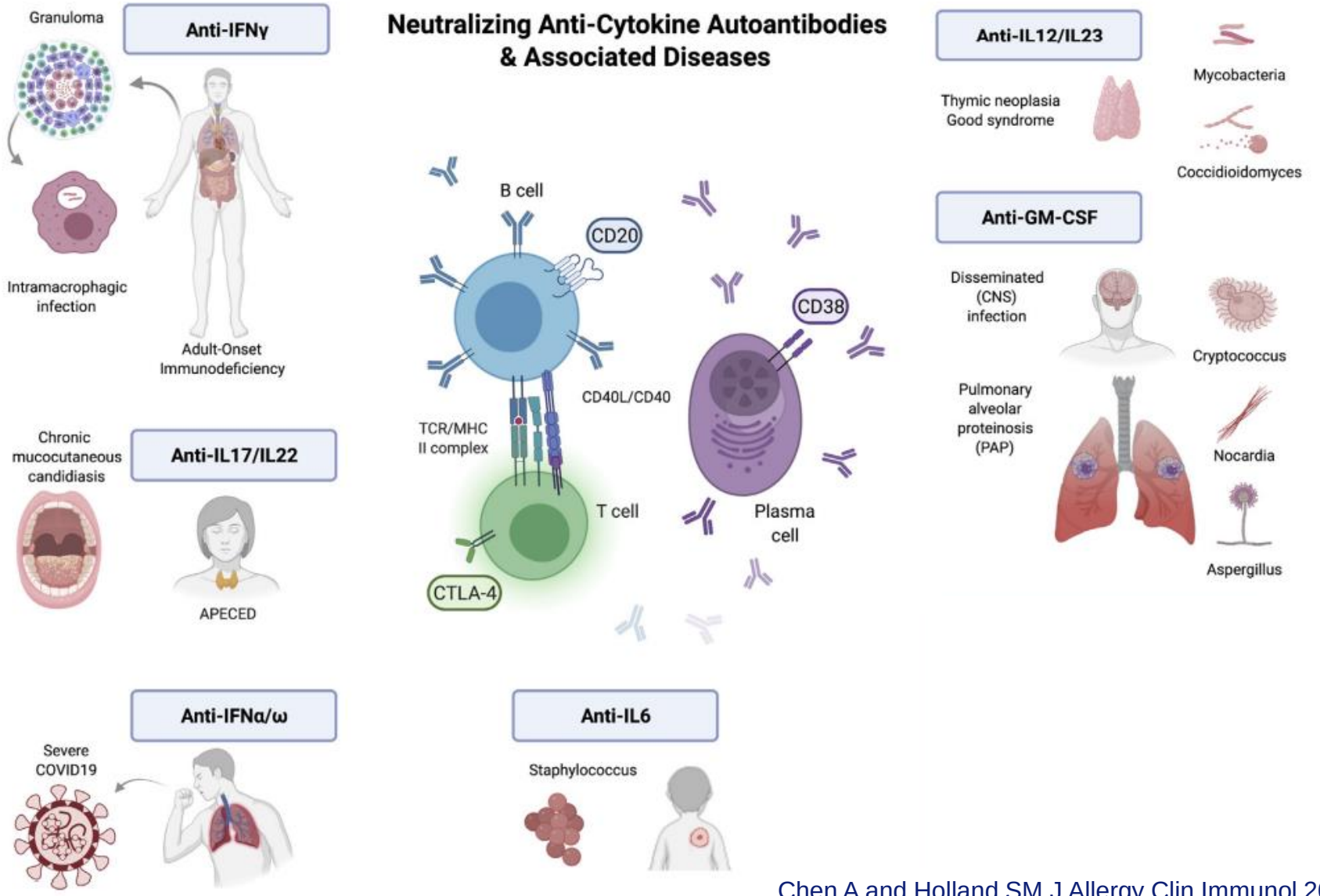
Ochoa S et al, Clin Infect Dis 2021;72:2206-2208

Plasmapheresis

Baerlecken N et al, 2009 Clin Infect Dis 2009;49:e76-e78

Time to infection clearance: years

Other anticytokine auto-antibodies



Chen A and Holland SM J Allergy Clin Immunol 2022;149:24-28

Summary

Low titer ACAA can occur in healthy controls and transiently upon infection: immunoregulatory function

High titer ACAA can cause autoimmune phenocopies of PID/IEI

Trigger of high titer ACAA is unknown

Adult onset severe/recurrent mycobacterial infections: measurement anti-IFNγ autoantibodies is indicated

(HIV-negative)

active infection associated with higher a-IFNγ-aAb

monitoring a-IFNγ-aAb: predict change of infection