



Anticytokine autoantibodies as the underestimated factors beneath infectious diseases

Croucher summer course on translational immunology

2026.07.23

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Institute of Immunology
& Translational Medicine



TRAF6 deficiency results in osteopetrosis and defective interleukin-1, CD40, and LPS signaling

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Severe impairment of interleukin-1 and Toll-like receptor signalling in mice lacking IRAK-4

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Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency

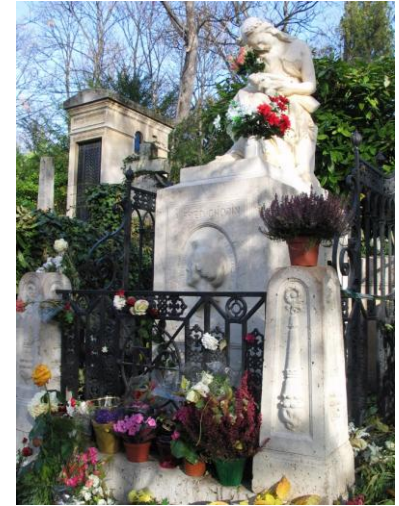
Capucine Picard,¹ Anne Puel,¹ Marion Bonnet,¹ Cheng-Lung Ku,¹ Jacinta Bustamante,¹ Kun Yang,¹ Claire Soudais,¹ Stéphanie Dupuis,¹ Jacqueline Feinberg,¹ Claire Fieschi,¹ Carole Elbim,² Remi Hitchcock,³ David Lammaz,⁴ Graham Davies,⁵ Abdulaziz Al-Ghonaum,⁶ Hassan Al-Rayes,⁶ Sulaiman Al-Jumaah,⁶ Sami Al-Hajjar,⁶ Ibrahim Zaid Al-Mohsen,⁶ Husn H. Frayha,⁶ Rajivi Rucker,³ Thomas R. Hawn,⁷ Alan Aderem,⁷ Haysam Tufenkeji,⁶ Soichi Haraguchi,³ Noorbibi K. Day,³ Robert A. Good,³ Marie-Anne Gougerot-Pocidalo,² Adrian Ozinsky,⁷ Jean-Laurent Casanova^{1,8*}

Members of the Toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) superfamily share an intracytoplasmic Toll–IL-1 receptor (TIR) domain, which mediates recruitment of the interleukin-1 receptor–associated kinase (IRAK) complex via TIR-containing adapter molecules. We describe three unrelated children with inherited IRAK-4 deficiency. Their blood and fibroblast cells did not activate nuclear factor κ B and mitogen-activated protein kinase (MAPK) and failed to induce downstream cytokines in response to any of the known ligands of TIR-bearing receptors. The otherwise healthy children developed infections caused by pyogenic bacteria. These findings suggest that, in humans, the TIR-IRAK signaling pathway is crucial for protective immunity against specific bacteria but is redundant against most other microorganisms.

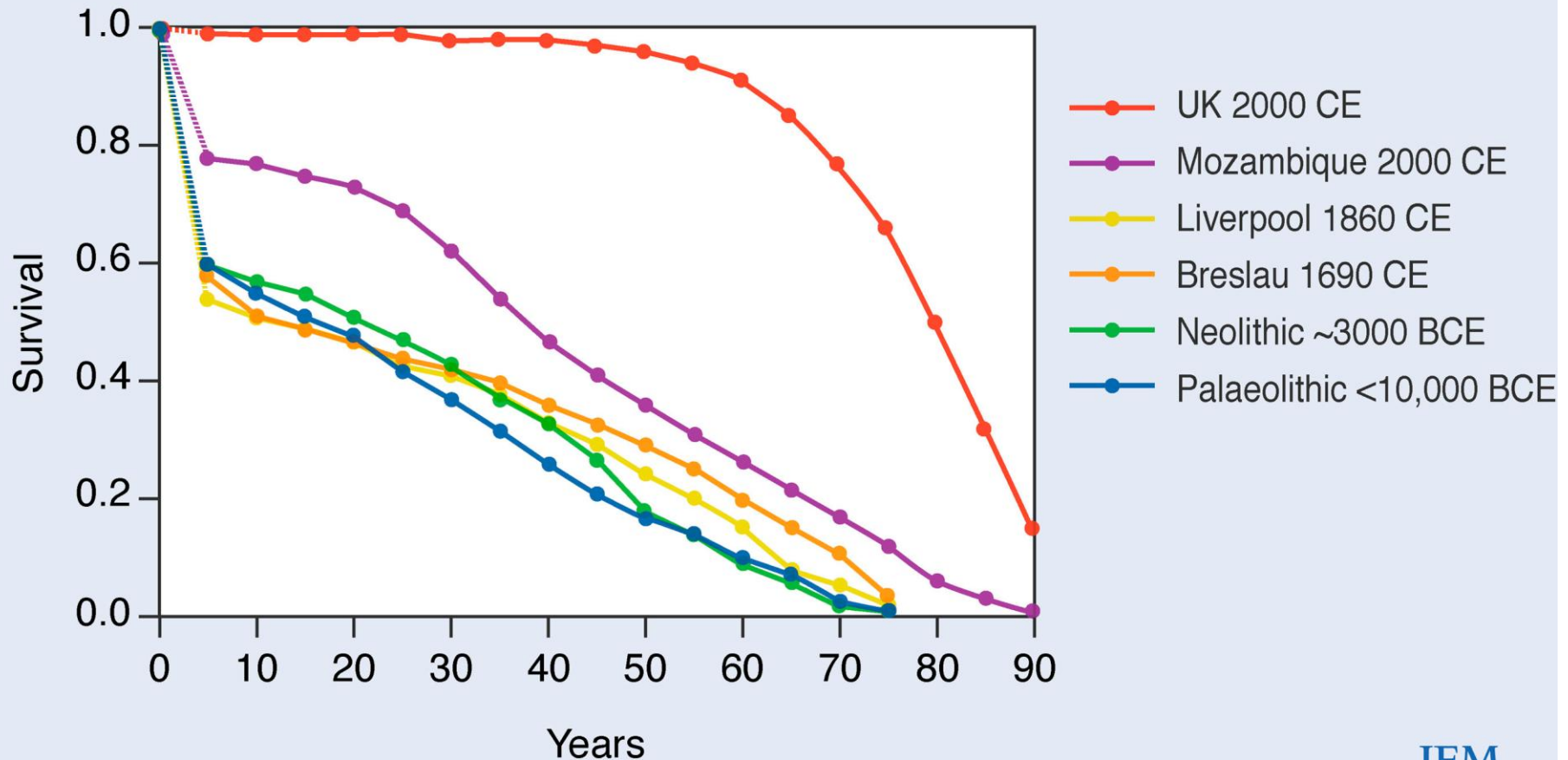
Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity

Cheng-Lung Ku,^{1,2} Horst von Bernuth,^{1,2,3} Capucine Picard,^{1,2,19} Shen-Ying Zhang,^{1,2} Huey-Hsuan Chang,^{1,2} Kun Yang,^{1,2} Maya Chrabieh,^{1,2} Andrew C. Issekutz,⁴ Coleen K. Cunningham,⁵ John Gallin,⁶ Steven M. Holland,⁶ Chaim Roifman,⁷ Stephan Ehl,⁸ Joanne Smart,⁹ Mimi Tang,⁹ Franck J. Barrat,¹⁰ Ofer Levy,^{11,13} Douglas McDonald,^{12,13} Noorbibi K. Day-Good,¹⁴ Richard Miller,¹⁵ Hidetoshi Takada,¹⁶ Toshiro Hara,¹⁶ Sami Al-Hajjar,¹⁷ Abdulaziz Al-Ghonaum,¹⁷ David Speert,¹⁸ Damien Sanlaville,²⁰ Xiaoxia Li,²² Frédéric Geissmann,^{2,23} Eric Vivier,²⁴ László Maródi,²⁵ Ben-Zion Garty,²⁶ Helen Chapel,²⁷ Carlos Rodriguez-Gallego,²⁸ Xavier Bossuyt,²⁹ Laurent Abel,^{1,2} Anne Puel,^{1,2} and Jean-Laurent Casanova^{1,2,21}

Infection is No. 1 killer for the human being



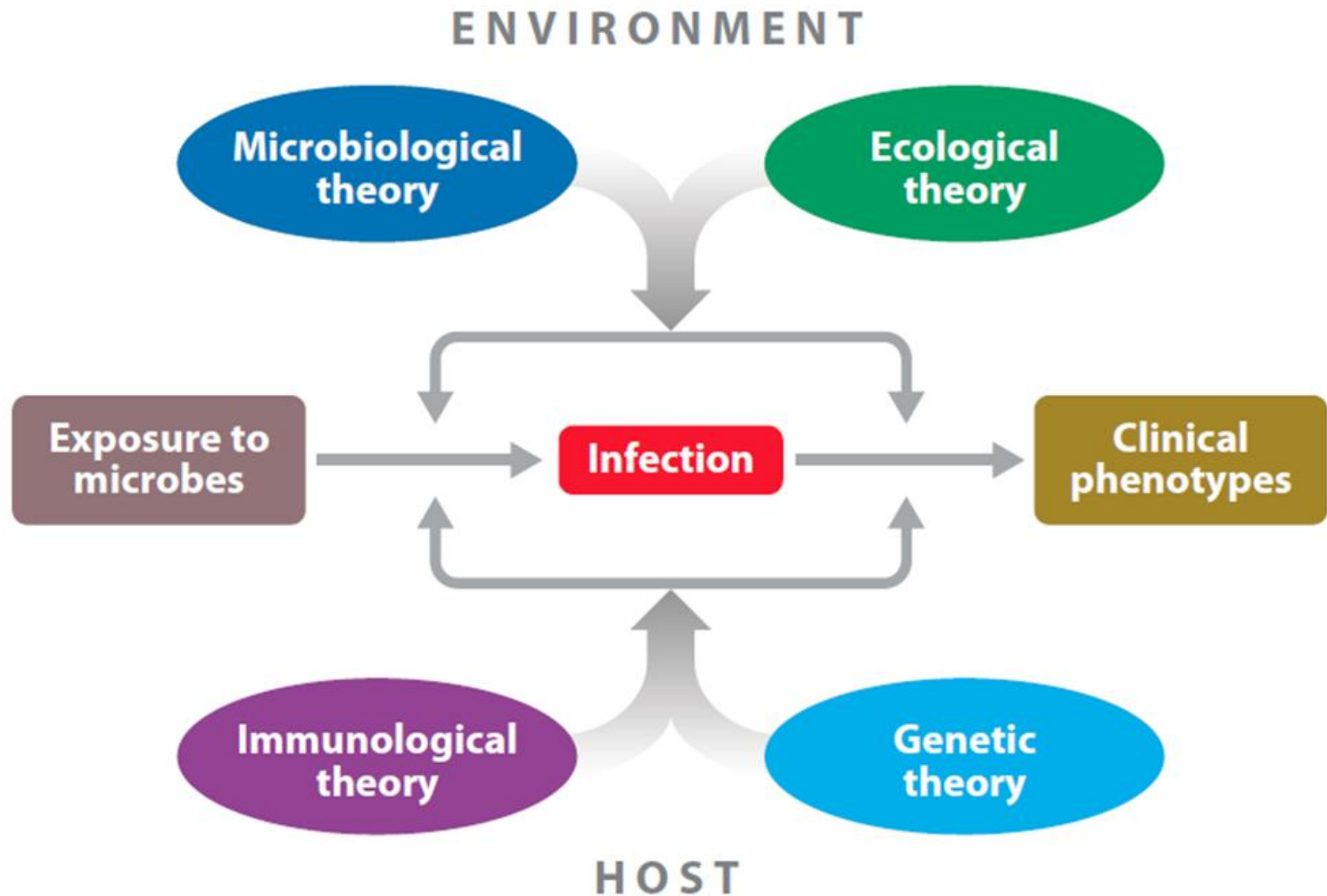
Our weakness



JEM

Infection is No. 1 killer for the human being

Infection diseases: not only microbe



Infectious diseases: no better model than human nature

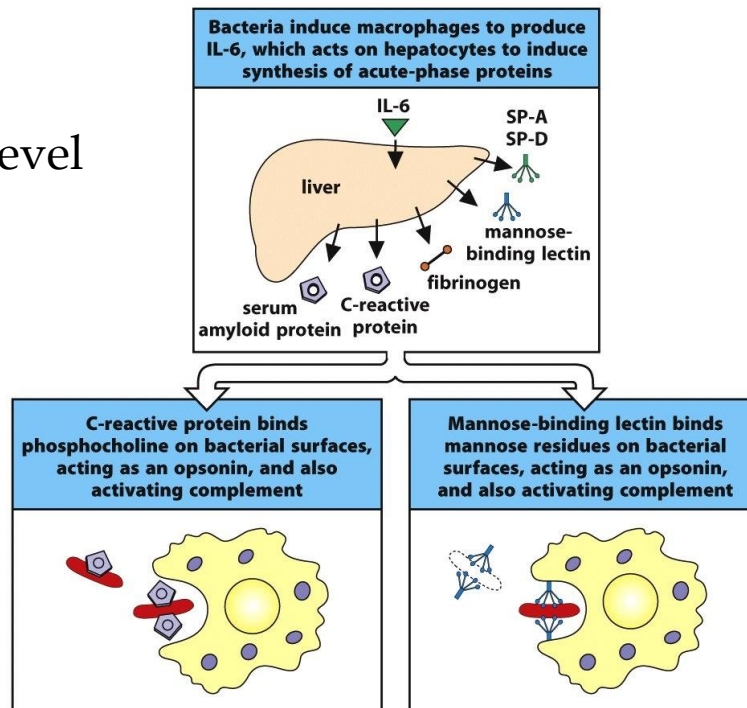
Mice, a very useful model for biomed studying, very close to human



But we are different
Particular for immune system

In mice:

C-reactive protein level is relative constant



In human:

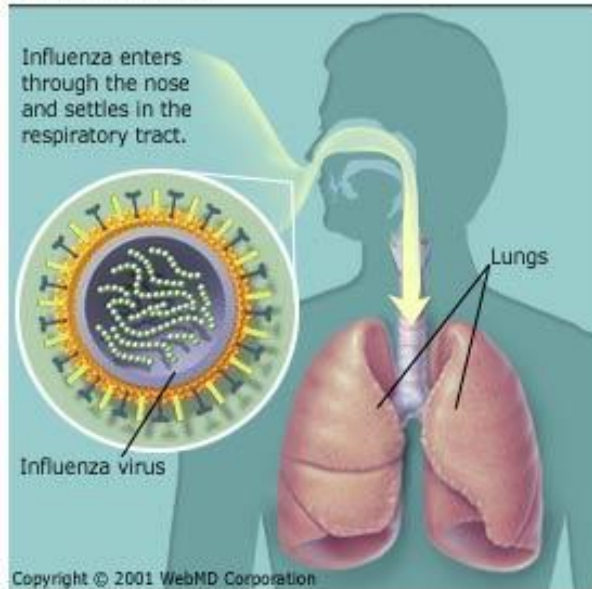
*C-reactive protein level is regulated by IL-6

* Mannose-binding protein is no crucial in human

Human and mice have separated from 95 million years ago.

Human got infected by nature, not needle

Influenza Virus



Nature **2002**. 416:750

Viral and bacterial infections

Mice were **infected intravenously with $1 \leq 10^6$ plaque-forming units of LCMV** (Armstrong strain). Sera obtained from LCMV-infected mice on day 3 after infection were quantified for IFN- γ levels by sandwich ELISA using a comparison with recombinant mouse IFN-g standards. To determine NK cell cytolytic activity, spleen cells of LCMV infected mice were prepared on day 3 after infection and assayed for lysis of YAC-1 cells in a standard 51Cr release assay for 4.5 h. Per cent specific lysis was determined from the activity in the culture supernatants according to the formula: $(\text{sample c.p.m.} - \text{spontaneous c.p.m.}) / (\text{total c.p.m.} - \text{spontaneous c.p.m.}) \leq 100$; where c.p.m. is counts per minute. For bacterial infections, *S. aureus* was cultured in trypticase soy medium, collected, and resuspended in PBS before use. **Mice were injected intraperitoneally with $1 \leq 10^7$ CFU viable *S. aureus***, and the survival of animals was monitored for 10 days.

Technical problem of infection model

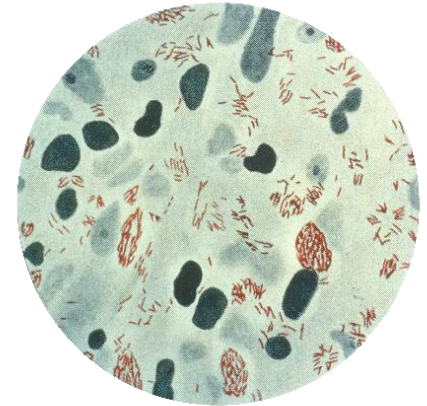
- Host tropism
- Dose
- Route of infection

Tuberculosis

- Strong pathogenic, however, only a small fraction of exposed individuals showed clinical manifestation

NTM (non tuberculosis mycobacterium)

- Ubiquitous organisms (Soil, water, domestic...), most are not pathogenic
- Susceptibility to NTM infection only in certain individuals
 - young and elderly (isolated: lymph node, lung....)
 - HIV/AIDS, immunocompromise condition (disseminated)
 - unknown



Different susceptibility and severity in exposed individual
→ Due to the different microbe strain?!

Different susceptibility and severity in exposed individual, host factors play critical roles?

Immunological conditions of children with BCG disseminated infection

SIR—For most children, inoculation of living BCG as a vaccine is harmless. However, disseminated infections caused by BCG have been occasionally reported. In most cases, infection has been shown not to be due to a reversal in virulence pattern of BCG; children with disseminated infection have been considered to have intrinsic susceptibility to BCG infection. However, which types of immunodeficiencies may result in disseminated BCG infection after vaccination is not known.

We first undertook a review of the published cases. 108 cases of disseminated BCG infection have been reported world wide since 1951. Despite the heterogeneity of the immunological investigations, 39 cases could be related to severe combined immunodeficiency (SCID) diseases, 11 to chronic granulomatous disease (CGD), four to AIDS, and one to complete Di George syndrome (CDGS). For three children, the immunological data were too inadequate to draw any conclusion. According to the available information, the immunological status of the remaining 50 children could not account for occurrence of disseminated BCG infection. These cases were thus tentatively classified as idiopathic.

To corroborate these findings, we next undertook a direct analysis of children within a more homogeneous series—ie, a retrospective study covering the 1974–94 period in France. The immunological status of 30 children with disseminated BCG infection was assessed. SCID was diagnosed in 13 and AIDS in two children. The remaining 15 children were tentatively classified as idiopathic in the absence of any feature indicating a well-defined immunodeficiency.

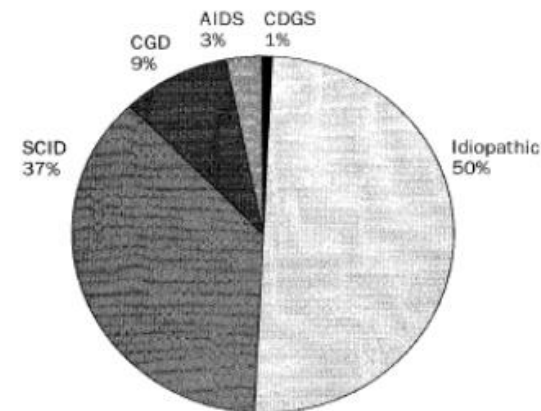


Figure: Immunological conditions of 121 children with disseminated BCG infection

The addition of published cases 1951–94 ($n=108$) to those from our retrospective study 1974–94 ($n=30$) results in 124 cases (several French cases have been previously published). Three children with BCG infection are not considered because of lack of immunological information. Of the remaining 121 children with disseminated BCG infection, 45 were found to have SCID, 11 CGD, four AIDS, one CDGS, and 60 were tentatively classified as idiopathic. All references available at our institution on request.

Taken together, these results establish that only four well-defined immunodeficiency conditions predispose to BCG infection: SCID, CGD, CDGS, and AIDS. They also reveal that about half the disseminated BCG infections occur without a well-defined underlying immunological defect.

Brief Report

INTERFERON- γ -RECEPTOR DEFICIENCY IN AN INFANT WITH FATAL BACILLE CALMETTE-GUÉRIN INFECTION

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JEAN-FRANÇOIS EMILE, M.D., Ph.D.,
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MICHAEL LEVIN, M.D., Ph.D.,
STÉPHANE BLANCHE, M.D., ERIC SEBOUN, Ph.D.,
ALAIN FISCHER, M.D., Ph.D.,
AND JEAN-LAURENT CASANOVA, M.D., Ph.D.

Molecular mechanism of mycobacterial infection in children

Mendelian susceptibility to mycobacterial diseases (MSMDs).

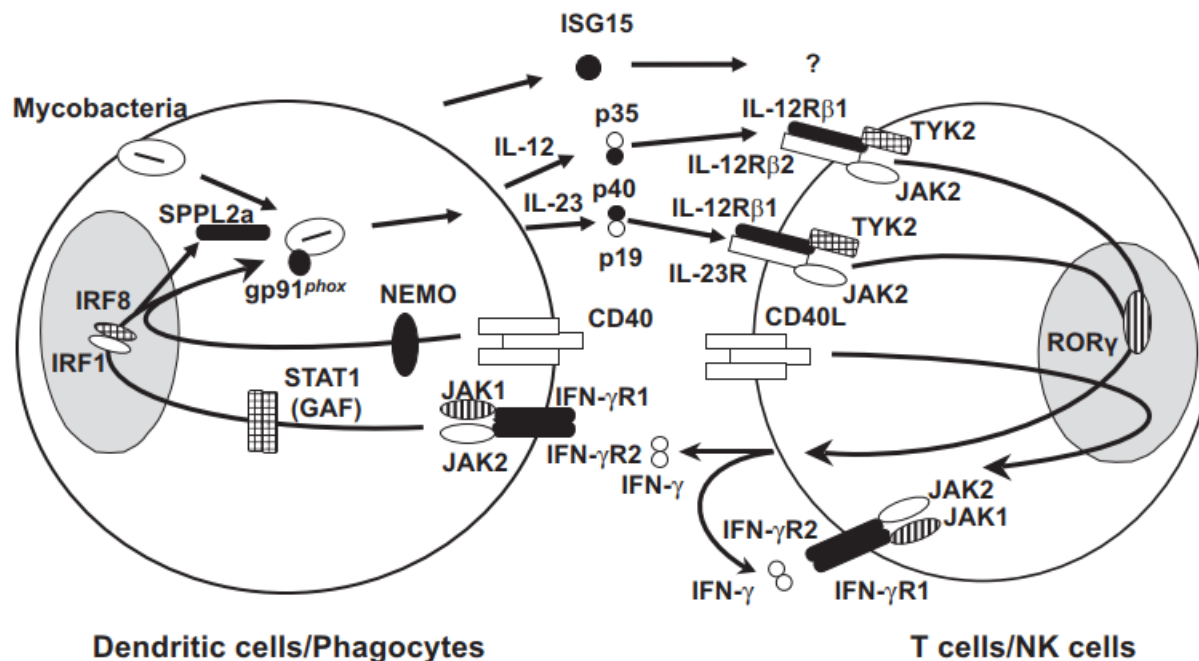
Patients suffered from

- Disseminated mycobacterial infection
- Salmonella

Inborn errors of the Interleukin (IL)-12/Interferon (IFN)- γ



MSMD and human immunity to mycobacteria



MSMD

- *ILRB1*
- *IL12B*
- *ISG15*
- *SPPL2A*
- *IRF8*
- *TYK2*
- *IFNGR1*
- *IFNGR1*
- *STAT1*
- *NEMO*
- *CYBB*

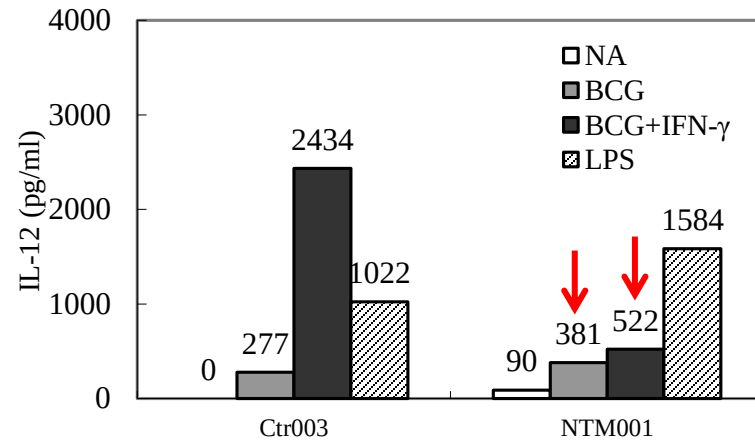
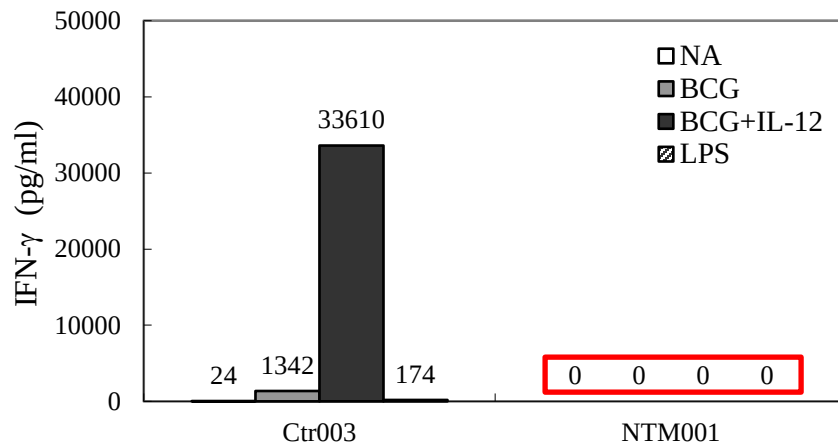
Syndromic MSMD

- *STAT1* (AR)
- *IRF8* (AR)
- *RORγ*
- *GATA2* (AD)

Adult disseminated NTM infection

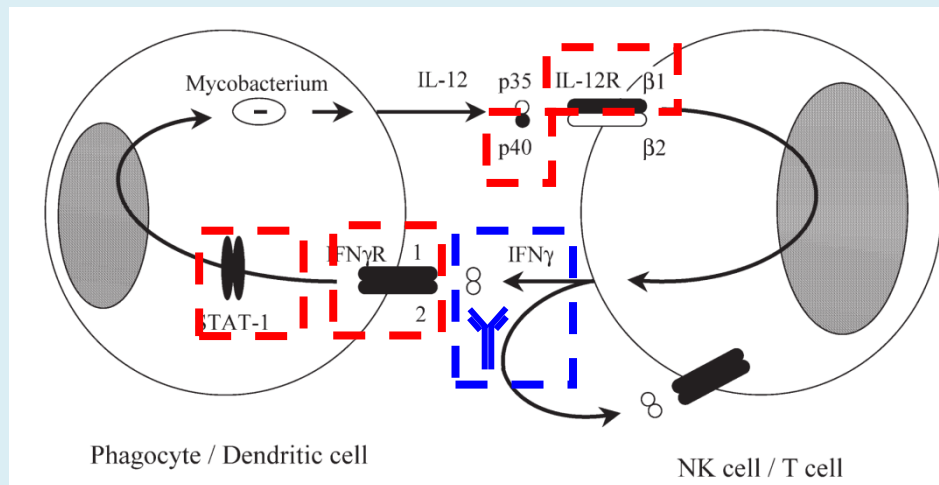
NTM01: Female, 50 yrs

Mycobacterium scrofulaceum



Mycobacterial infection

Child: Inborn genetic defect



Adult: anti-IFN-γ autoantibodies



Rainer Doffinger,
Clin Infect Dis 2004



Steven M Holland,
J Immunol 2005



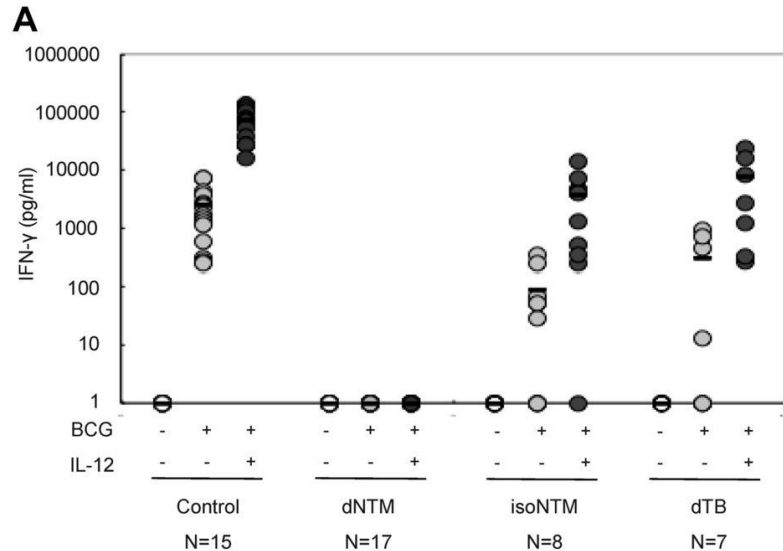
Michel Levin,
J Clin Invest 2005



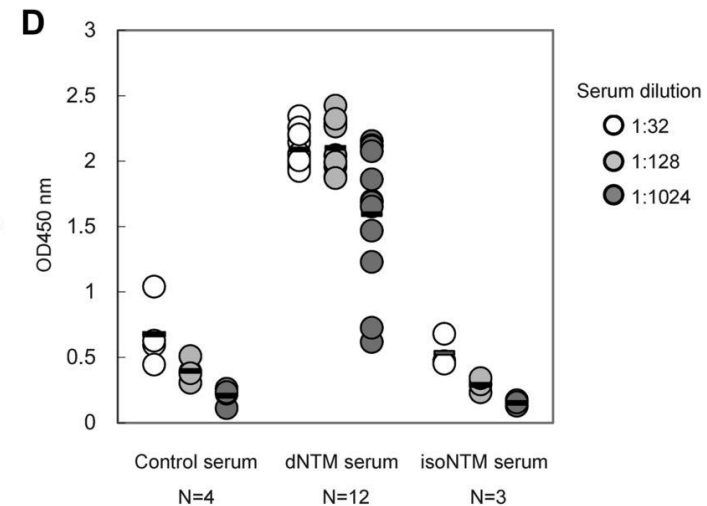
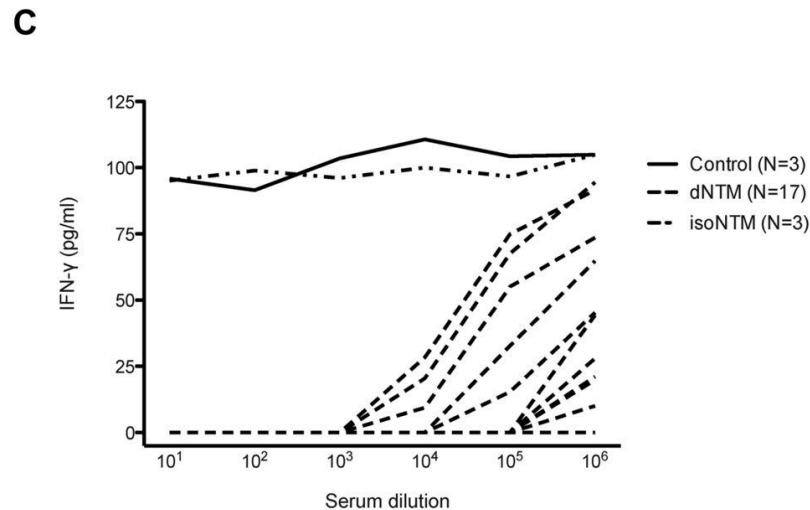
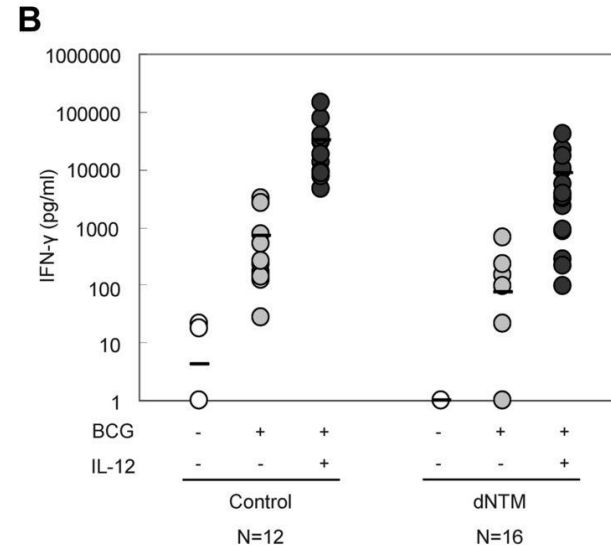
Conny Hoflich,
Blood 2005

High Prevalence of anti-IFN- γ autoantibodies in Taiwanese patients with disseminated NTM infection (dNTM)

Whole Blood (with plasma)

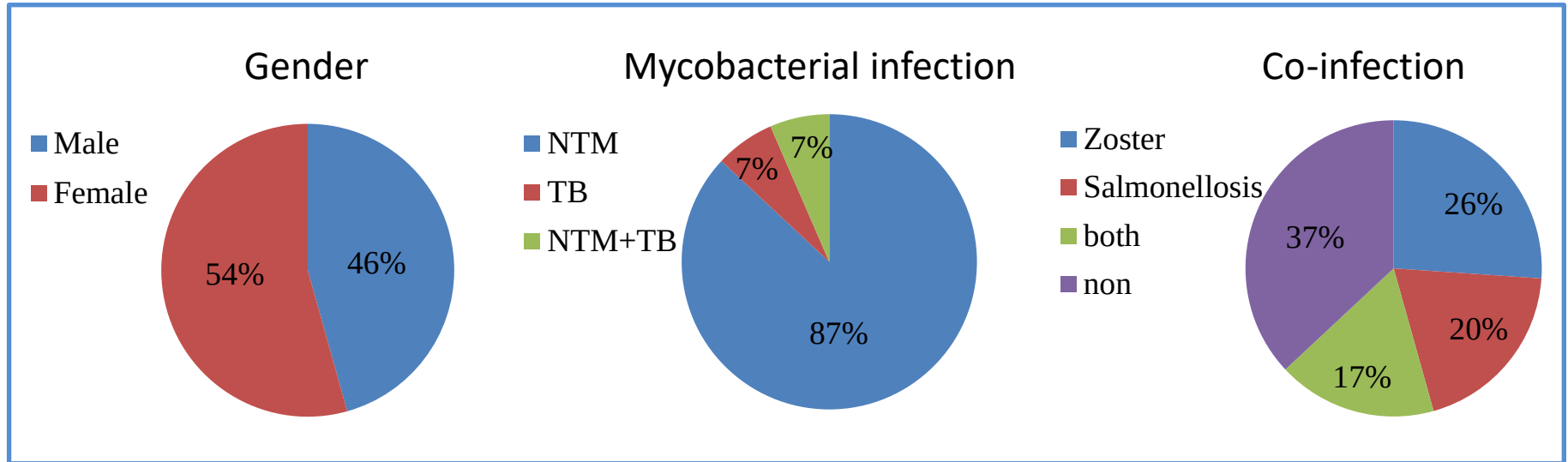


PBMCs (without plasma)



Clinical feature of patients with anti-IFN- γ autoantibodies

- We had found 133 cases, the biggest single cohort in Taiwan, maybe also for world-wide
- 46 cases clinical information summarize



Other Signs

Opportunistic infection

- *T. marneffe*i (4)
- Legionellosis (2)
- Aspergillosis (1)
- *S. Aureus* (1)

Autoimmune

- Hypothyroidism (2)
- Behcet disease (1)
- Sweet's syndrome (1)

Malignancy

- Peripheral T-cell lymphoma (PTCL) (3)
- Langerhans' cell histiocytosis X (1)

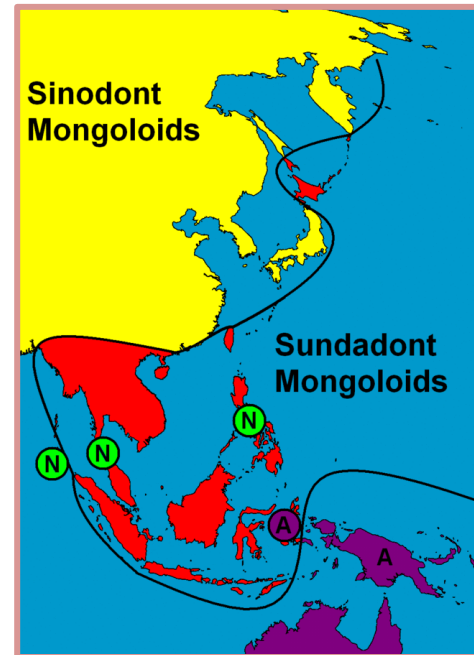
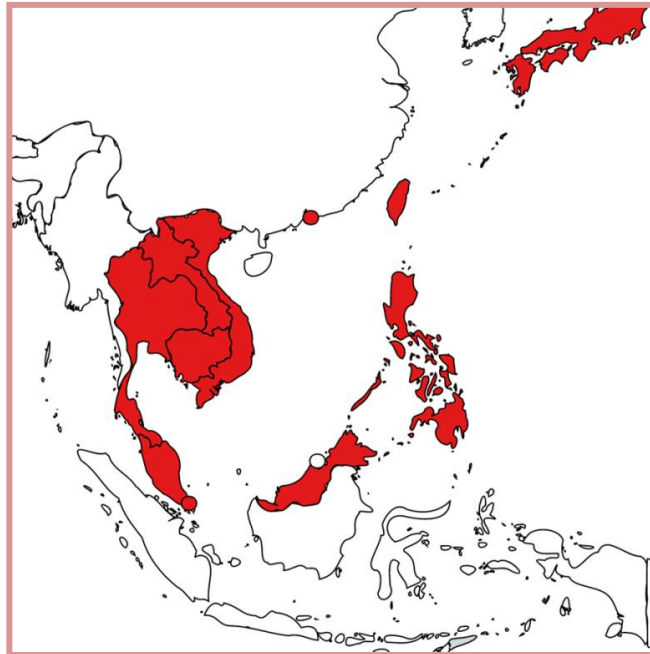
Characteristics of Patients with Disseminated Non-tuberculosis Mycobacterium Infections

Pt.	Age	Sex	Onset	Pathogens	Laboratory data
1	54	M	50 yr	Mycobacterium Salmonella Penicillium marneffeii	HIV (-), ANA (-); RA<20; SSA (-), SSB (-), C3/C4:199/74.5, C-ANCA (-), P-ANCA (-), Coomb's test (-), HLA-B27 (-), IgG/A/M: 1980/159/65.8 (08/10),
2	50	F	47 yr	Mycobacterium	AFP: 27.3, CEA:3.26, CA-125: 70, CA-199:3.72, IgG/IgA/IgM/IgE: 1310/458/137/27.4
3	68	M	18 yr	Mycobacterium Salmonella enteritidis B	ANA (-), anti-nDNA: 1.9, RA: 88.7, C3/C4: 202/25.1, C-ANCA (+), P-ANCA (-), CEA: 0.46, SCC: 12.8; IgG/A/M/E: 2980/968/94/173
4	46	F	44 yr	Salmonella enteritidis D Mycobacterium	SSA/SSB (-), IgG/A/M: 1770/3.9/89.2, BM(-), IEP (-)
5	55	M	53 yr	<i>Mycobacterium terrae</i>	C3/C4: 210/27, RF<20, ANA-1:40, AFP: 1.7, CEA:1.93, PSA:1.037, CA19-9:15.9, SCC: 0.9 IgG/A/M/E: 1870/312/116/11.52,
6	81	M	81 yr	Nontuberculous mycobacterium	ANA (-), RA<20, IgG/A/M: 1780/432/92.6 IgE:521.70, C3/C4: 131/36.1 AFP:2.73, CEA: 0.84, PSA: 17.899, CA199: 32
7	66	M	61 yr	Nontuberculous mycobacterium	HIV (-), RF<20, ANA (-), Ig G/A/M-1340/367/55.6, C3/C4-115/27.2, IgE-388.91, , CEA-1.22, , CA199-10.2, PSA-1.23, CA125-117.9
8	87	M	84 yr	<i>M. scrofulaceum</i> <i>S. aureus</i>	ANA-1:40, APF-3.61, CEA-1.72, PSA-3.14, CA199-12.8,
9	48	M	44 yr	<i>Mycobacterium avium</i> complex, <i>S. enteritidis</i>	WBC: 7120 (54.4/29.2/4.9/10.5/1)
10	61	F	59 yr	Nontuberculous mycobacterium	IgG/A/M: 1550/206/108, RA<20, C3/C4: 171/64; ANA: 1:40, AFP: 1.92, CEA: 1.44, CA-125: 9.5, CA19-9: 4.1
11	49	M	48 yr	<i>Mycobacterium kansasii</i>	HIV (-), colonoscope: polyps, AFP: 1.45, CEA: 1.14, PSA: 5.671, CA19-9: 9.4; ANA: 1:40, IgG/A/M: 1990/191/182, RA<20, C3/C4: 166/27.9
12	56	F	48 yr	Nontuberculous mycobacterium	AFP: 1.7, CEA<0.45, SCC:0.5, IgG/A/M: 2340/639/124, RA<20, ANA: negative, HIV (-), nomral thyroid function

Strongly associated with HLA-DRB1*15:02/16:02 and HLA-DQB1*05:01/05:02 across Southeast Asia

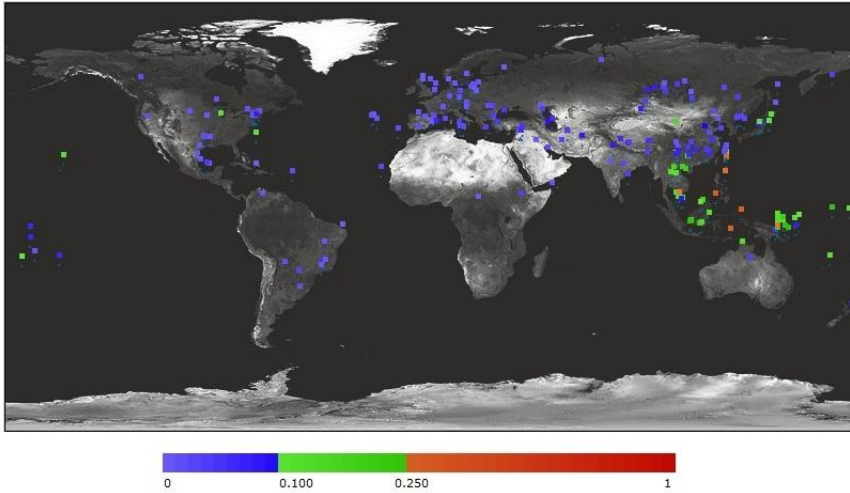
Allele type	Control		Patient		χ^2	P_{χ^2}	Fisher exact P value	OR (95% CI)	P_{logistic}	P_{FDR}
	Count*	%†	Count*	%†						
Thailand	N = 101		N = 78							
DRB1*15:02	25	12.38	67	42.95	43.0875	5.23×10^{-11}	8.26×10^{-11}	5.33 (3.15-9.01)	4.26×10^{-10}	1.02×10^{-8}
DRB1*16:02	20	9.90	46	29.49	22.4560	2.15×10^{-6}	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}

Origin	HLA-DRB1		HLA-DQB1	
Hong Kong	15:02	16:02	05:02	05:02
	16:02	16:02	05:02	05:02
	04:05	15:02	03:02	05:02
	03:01	16:02	02:01	05:02
	16:02	16:02	05:02	05:02
	15:01	16:02	05:02	06:01
	09:01	16:02	03:03	05:02
The Philippines	12:02	16:02	03:01	05:02
	04:05	15:02	05:02	05:02
	15:02	15:02	05:02	06:01
	15:02	15:02	05:01	05:02
	15:02	15:02	05:02	05:02
	14:54	15:02	05:02	05:03
	15:02	15:02	05:02	05:02
Vietnam	15:02	15:02	05:01	05:02
	15:01	16:02	05:02	06:01
	09:01	09:01	03:03	03:03
	04:05	16:02	04:02	05:02
Liao	15:02	16:02	05:01	05:02
	14:54	15:02	05:02	05:02
	15:02	15:02	05:01	05:02
United States	15:02	16:02	05:02	05:02
	04:01	13:02	03:01	06:09

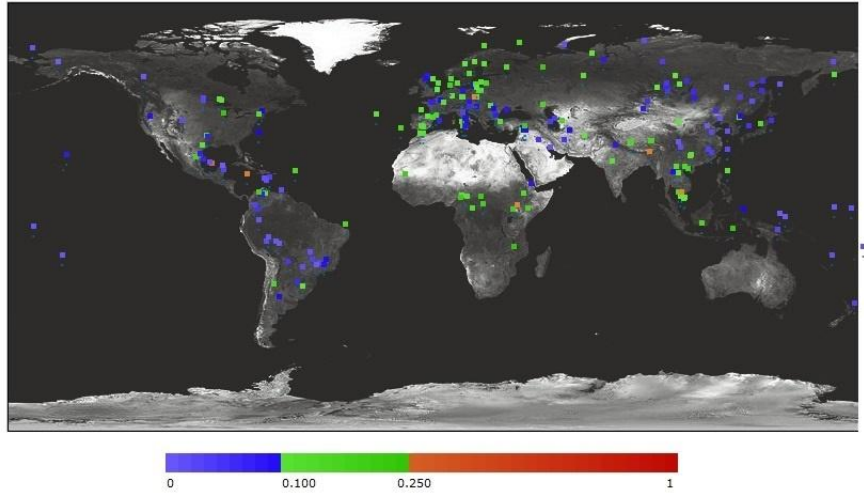


Frequency of DRB1*15:02, 16:02 and DQB1*05:01, *05:02

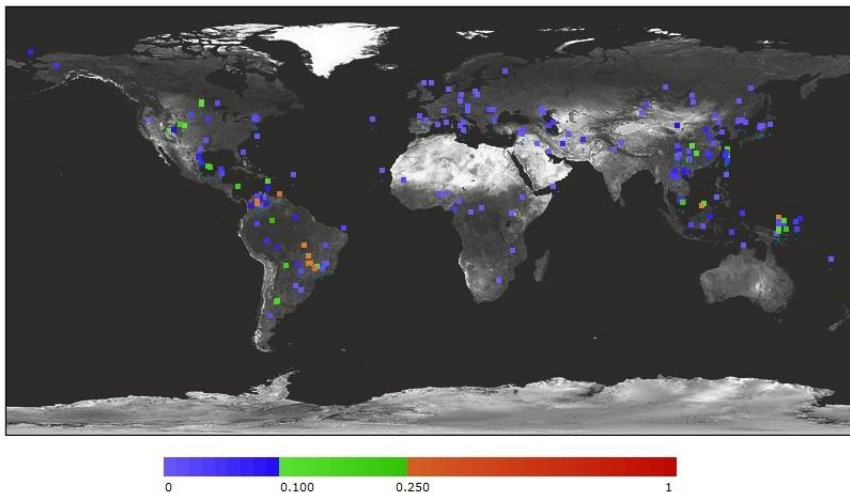
DRB1*15:02



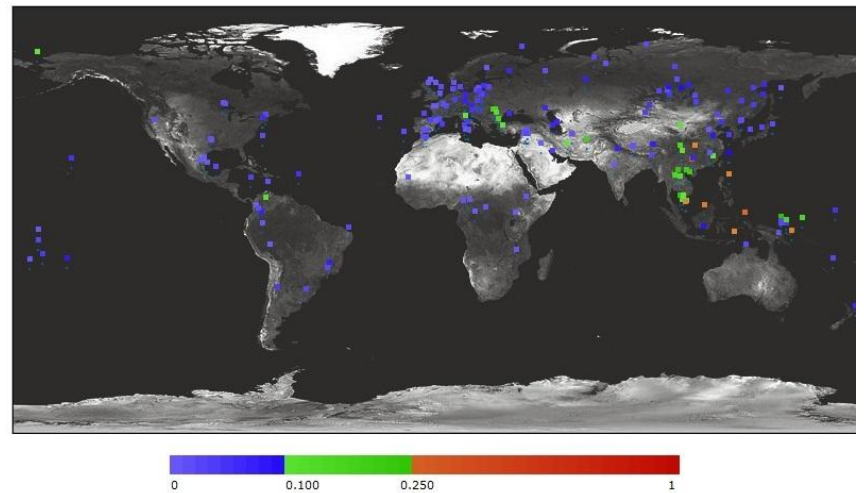
DQB1*05:01



DRB1*16:02

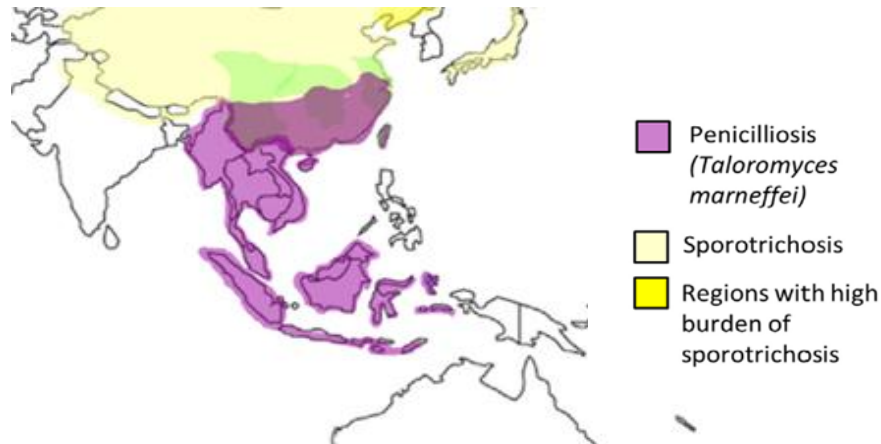


DQB1*05:02

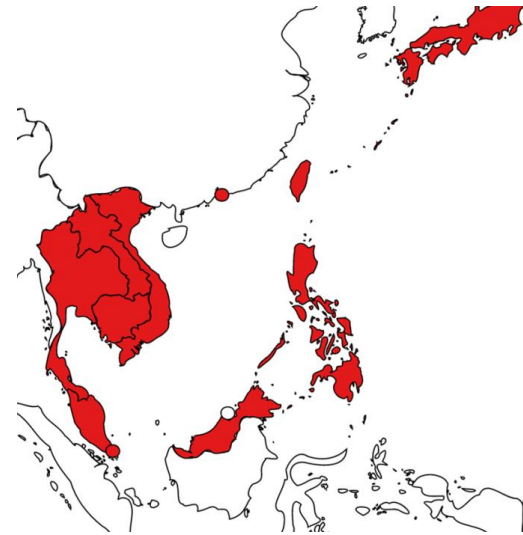


Anti-IFN- γ autoantibodies underlie the fungal infection

T. marneffei distribution



Anti-IFN- γ autoAbs distribution



frontiers
in Immunology

REVIEW
published: 28 June 2017
doi: 10.3389/fimmu.2017.00735



Cellular and Molecular Defects Underlying Invasive Fungal Infections—Revelations from Endemic Mycoses

Pamela P. Lee¹ and Yu-Lung Lau^{1,2*}

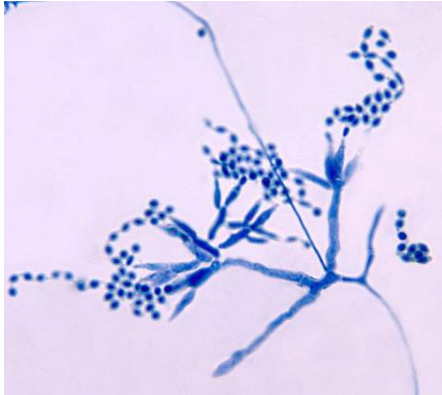
Talaromyces marneffei
Aspergillus spp.
Cryptococcus neoformans

Pathogens other than mycobacterial species

Pathogen	No of Patients (%)
Non-typhoid Salmonella species	18/45 (40.0)
<i>Legionella pneumophila</i>	1/45 (2.2)
<i>Staphylococcus aureus</i>	1/45 (2.2)
<i>Talaromyces marneffei</i>	4/45 (8.9)
<i>Aspergillus</i> species	1/45 (2.2)
<i>C. neoformans</i>	1/45 (2.2)
Epstein-Barr virus	1/45 (2.2)

Talaromyces marneffei (Penicillium marneffei)

Dimorphic fungus



Natural host: bamboo rat



Disease: Penicilliosis

Site: Skin lesions in tropics, pneumonia, systemic disease

Outcome: Lethal without treatment with anti-fungal drug

Patients: immunocompromised individuals

- advance HIV patients
- children with primary immunodeficiency (GOF STAT1; IFNGR; CD40L; gp91)



Progressive Disseminated Penicilliosis Caused by *Penicillium marneffei*

Report of Eight Cases and Differentiation of the Causative Organism from *Histoplasma capsulatum*

ZHOUJIN DENG, M.D. AND DANIEL H. CONNOR, M.D.

Eight patients with fatal penicilliosis caused by *Penicillium marneffei* are reported. All were natives of southern rural Guangxi, and none had a predisposing illness or evidence of altered immunity. The distinctive features of *P. marneffei* include proliferation of yeast-like cells within histiocytes, followed by the development of focal necrosis and, eventually, large abscesses. Outside the histiocytes, the fungi elongate, become slightly curved, and form septa. *In vitro*, *P. marneffei* produces a pigment which diffuses into the culture medium. The differentiation between *P. marneffei* and *Histoplasma capsulatum* is described, and possible reservoirs for *P. marneffei* are discussed. (Key words: Penicilliosis; *Penicillium marneffei*; Fatal mycosis; Systemic mycosis; China) Am J Clin Pathol 1985; 84: 323-327

PENICILLIUM MARNEFFEI was first isolated from a lesion in the liver of a bamboo rat (*Rhizomys sinensis*) in Vietnam.¹ The first infection in humans happened when Segretain accidentally inoculated his finger with this isolate.² The first natural infection was reported by DiSalvo and co-workers,³ and occurred in an American missionary who had returned from Vietnam. Thus, the geographic source of the organisms was probably Vietnam. Guangxi Province in the People's Republic of China borders Vietnam and has a similar climate. During the past 20 years (1964-1983 inclusive), we have identified eight patients in Guangxi with penicilliosis. The first was studied in 1964, and the next ones almost ten years later—in 1973. Much of the intervening time was during the cultural revolution (1966-1976), when academic endeavors were suppressed. Autopsy was performed on five patients and biopsy specimens taken from the other three subjects (Table 1). In each patient the infection was disseminated, progressive, and fatal.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. Address reprint requests to Dr. Connor, Department of Infectious and Parasitic Disease Pathology, Armed Forces Institute of Pathology, Washington, D.C. 20306-6000.

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Pus from a cutaneous abscess of one patient (#7) grew *P. marneffei*.

Clinical Data

The patients ranged in age from 11 to 40 years old, and the average age was 24.4 years. There were seven men and one woman. Five were farmers and one each a carpenter, barber, and schoolboy. All lived in southern rural Guangxi.

Clinical onset was acute with high fever, chills, and leukocytosis. The high fever recurred throughout the course of the disease and was accompanied by cough, weakness, loss of weight, anemia, hepatomegaly, and lymphadenopathy. Each patient had anemia with hemoglobin levels of 5 to 7 g/dL. Erythrocyte counts were 1,300,000 to 300,000 per mm³. Total leukocyte counts ranged from 18,000 to 48,000 per mm³. Segmented neutrophils were 70% to 94%. Livers were palpable 2 to 4 cm below the right costal margin. Spleens were infrequently palpable. Superficial lymph nodes were enlarged from 0.5 to a maximum of 1.5 cm. They were soft, movable, and nontender. The course of the illness ranged from 2 months to 3 years, the average duration being 10.6 months. None of these patients was immunosuppressed, nor did any have debilitating disease.

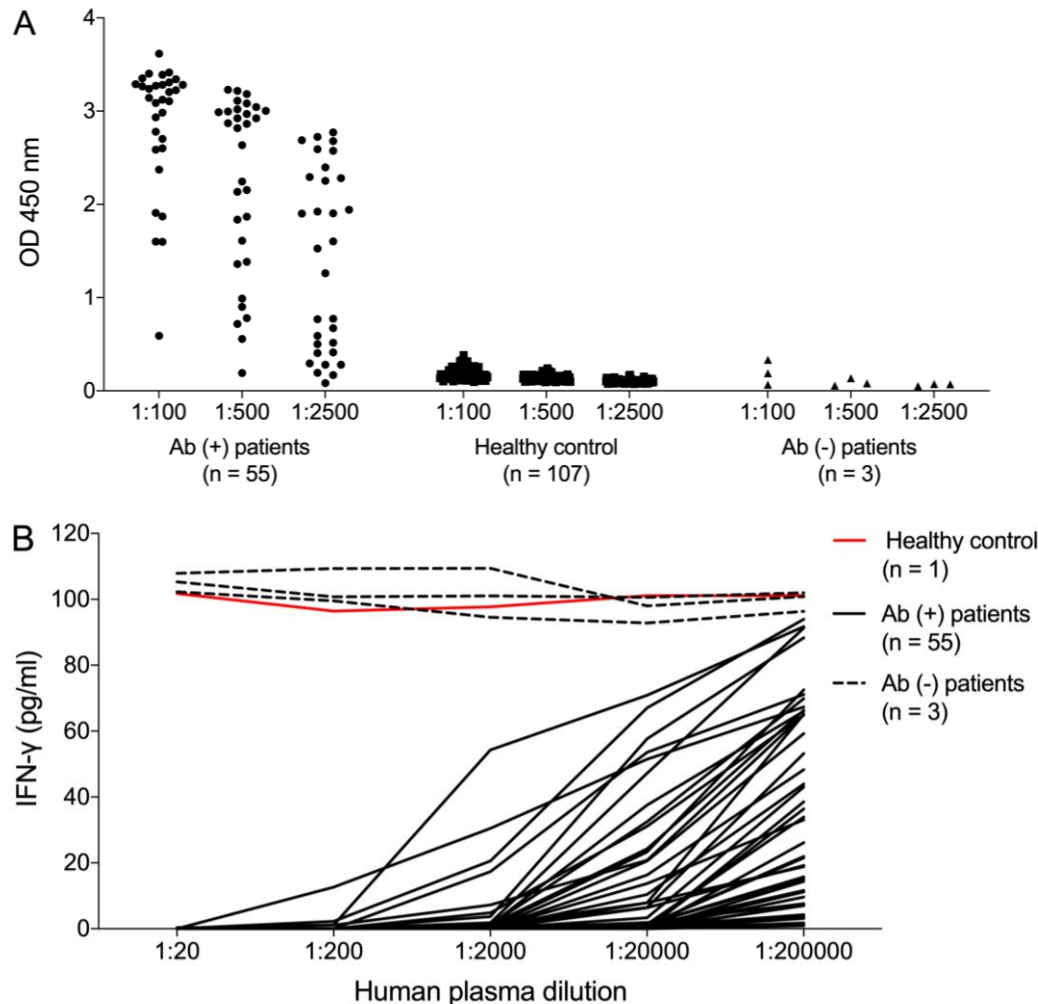
Mycology

P. marneffei is a dimorphic fungus that grows as small yeast-like cells in tissue and in culture on rich media at 37 °C. It grows in mycelial form at 25 °C and as short hyphal elements in pulmonary cavities. *P. marneffei* produces a fast-growing, grayish floccose colony with

T. marneffei distribution



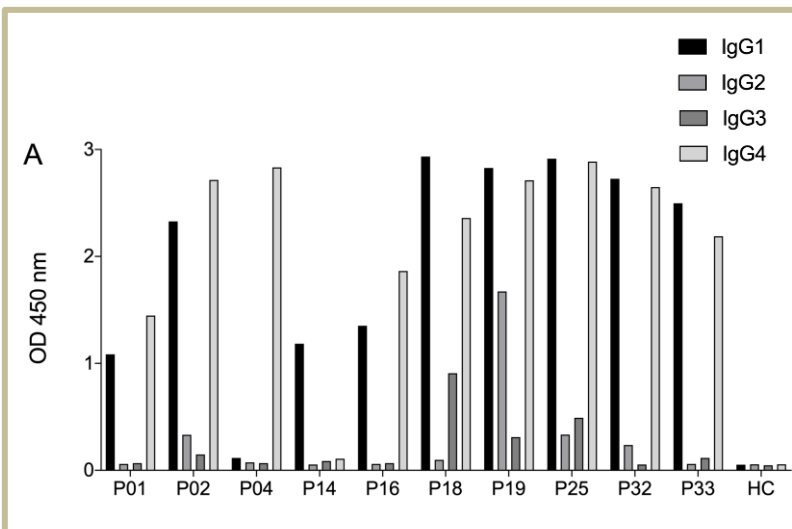
Anti-IFN- γ autoantibodies underlie *T. marneffei* infection



High prevalence (55/58) anti-IFN- γ autoantibodies in *T. marneffei* infection patients without HIV or known immune incompetent



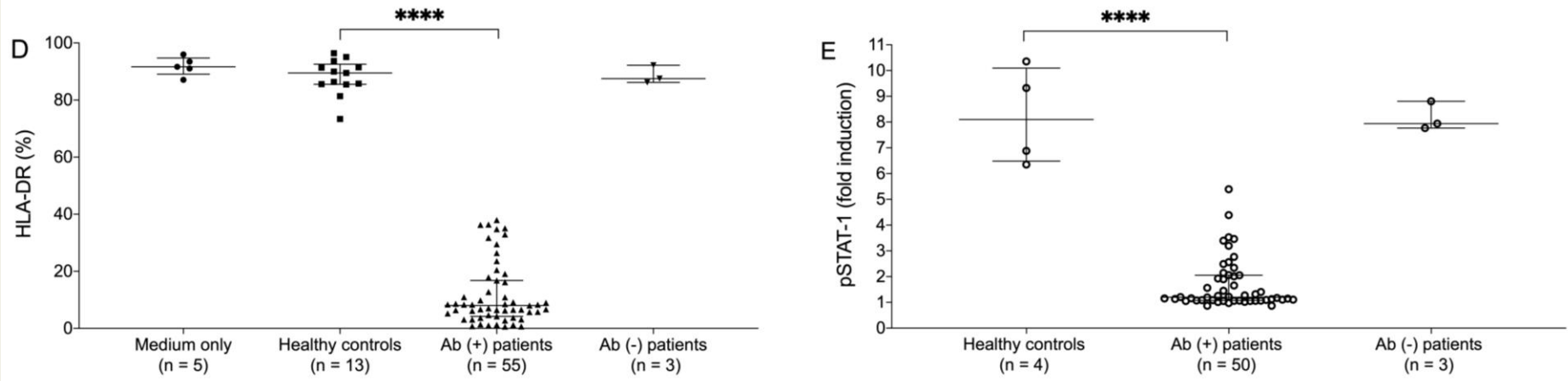
Ding, Jing Ya



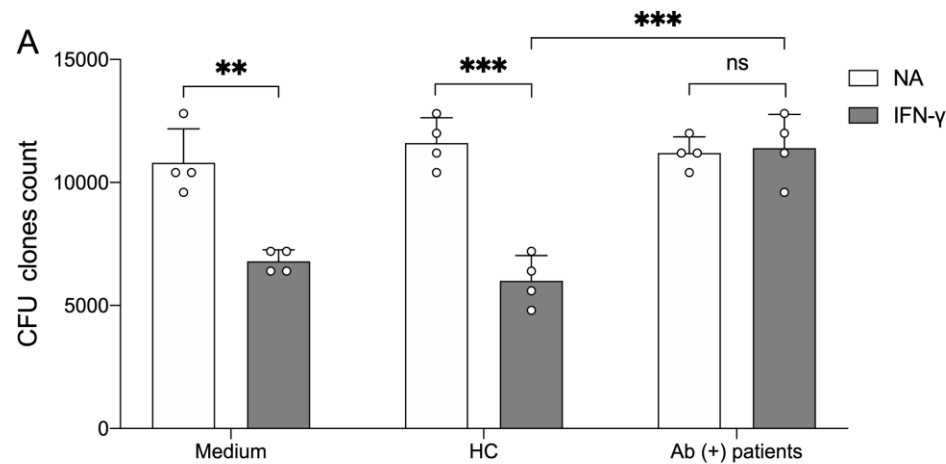
IgG1 and IgG4 are the major subclass of autoAbs

Neutralizing anti-IFN- γ autoAbs impair anti-*T. marneffei* Immunity

IFN- γ neutralizing assays



IFN- γ -mediated *T. marneffei* killing



Clinical features of *T. marneffei* infection with anti-IFN- γ autoantibodies

Clinical features	Number (n = 55)	Percentage (%)
Symptoms/signs		
Fever	47	85.5%
Leukocytosis	46	83.6%
Cough	44	80.0%
Weight loss	43	78.2%
Lymphadenopathy	42	76.4%
Anemia	34	61.8%
Thrombocytosis	30	54.5%
Cutaneous or subcutaneous lesion	28	50.9%
Misdiagnosed as tuberculosis	28	50.9%
Malaise	25	45.5%
Arthritis or arthralgia	19	34.5%
Lymphopenia	13	23.6%
Abdominal pain or diarrhea	11	20.0%
Chest pain	11	20.0%
Dyspnea	11	20.0%
Hepatomegaly	9	16.4%
Thrombocytopenia	7	12.7%
Splenomegaly	6	10.9%
Hemoptysis	5	9.1%
Osteomyelitis	2	3.6%
Organ involvement		
Lung/pleura	55	100.0%
Lymph node	43	78.2%
Skin	26	47.3%
Bone/joints	13	23.6%
Liver	8	14.5%
Spleen	5	9.1%

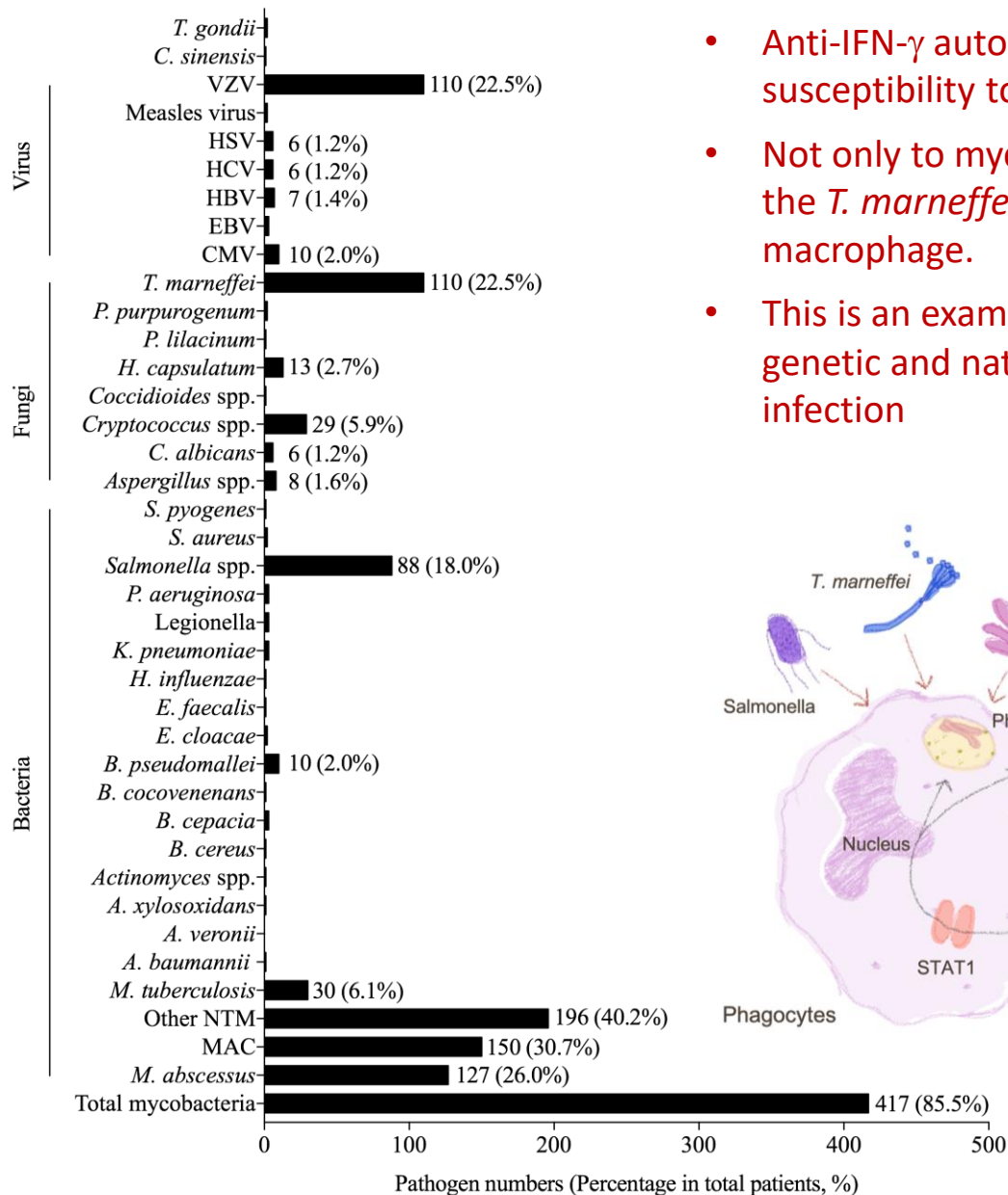
Pathogens other than *T. marneffei* from patients with anti-IFN- γ

Pathogen	Number of Patients (%)
VZV	8 (14.5)
NTM	7 (12.7)
<i>Salmonella</i> spp.	4 (7.3)
CMV	3 (5.5)
<i>Candida albicans</i>	3 (5.5)
<i>M. Tuberculosis</i>	3 (5.5)
<i>K. pneumoniae</i>	3 (5.5)
<i>Aspergillus</i>	1 (1.8)

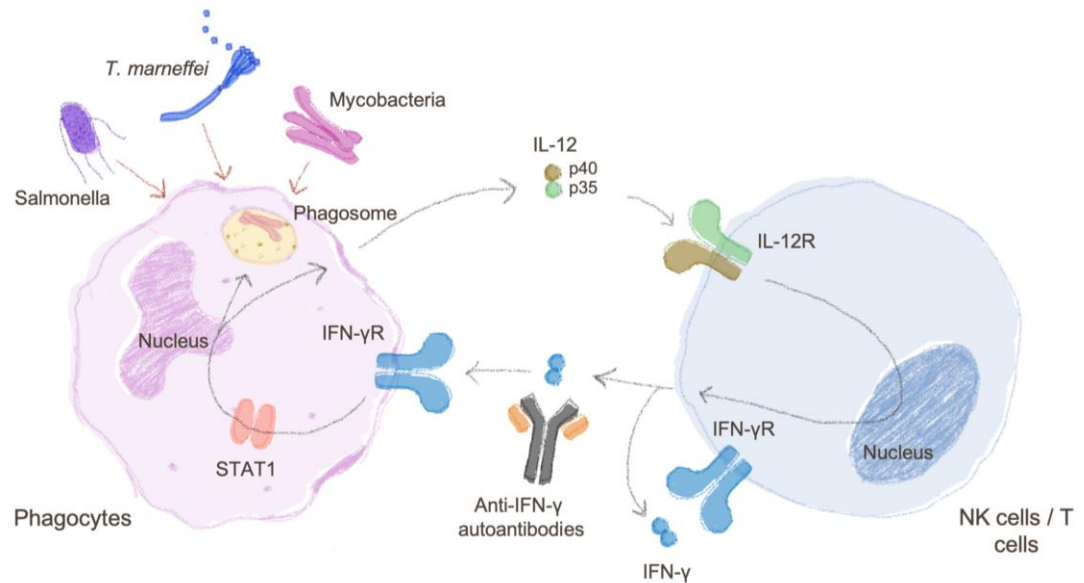
- Mortality: 13/43 (30.2%)
- Recurrent infection: 19/30 (63%)
- Reactive skin lesions : 7/55 (12.7%)



Anti-IFN- γ autoAbs: Late-onset Immunodeficiency



- Anti-IFN- γ autoantibodies are the underlie etiology for the susceptibility to *T. marneffeii*
- Not only to mycobacterium, IFN- γ pathway is critical to control the *T. marneffeii* and maybe for other fungal through activation macrophage.
- This is an example to demonstrate the impact of population genetic and natural environment to the host immunity against infection



Whether Autoantibodies recognize a major region in IFN- γ peptide ?

Synthetic peptides covered full IFN- γ

Peptide 1 Q D P Y V K E A E N L K K Y F N A G H S D V A D N G T L F L

Peptide 2 D N G T L F L G I L K N W K E E S D R K I M Q S Q I V S F Y

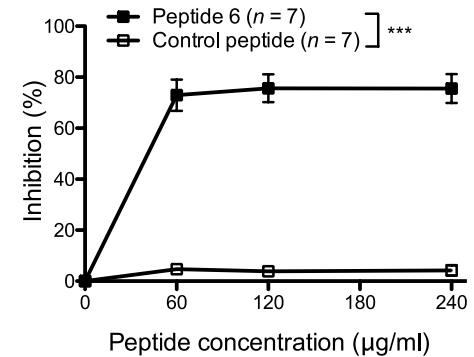
Peptide 3 S Q I V S F Y F K L F K N F K D D Q S I Q K S V E T I K E D

Peptide 4 V E T I K E D M N V K F F N S N K K K R D D F E K L T N Y S

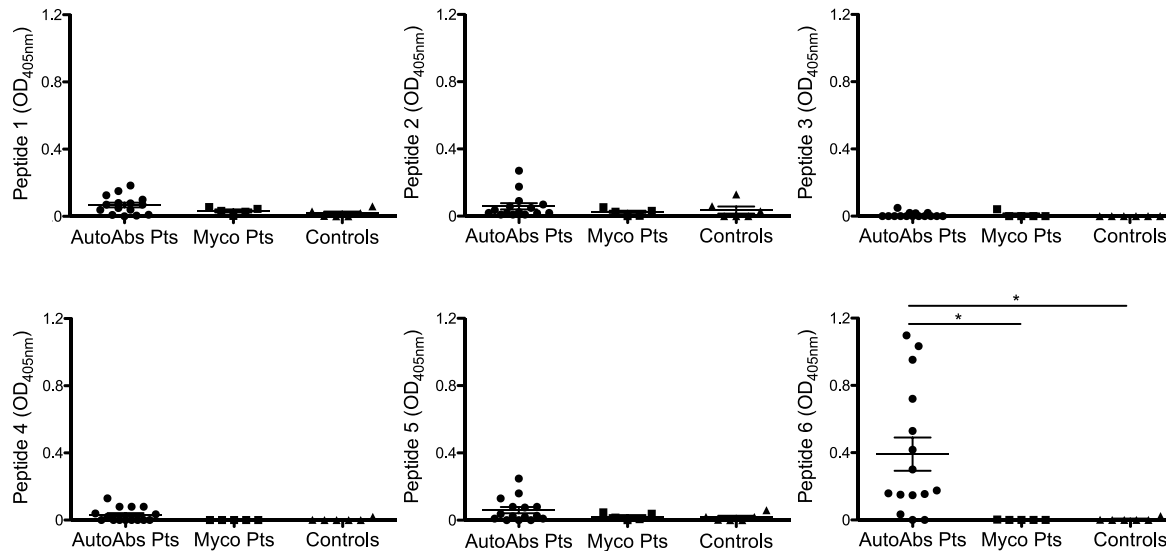
Peptide 5 F E K L T N Y S V T D L N V Q R K A I H E L I Q V M A E L S

Peptide 6 I Q V M A E L S P A A K T G K R K R S Q M L F R G R R A S Q

Binding competition assay



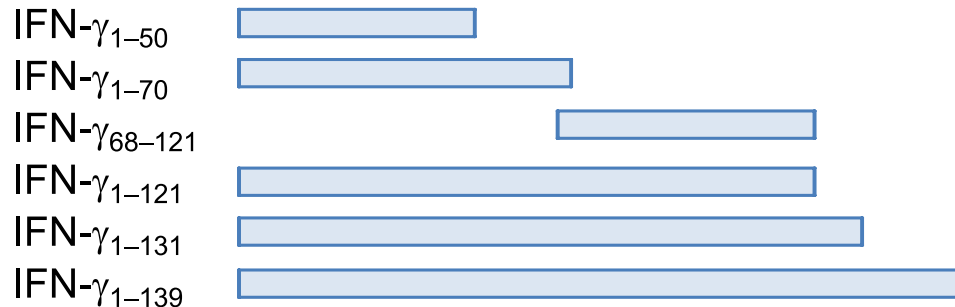
Peptide Scan



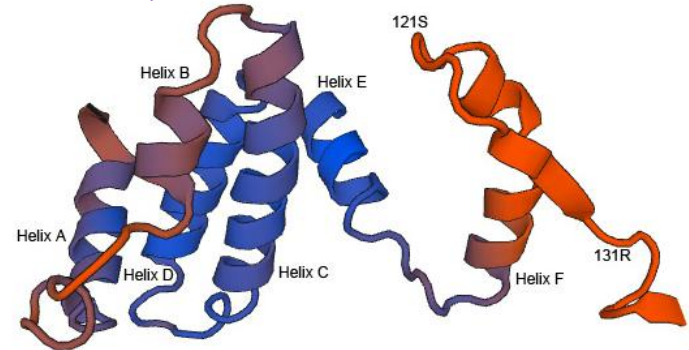
Lin, Nat Med 2016

Autoantibodies recognize the IFN- γ protein deletion clone

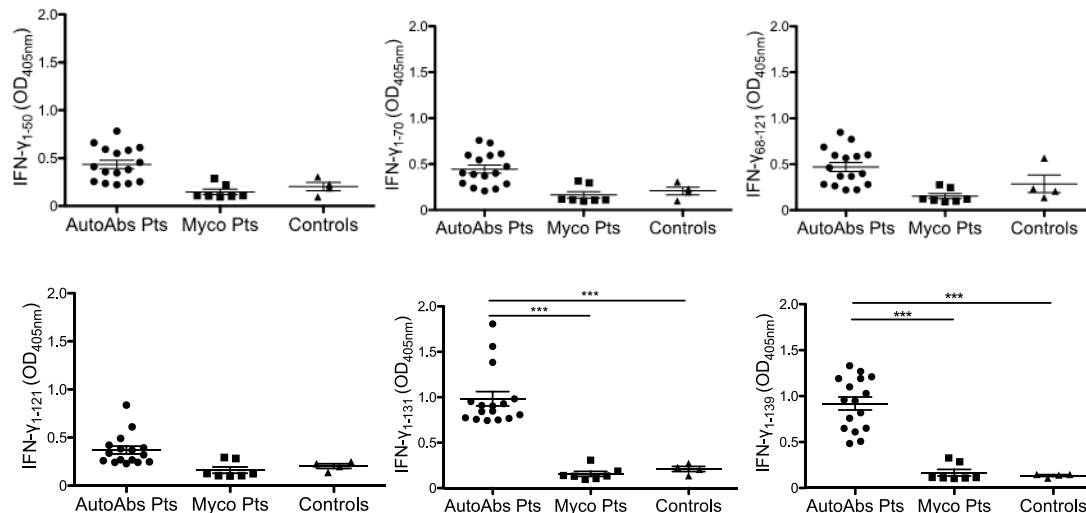
IFN- γ deletion clones



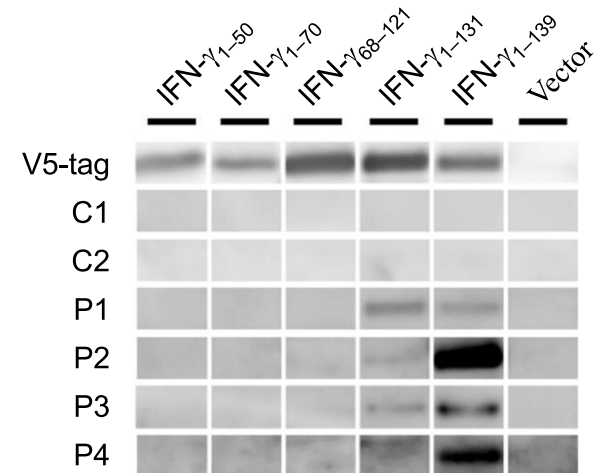
IFN- γ structure



Binding of autoAbs to IFN- γ deletion clone (ELISA)



(Western blot)



P121-131 (SPAAGTGKRKR) recognized by anti-IFN- γ AutoAbs

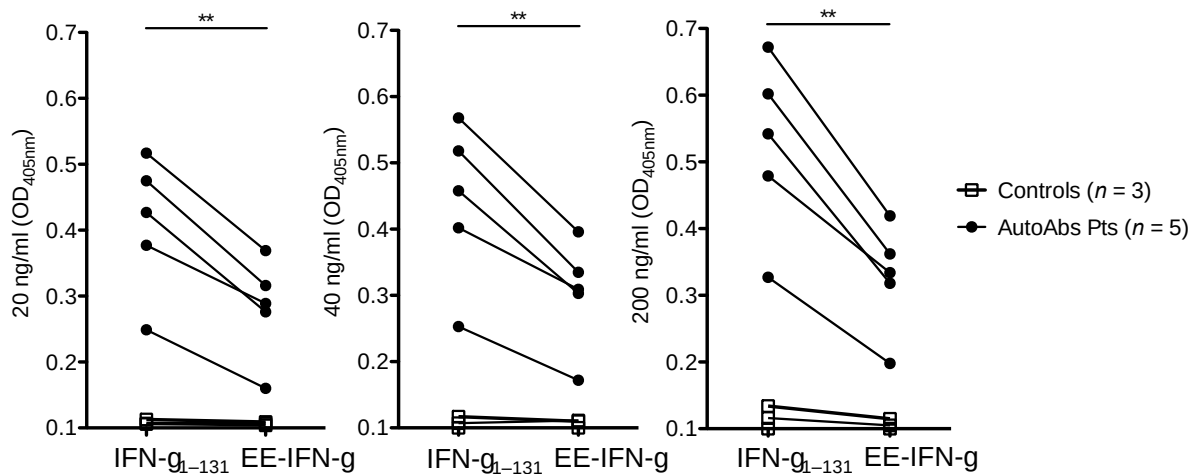
The critical motif in P₁₂₁₋₁₃₁ for AutoAbs binding

C-terminal a.a. alignment of IFN- γ

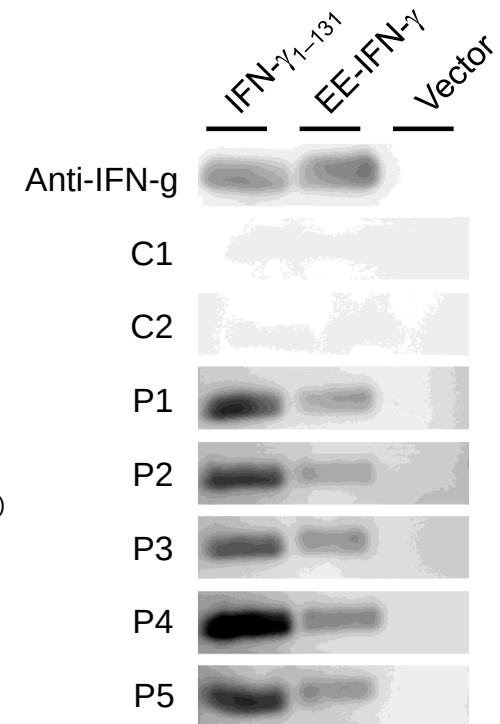
	116	121	127	
<i>B. taurus</i>	VMNDLSPKSNLR	RKRKRS	QNLFRGRR	ASM
<i>E. caballus</i>	VMNDLSPKANLR	RKRKRS	QNPFRGRR	ALQ
<i>S. scrofa</i>	VMNDLSPRSNLR	RKRKRS	QTMFQGQR	ASK
<i>G. gallus</i>	ILQKLVDPP	SFKRKRS	QSQRRC	CNC
<i>M. musculus</i>	VVHQLLPES	SLRKRKRS	RC	
<i>H. sapiens</i>	VMAELSPA	AKTGKRKRS	QMLFRGRR	ASQ
EE-IFN- γ	VMAELLPE	SSLRKRKR		

Epitope-Erased-IFN- γ

Decreased binding affinity of EE-IFN- γ to AutoAbs (ELISA)



(Western blot)

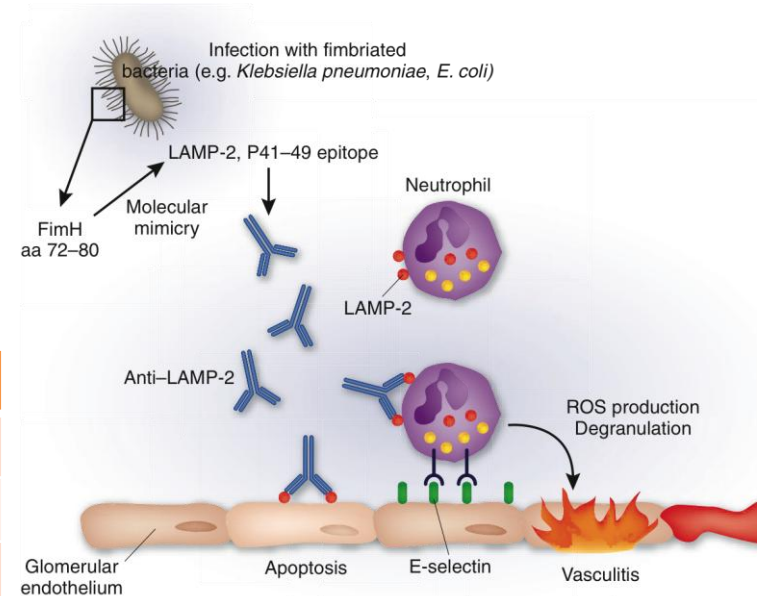


The origin of AutoAbs against IFN- γ

Example of Molecular Mimicry: Autoantibodies to neutrophil cytoplasmic antigens (ANCA)

If Molecular Mimicry happened :

Patient:	need to be infected or “exposed” to microbe
Autoantibodies	limited epitopes found on antigen
Antigen	A similar structure/sequence found in microbe



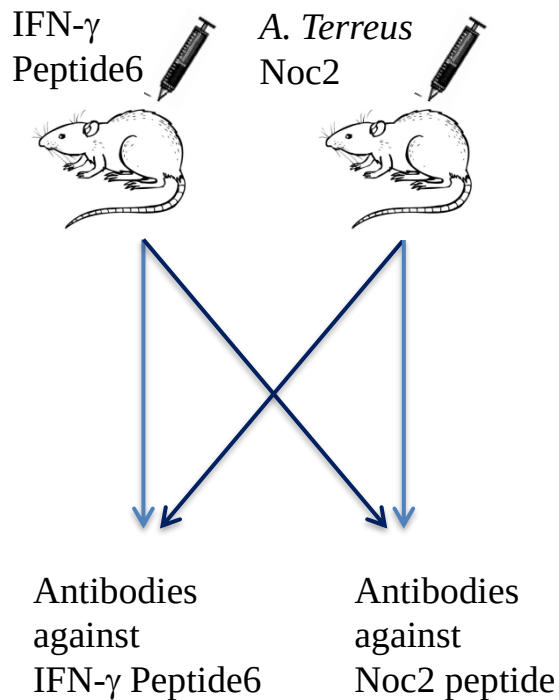
Blast of P₁₂₁₋₁₃₃ in NCBI database

Protein	Species	AA		AA	Positive	Accession code
IFN- γ P ₁₂₅₋₁₃₃	<i>Homo sapiens</i>	125	AAKTGKRKRSQML	133	-	GI:56786138
Ribosome assembly protein Noc2	<i>Aspergillus terreus</i>	105	TPKTGKRKRSEQQ	113	9/9(100%)	GI:115397505
Ribosome assembly protein Noc2	<i>Aspergillus fumigatus</i>	100	TPKIGKRKRSEEQ	108	8/9(89%)	GI:159131733
Ribosome assembly protein Noc2	<i>Aspergillus flavus</i>	102	TPKTGKRKRTEEQ	110	8/9(89%)	GI:238483989
Ribosome assembly protein Noc2	<i>Aspergillus nidulans</i>	103	SPKIGKRKRSETQ	111	8/9(89%)	GI:17517347
Ribosome assembly protein Noc2	<i>Aspergillus niger</i>	102	TPKIGKRKRSEDEQ	110	7/9(78%)	GI:317025642

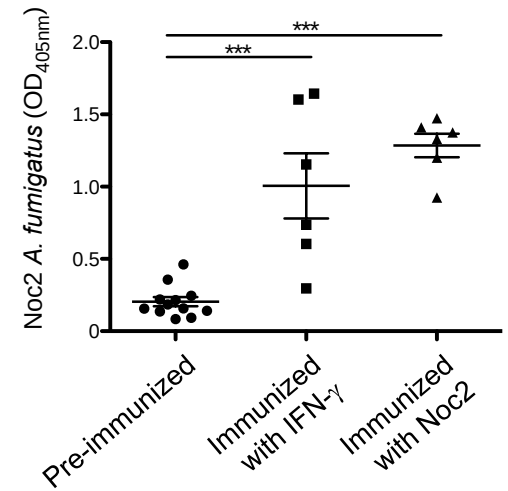
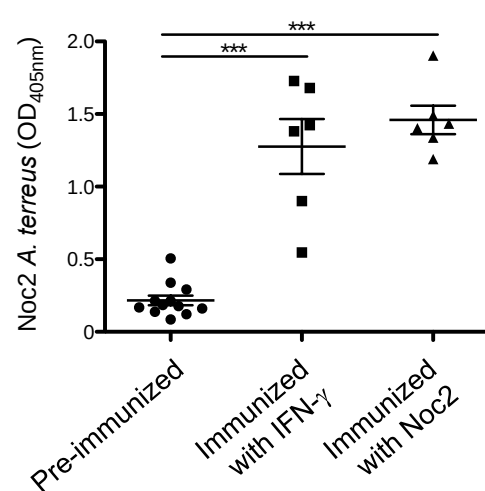
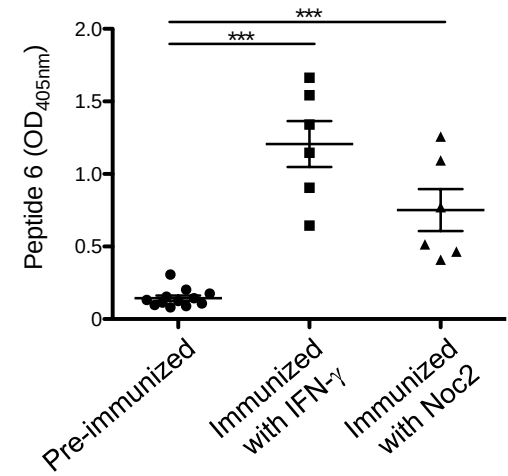
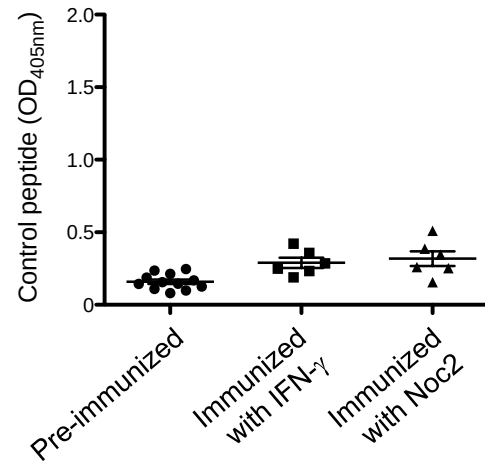
The P₁₂₅₋₁₃₃ epitope was 100% positive homology to amino acids 105–113 of the ribosome assembly protein Noc2 of *A. terreus*

Anti-Noc2 antibodies cross-react with IFN- γ *in vivo*?

Rat immunized by IFN- γ peptide 6 or Noc2 peptide



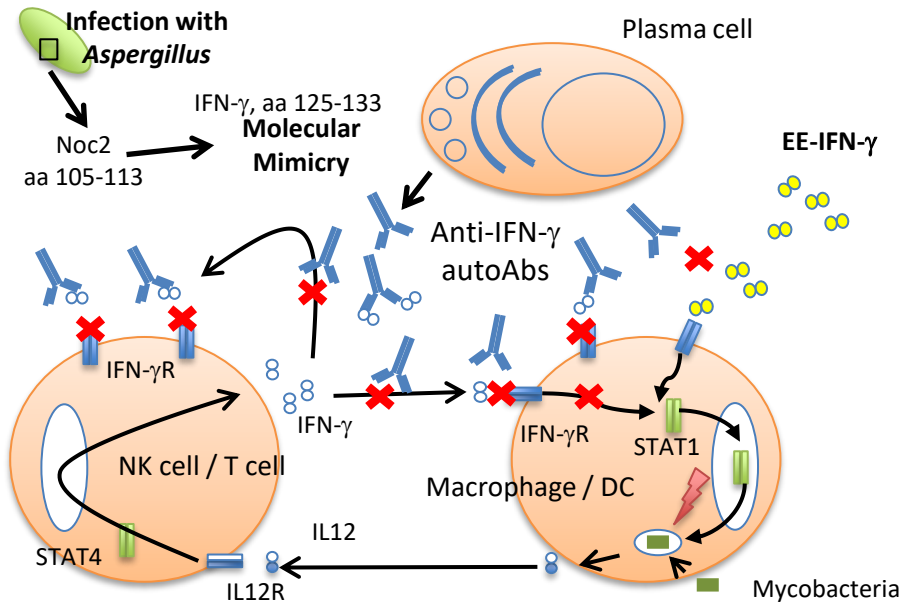
Binding of sera to NOC2 or IFN- γ



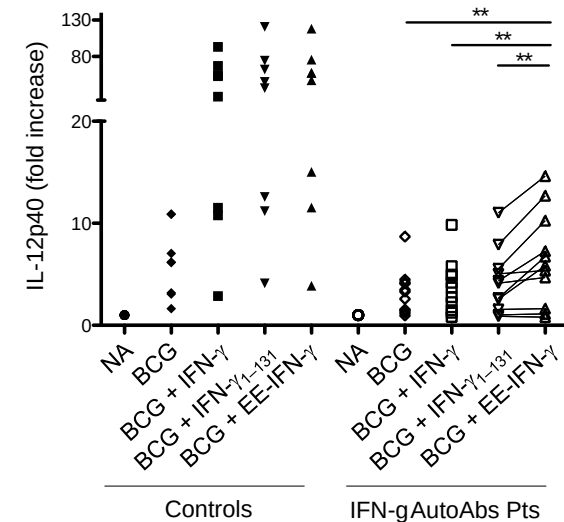
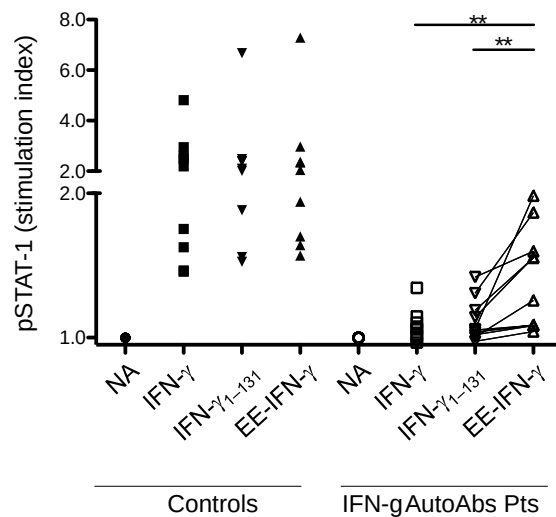
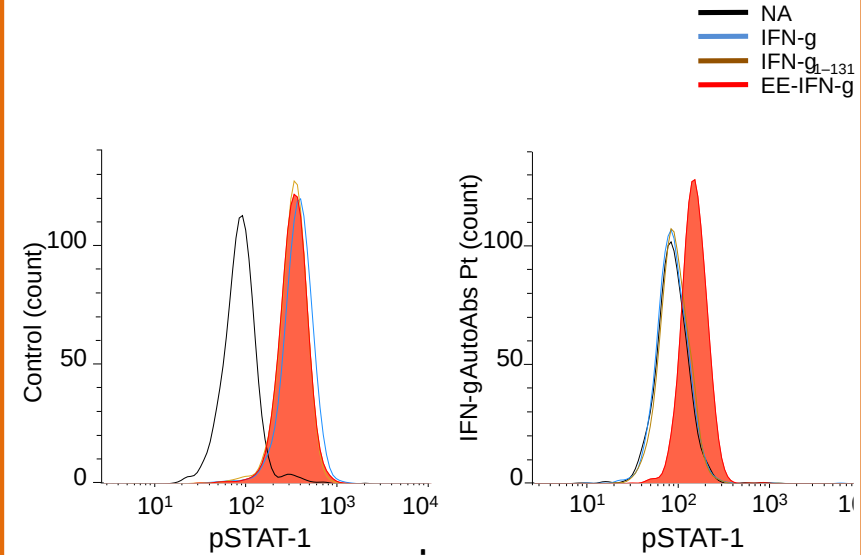
Antibodies induced by *Aspergillus* Noc2 cross-react with IFN- γ and *vice versa*.

The epitope-erased-IFN- γ to treat mycobacterial infection

Clean infection by activation IFN- γ signal, not autoAbs

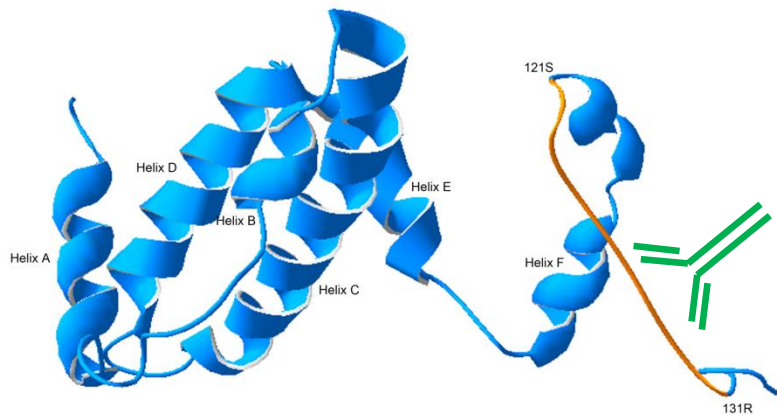


EE-IFN- γ induced STAT-1 phosphorylation in patients' whole blood

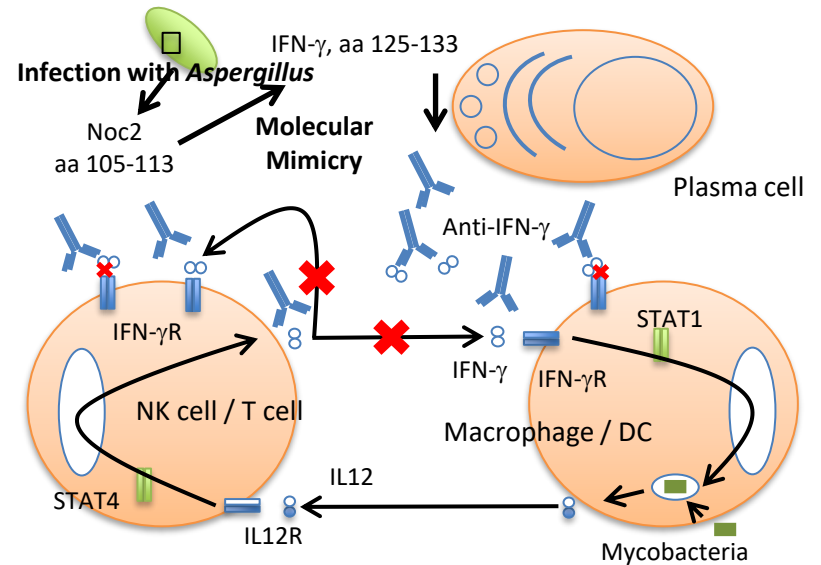


Summary

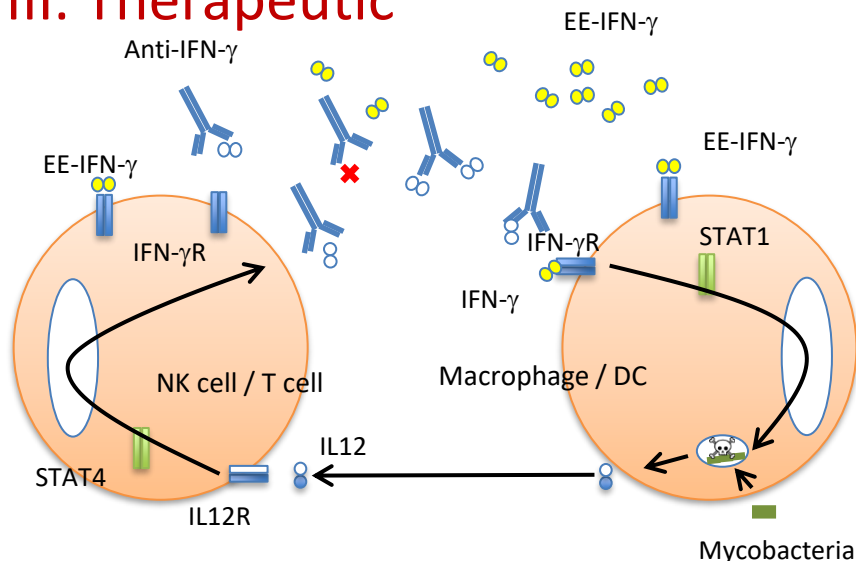
I. AutoAb against C-terminal



II. Molecular mimicry



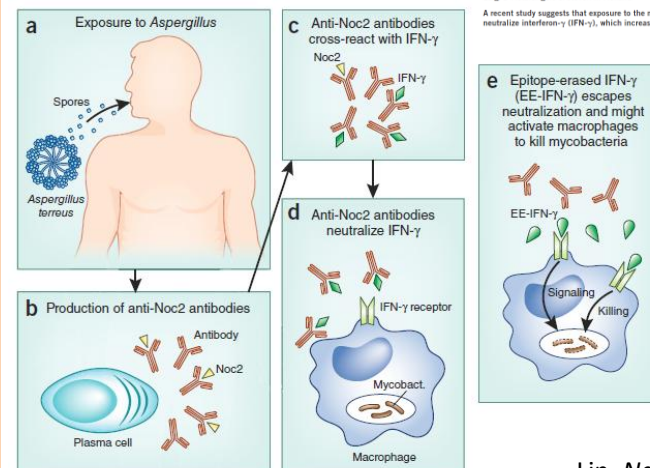
III. Therapeutic



NEWS AND VIEWS

Friendly fire: anti-cytokine antibodies elicited by microbes

Luigi D Notarangelo & Steven M Holland
A recent study suggests that exposure to the mold *Aspergillus* induces the production of antibodies that neutralize interferon- γ (IFN- γ), which increases the risk of mycobacterial disease.



Concomitant autoimmunity and late cancers in adult-onset immunodeficiency due to neutralizing anti-IFN- γ autoantibodies

Wan-Ting Tsai^{1,2}, Chih-Yun Cheng³, Hsin-Yun Sun¹, Bei-Chia Guo¹, Ying-Chieh Chiang¹, Chiao-Feng Cheng¹, Yi-Hua Pan¹, Un-In Wu¹, Jann-Tay Wang¹, Wang-Huei Sheng¹, Aristine Cheng^{1*}, Yee-Chun Chen¹ and Shan-Chwen Chang¹

¹Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan, ²Department of Internal Medicine, Taipei City Hospital, Zhongxiao Branch, Taipei, Taiwan, ³Department of Internal Medicine, National Taiwan University Hospital, Hsinchu Branch, Hsinchu, Taiwan

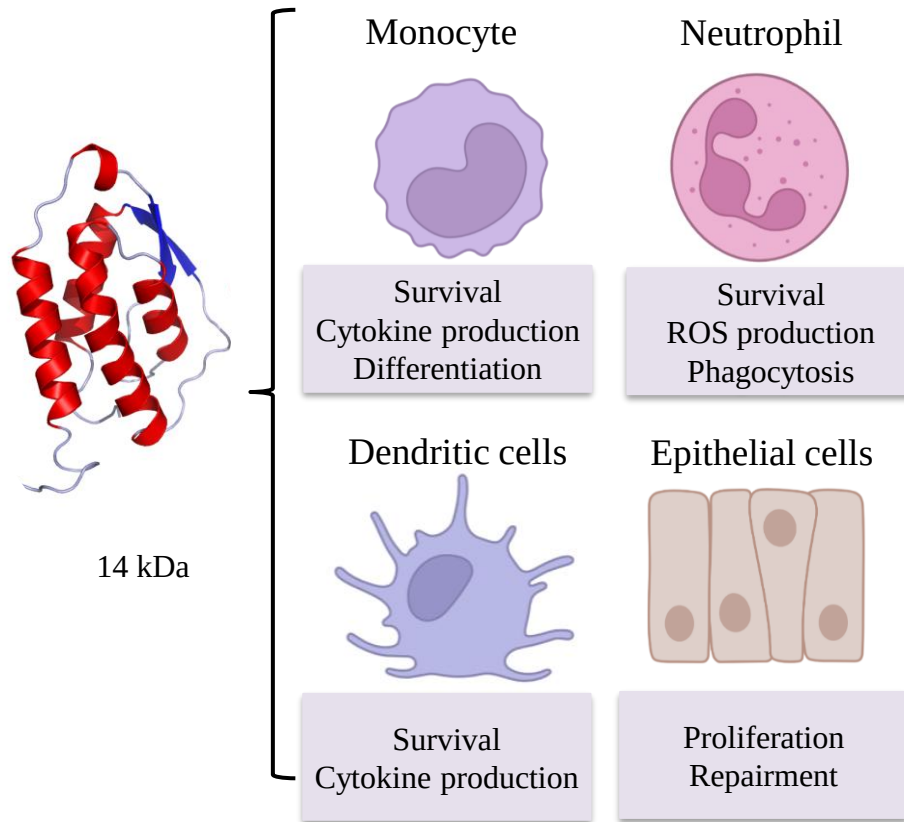
- IFN- γ considered play critical role in anti tumor immunity.
- However, little genetic evidence in human supports.

TABLE 1 Characteristics of 40 patients with neutralizing anti-IFN- γ autoantibodies in relation to concomitant autoimmune disease (AiD).

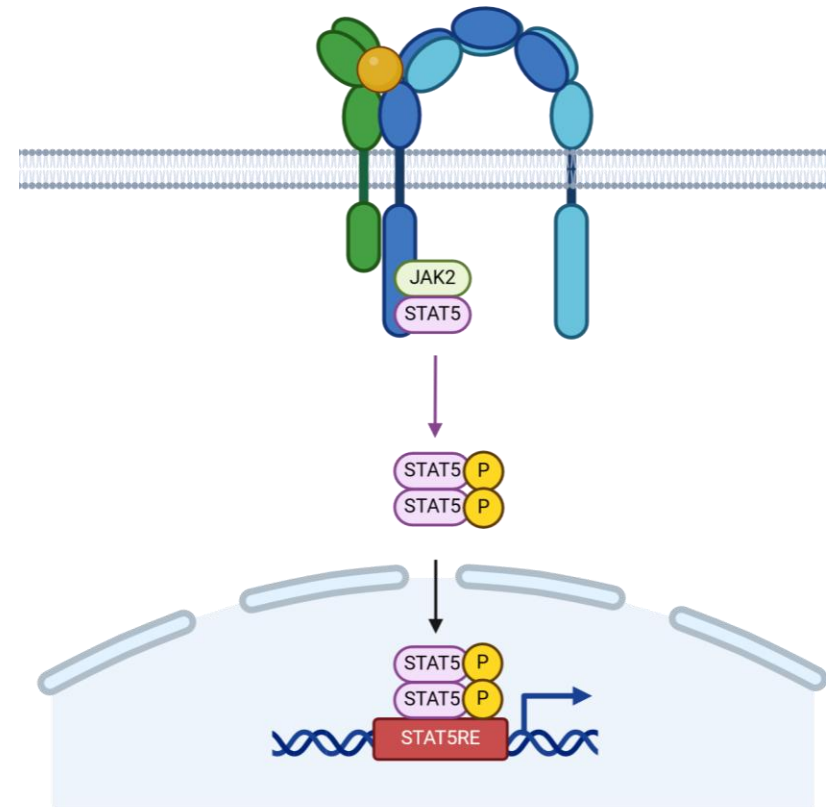
Variables	Overall	With AiD	Without AiD	p value
Basic profile				
Patient number, n	40	23	17	NA
Age, year (median [IQR])	56.5 (52.5-63.5)	54 (42-58)	59 (56-65)	0.019
Men, n (%)	21 (52.5)	8 (34.8)	13 (76.5)	0.012
Positive autoimmune markers, n (%)	37 (92.5)	23 (100.0)	14 (82.4)	0.069
Titer of binding anti-IFN- γ autoantibody, median (IQR)	9775 (8964-11862)	9857 (8452-11999)	9693 (9308-10310)	0.775
Titer of neutralizing anti-IFN- γ autoantibody ^a , median (IQR)	1:64 (1:16 - 1:256)	1:64 (1:16 - 1:256)	1: 64 (1:64- 1:128)	0.278
Any comorbidities, n (%)				
GERD or gastric ulcer	25 (62.5)	15 (65.2)	10 (58.8)	0.749
Chronic hepatitis B infection	5 (12.5)	2 (8.7)	3 (17.6)	0.634
Malignancy	10 (25.0)	8 (34.8)	2 (11.8)	0.145
Hodgkin's lymphoma	1 (2.5)	1 (4.3)	0 (0.0)	1.000
Papillary thyroid cancer	2 (5.0)	2 (8.7)	0 (0.0)	0.499
Genitourinary/gynecologic	4 (10.0)	3 (13.0)	1 (5.9)	0.624
Other malignancies ^b	4 (10.0)	2 (8.7)	2 (11.8)	1.000
Hypertension	9 (22.5)	4 (17.4)	5 (29.4)	0.456
Diabetes	9 (22.5)	4 (17.4)	5 (29.4)	0.456
COPD	1 (2.5)	0 (0.0)	1 (5.9)	0.425
Congestive heart failure	0 (0.0)	0 (0.0)	0 (0.0)	NA
Chronic hepatitis C	2 (5.0)	1 (4.3)	1 (5.9)	1.000
Chronic kidney disease	3 (7.5%)	2 (8.7%)	1 (5.9%)	1.000

Pleiotropic effects and signaling transduction of GM-CSF

GM-CSF is a hematopoietic cell regulator



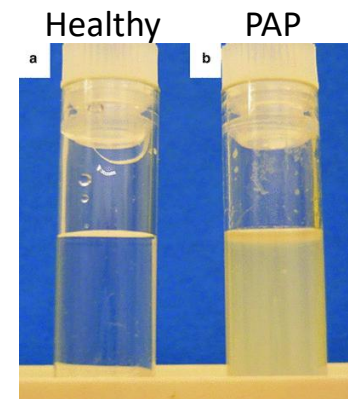
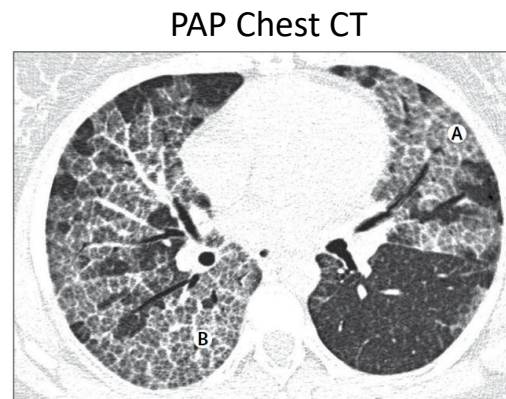
GM-CSF binds GMR α and GMR β c to trigger JAK2-STAT5 signaling activation



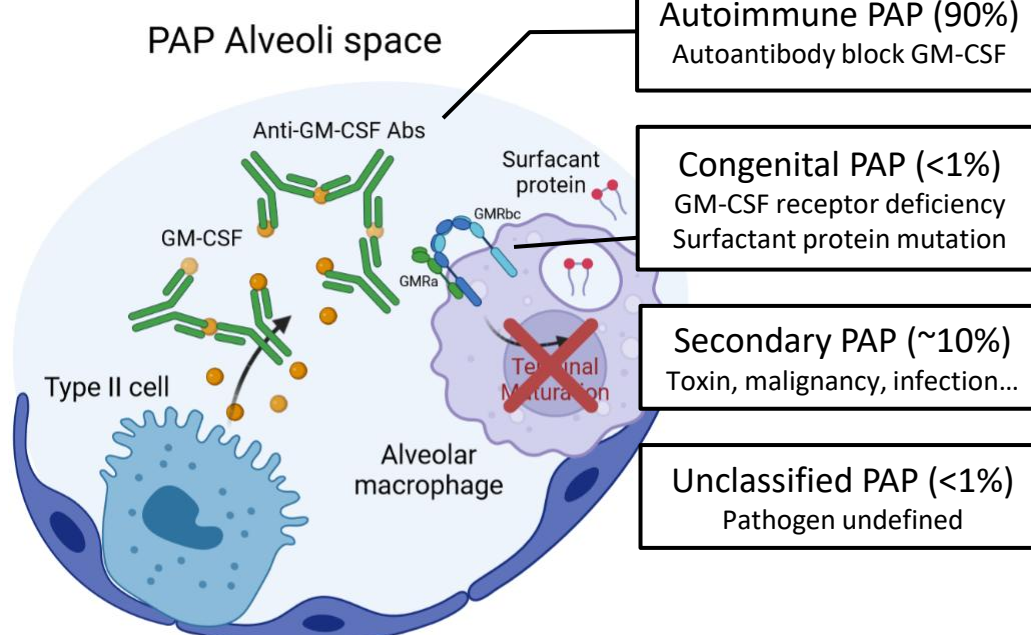
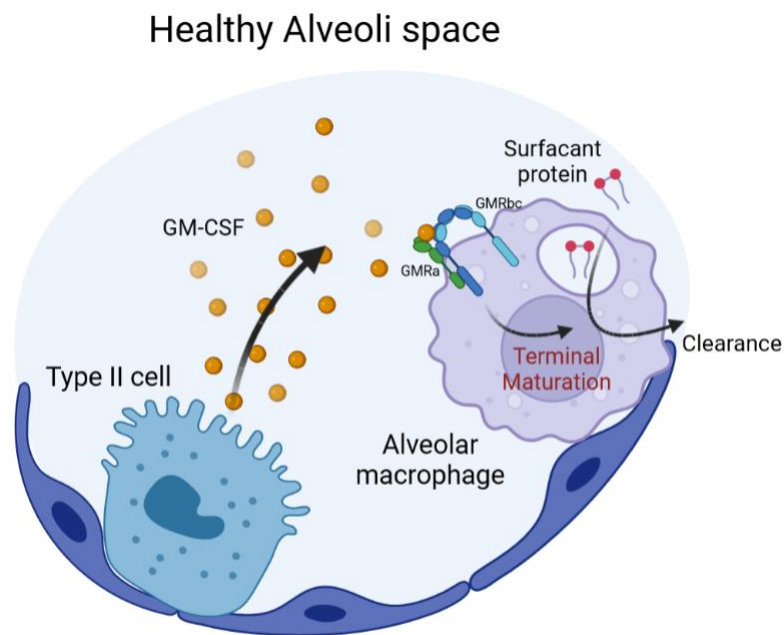
Pulmonary alveolar proteinosis (PAP) and GM-CSF autoAbs

Pulmonary alveolar proteinosis (PAP)

- Pulmonary autoimmune disease
- Diagnosis
 - (1) Ground-glass opacification of chest CT
 - (2) Milky like bronchoalveolar lavage fluid
 - (3) Surfactant protein accumulation



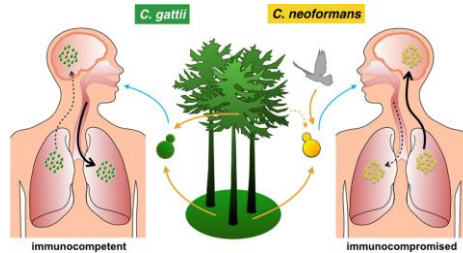
Critical pathogenesis of PAP: GM-CSF signaling blockade



Infection phenotype of GM-CSF autoAbs: Cryptococcosis and Nocardiosis

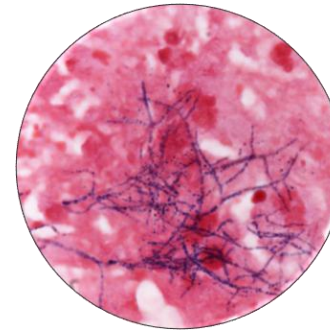
Cryptococcus spp.

- A fungal pathogen infectious disease
- *C. neoformans* in immunocompromised people (ex. HIV)
- *C. gattii* in immunocompetent people
- Cause severe pneumonia and meningitis

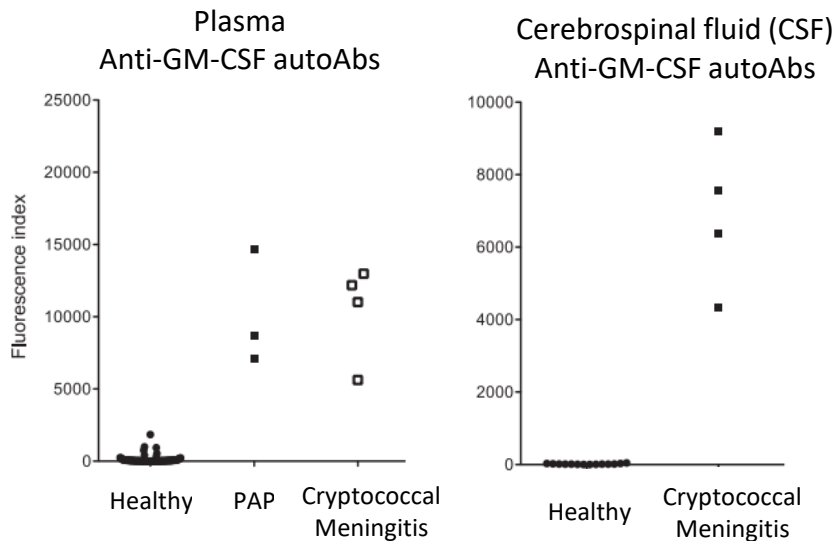


Nocardia spp.

- A bacterial pathogen.
- *N. asteroides*, *N. farcinica*, *N. brasiliensis* are common found in human.
- Mostly be found in immune-compromised patients.
- Commonly Infected location: brain and pulmonary.



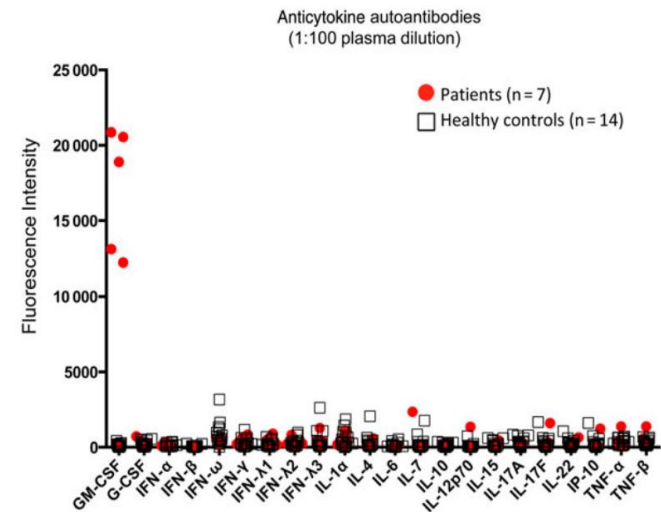
GM-CSF autoAbs in cryptococcosis



Rosen, *J Immunol* 2013

GM-CSF autoAbs in nocardiosis

Multiplex screening of **immunocompetent** nocardiosis patients



Rosen, *Clin Infect Dis* 2014

Infection phenotype of GM-CSF autoAbs in different ethnic cohort

ORIGINAL ARTICLE

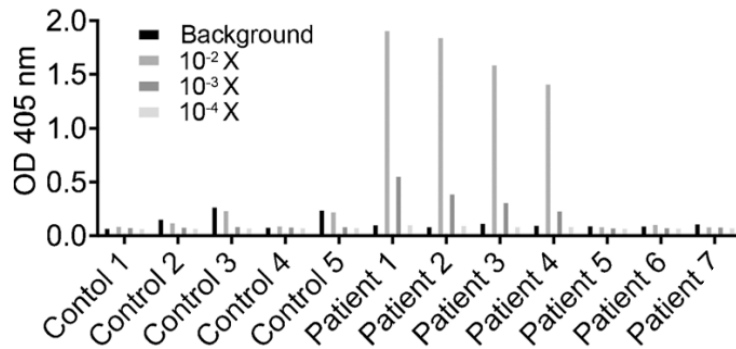
Disseminated Cryptococcosis Due to Anti-Granulocyte-Macrophage Colony-Stimulating Factor Autoantibodies in the Absence of Pulmonary Alveolar Proteinosis

Chen-Yen Kuo^{1,2} · Shang-Yu Wang^{1,3} · Han-Po Shih¹ · Kun-Hua Tu^{1,4} · Wen-Chi Huang⁵ · Jing-Ya Ding¹ · Chia-Hao Lin¹ · Chun-Fu Yeh^{1,6} · Mao-Wang Ho^{7,8} · Shi-Chuan Chang⁹ · Chi-Ying He^{1,10} · Hung-Kai Chen¹¹ · Chen-Hsuan Ho¹¹ · Chen-Hsiang Lee⁵ · Chih-Yu Chi^{1,7,8} · Cheng-Lung Ku^{1,6,12,13}

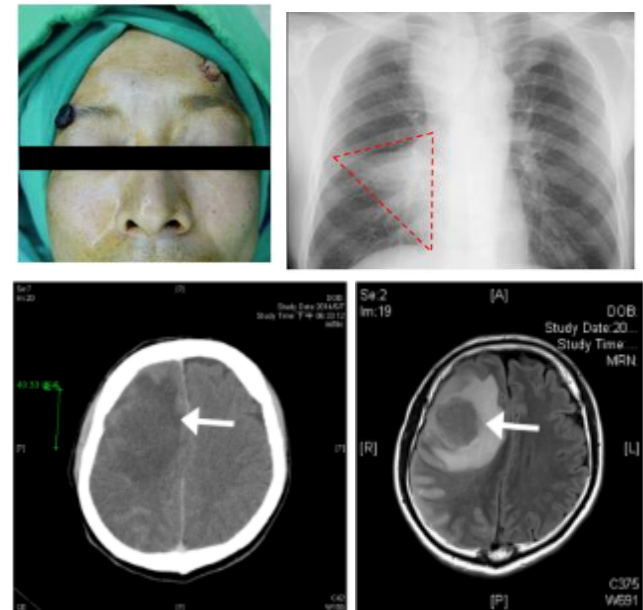
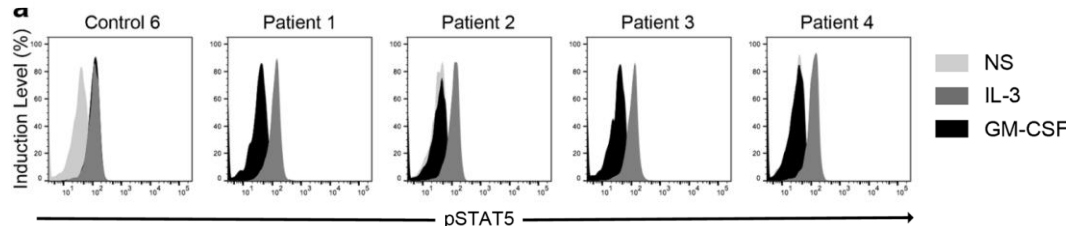


Kuo, Chen-Yen

GM-CSF autoAbs screening in Taiwan cryptococcosis



GM-CSF autoantibodies neutralizing abilities



CNS Cryptococcosis as major manifestation

Table 1 Demographics, laboratory data, treatment, and outcome of patients with cryptococcal infection and anti-GM-CSF autoantibodies

Clinical parameter	Patient 1	Patient 2	Patient 3	Patient 4
Age at diagnosis (years)	37	40	59	37
Sex	Male	Male	Female	Male
Underlying disease	No	Allergic rhinitis, asthma, gout	Hypertension	Chronic hepatitis C
Presenting symptoms	Headache, vomiting, blurred vision, seizure	Headache, left limb weakness, confusion	Blurred vision	Fever, cough Headache, vomiting
Infection site	CNS, skin, lung	CNS, lung	Eye	CNS, lung
Peripheral total WBC count (cells/ μ l) (3900–10,600)	17,230	10,700	8100	14,900
Granulocytes (cells/ μ l) (1638–7844)	15,558	7522	5848	12,248
Lymphocytes (cells/ μ l) (780–5936)	999	2215	1547	1579
Monocytes (cells/ μ l) (0–1272)	637	717	510	939
Serum cryptococcal antigen	>1:1024	1:512	1:64	1:256
Cerebrospinal fluid data				
Opening pressure (mm H ₂ O)	>60	NA	NA	130
WBC (cells/mm ³)	40	NA	NA	534
Granulocyte (cells/mm ³)	5	NA	NA	48
Lymphocytes (cells/mm ³)	10	NA	NA	459
Monocytes (cells/mm ³)	24	NA	NA	27
Microbiology	India ink (+) Cryptococcal antigen (>1:1024) and culture (+)	Cryptococcal fungal spores and culture (+)	Cryptococcal antigen (1:64)	Cryptococcal antigen (1:256)
Protein (mg/dl)	144.7	NA	NA	92
Glucose (mg/dl)	<10	NA	NA	34
PAP	No	No	No	No
HIV Ab	Negative	Negative	Negative	Negative
Antifungal agents	AmB + 5-FC for 3 months	AmB + 5-FC for 3 months; then fluconazole	AmB (intraocular); then voriconazole	AmB + 5-FC; then fluconazole
Outcome and sequelae	Hydrocephalus, status epilepticus, coma, death	Hydrocephalus, focal seizure, left hemiplegia	Impaired vision	No sequelae

CNS central nervous system, WBC white blood cell, PAP pulmonary alveolar proteinosis, HIVAb human immunodeficiency virus antibody, AmB amphotericin B, 5-FC 5-fluorocytosine, NA not available

Cryptococcus gattii Infection as the Major Manifestation in Taiwan

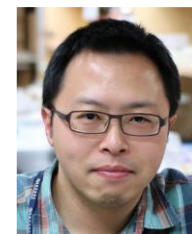
	GM-CSF Abs (-)	GM-CSF Abs (+)	p value
Number	12	14	
Age (yrs.) (median [IQR])	57 [36~73]	55 [40~61]	0.571
Sex = male (%)	7 (58.3)	12 (85.7)	0.190
Autoimmune disease (%)	1 (8.3)	2 (14.3)	1.000
Chronic infection (%)	5 (41.7)	4 (28.6)	0.683
Risks of host [#] (%)	3 (25.0)	0 (0.00)	0.085
Solid organ or stem cell transplant recipient	0 (0.00)	0 (0.00)	NA
Hematologic malignancy	2 (16.7)	0 (0.00)	0.203
Immunosuppressive therapy	1 (8.3)	0 (0.00)	0.462
End-stage liver or renal disease	1 (8.3)	0 (0.00)	0.462
WBC (10 ³ μ L) (median [IQR])	10.00 [5.25, 15.05]	10.30 [7.70, 14.70]	0.685
CRP (mg/dL) (median [IQR])	4.63 [0.47, 13.02]	0.28 [0.14, 4.42]	0.218
CCI score (median [IQR])	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.69

C. species (%) <0.001

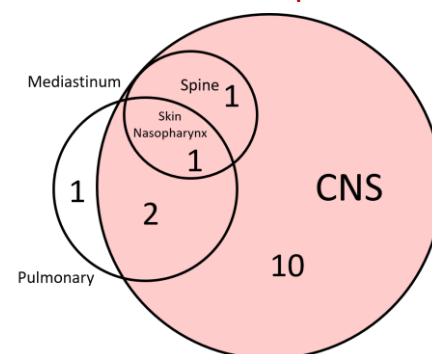
<i>C. gattii</i>	0 (0.00)	11 (78.6)
<i>C. neoformans</i>	10 (83.3)	0 (0.00)
<i>Cryptococcus spp</i> *	2 (16.7)	3 (21.4)

ICU stay (%)	9 (75.0)	4 (28.6)	0.047
Length of stay (days) (median [IQR])	47.50 [32.00, 81.00]	44.50 [26.00, 73.75]	0.817
Mortality (%)	2 (16.7)	1 (7.10)	0.580

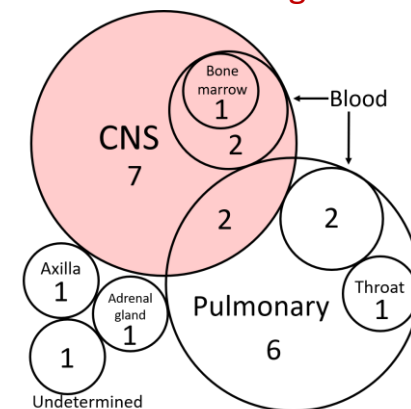
[#]Risk factors proposed by consensus from European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC). *Exact species could not be confirmed. CNS, central nervous system; anti-GM-CSF Abs, anti-granulocyte-macrophage colony-stimulating factor autoantibodies; IQR, interquartile range; WBC, white blood cell count; CRP, c-reactive protein; CCI, Charlson comorbidity index; *Cryptococcus*; ICU, intensive care unit; p value < 0.05 was significant



GM-CSF autoAbs positive



GM-CSF autoAbs negative

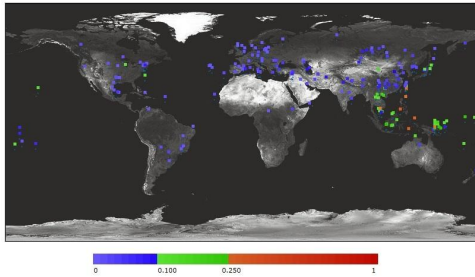


GM-CSF autoAbs are not associated with specific HLA type

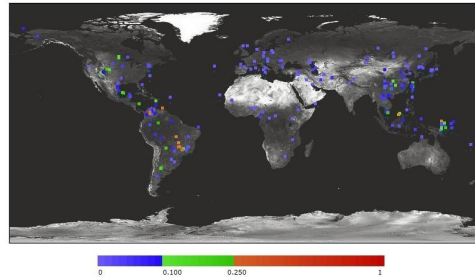
Anti-IFN- γ autoAbs were strongly associated HLA
DRB1 15:02 and 16:02

Allele type	Control		Patient		χ^2	P_{χ^2}	Fisher exact P value
	Count*	%†	Count*	%†			
Thailand	N = 101		N = 78				
DRB1*15:02	25	12.38	67	42.95	43.0875	5.23×10^{-11}	8.26×10^{-11}
DRB1*16:02	20	9.90	46	29.49	22.4560	2.15×10^{-6}	3.81×10^{-6}
DQB1*05:01	21	10.40	51	32.69	27.2348	1.80×10^{-7}	2.57×10^{-7}
DQB1*05:02	44	21.78	65	41.67	16.4347	.0001	.0001
Taiwan	N = 102		N = 44				
DRB1*15:02	2	0.98	11	12.50	19.1789	1.19×10^{-5}	.0001
DRB1*16:02	17	8.33	38	43.18	48.8374	2.78×10^{-12}	2.53×10^{-11}
DQB1*05:01	7	3.43	10	11.36	7.0552	.0079	.0127
DQB1*05:02	25	12.25	42	47.73	43.7541	3.72×10^{-11}	2.21×10^{-10}

DRB1*15:02



DRB1*16:02



High prevalence found in
Southeast Asia and South
China; associated with
specific HLA alleles found
in Baiyue

HLA analysis of 21 GM-CSF
autoantibody-positive patient in Taiwan

HLA	Patient (2n=42)	Control (2n=1008)	P-value	
DRB1*03:01	0.048 (2)	0.087 (87)	0.572	DRB1
DRB1*07:01	0.024 (1)	0.028 (28)	1.000	
DRB1*08:03	0.167 (7)	0.086 (86)	0.089	
DRB1*09:01	0.143 (6)	0.166 (167)	0.834	
DRB1*11:01	0.071 (3)	0.080 (80)	1.000	
DRB1*12:01	0.024 (1)	0.033 (33)	1.000	
DRB1*12:02	0.095 (4)	0.086 (86)	0.777	
DRB1*13:12	0.024 (1)	0.006 (6)	0.249	
DRB1*14:01/54	0.095 (4)	0.039 (39)	0.088	
DRB1*14:05	0.024 (1)	0.022 (22)	0.613	
DRB1*14:07	0.024 (1)	0 (0)	0.040	DQB1
DRB1*15:01	0.167 (7)	0.068 (68)	0.025	
DRB1*15:02	0.048 (2)	0.023 (23)	0.264	
DRB1*16:02	0.048 (2)	0.048 (48)	1.000	
DQB1*02:01	0.048 (2)	0.086 (86)	0.571	
DQB1*02:02	0.024 (1)	0.024 (24)	1.000	
DQB1*03:01	0.214 (9)	0.212 (213)	1.000	
DQB1*03:03	0.143 (6)	0.171 (172)	0.834	
DQB1*04:01	0.024 (1)	0.069 (69)	0.356	
DQB1*05:01	0.024 (1)	0.025 (25)	1.000	
DQB1*05:02	0.119 (5)	0.093 (94)	0.586	DPB1
DQB1*05:03	0.095 (4)	0.049 (49)	0.157	
DQB1*06:01	0.238 (10)	0.107 (108)	0.020	
DQB1*06:02	0.071 (3)	0.034 (34)	0.181	
DPB1*01:01	0.025 (1)	0.001 (1)	0.075	
DPB1*02:01	0.150 (6)	0.172 (173)	0.833	
DPB1*02:02	0.025 (1)	0.085 (85)	0.246	
DPB1*03:01	0.025 (1)	0.054 (54)	0.718	
DPB1*04:01	0.050 (2)	0.081 (81)	0.764	
DPB1*05:01/135:01	0.575 (23)	0.437 (440)	0.104	
DPB1*13:01/107:01	0.050 (2)	0.066 (66)	1.000	DPB1
DPB1*19:01	0.025 (1)	0.013 (13)	0.422	
DPB1*21:01	0.075 (3)	0.019 (19)	0.048	

Lo and Wang, *J Clin Immunol* 2022

GM-CSF autoAbs PAP and cryptococcosis are not overlapping

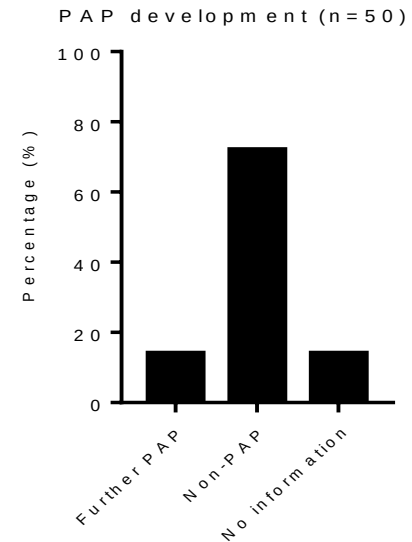
Taiwan real-world data

National Health Insurance Research Database

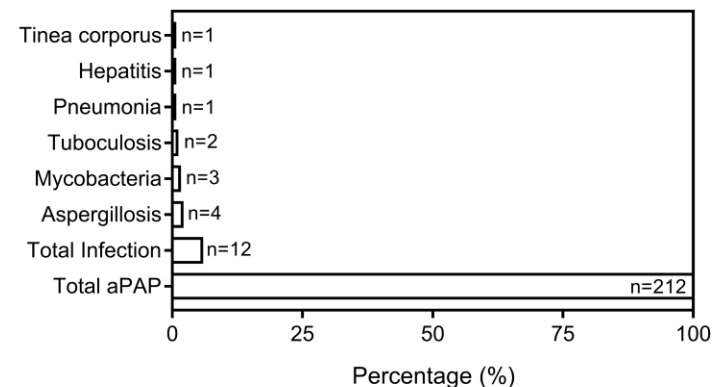
Year	PAP n/1,000,000 (%)	Cryptococcal meningitis n/1,000,000 (%)	Intersection of A and B
1996	0 (0.00)	5 (1.99)	0 (0.00)
1997	1 (7.69)	2 (0.80)	0 (0.00)
1998	0 (0.00)	11 (4.38)	0 (0.00)
1999	1 (7.69)	10 (3.98)	0 (0.00)
2000	0 (0.00)	10 (3.98)	0 (0.00)
2001	0 (0.00)	14 (5.58)	0 (0.00)
2002	2 (15.4)	19 (7.57)	0 (0.00)
2003	0 (0.00)	9 (3.59)	0 (0.00)
2004	0 (0.00)	22 (8.76)	0 (0.00)
2005	3 (23.1)	24 (9.56)	0 (0.00)
2006	0 (0.00)	9 (3.59)	0 (0.00)
2007	1 (7.69)	17 (6.77)	0 (0.00)
2008	1 (7.69)	13 (5.18)	0 (0.00)
2009	2 (15.4)	14 (5.58)	0 (0.00)
2010	0 (0.00)	20 (7.97)	0 (0.00)
2011	1 (7.69)	29 (11.6)	0 (0.00)
2012	1 (7.69)	23 (9.16)	0 (0.00)
Total	13 (100)	251 (100)	0 (0.00)

Literature review of GM-CSF

autoAbs positive cryptococcosis



Japanese autoimmune PAP cohort



No difference of autoAb's composition, titer and, neutralizing

**Cryptococcosis with
anti-GM-CSF autoantibodies**

	IgG subclass					Immunoglobulin isotype		
	IgG	IgG1	IgG2	IgG3	IgG4	IgA	IgM	IgE
P1	⊙	⊙	⊙	⊙	⊙			
P2	⊙	⊙		⊙				
P3	⊙	⊙			⊙			
P4	⊙	⊙		⊙				
P5	⊙	⊙			⊙			
P6	⊙	⊙			⊙		⊙	
P7	⊙	⊙		⊙				
P8	⊙	⊙						
P9	⊙	⊙			⊙			
P10	⊙	⊙		⊙	⊙			
P11	⊙	⊙		⊙	⊙			
P12	⊙	⊙		⊙			⊙	
P13	⊙	⊙			⊙		⊙	
P14	⊙	⊙						
P15	⊙	⊙			⊙		⊙	

**PAP with
anti-GM-CSF autoantibodies**

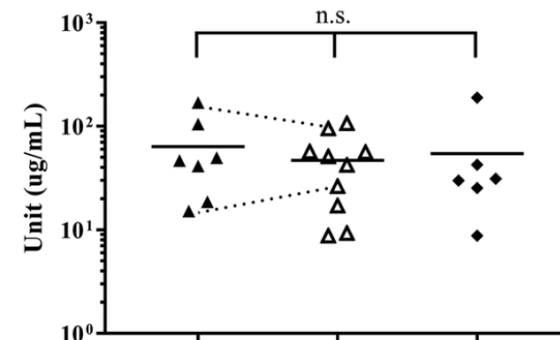
	IgG subclass					Immunoglobulin isotype		
	IgG	IgG1	IgG2	IgG3	IgG4	IgA	IgM	IgE
PAP1	⊙	⊙		⊙				
PAP2	⊙	⊙		⊙	⊙			
PAP3	⊙	⊙						
PAP4	⊙	⊙			⊙			
PAP5	⊙	⊙			⊙			
PAP6	⊙	⊙			⊙			

⊙ denoted positive.

For IgG, IgA, IgE, IgG1, IgG2, IgG3 and IgG4 positive meaning: signal – background value > 0.1.

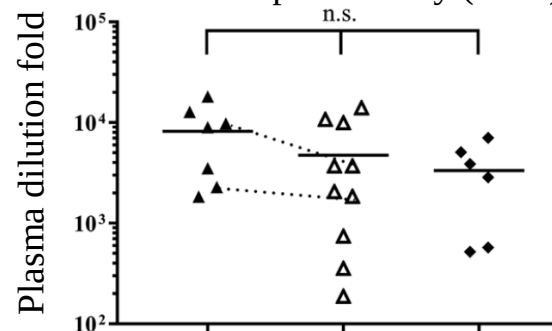
For IgM positive meaning: signal – background value > 0.4.

Autoantibodies titer

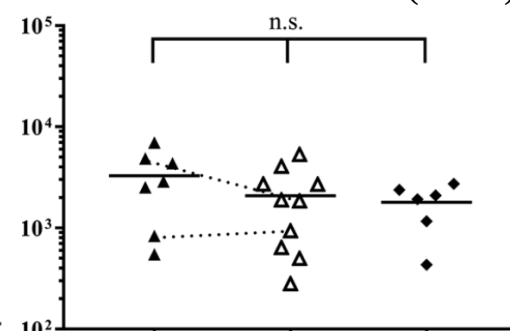


Neutralizing

STAT5 reporter assay (IC50)



TF-1 Cell Proliferation (EC50)



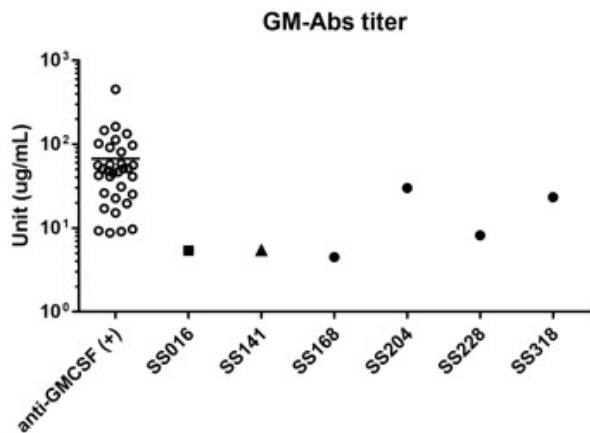
▲ Active Crypto △ Inactive Crypto ◆ PAP

Ant-GM-CSF Abs in patient with Sjögren syndrome

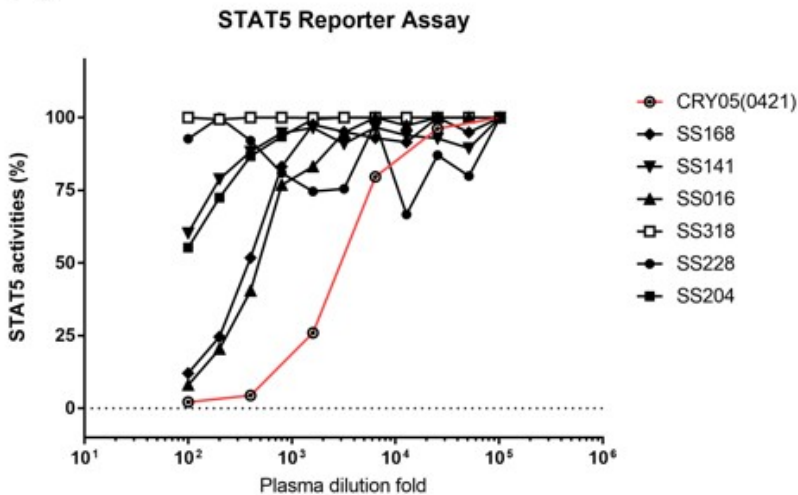
Sjögren's syndrome (SS): A systemic autoimmune disease characterized by dry eyes and dry mouth.

Yu-Fang Lo
20191122

(A)



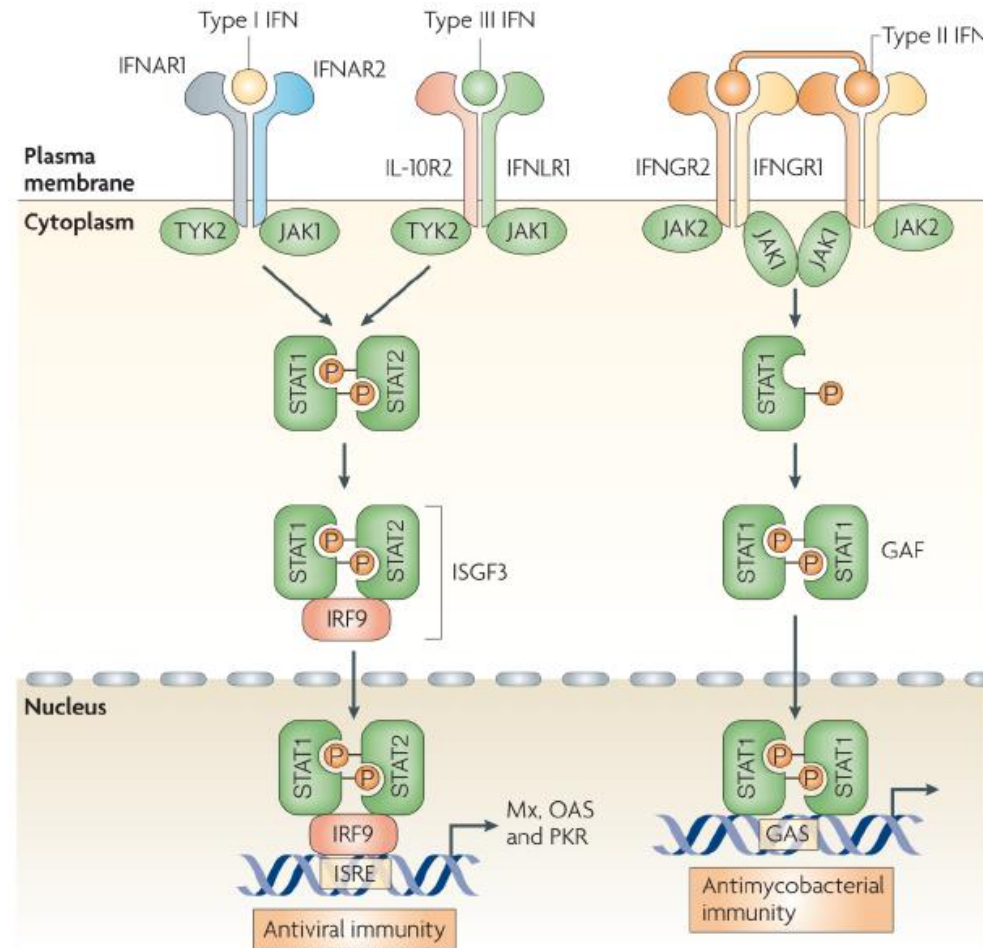
(B)



(C)

Patient number	GM-Abs	
	Titer (ug/mL)	IC50 (dilution fold)
SS016	5.4	470.4
SS141	5.5	132.7
SS168	4.5	406.3
SS204	30.1	155.2
SS228	8.2	Non-neutralizing
SS318	23.4	Non-neutralizing
CRY005 (PC)	51.2	3672

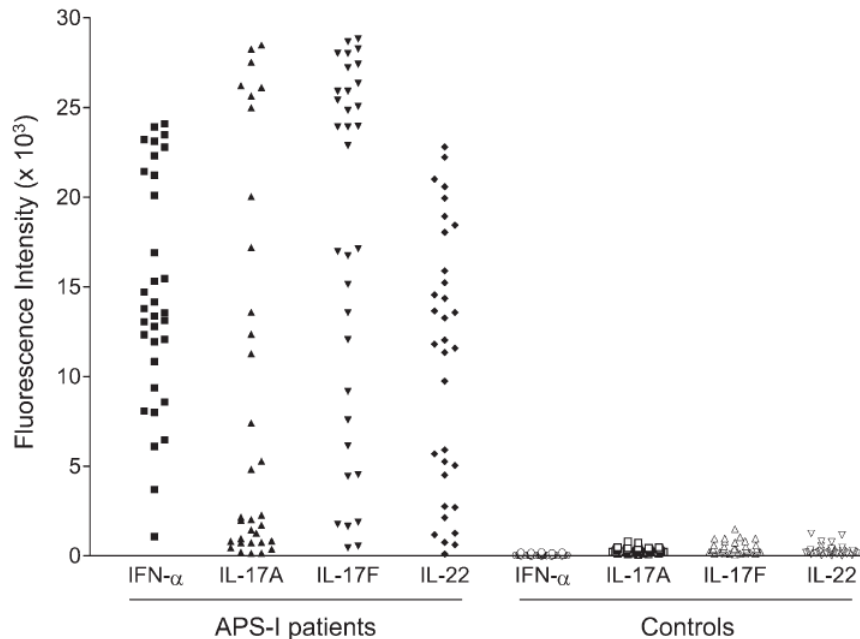
Type I interferon



- IFN α (IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFNA8, IFNA10, IFNA13, IFNA14, IFNA16, IFNA17 and IFNA21), IFN ω (IFNW1), IFN ϵ (IFNE), IFN κ (IFNK) and IFN β (IFNB1)
- IFN α is the master IFN produced by pDC; and IFN β is expressed in most cells.
- The receptors (IFNAR1, IFNAR2) are widely expressed in most cell types.

Anti-IL-17 and type I IFN autoAbs cause mucocutaneous candidiasis in APS-I

APS-I: Autoimmune Polyendocrine Syndrome type I (Also called APECED, mutated in *AIRE*)



Brief Definitive Report

Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I

Anne Puel,^{1,2} Rainer Döflinger,³ Angels Natividad,^{1,2} Maya Chrabieh,^{1,2} Gabriela Barcenas-Morales,⁴ Capucine Picard,^{1,2,5} Aurélie Cobat,^{1,2} Marie Ouachée-Chardin,⁸ Antoine Toulon,^{2,6} Jacinta Bustamante,^{1,2} Saleh Al-Muhsen,⁹ Mohammed Al-Owain,¹⁰ Peter D. Arkwright,¹¹ Colm Costigan,¹² Vivienne McConnell,¹³ Andrew J. Cant,¹⁴ Mario Abinun,¹⁴ Michel Polak,^{2,15} Pierre-François Bougnères,¹⁶ Dinakantha Kumararatne,³ László Marodi,¹⁷ Amit Nahum,¹⁸ Chaim Roifman,¹⁸ Stéphane Blanche,^{2,7} Alain Fischer,^{2,7,19} Christine Bodemer,^{2,6} Laurent Abel,^{1,2,20} Desa Lilic,²¹ and Jean-Laurent Casanova^{1,2,7,20}

¹Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Institut National de la Santé et de la Recherche Médicale (INSERM), U550, 75015 Paris, France

High titers of auto-Abs against IFN-α, IL-17A, IL-17F, and IL-22

→ Lost of self-tolerance (autoimmune disease) might induce the production of Anticytokine Abs, which might cause the clinical infectious problems

TLR3-dependent type I IFN immunity in RECs and TLR7-dependent type I IFN immunity in pDCs are strong determinants of protection against SARS-CoV-2

Science

RESEARCH ARTICLE

Cite as: Q. Zhang *et al.*, *Science* 10.1126/science.abd4570 (2020)

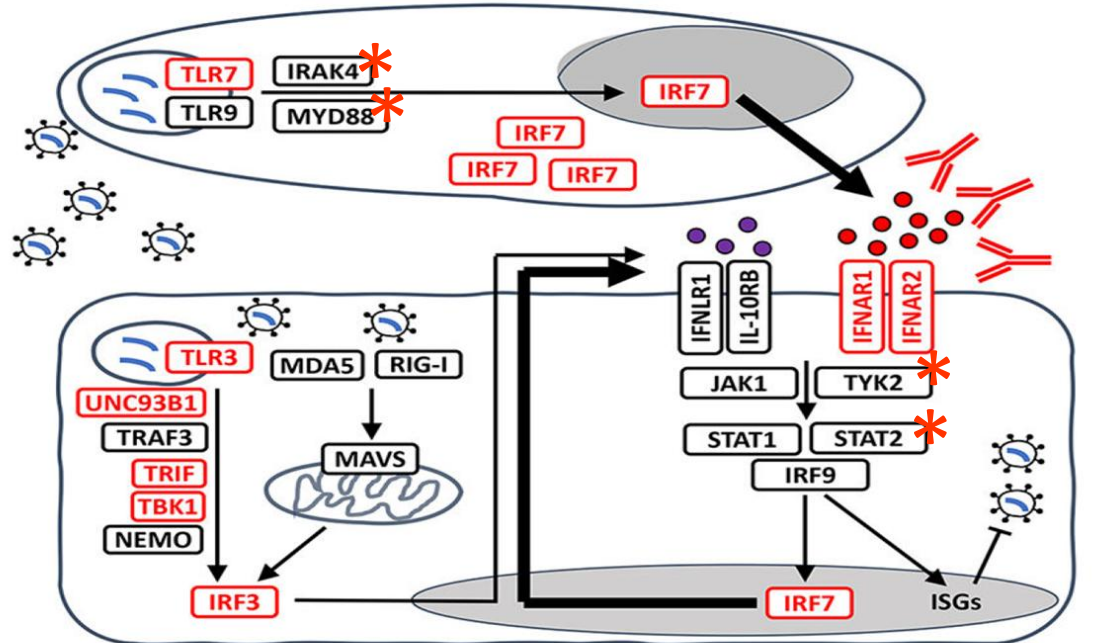
Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

Qian Zhang¹, Paul Bastard^{2,3*}, Zhiyong Liu^{1*}, Jérémie Le Pen^{4*}, Marcela Moncada-Velez^{1*}, Jie Chen^{1*}, Masato Ogishi^{1*}, Ira K. D. Sabli^{1*}, Stephanie Hodeib^{1*}, Cecilia Koro^{1*}, Jérémie Rosain^{2,3*}, Kaya Bilguvar^{1*}, Junqiang Ye^{1*}, Alexandre Bolze^{1*}, Benedetta Bigio^{1*}, Rui Yang^{1*}, Andrés Augusto Arias^{1,5,10*}, Qinhua Zhou^{1*}, Yu Zhang^{11,12*}, Fanny Onodi^{1*}, Sarantis Korniotis^{1*}, Léa Karp^{1*}, Quentin Philippot^{2,3}, Marwa Chbihi^{2,3}, Lucie Bonnet-Madin^{1*}, Karim Dorgham^{1*}, Nikola Smith^{1*}, William M. Schneider^{1*}, Brandon S. Razoosky^{1*}, Hans-Heinrich Hoffmann^{1*}, Eleftherios Michailidis^{1*}, Leen Moens^{1*}, Ji Eun Han^{1*}, Lazaro Lorenzo^{2,3}, Lucy Bizien^{2,3}, Philip Meade^{1*}, Anna-Lena Neehus^{2,3}, Aileen Camille Ugurbil^{1*}, Aurélien Corneau^{1*}, Gaspard Kerner^{2,3}, Peng Zhang^{1*}, Franck Rapaport^{1*}, Yoann Seeluthner^{2,3}, Jeremy Manry^{2,3}, Cecile Masson^{1*}, Yohann Schmitt^{1*}, Agatha Schlüter^{1*}, Tom Le Voyer^{2,3}, Taushif Khan^{2*}, Juan Li^{1*}, Jacques Fellay^{2,3,24,25}, Lucie Roussel^{1*}, Mohammad Shahrooee^{27,28}, Mohammed F. Alosaimi²⁹, Davood Mansouri^{30,31,32}, Haya Al-Saud³³, Fahd Al-Mulla³⁴, Feras Almourfi³⁵, Saleh Zaid Al-Muhsen³⁶, Fahad Alshime³⁷, Saeed Al Turki^{38,39}, Rana Hasanato³⁹, Diederik van de Beek³⁸, Andrea Biondi³⁹, Laura Rachele Bettini³⁹, Mariella D'Angio³⁹, Paolo Bonfanti⁴⁰, Luisa Imberti⁴¹, Alessandra Sottini⁴¹, Simone Paghera⁴¹, Eugenia Quiros-Roldan⁴², Camillo Rossi⁴³, Andrew J. Oler⁴⁴, Miranda F. Tompkins⁴⁵, Camille Alba⁴⁵, Isabelle Vandernoot⁴⁵, Jean-Christophe Goffard⁴⁵, Guillaume Smits⁴⁶, Isabelle Migotte⁴⁶, Filomeen Haerynck⁴⁶, Pere Soler-Palacin⁴⁶, Andrea Martin-Nalda⁴⁶, Roger Colobran⁴⁷, Pierre-Emmanuel Morange⁴⁷, Sevgi Keles⁴⁸, Fatma Çölkese⁴⁸, Tayfun Özcelik⁴⁹, Kadriye Kart Yasar⁴⁹, Sevtap Senoglu⁴⁹, Şemsi Nur Karabela⁴⁹, Carlos Rodriguez Gallego^{50,51}, Giuseppe Novelli⁵⁰, Sami Hraiech⁴⁹, Yacine Tandjaoui-Lambiotte^{52,53}, Xavier Duval^{53,54}, Cédric Laouénan^{53,54}, COVID-STORM Clinicians¹, COVID Clinicians¹, Imagine COVID Group¹, French COVID Cohort Study Group¹, CoV-Contact Cohort¹, Amsterdam UMC Covid-19 Biobank¹, COVID Human Genetic Effort¹, NIAID-USUHS/TAGC COVID Immunity Group¹, Andrew L. Snow⁵⁵, Clifton L. Dalgard^{45,56}, Joshua Milner⁵⁶, Donald C. Vinh⁵⁶, Trine H. Mogensen^{49,70}, Nico Marr^{23,71}, Andrés N. Spaan⁷², Bertrand Boisson^{1,2,3}, Stéphanie Boisson-Dupuis^{1,2,3}, Jacinta Bustamante^{1,2,3,73}, Anne Puel^{1,2,3}, Michael Ciancanelli^{1,74}, Isabelle Meyts^{1,7,75}, Tom Maniatis^{7,76}, Vassili Soumelis^{13,77}, Ali Amara^{1*}, Michel Nussenzweig^{78,79}, Adolfo García-Sastre^{18,80,81,82}, Florian Krammer^{1*}, Aurora Pujol^{1*}, Darragh Duffy^{1*}, Richard Lifton^{83,84,85}, Shen-Ying Zhang^{1,3,24}, Guy Gorochoy^{1*}, Vivien Béziat^{1,2,24}, Emmanuelle Jouanguy^{1,2,24}, Vanessa Sancho-Shimizu^{1*}, Charles M. Rice^{1*}, Laurent Abel^{1,2,24}, Luigi D. Notarangelo^{11,12}, Aurélie Cobat^{1,2,24}, Helen C. Su^{11,12}, Jean-Laurent Casanova^{1,2,3,79,86}§

Gene	Inheritance	Genetic form	Genotype	Gender	Age (year)	Ancestry/Residence	Outcome
TLR3	AD	Known	p.Ser339fs/WT	M	40	Spain	Survived
TLR3	AD	Known	p.Pro554Ser/WT	M	68	Italy	Survived
TLR3	AD	Known	p.Trp769*/WT	M	77	Italy	Survived
TLR3	AD	Known	p.Met870Val/WT	M	56	Colombian/Spain	Survived
UNC93B1	AD	New	p.Glu96*/WT	M	48	Venezuelan/Spain	Survived
TICAM1	AD	Known	p.Thr41le/WT	M	49	Italy	Survived
TICAM1	AD	Known	p.Ser60Cys/WT	F	61	Vietnamese/France	Survived
TICAM1	AD	Known	p.Gln392Lys/WT	F	71	Italy	Deceased
TBK1	AD	Known	p.Phe24Ser/WT	F	46	Venezuelan/Spain	Survived
TBK1	AD	Known	p.Arg308*/WT	M	17	Turkey	Survived
IRF3	AD	Known	p.Glu49del/WT	F	23	Bolivian/Spain	Survived
IRF3	AD	Known	p.Asn146Lys/WT	F	60	Italy	Survived
IRF7	AR	Known	p.Pro364fs/p.Pro364fs	F	49	Italian/Belgium	Survived
IRF7	AR	Known	p.Met371Val/p.Asp117Asn	M	50	Turkey	Survived
IRF7	AD	New	p.Arg7fs/WT	M	60	Italy	Survived
IRF7	AD	New	p.Gln185*/WT	M	44	France	Survived
IRF7	AD	New	p.Pro246fs/WT	M	41	Spain	Survived
IRF7	AD	New	p.Arg369Gln/WT	M	69	Italy	Survived
IRF7	AD	New	p.Phe95Ser/WT	M	37	Turkey	Survived
IFNAR1	AR	Known	p.Trp73Cys/Trp73Cys	M	38	Turkey	Survived
IFNAR1	AR	Known	p.Ser422Arg/Ser422Arg	M	26	Pakistan/Saudi Arabia	Deceased
IFNAR1	AD	New	p.Pro335del/WT	F	23	Chinese/Italy	Survived
IFNAR2	AD	New	p.Glu140fs/WT	F	54	Belgium	Survived

AD: autosomal dominant; AR: autosomal recessive; WT: wild-type.

Plasmacytoid dendritic cells



Respiratory epithelial cells

*: additional identified genes associated with severe COVID-19 pneumoniae

- Gene involved in the related pathway also reported to cause the susceptibility to viral infection
Ex: HSV, influenza, yellow fever vaccine....

Zhang, *Nature* 2022; García-García, *J Exp Med* 2023; Zhang, *J Exp Med* 2022

Anti-Type I IFN autoAbs underlie severe COVID-19 pneumonia

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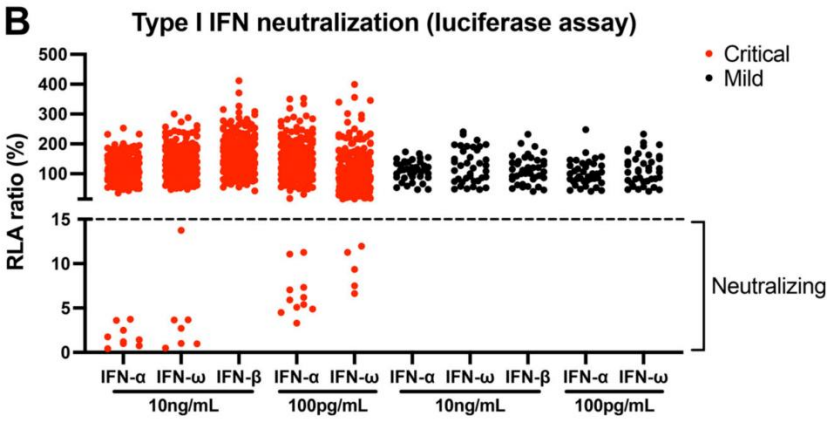
Cite as: P. Bastard *et al.*, *Science* 10.1126/science.abb4585 (2020).

Auto-antibodies against type I IFNs in patients with life-threatening COVID-19

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Autoantibodies against type I IFNs in patients with critical influenza pneumonia

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Patient	Auto-Abs					Gender	Age (yr)	Residence	Influenza pneumonia severity	Viral strain	Vaccinated	Clinical history	Outcome
	IFN-α (10 ng/ml)	IFN-α (100 pg/ml)	IFN-ω (10 ng/ml)	IFN-ω (100 pg/ml)	IFN-β (10 ng/ml)								
P1	+	+	+	+	-	M	73	Greece	Bilateral lung infiltrates, noninvasive mechanical ventilation	IAV (H3)	NA	COPD, sleep breathing disorder, cardiovascular disease, heart failure, hypertension, dyslipidemia	Survived
P2	+	NA	+	NA	-	F	67	Belgium	Admitted to ICU, noninvasive ventilation for 5 d	IAV	NA	Rheumatoid arthritis under methotrexate, local nasal corticosteroids	Survived
P3	+	+	+	+	-	M	28	Belgium	Admitted to ICU, invasive ventilation for 10 d	IAV	NA	Hypothyroidism, GI reflux, urolithiasis, limited metabolic syndrome (new-observation HbA1c 6.2%)	Survived
P4	+	+	+	+	-	F	56	Spain	ARDS	IAV (H1N1)	No		NA
P5	+	+	+	+	-	M	62	Spain	ARDS	NA	NA		NA
P6	+	+	+	+	-	M	62	France	Admitted to ICU, intubated	IAV	NA		Survived
P7	+	+	-	+	-	M	55	France	Admitted to ICU, intubated	IAV	NA		Survived
P8	+	+	-	-	-	M	70	France	Admitted to ICU, intubated	IAV	NA		Survived
P9	+	+	-	-	-	M	40	France	Admitted to ICU, ARDS, intubated, ECMO	IAV (H1N1)	NA	Meningitis at 3 mo of age	Survived
P10	-	+	-	+	-	M	6	Israel	Admitted to ICU, ARDS	IAV (H1N1)	No	Diagnosed with mitochondrial complex I deficiency (family history showed brother died of RSV infection at 3 mo of age)	Survived
P11	-	+	-	-	-	F	48	France	Admitted to ICU, intubated	IAV	NA		Survived
P12	-	+	-	-	-	M	39	France	Admitted to ICU, intubated, ECMO	IAV	NA		NA
P13	-	+	-	-	-	M	70	France	Admitted to ICU	IAV	NA		Survived
P14	+	+	+	+	+	M	55	Chile	Hospitalized with oxygen therapy	IAV	No	Dyslipidemia	Survived
P15	+	+	+	+	+	M	6	France	Intubated for hypoxemia influenza pneumonia, with secondary bacterial infection, intubated	IAV (H1N1)	NA	Failure to thrive, ulcerative digestive lesions due to disseminated CMV infection	Deceased
P16	+	+	+	+	+	F	1.3	Belgium	ARDS, intubated	IAV (H1N1)	No	Diarrhea after oral rotavirus vaccine and skin eruption after MMRV vaccine, autoimmune hemolytic anemia, autoimmune pancreatitis	Deceased
P17	+	+	+	+	-	M	43	Chile	Admitted to ICU, intubated	IAV (H1)	No	Chikungunya (2015) in Colombia	Survived
P18	+	+	+	+	-	M	64	Chile	Hospitalized with oxygen therapy	IAV (H3)	No	Dyslipidemia, infrarenal abdominal aortic aneurysm	Survived
P19	+	+	+	+	-	M	81	Chile	Hospitalized	IAV (H3)	Yes		Survived
P20	+	+	+	+	-	M	83	Spain	Hospitalized	IAV (H3)	Yes	Diabetes	Survived
P21	+	+	-	+	-	F	85	Chile	Admitted to ICU, intubated	IAV (H1)	No	Obesity, arterial hypertension, asthma	Survived
P22	+	+	-	-	-	F	91	Spain	Hospitalized with oxygen therapy	IAV (H1N1)	No	Asthma, heart disease, diabetes	Survived
P23	-	-	+	+	-	M	8	Taiwan	Admitted to ICU with oxygen therapy	IAV	NA	Sister died of encephalitis due to IAV (H1N1)	Survived

Type I IFN deficiency and severe viral diseases

RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Autoantibodies against type I IFNs in patients with life-threatening COVID-19

Bastard P et al., Sci, 2020



BRIEF DEFINITIVE REPORT

Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine

Bastard P et al., J. Exp. Med, 2021



ARTICLE

Autoantibodies against type I IFNs in patients with critical influenza pneumonia

Qian Z et al., J. Exp. Med, 2022



ARTICLE

Autoantibodies neutralizing type I IFNs underlie West Nile virus encephalitis in ~40% of patients

Gervais A et al., J. Exp. Med, 2023



BRIEF DEFINITIVE REPORT

Autoantibodies neutralizing type I IFNs underlie severe tick-borne encephalitis in ~10% of patients

Gervais A et al., J. Exp. Med, 2024

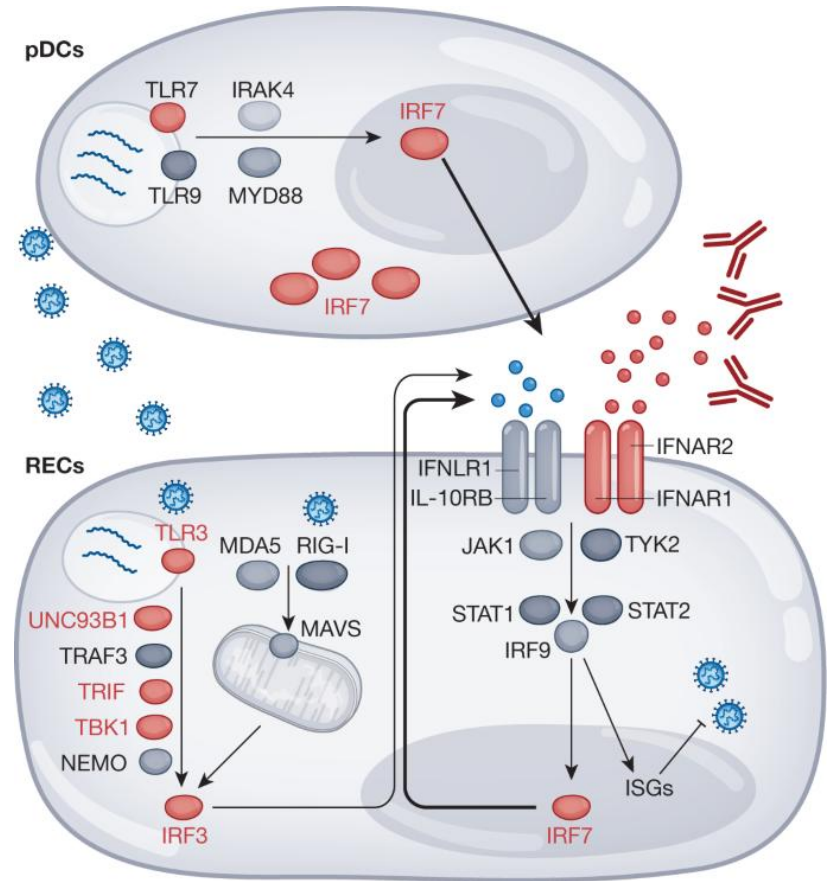


BRIEF DEFINITIVE REPORT

Auto-Abs neutralizing type I IFNs in patients with severe Powassan, Usutu, or Ross River virus disease

Gervais A et al., J. Exp. Med, 2024

Anti-IFN-I autoantibodies



- ~ 30 % of patients with adverse effects to YF vaccines
- ~ 15% of patients with critical COVID-19 pneumonia
- ~ 20 % of patients with COVID19 death
- ~ 5 % of patients < 70 yr with critical influenza pneumonia
- ~ 40 % of patients with West Nile virus encephalitis
- ~ Severe tick-borne encephalitis (~10%)

Anti-Type I IFN autoAbs cause the predispose to viral infections

	OR [95% CI]		
	Children under 18 years old	Adults under 65 or 70 years old	Adults over 65 or 70 years old
Critical COVID-19			
IFN- β 10 ng/mL	4.9 [0–95.1]		
IFN- α 10 ng/mL	40.6 [6.4–429.8]		
IFN- ω 10 ng/mL	7.7 [1.8–26.7]		
IFN- α 100 pg/mL	28.2 [8.8–101.3]		
IFN- ω 100 pg/mL	4.2 [2–7.9]		
IFN- α or IFN- ω 10 ng/mL	9.2 [2.6–29.1]	48.1 [34.4–67.2]	7 [5.4–9.0]
IFN- α and IFN- ω 10 ng/mL	68 [5.4–9435.4]	160 [69.3–369.3]	13 [8.8–19.3]
IFN- α or IFN- ω 100 pg/mL	5.3 [2.8–9.6]	12.3 [9.4–16.0]	5.1 [4.0–6.4]
IFN- α and IFN- ω 100 pg/mL	19.4 [4.7–87.8]	184.9 [45.7–748.3]	7 [5.1–9.7]
Critical flu			
IFN- β 10 ng/mL	–	1.1 [0.1–19.8]	2.3 [0.1–51]
IFN- α 10 ng/mL	–	52.1 [22.3–121.8]	1.8 [0.5–6.3]
IFN- ω 10 ng/mL	–	24.9 [9.9–62.4]	1.3 [0.2–6.5]
IFN- α 100 pg/mL	–	17.5 [8.4–36.6]	1.1 [0.4–3.3]
IFN- ω 100 pg/mL	–	5.5 [2.5–11.9]	0.5 [0.1–2.8]
IFN- α or IFN- ω 10 ng/mL	–	23.4 [10.7–51.4]	1.2 [0.3–4.4]
IFN- α and IFN- ω 10 ng/mL	–	139.9 [42.3–462.5]	2.5 [0.5–13.1]
IFN- α or IFN- ω 100 pg/mL	–	5.7 [3–11.1]	0.8 [0.3–2.4]
IFN- α and IFN- ω 100 pg/mL	–	77 [22.4–264.4]	0.9 [0.2–4.8]
WNVD			
IFN- β 10 ng/mL	–		
IFN- α 10 ng/mL	–	185.6 [96–359]	54.7 [39.8–75]
IFN- ω 10 ng/mL	–	139.2 [77.6–249.7]	42.4 [30.2–59.6]
IFN- α 100 pg/mL	–	54.8 [29.6–101.6]	28.3 [20.9–38.4]
IFN- ω 100 pg/mL	–	25 [15.4–40.6]	28.2 [20.6–38.6]
IFN- α or IFN- ω 10 ng/mL	–	80.5 [48.6–133.3]	40.9 [30.5–55]
IFN- α and IFN- ω 10 ng/mL	–	558.1 [201.7–1544.1]	82.9 [55.2–124.6]
IFN- α or IFN- ω 100 pg/mL	–	16.8 [10.7–26.3]	22.2 [16.7–29.6]
IFN- α and IFN- ω 100 pg/mL	–	304.6 [99.4–933.3]	43.9 [30.8–62.5]
WNF			
IFN- β 10 ng/mL	–		
IFN- α 10 ng/mL	–	78.7 [26.1–237.5]	6.6 [1.9–22.2]
IFN- ω 10 ng/mL	–	58.8 [22.3–155.1]	5.4 [1.3–23.2]
IFN- α 100 pg/mL	–	30.1 [11.8–76.9]	3.2 [0.9–10.6]
IFN- ω 100 pg/mL	–	14.5 [6.9–30.4]	5.2 [1.8–15.2]
IFN- α or IFN- ω 10 ng/mL	–	36.2 [15.1–86.3]	4.8 [1.4–16]
IFN- α and IFN- ω 10 ng/mL	–	229.1 [53.4–983.7]	11.7 [2.7–51.2]
IFN- α or IFN- ω 100 pg/mL	–	11.8 [6–23.1]	3.1 [1.1–9]
IFN- α and IFN- ω 100 pg/mL	–	114.4 [27.7–472.5]	6.8 [2–23.1]

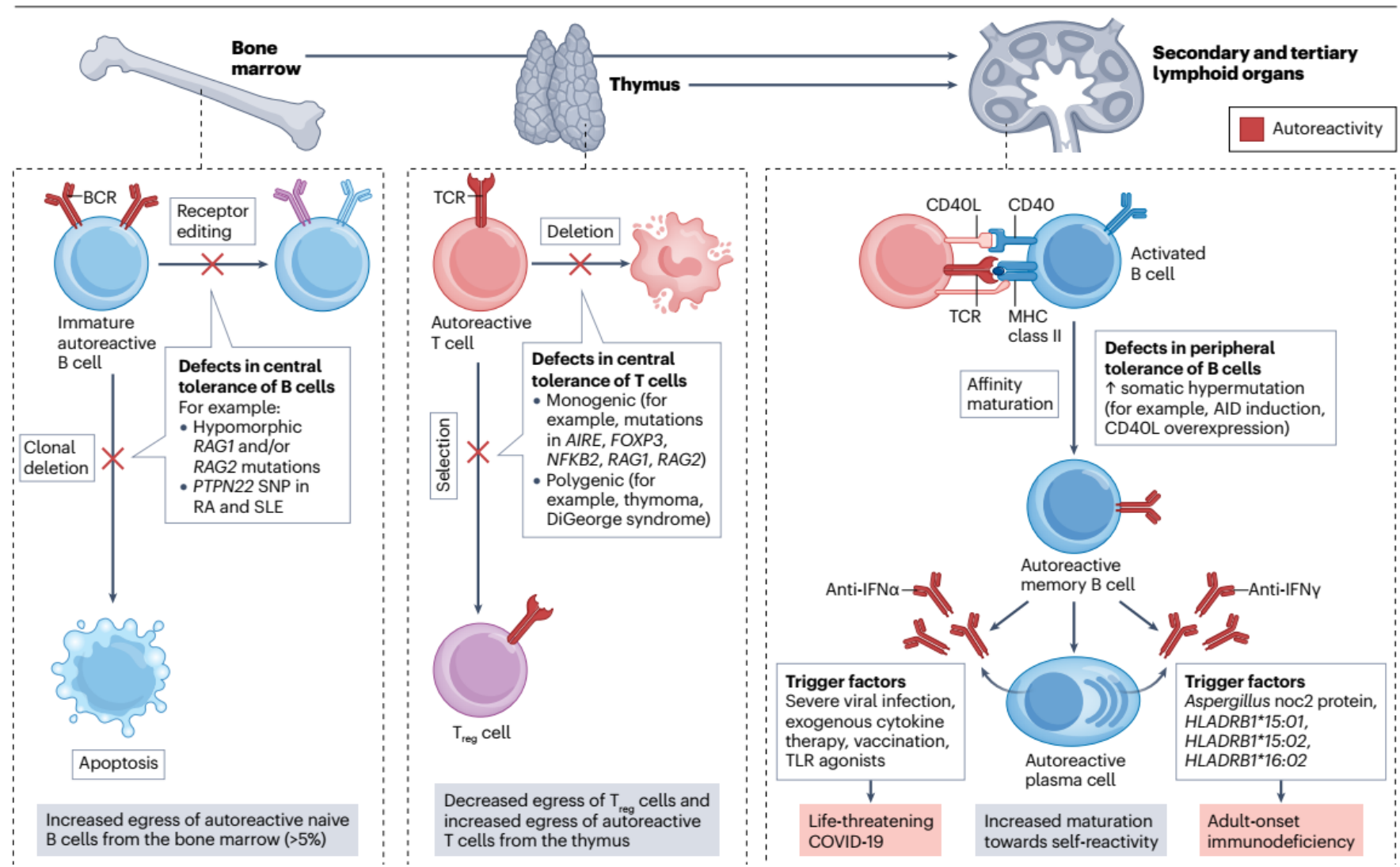
Note: The age cutoffs for the cohorts differed: critical COVID-19: 65 years old, critical flu: 65 years old, WNVD: 70 years old, WNF: 70 years old.

Genetic factors for the ACADs

Table 1 | Anti-cytokine autoantibodies in inborn and acquired errors of immunity

Gene	Inborn or acquired errors of immunity	Cytokine target of ACAAs	Disease associations
Defects in central tolerance of B cells			
RAG1 and/or RAG2	Delayed onset combined immunodeficiency with granulomas and/or autoimmunity	IFNα, IFNβ, IFNω, IL-12/23p40, IL-22, TNF, IFNγ, IL-6	Recurrent sinopulmonary infections, often followed by bronchiectasis; severe <i>Herpesviridae</i> infections (in particular VZV, CMV and EBV), molluscum contagiosum and warts owing to HPV infection; chronic multifocal osteomyelitis ^{9,56}
Polygenic (for example, PTPN22)	Rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis	IFNα, IFNβ, TNF, IL-1, IL-6, IL-12, IL-23, IFNγ	Poorly studied; some associated with relapses and immunopathology, some associated with remissions and amelioration of autoimmunity ^{76,106}
Defects in central tolerance of T cells			
AIRE	Autoimmune polyglandular syndrome type 1 (APS1, also known as APECED)	IFNα (particularly, IFNA2, IFNA4, IFNA6, IFNA17), IFNω, IL-17A, IL-17F and IL22 and IL-6	Chronic mucocutaneous candidiasis; prolonged <i>Herpesviridae</i> reactivations; some develop severe COVID-19; decreased severity of type 1 diabetes ^{17,25,27,35,42,196}
Polygenic (for example, GTF2I)	Thymoma and myasthenia gravis	IFNα, IFNω, IL-12/23p40, IL-12p70 and IL-23p60, IL-17A, IL-17F, IL-22	Chronic mucocutaneous candidiasis, <i>Herpesviridae</i> reactivations, yellow fever vaccine-associated visceral disease, viral and <i>Pneumocystis</i> pneumonias, recurrent sinopulmonary infections, bronchiectasis, cerebral and disseminated intracellular infections (toxoplasmosis, histoplasmosis, coccidioidomycosis and mycobacterial) ^{49,50,58,197,198}
RAG1 and/or RAG2	Delayed onset combined immunodeficiency with granulomas and/or autoimmunity	IFNα, IFNβ, IFNω, IL-12/23p40, IL-22, TNF, IFNγ, IL-6	Recurrent sinopulmonary infections, often followed by bronchiectasis; severe <i>Herpesviridae</i> infections (in particular VZV, CMV and EBV), molluscum contagiosum and warts owing to HPV infection; chronic multifocal osteomyelitis ⁹
NFKB2	Common variable immunodeficiency	IFNα, IFNβ, IFNω, IL-12/23p40, IL-23	Recurrent deep-seated pyogenic bacterial infections, recurrent sinopulmonary infections, severe herpes vegetans and molluscum contagiosum ^{44,199}
FOXP3	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome	IFNα, IL-17	Severe COVID-19; respiratory and gastrointestinal infections ¹⁹
Defects in peripheral tolerance of B cells			
NEMO	Incontinentia pigmenti	IFNα	Severe COVID-19; viral respiratory tract infections ²⁰⁰
Polygenic (for example, CD40L, AID, HLADR, HLADQ)	Common variable immunodeficiency, systemic lupus erythematosus, adult-onset immunodeficiency syndrome associated with IFNγ autoantibodies	G-CSF, erythropoietin, TGFβ1–TGFβ3, IL-2, IL-15, IL-12, IL-23, IFNγ, IFNα, BAFF	Memory B cells are highly enriched in VH4-34 expressing clones that lack tolerizing somatic mutations ^{56,69,201}

Genetic factors for the ACADs



Host factors for the susceptibility of Severe SARS-CoV-2 and other viral Infection in Taiwanese Children

Children with severe viral infection

(SARS-CoV-2, MIS-C, HSV encephalitis, influenza, adenovirus, enterovirus....)



Inborn errors of antiviral type I IFN immunity

- Functional screening
- Whole exomic sequence
- Whole genomic sequence



Anticytokine autoantibodies

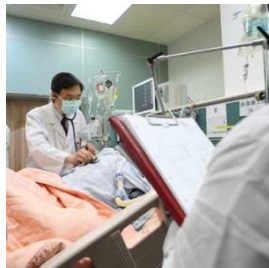
- Functional screening
- Autoantibody detection



Mechanical studying



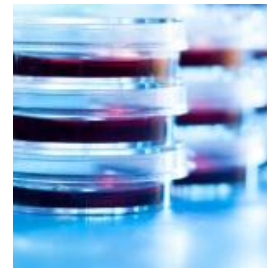
Genetic



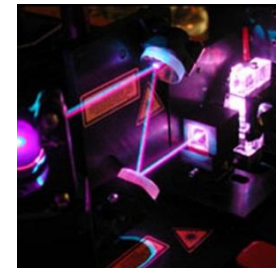
Clinical analysis



Biochemical assay



In vitro assay



High dimension

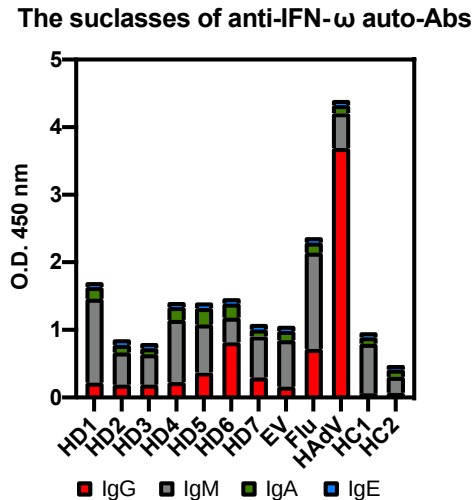
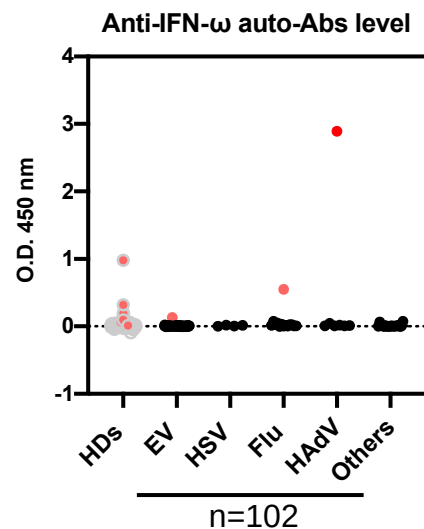


Animal model

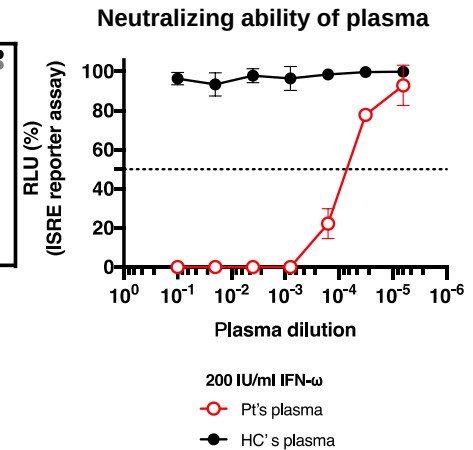
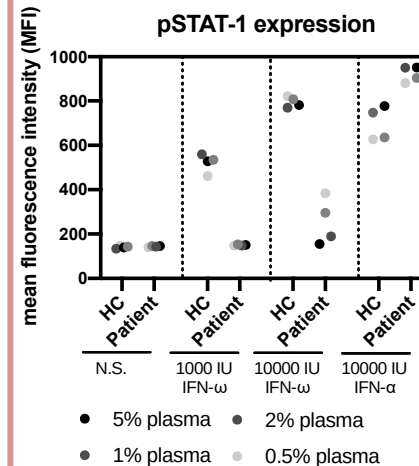
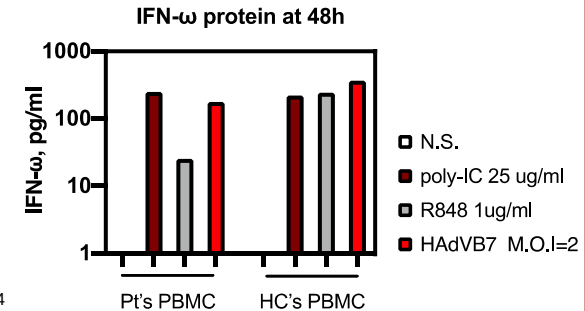
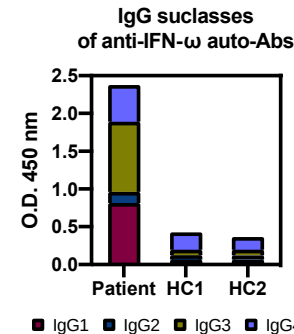
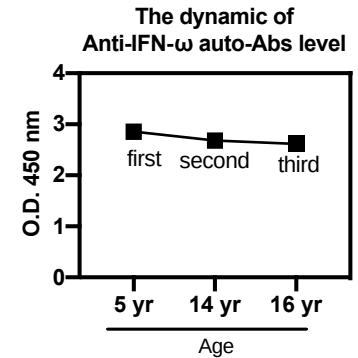
Anti-type I IFN Auto-Abs underlie the severe viral infection



Children (≤18yr)	Numbers	anti-IFN- ω auto-Ab (Positive number)	anti-IFN- ω auto-Ab (percentage)
Health (HDs)	455	7	7/455 (1.5%)



5y6 m/o, male
adenovirus serotype B7

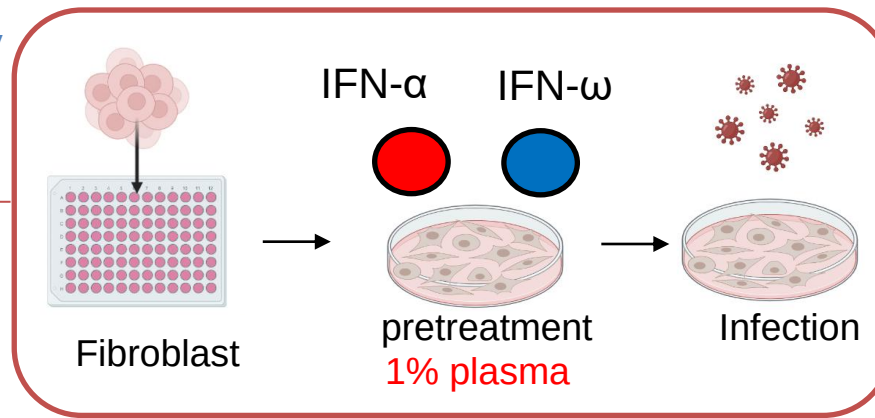


Anti-type I IFN Auto-Abs underlie the severe viral infection

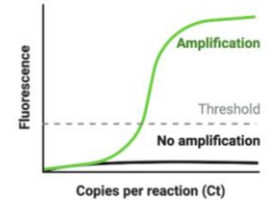
Virus induced-cell death assay



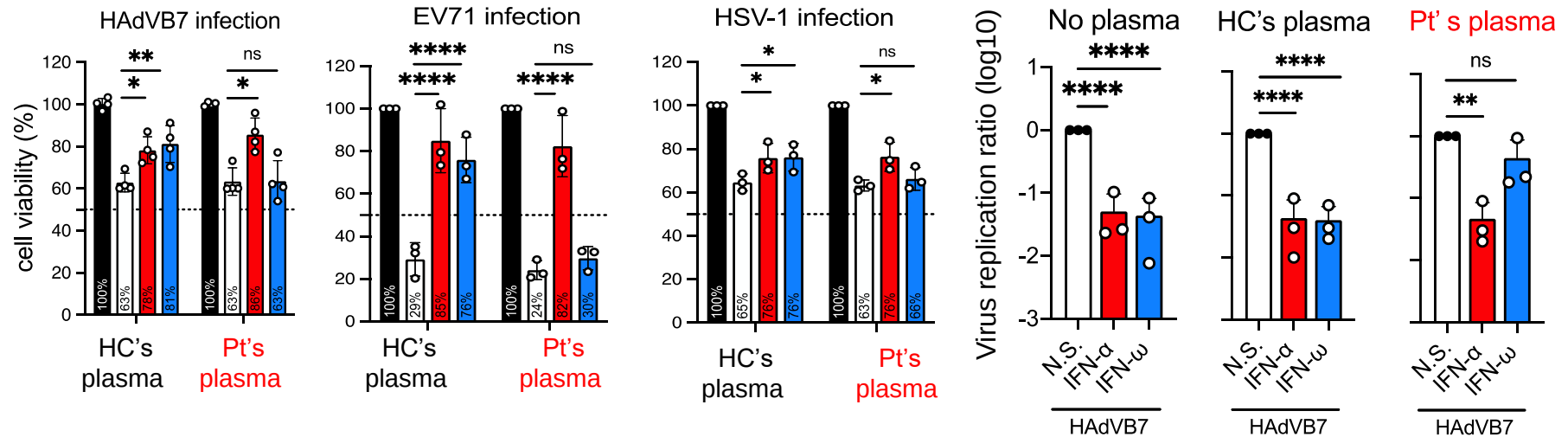
cell viability by CCK8



Virus replication assay



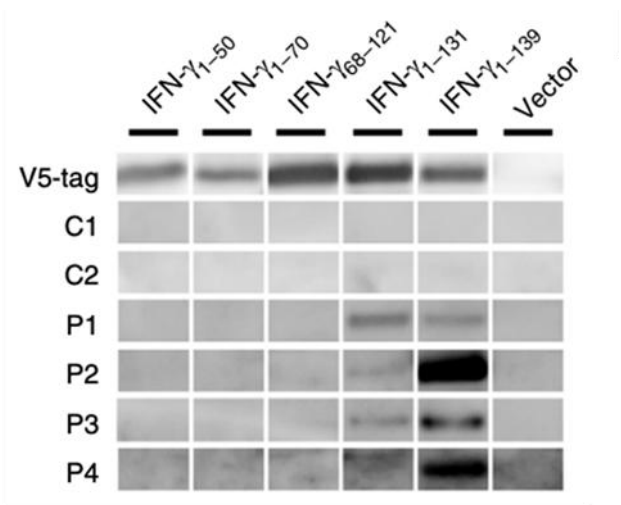
Viral load of HAdVB7 by qPCR



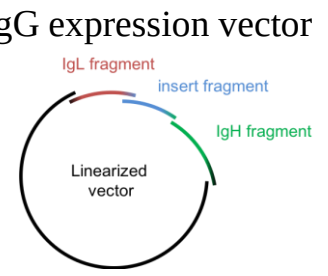
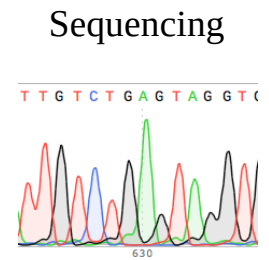
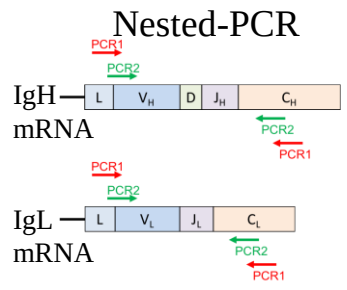
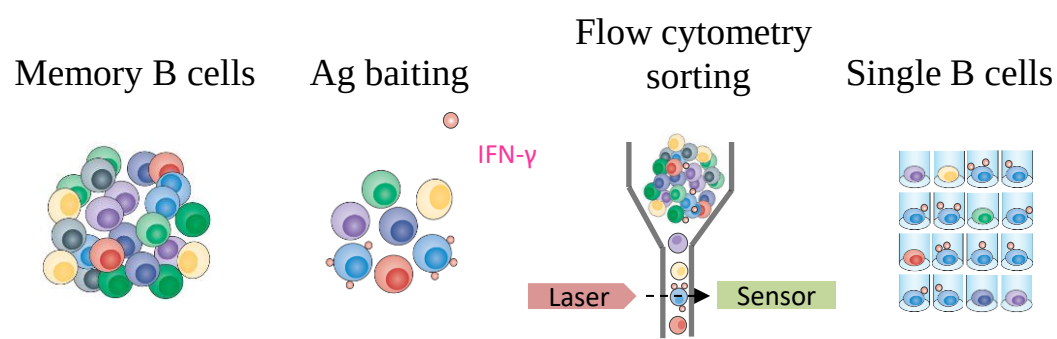
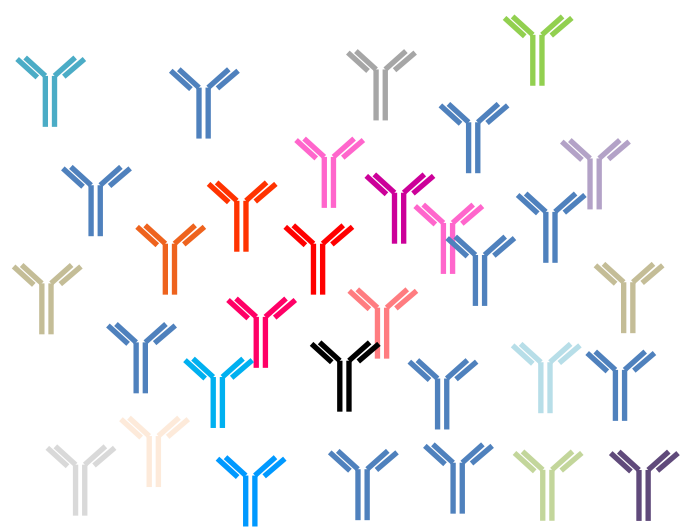
Our findings suggest that anti-IFN- ω autoantibodies is the underlie mechanism for the severe adenoviral pneumonia in children, and highlight the non-redundant IFN- ω effect to adenoviral infection

Cloning antibodies by single human B cell capture method

Method of isolation of human antibody

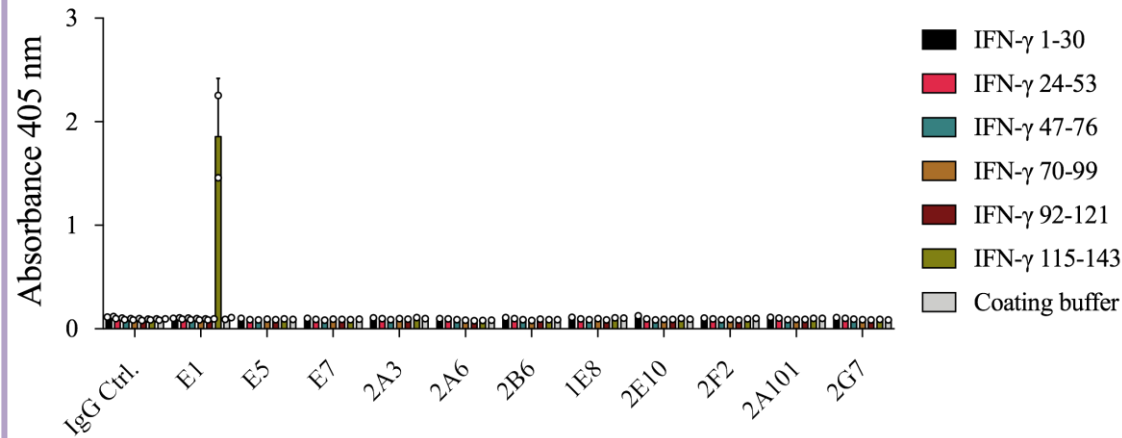


Human Plasma

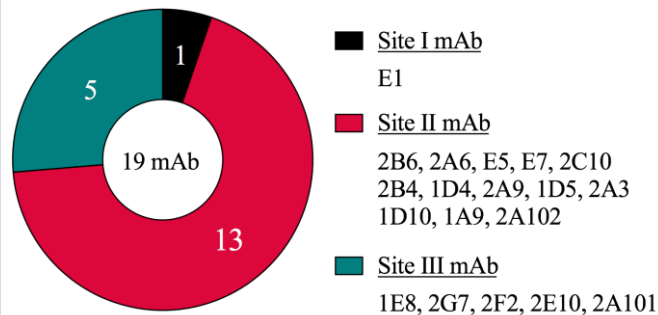
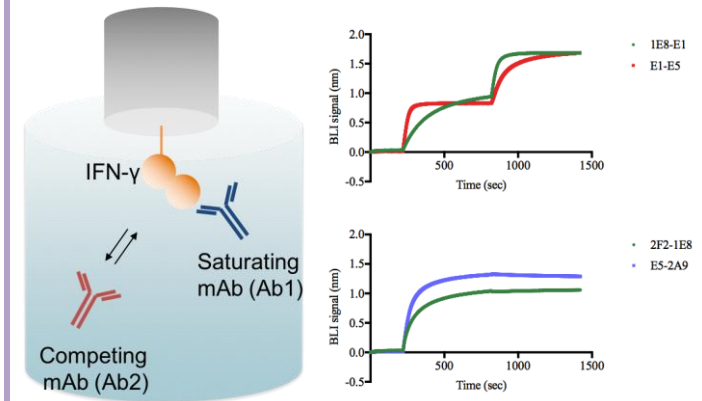


Scheid, *Nature* 2009; Chen, *J Allergy Clin Immunol* 2016

Anti-IFN- γ mAbs are categorized into 3 binding epitopes



Epitope Binning



	2A101	2G7	1E8	2E10	2F2	E1	E5	E7	1D4	1D5	2A6	2A9	1D10	2A3	2A102	2B4	2B6	2C10	1A9
2A101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2G7	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1E8	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2E10	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2F2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
E1	+	++	+	++	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
E5	-	-	++	++	++	++	-	-	-	-	-	-	-	-	-	-	-	-	-
E7	-	-	+	++	++	++	-	-	-	-	-	-	-	-	-	-	-	-	-
1D4	-	-	++	-	-	++	-	-	-	-	-	-	-	-	-	-	-	-	-
1D5	-	-	-	-	-	++	-	-	-	-	-	-	-	-	-	-	-	-	-
2A6	-	-	-	-	+	++	-	-	-	-	-	-	-	-	-	-	-	-	-
2A9	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-
1D10	-	-	-	++	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2A3	-	-	++	++	++	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2A102	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
2B4	-	-	-	-	+	++	-	-	-	-	-	-	-	-	-	-	-	-	-
2B6	+	++	++	++	++	++	-	-	-	-	-	-	-	-	-	-	-	-	-
2C10	-	-	-	-	++	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1A9	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

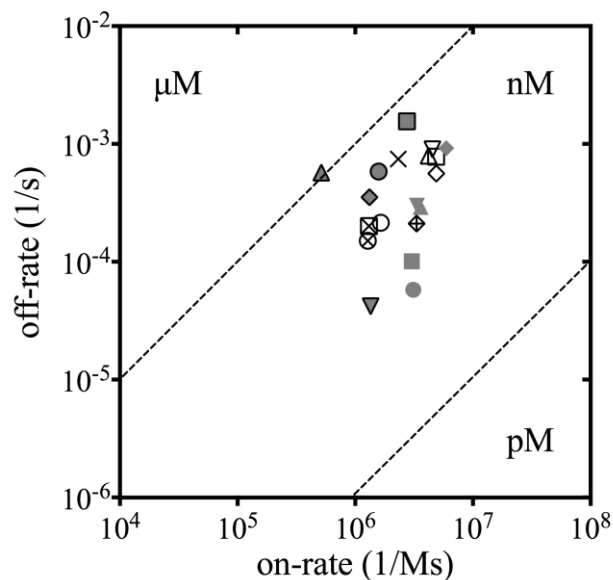
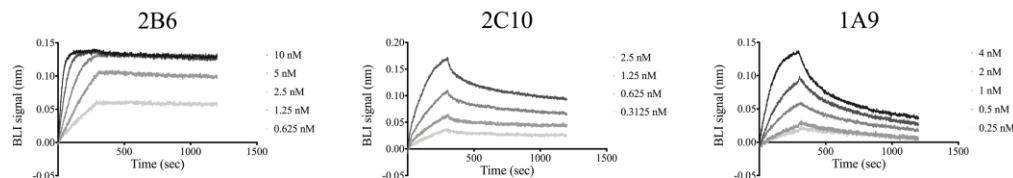
-, no binding detected or too low to be determined;
+, binding nm shift < 0.5; ++, binding nm shift > 0.5

Extreme High Affinity anti-IFN- γ mAbs with nM Scale

Binding affinity

Strong

Weak

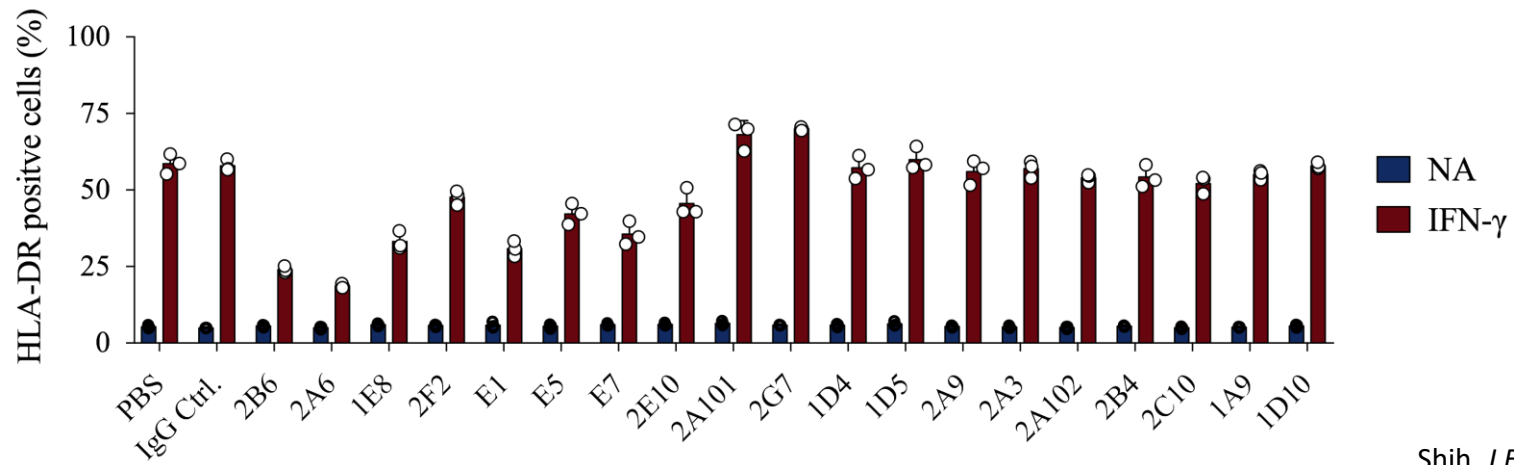
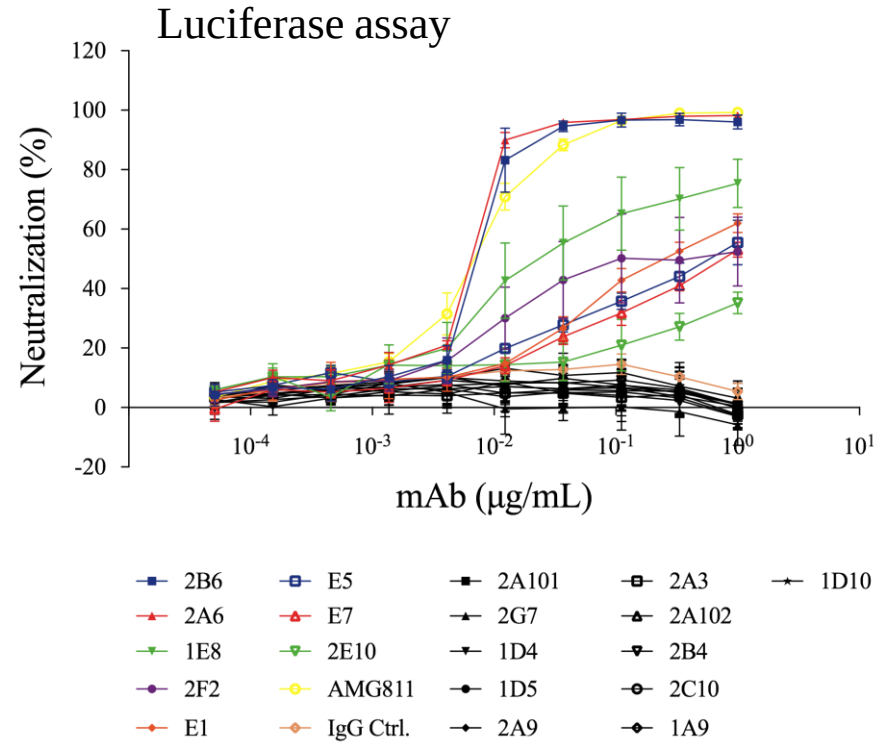
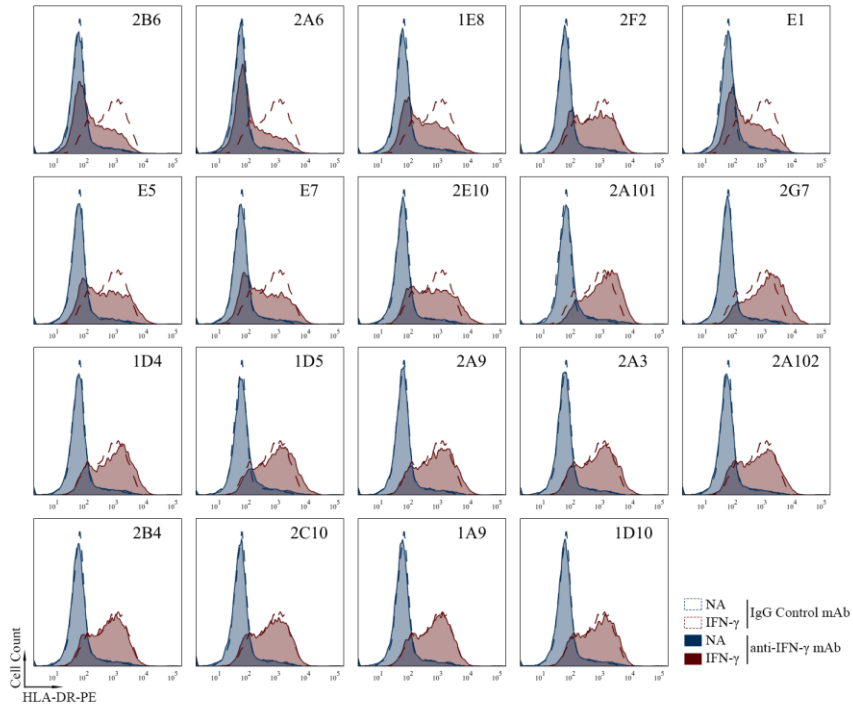


- ◆ E1 ◆ 2A3
- 2B6 ● 1D10
- 2A6 ■ 1A9
- ▲ E5 ▲ 2A102
- ▼ E7 ▼ 1E8
- ◇ 2C10 ◇ 2G7
- 2B4 ⊗ 2F2
- 1D4 ⊠ 2E10
- △ 2A9 × 2A101
- ▽ 1D5

mAb	Ka (1/Ms)	Kd (1/s)	KD (M)
2B6	3.11E+06	5.79E-05	1.86E-11
1E8	1.35E+06	4.19E-05	3.10E-11
2A6	3.02E+06	1.01E-04	3.33E-11
2G7	3.32E+06	2.11E-04	6.36E-11
E5	3.59E+06	2.93E-04	8.17E-11
E7	3.34E+06	2.99E-04	8.96E-11
2C10	4.88E+06	5.61E-04	1.15E-10
2F2	1.28E+06	1.51E-04	1.18E-10
2B4	1.65E+06	2.15E-04	1.31E-10
2E10	1.31E+06	2.01E-04	1.53E-10
E1	5.93E+06	9.22E-04	1.56E-10
1D4	4.87E+06	7.81E-04	1.60E-10
2A9	4.20E+06	7.95E-04	1.89E-10
1D5	4.53E+06	9.01E-04	1.99E-10
2A3	1.32E+06	3.53E-04	2.68E-10
2A101	2.32E+06	7.45E-04	3.21E-10
1D10	1.58E+06	5.84E-04	3.70E-10
1A9	2.75E+06	1.56E-03	5.69E-10
2A102	5.15E+05	5.73E-04	1.11E-09

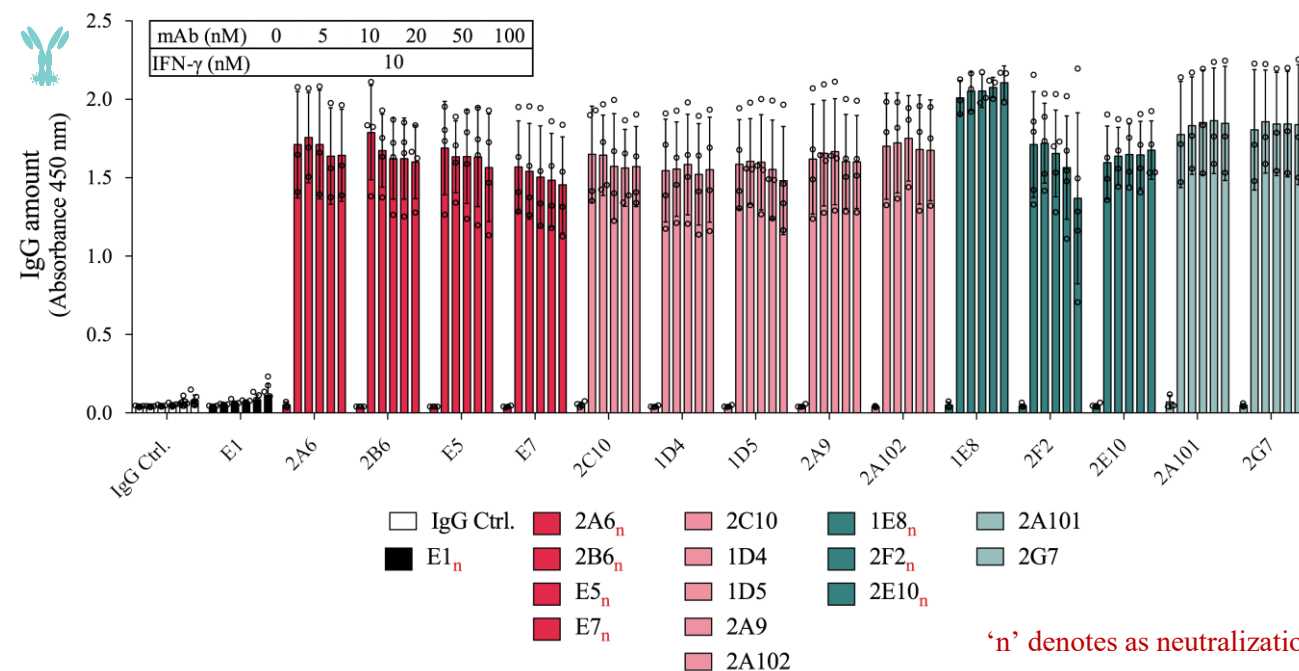
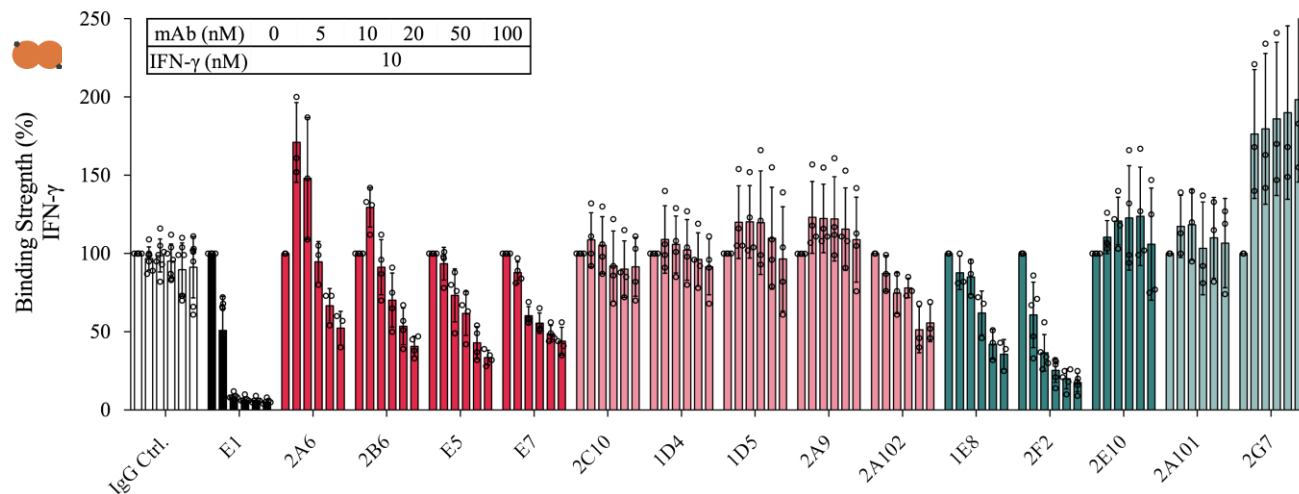
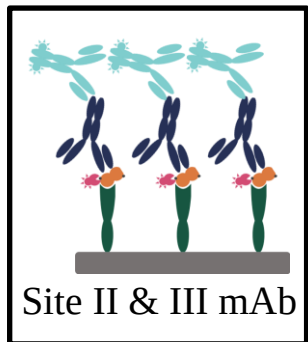
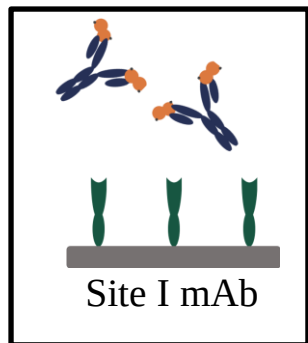
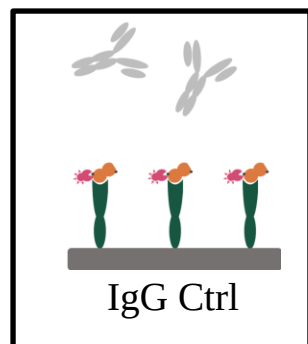
Potent neutralizing anti-IFN- γ mAbs *in-vitro*

THP-1 HLA-DR assay



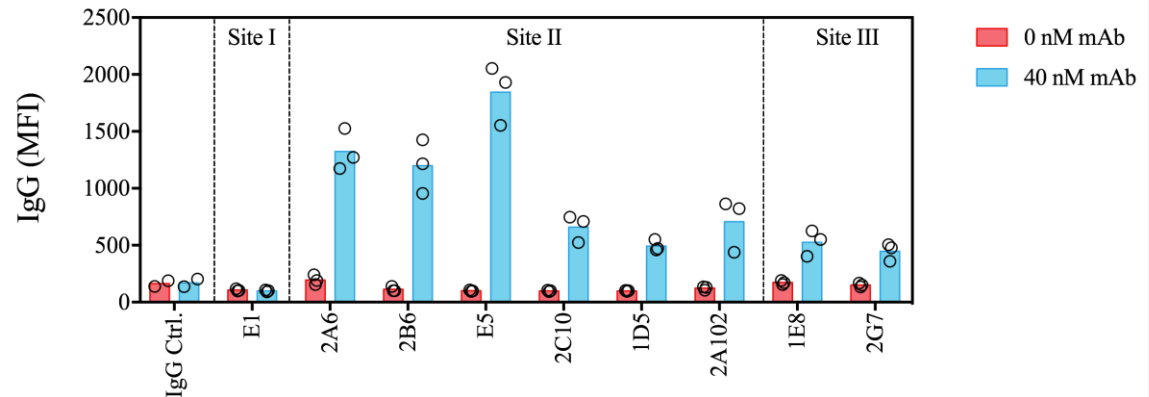
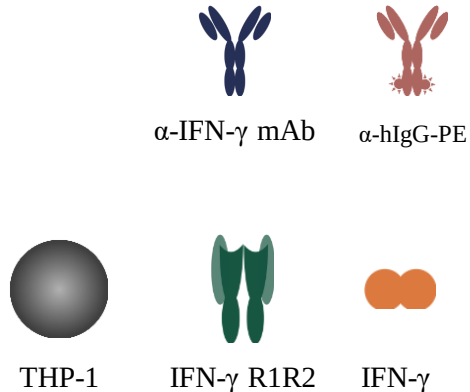
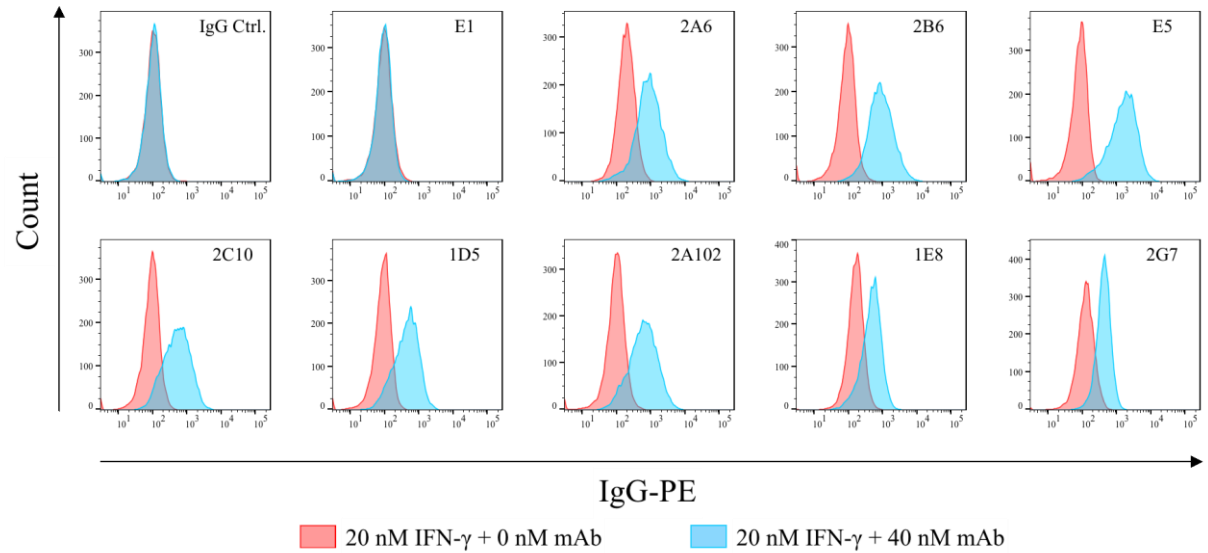
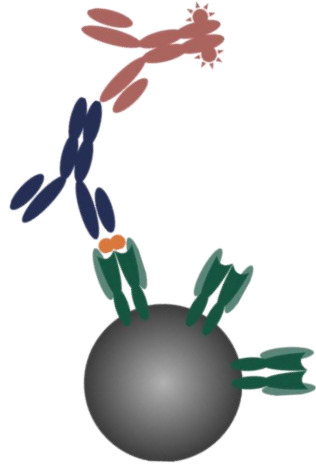
Site I mAb directly disrupt the IFN- γ and its R1 binding

In-vitro IFN- γ R1 ELISA



'n' denotes as neutralization

The site II & III mAbs anchoring on the cell through IFN- γ



Site	—	I	II	II	II	II	II	II	III	III
Neutralization	—	+	+	+	+	—	—	—	+	—

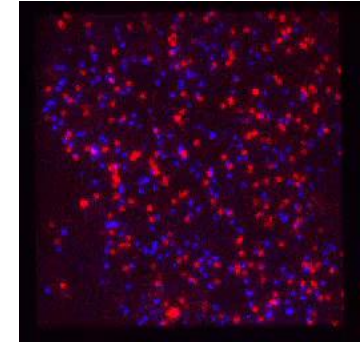
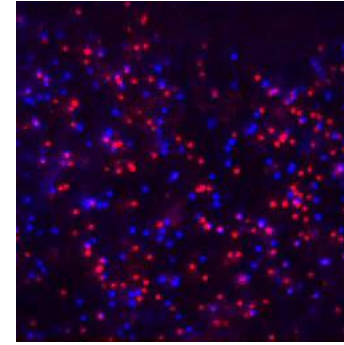
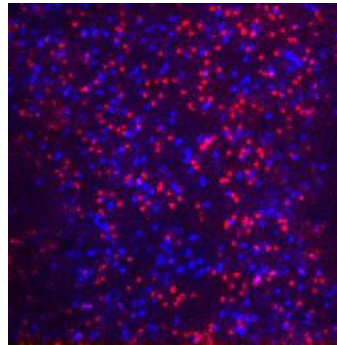
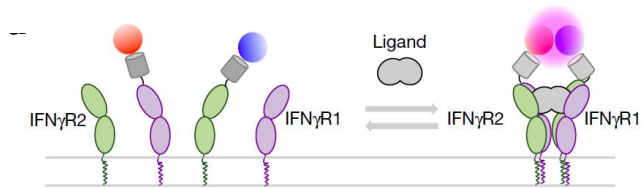
Site II 2B6(K3) clone strongly prevents IFNGR hetero-dimerization

IFN- γ R1-IFN- γ R2 dimerization

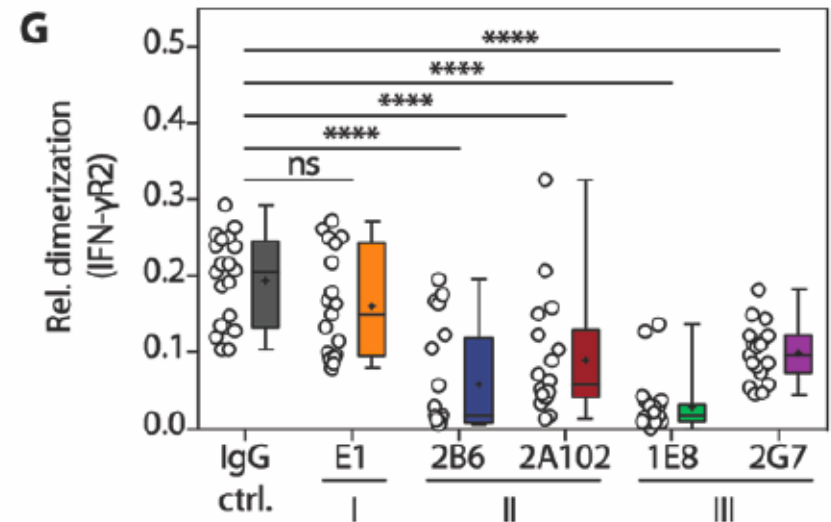
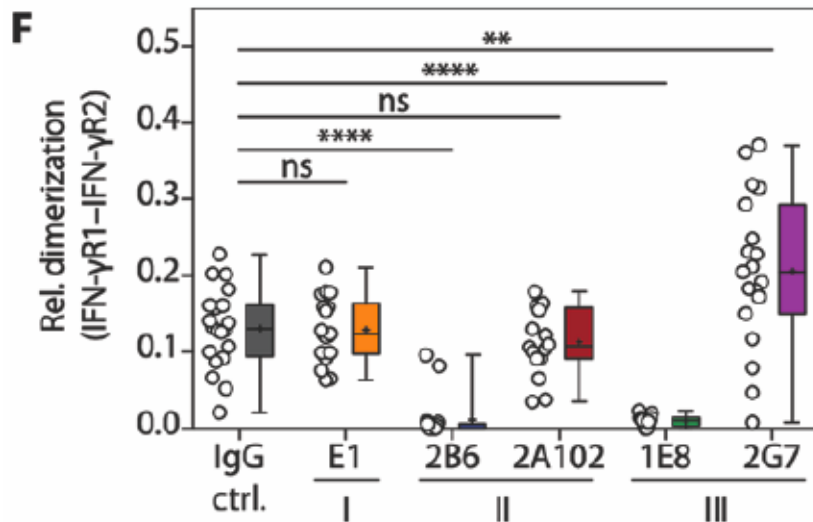
unstimulated

+IFN- γ

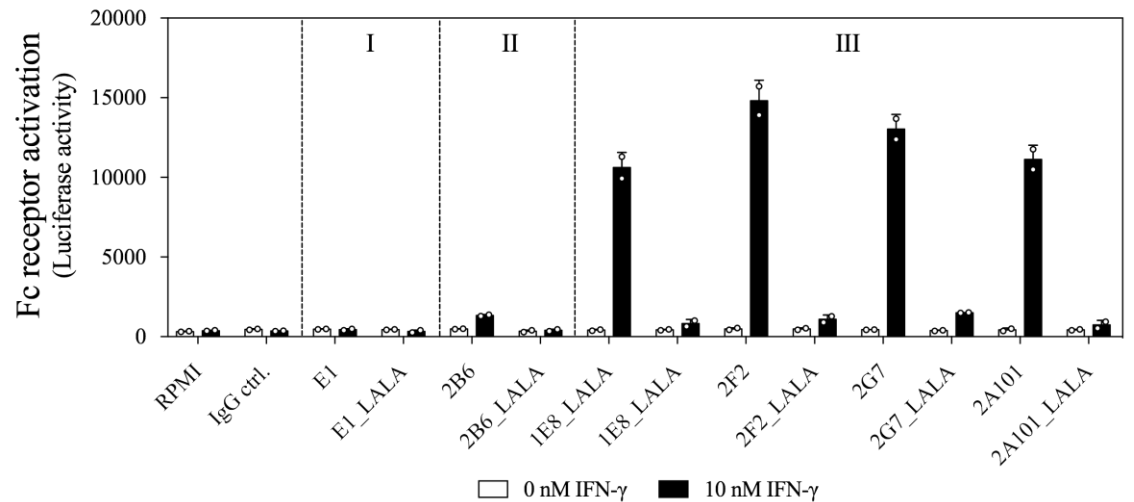
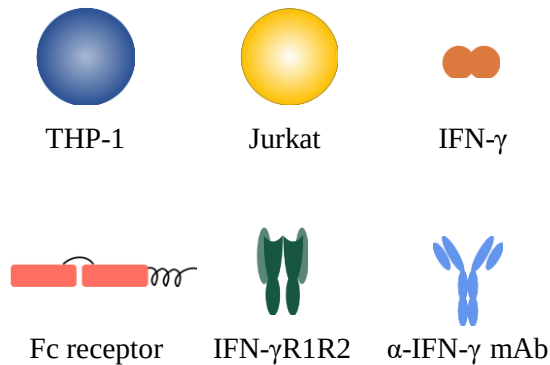
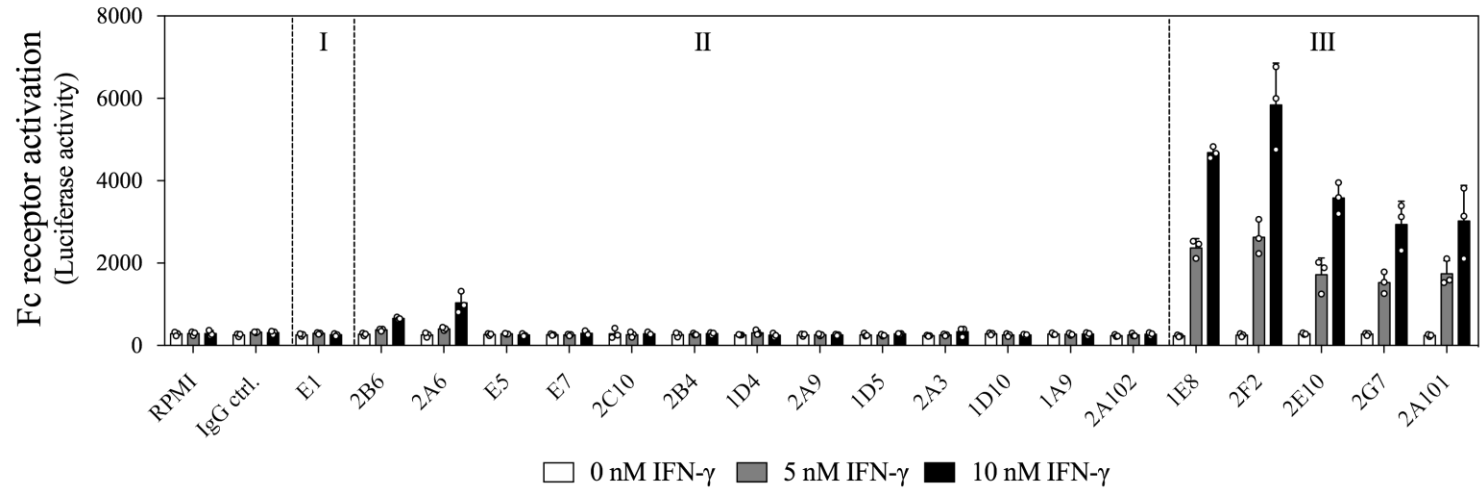
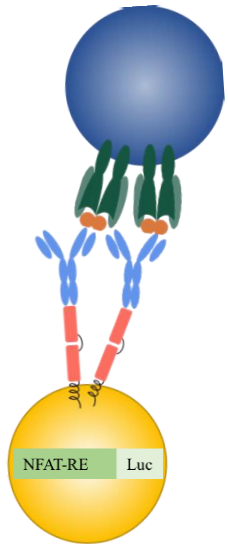
pre-incubated
IFN- γ + 2B6



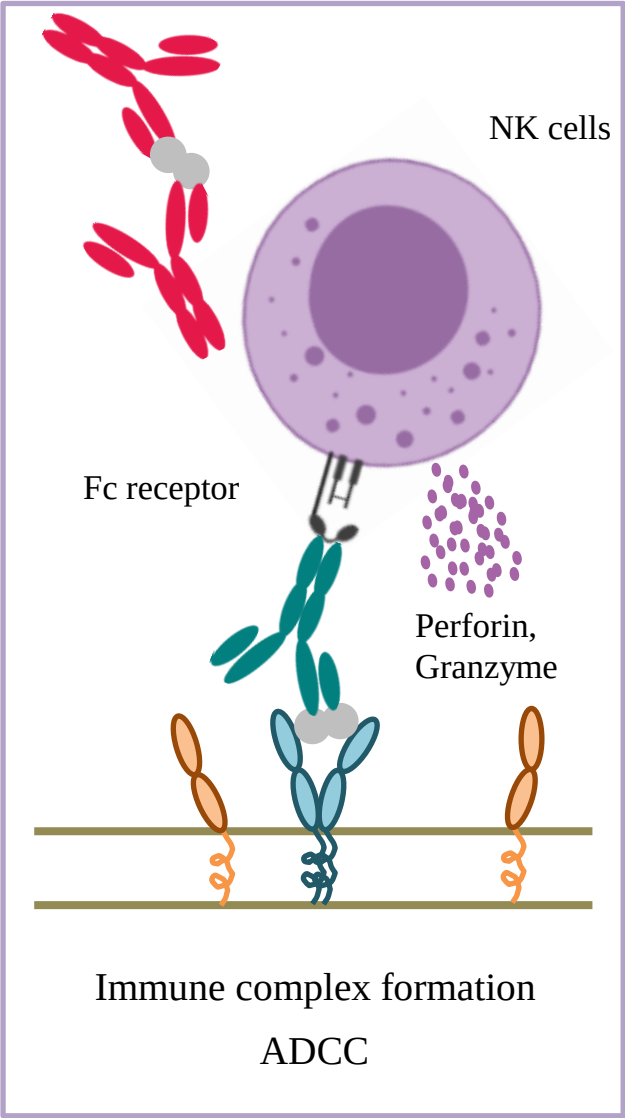
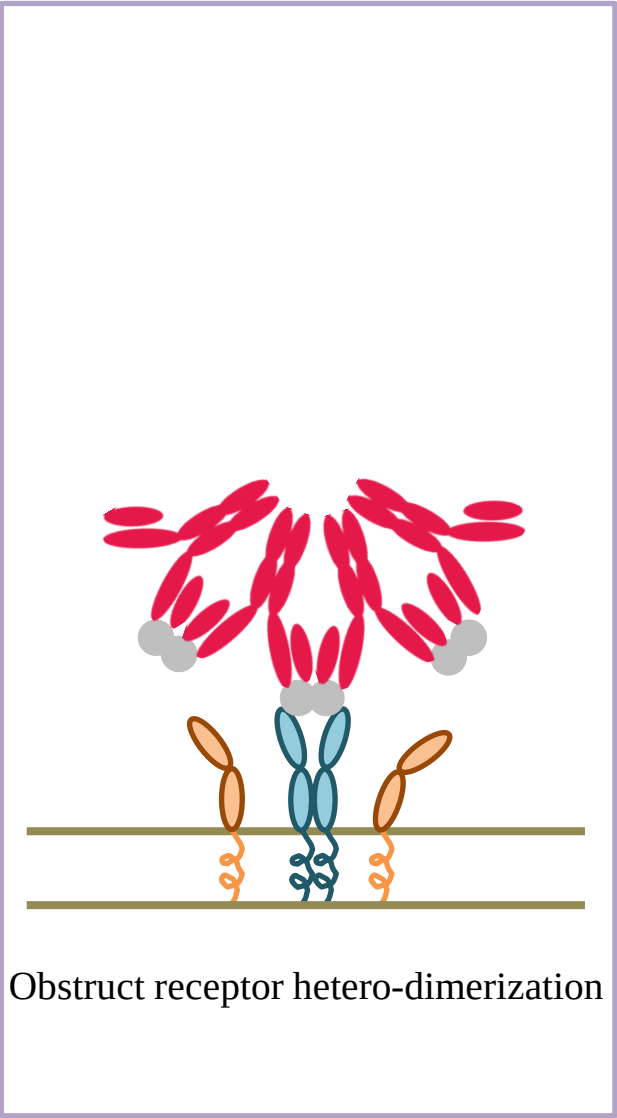
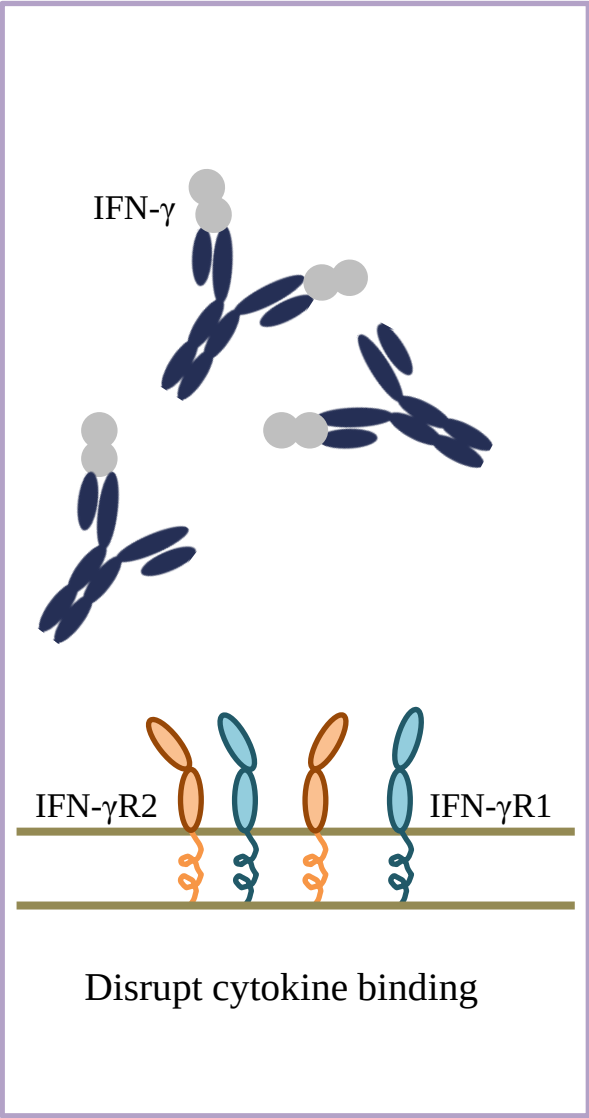
Osnabrück University
Jacob Piehler, Ph.D.



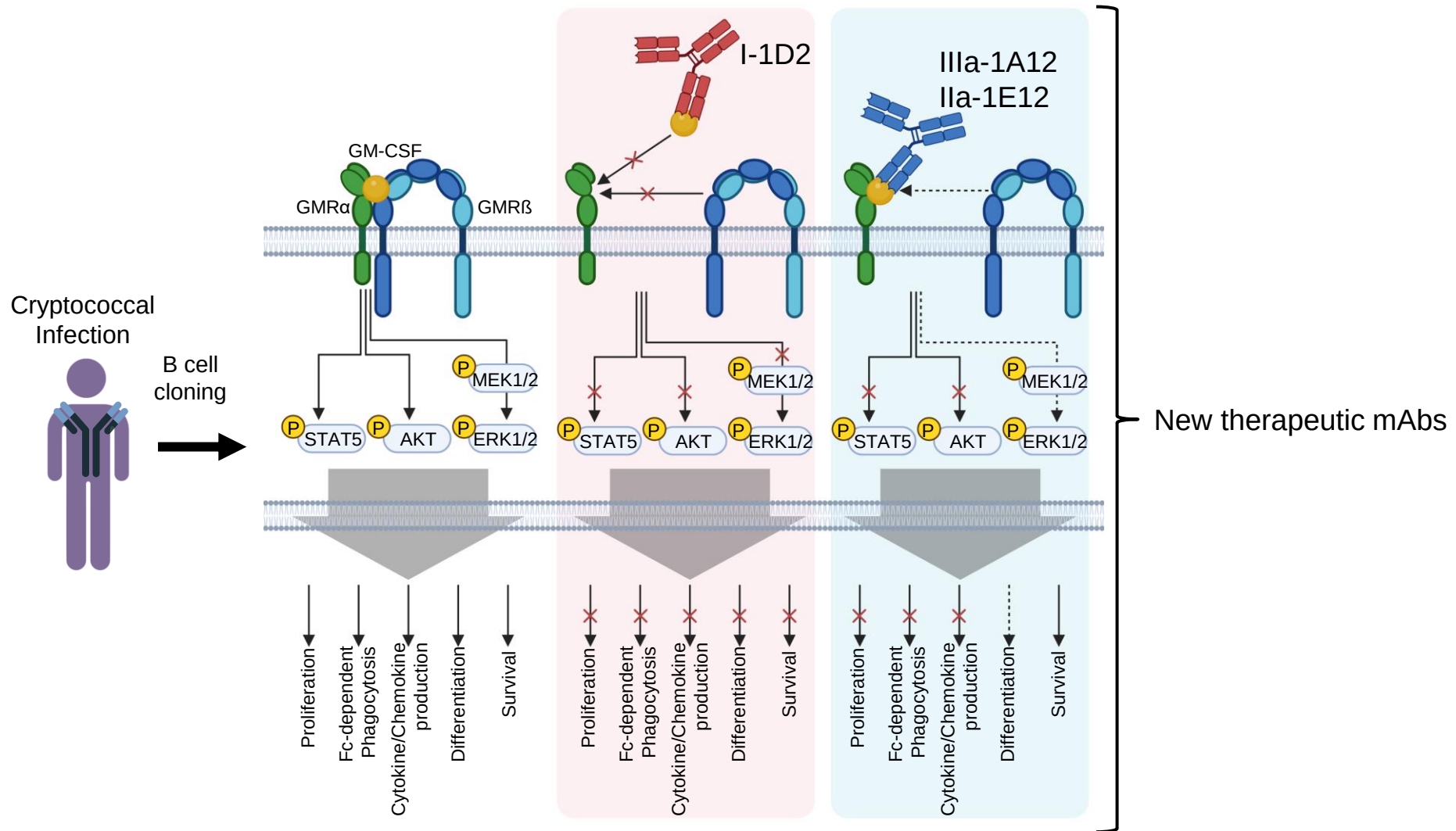
Site III mAbs activate Fc receptor through exposed Fc region



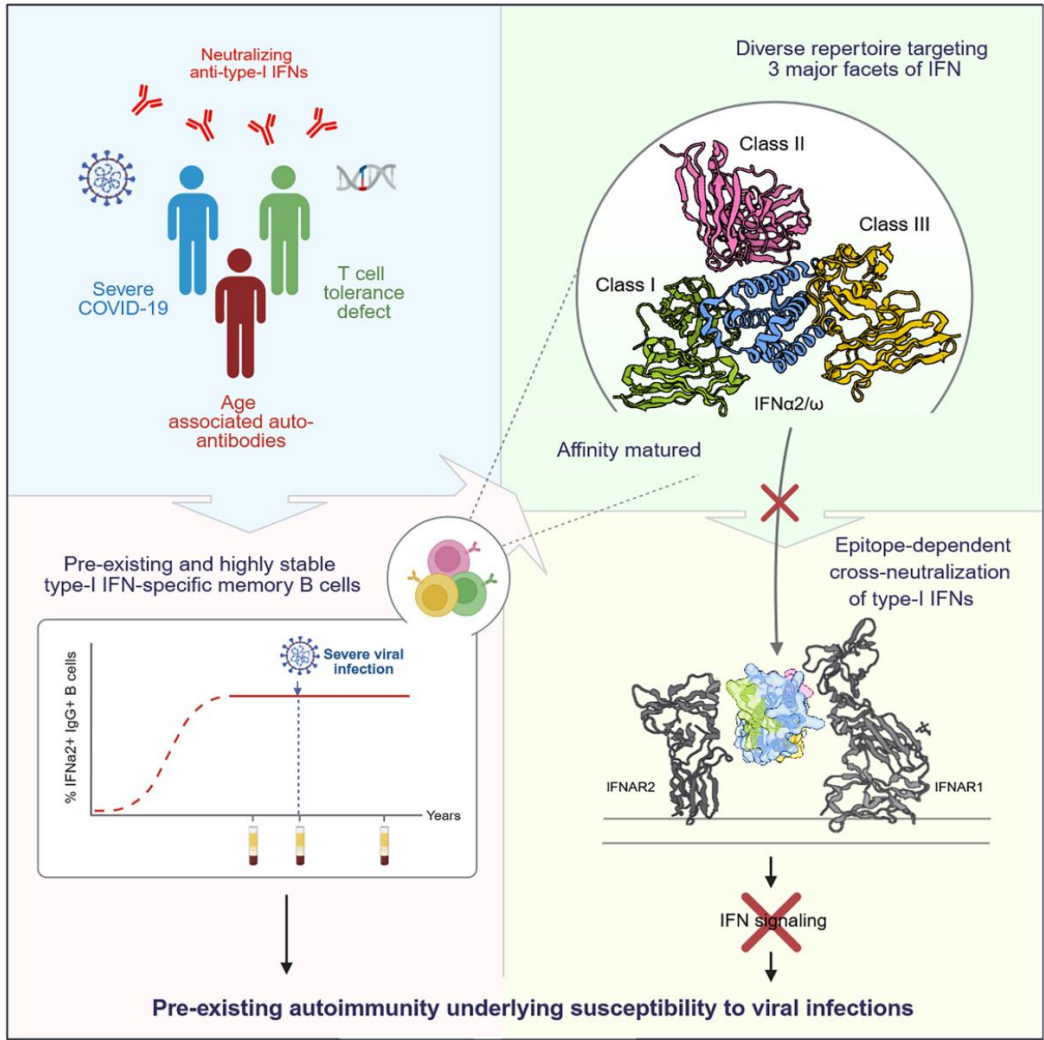
Mode of actions of AIGAs



Conclusion

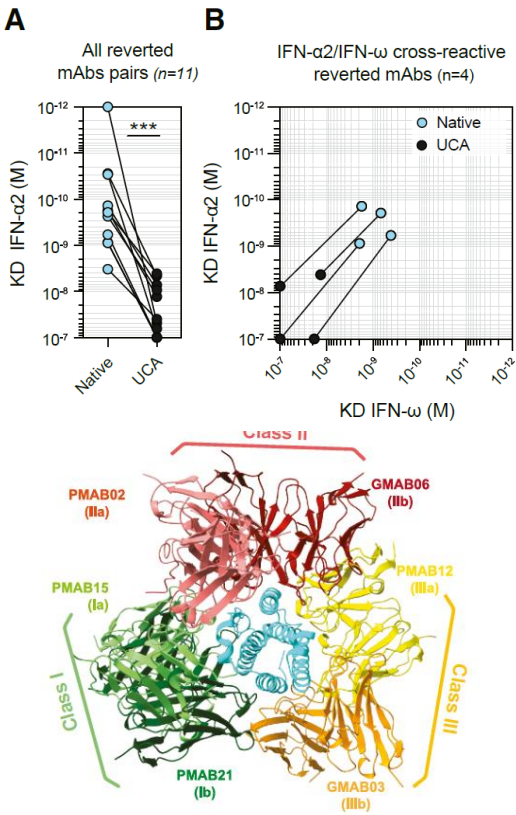


Cloning of anti-type I IFN autoantibodies



Article Affinity-matured B cell responses neutralizing type-I interferons underlie severe viral infections

Morgane Fournier,^{1,56} Matthias Vanderkerken,^{1,56} Karim Dorgham,^{2,56} Paul Bastard,^{3,4,5,6,56} Olivia Ahouzi,^{7,56} Stephane Duquerry,^{7,5,56} Ngoc Khanh Nguyen,^{2,56} Manon Broutin,¹ Manon Charlet,¹ Alexis Vandenberghe,^{1,9} Paolo Van Endert,¹ Lucy Bizien,^{3,4} Omaira Da Mata-Jardin,² Andrés Ferriño-Iriarte,⁷ Ahmed Haouz,¹⁰



- High-affinity type-I IFN-specific memory B cells preexist severe viral infection
- IFN-α2/ω neutralization potential is gained through extended affinity maturation
- Pathogenic auto-Abs target three major antigenic sites on type-I IFNs
- Structural atlas of anti-IFN mAbs highlights epitope restricted cross-reactivity

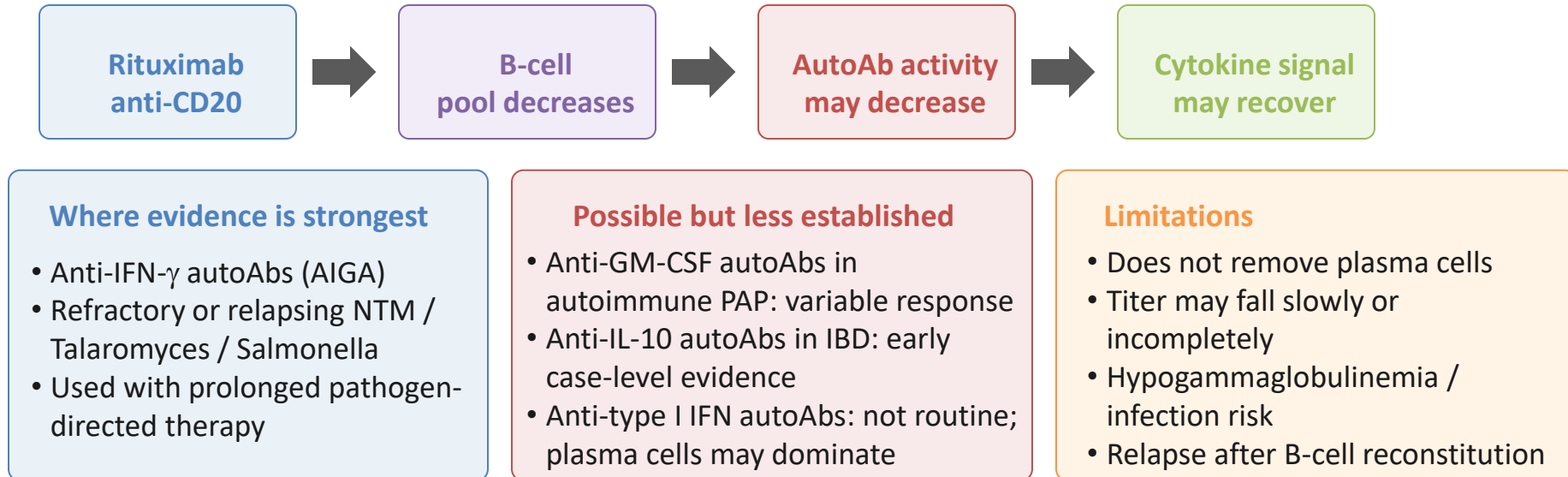
Persistent infection despite of antibiotic treatment

Patient	Species of NTM	Used antibiotics	Maintenance therapy	Outcome
1	<i>M. scrofulaceum</i> , <i>M. abscessus</i>	AZ, CIP, CLA, EMB, LVX, RFB	CLA+LVX	Persistent infection
2	MAC	CLA, EMB, RFB, RMP	CLA+EMB	Persistent infection
3	<i>M. goodii</i> , <i>M. abscessus</i>	AN, CLA, CIP, EMB, FOX, MXF, RMP, TE, TG	CLA+RMP+TG	Persistent infection
4	<i>M. abscessus</i>	AN, CIP, CLA, EMB, INH, RMP	—	Cured
5	<i>M. abscessus</i>	AZ, CIP, FOX, MIN, TG	AZ+CIP	Persistent infection
6	<i>M. terrae</i> complex	AZ, CLA, EMB, INH, PZA, RMP	—	Cured
7	Unidentified	CLA, E, EMB, INH, RMP	—	Cured
8	<i>M. scrofulaceum</i>	CLA, EMB, INH, LVX, RMP	—	Cured
9	MAC	AZ, CLA, CIP, EMB, LVX, MIN, RMP	MIN+RFB	Persistent infection
10	Unidentified	AN, AZ, CLA, EMB, FOX, INH, PZA, RFB, RMP	AZ+EMB+INH+RFB	Persistent infection
11	<i>M. kansasii</i>	AN, CLA, EMB, FOX, INH, LZD, MXF, RMP, TG	—	Cured
12	Unidentified	CLA, EMB, INH, MXF, PZA, RMP	CLA+MXF	Persistent infection
13	<i>M. abscessus</i>	AN, AZ, CIP, CLA, EMB, INH, IPM, LVX, MIN, MXF, RMP	AZ+CEF+CIP	Persistent infection
14	Unidentified	EMB, INH, PZA, RMP	—	Cured
15	MAC	CLA, EMB, INH, PZA, RMP	NA	Unknown
16	<i>M. abscessus</i>	AN, AZ, CEF, CLA, IPM, LVX, MIN, TG	AZ+CEF+LVX	Persistent infection
17	<i>M. abscessus</i> , <i>M. szulgai</i>	AN, CIP, CLA, EMB, FOX, INH, IPM, LVX, RMP	Unknown	Persistent infection
18	<i>M. abscessus</i>	CLA, EMB, INH, MIN, MXF, RMP	CLA+MIN	Persistent infection
19	<i>M. goodii</i>	AN, CLA, EMB, RMP	CLA+EMB	Persistent infection
20	MAC	CLA, EMB, LVX, RMP	AZ+RMP	Persistent infection
21	<i>M. abscessus</i>	CLA, EMB, INH, PZA	CEF+CLA+DOX	Persistent infection
22	Unidentified	CLA, EMB, RMP	Unknown	Persistent infection
23	MAC	CLA, EMB, INH, LVX, MXF, PZA, RMP	CLA+EMB+LVX+RMP	Persistent infection
24	<i>M. fortuitum</i>	CLA, INH, RMP, SXT	—	Cured
25	MAC	AZ, DOX, EMB, IPM, MXF, RFB, SXT	AZ+EMB+MXF+RFB	Persistent infection
26	Unidentified	AZ, CIP, EMB, INH, PZA, RFB, RMP	AZ+EMB	Persistent infection
27	MAC	CIP, CLA, EMB, RFB, RMP	INH+RMP	Persistent infection
28	<i>M. abscessus</i>	AN, AZ, CLA, DOX, TG	CLA	Persistent infection
29	<i>M. abscessus</i>	AN, CIP, CLA, IPM, LZD, MIN, MXF	AZ+DOX+LVX	Persistent infection
30	MAC	AN, CLA, EMB, FOX, IPM, MXF, RFB, TG	NA	Unknown
31	MAC	CEF, CLA, EMB, LVX, MXF, RMP, SXT	CLA+EMB+RMP	Persistent infection
32	MAC	AN, CLA, EMB, INH, RFB, RMP, TG	CLA+EMB+RFB	Persistent infection
33	Unidentified	CLA, EMB, MXF, RMP	CLA+MXF+RMP	Persistent infection
34	Unidentified	NA	NA	Unknown
35	<i>M. abscessus</i>	INH, RMP, EMB, AZ, CIP	NA	Unknown
36	Unidentified	NA	NA	Unknown
37	Unidentified	NA	NA	Unknown
38	Unidentified	NA	NA	Unknown
39	<i>M. abscessus</i>	IPM, AN, CLA, MXF, LVX, MIN, AZ, SXT, LZD	CLA+LZD+MXF	Persistent infection
40	MAC, <i>M. abscessus</i> , <i>M. kansasii</i> , <i>M. chelonae</i>	IPM, AN, CLA, EMB, RMP, INH, LVX, MIN, MXF	—	Cured
41	MAC	NA	NA	Unknown
42	Unidentified	NA	NA	Unknown
43	MAC, <i>M. kansasii</i>	RFB, DOX, CLA, LZD, SXT, LVX, IPM, AN	RFB+DOX+CLA	Persistent infection
44	Unidentified	CLA, EMB, INH, RMP, TG, LZD, SXT, CIP	—	Cured
45	Unidentified	INH, RMP, EMB, CLA	INH+RMP+EMB+CLA	Persistent infection

B-cell depletion as a precision treatment strategy for ACAD

Rationale

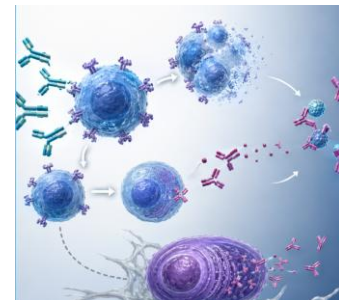
ACADs are driven by pathogenic autoantibodies. Depleting CD20+ B cells can reduce new autoantibody production, but long-lived plasma cells may persist.



Monitoring

- Clinical response
- neutralizing activity
- cytokine signaling rescue
- CD19/CD20 count
- IgG level
- cultures / imaging

B-cell depletion is most rational when active B cells sustain pathogenic cytokine-neutralizing antibodies; persistent plasma-cell antibody production may require other strategies.



Inhibitory Decoy to restore cytokine's function

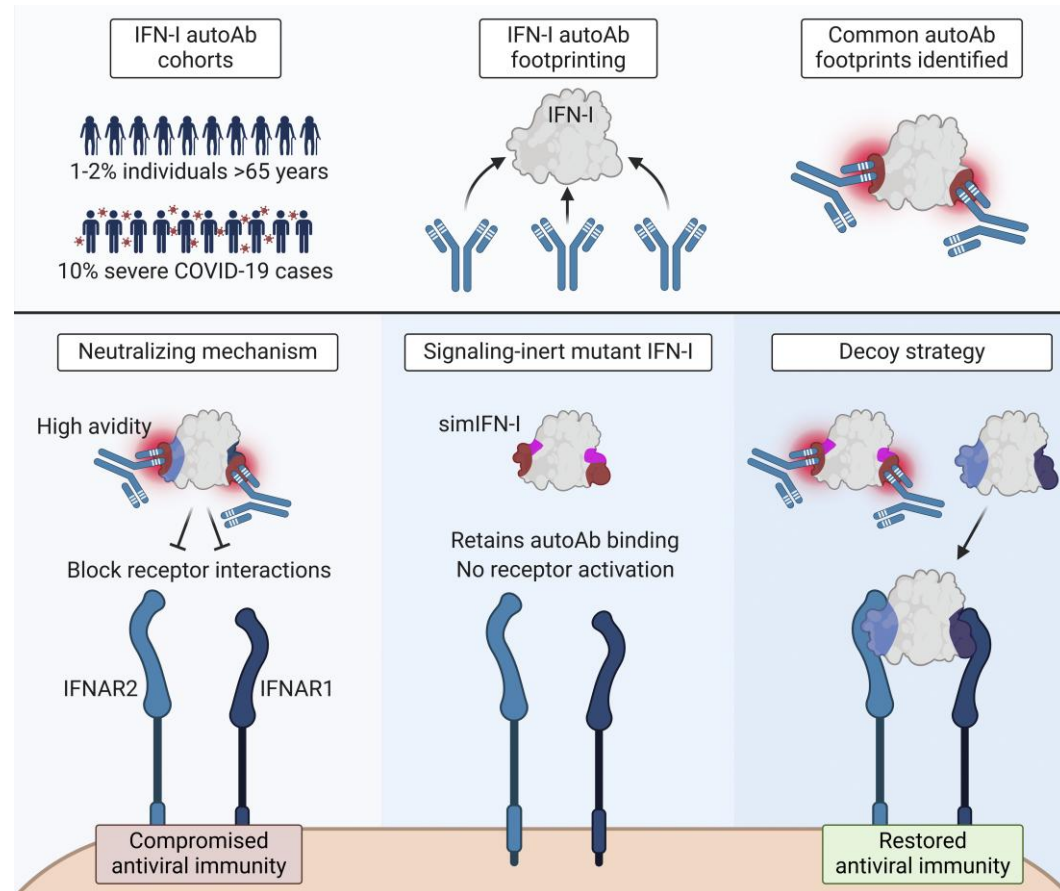


ARTICLE

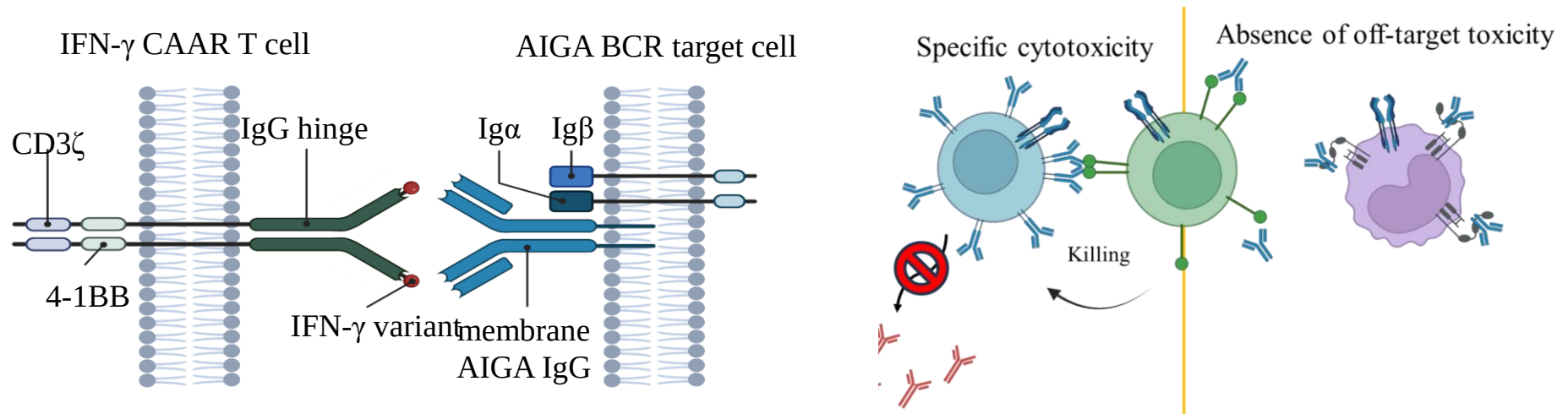
Type I interferon autoantibody footprints reveal neutralizing mechanisms and allow inhibitory decoy design

Kevin Groen¹, Roger Kuratli², Jannik Enkelmann¹, Sonja Fernbach¹, Pedro D. Wendel-Garcia², Willy I. Staiger³, Marylène Lejeune⁴, Esther Sauras-Colón⁵, Ferran Roche-Campo⁶, Paraskevas Filippidis⁷, Andri Rauch⁸, Swiss HIV Cohort Study, Alexandra Trkola², Huldrych F. Günthard^{1,3}, Roger D. Kouyos^{1,3}, Silvio D. Bruggen⁹, and Benjamin G. Hale¹

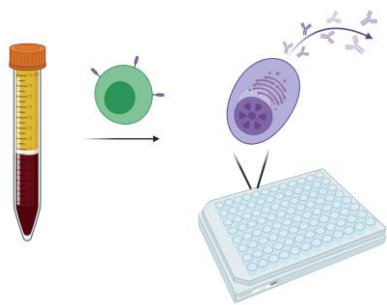
Autoantibodies neutralizing type I interferons (IFN-Is; IFN α or IFN ω) exacerbate severe viral disease, but specific treatments are unavailable. With footprint profiling, we delineate two dominant IFN-I faces commonly recognized by neutralizing IFN-I autoantibody-containing plasmas from aged individuals with HIV-1 and from individuals with severe COVID-19. These faces overlap with IFN-I regions independently essential for engaging the IFNAR1/IFNAR2 heterodimer, and neutralizing plasmas efficiently block the interaction of IFN-I with both receptor subunits in vitro. In contrast, non-neutralizing autoantibody-containing plasmas limit the interaction of IFN-I with only one receptor subunit and display relatively low IFN-I-binding avidities, thus likely hindering neutralizing function. Iterative engineering of signaling-inert mutant IFN-Is (simIFN-Is) retaining dominant autoantibody targets created potent decoys that prevent IFN-I neutralization by autoantibody-containing plasmas and that restore IFN-I-mediated antiviral activity. Additionally, microparticle-coupled simIFN-Is were effective at depleting IFN-I autoantibodies from plasmas, leaving antiviral antibodies unaffected. Our study reveals mechanisms of action for IFN-I autoantibodies and demonstrates a proof-of-concept strategy to alleviate pathogenic effects.



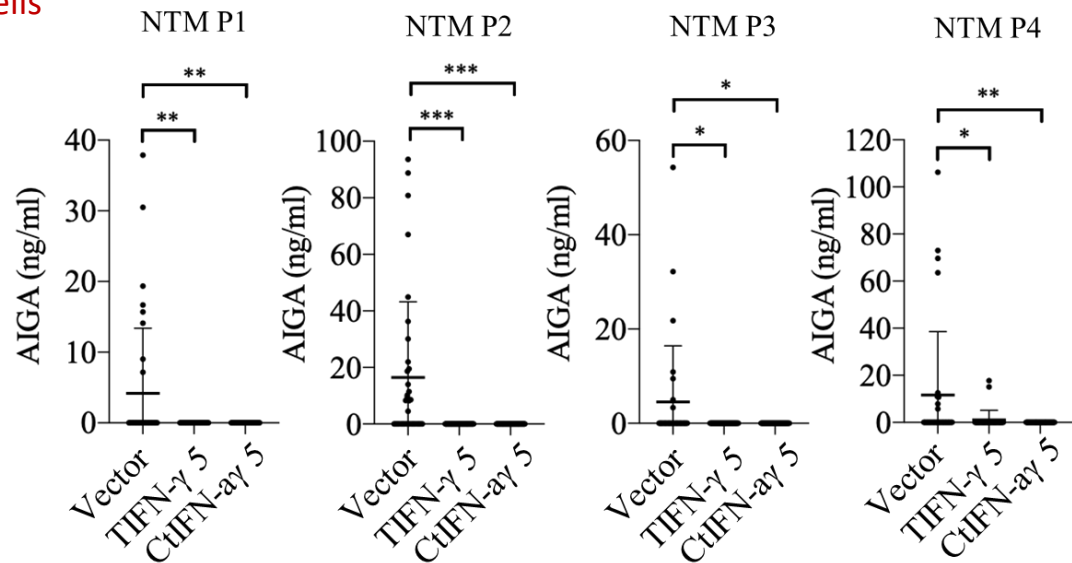
Chimeric autoantibody receptor (CAAR) T cells for targeted therapy of anti-IFN- γ autoantibodies diseases



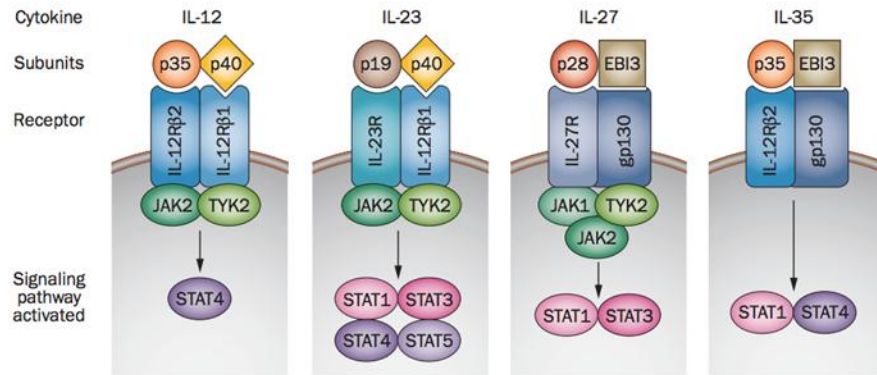
Clonal dissection of AIGA memory B cells after IFN- γ CAAR T cells treatment



10^5 PBMCs each well
E:T ratio: 1:30
Time: 10 days



Anti-IL-12 autoantibodies and infections



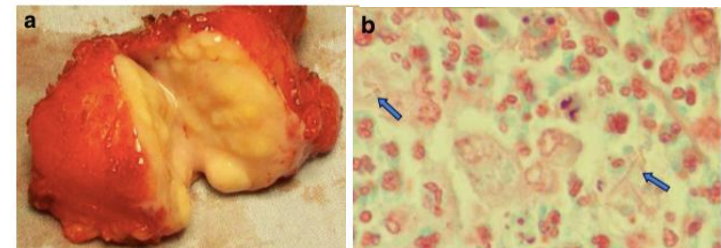
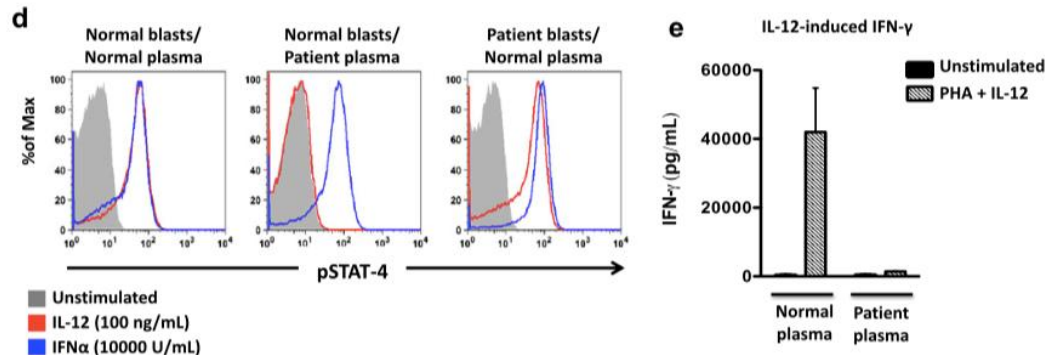
- Only few cases had been reported.
- Most cases are non-neutralizing and be reported in thymoma patients.

J Clin Immunol (2013) 33:1057–1061
DOI 10.1007/s10875-013-9908-z

ASTUTE CLINICIAN REPORT

Recurrent *Burkholderia gladioli* Suppurative Lymphadenitis associated with Neutralizing Anti-IL-12p70 Autoantibodies

Bich-Thuy T. Sim • Sarah K. Browne • Marguerite Vigliani • Dalila Zachary •
Lindsey Rosen • Steven M. Holland • Steven M. Opal



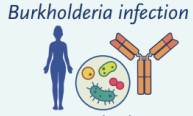
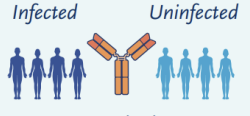
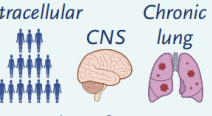
Anti-IL-12 autoantibodies and infections

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anti-Interleukin-23 Autoantibodies in Adult-Onset Immunodeficiency

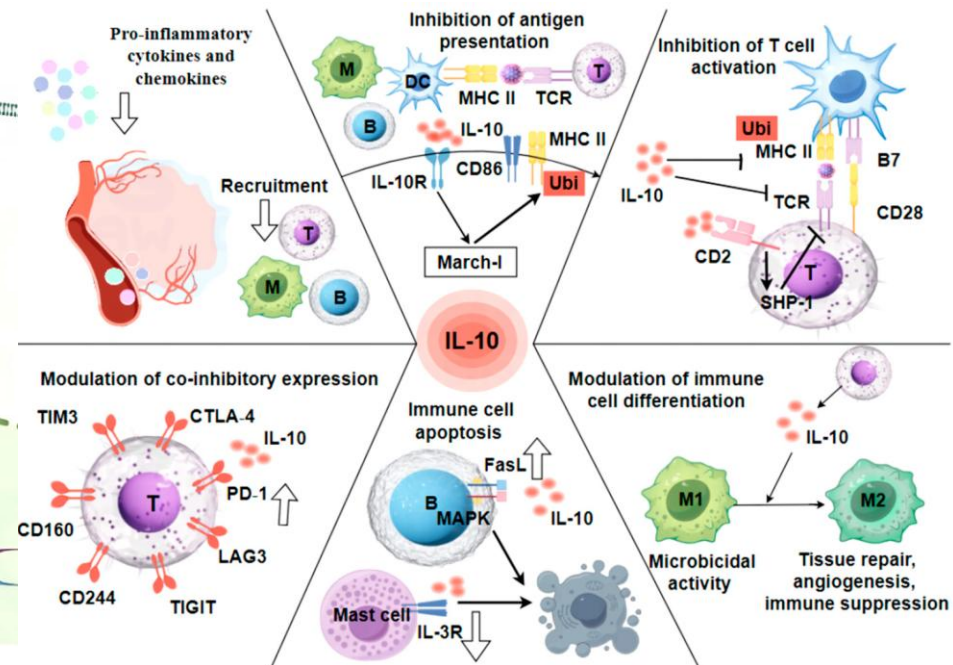
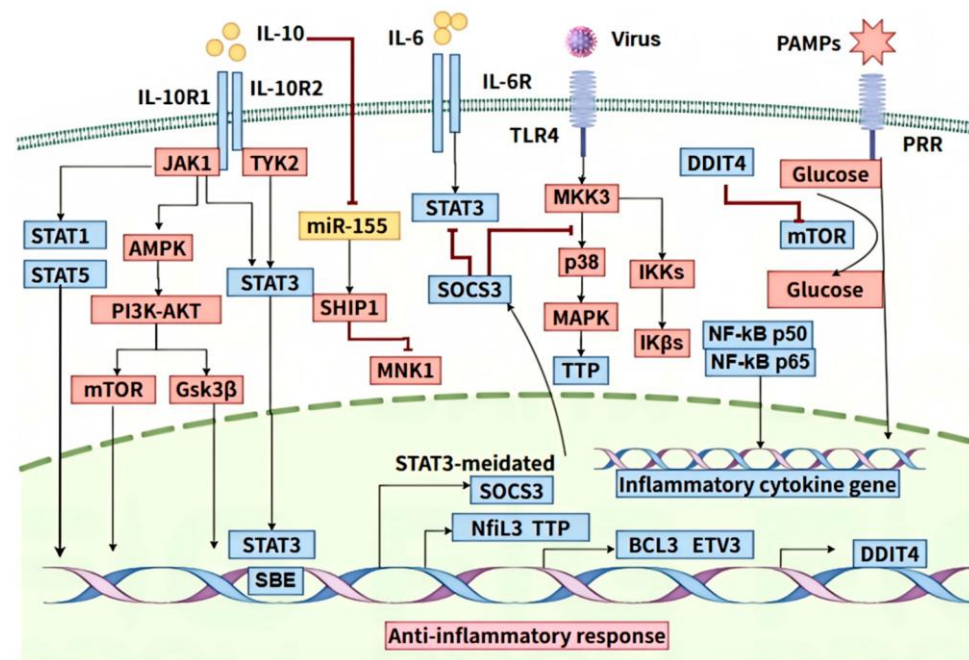
Aristine Cheng, M.D., Anuj Kashyap, B.A., Helene Salvator, M.D., Ph.D., Lindsey B. Rosen, Ph.D., Devon Colby, B.S., Fatemeh Ardeshir-Larijani, M.D., Patrick J. Loehrer, M.D., Li Ding, M.D., Saul O. Lugo Reyes, M.D., Sean Riminton, M.D., Ph.D., Madison Ballman, B.A., Joseph M. Rocco, M.D., Beatriz E. Marciano, M.D., Alexandra F. Freeman, M.D., Sarah K. Browne, M.D., Amy P. Hsu, Ph.D., Adrian Zelazny, Ph.D., Arun Rajan, M.D., Irini Sereti, M.D., Christa S. Zerbe, M.D., Michail S. Lionakis, M.D., Sc.D., and Steven M. Holland, M.D.

	INDEX PATIENT	DISCOVERY	VALIDATION	EXPANSION	OTHER COHORTS
Patient	 Burkholderia infection Anti-interleukin-12 N=1	 Infected Uninfected Anti-interleukin-12 N=30	 Infected Uninfected Thymoma N=91	 Intracellular CNS Chronic lung Similar infections N=128	 Healthy CMC Viral No similar infections N=971
Hypothesis	Anti-interleukin-12 may cross-react and neutralize interleukin-23 owing to the common p40	Does neutralization of interleukin-23 occur in other patients with anti-interleukin-12? And is this a phenotype?	Can we validate these findings in a larger cohort of patients with thymoma?	Can we find anti-interleukin-23 in similarly infected patients in the absence of anti-interleukin-12 or thymoma?	Can we show that anti-interleukin-23 is uncommon in healthy persons and in controls with other infections?
Methods	Perform multiplex binding and functional assays	Perform multiplex binding and functional assays, IgG deletion assay, and clinical data review	Perform blinded testing for anti-interleukin-23, predict infection status, and calculate true positive and negative accuracy of anti-interleukin-23	Screen other patients with MSMD-like intracellular, unusual CNS, or fungal infections for anti-interleukin-23	Screen healthy blood donors and patients with CMC or Covid-19 for anti-interleukin-23
Findings	Index patient had bioactive anti-interleukin-23	Neutralization of interleukin-23 occurred in 50% of patients with anti-interleukin-12 who had invasive mycobacterial, fungal, or bacterial infections	Neutralization of interleukin-23 occurred in 50% of patients with thymoma who had invasive infections (overall accuracy, 81%)	Neutralization of interleukin-23 occurred in 2 patients (without anti-interleukin-12 or thymoma) who had unusual CNS infections	Neutralization of interleukin-23 occurred in <2% of healthy controls or patients with unrelated viral or mucosal infections

- Anti-IL12/23 and IL23 drug showed a high safety in preclinical study and real-world
- A possible co-founding factor of thymoma and infections

IL-10 and autoinflammatory diseases

IL-10, a suppressive cytokine



IL-10 deficiency and Inflammatory Bowel Diseases

ORIGINAL ARTICLE

Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor

Erik-Oliver Glocker, M.D., Daniel Kotlarz, M.D., Kaan Boztug, M.D., E. Michael Gertz, Ph.D., Alejandro A. Schäffer, Ph.D., Fatih Noyan, Ph.D., Mario Perro, M.Sc., Jana Diestelhorst, B.Sc., Anna Allroth, M.D., Dhaarini Murugan, M.Sc., Nadine Hätscher, B.Sc., Dietmar Pfeifer, M.D., Karl-Walter Sykora, M.D., Martin Sauer, M.D., Hans Kreipe, M.D., Martin Lacher, M.D., Rainer Nustede, M.D., Cristina Woellner, M.Sc., Ulrich Baumann, M.D., Ulrich Salzer, M.D., Sibylle Koletzko, M.D., Neil Shah, M.D., Anthony W. Segal, M.D., Axel Sauerbrey, M.D., Stephan Buderus, M.D., Scott B. Snapper, M.D., Ph.D., Bodo Grimbacher, M.D., and Christoph Klein, M.D., Ph.D.

ABSTRACT

BACKGROUND

The molecular cause of inflammatory bowel disease is largely unknown.

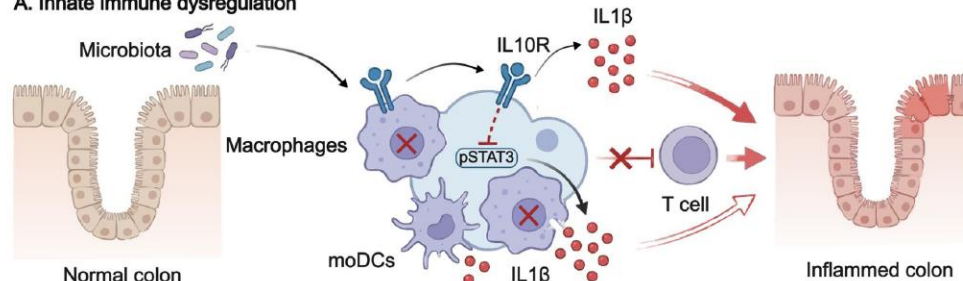
METHODS

We performed genetic-linkage analysis and candidate-gene sequencing on samples from two unrelated consanguineous families with children who were affected by early-onset inflammatory bowel disease. We screened six additional patients with early-onset colitis for mutations in two candidate genes and carried out functional assays in patients' peripheral-blood mononuclear cells. We performed an allogeneic hematopoietic stem-cell transplantation in one patient.

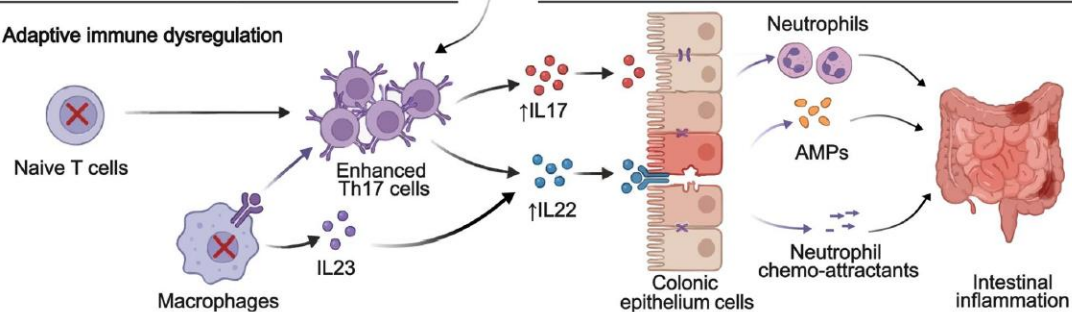
RESULTS

In four of nine patients with early-onset colitis, we identified three distinct homozygous mutations in genes *IL10RA* and *IL10RB*, encoding the IL10R1 and IL10R2 proteins, respectively, which form a heterotetramer to make up the interleukin-10 receptor. The mutations abrogate interleukin-10–induced signaling, as shown by deficient STAT3 (signal transducer and activator of transcription 3) phosphorylation on stimulation with interleukin-10. Consistent with this observation was the increased secretion of tumor necrosis factor α and other proinflammatory cytokines from peripheral-blood mononuclear cells from patients who were deficient in IL10R subunit proteins, suggesting that interleukin-10–dependent “negative feedback” regulation is disrupted in these cells. The allogeneic stem-cell transplantation performed in one patient was successful.

A. Innate immune dysregulation



B. Adaptive immune dysregulation



IL-10 blockade by autoantibodies as an acquired phenocopy

BRIEF REPORT

Neutralizing Autoantibodies against Interleukin-10 in Inflammatory Bowel Disease

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SUMMARY

We discovered high-titer neutralizing autoantibodies against interleukin-10 in a child with infantile-onset inflammatory bowel disease (IBD), a phenocopy of inborn errors of interleukin-10 signaling. After B-cell-depletion therapy and an associated decrease in the anti-interleukin-10 titer, conventional IBD therapy could be withdrawn. A second child with neutralizing anti-interleukin-10 autoantibodies had a milder course of IBD and has been treated without B-cell depletion. We conclude that neutralizing anti-interleukin-10 autoantibodies may be a causative or modifying factor in IBD, with potential implications for therapy. (Funded by the National Institute for Health and Care Research and others.)

INTERLEUKIN-10 SERVES AS AN ANTIINFLAMMATORY CYTOKINE WITH A crucial role in controlling intestinal inflammation. Biallelic loss-of-function variants of interleukin-10 (encoded by *IL10*) or its receptor subunits (encoded by *IL10RA* and *IL10RB*) lead to severe infantile-onset ulcerating intestinal inflammation with fistulizing disease.^{1,2} Most patients with this condition present with infantile-onset enterocolitis, and in some cases the condition may manifest with additional features such as folliculitis, arthritis, and B-cell lymphoma.^{1,2} This phenotype and the curative potential of hematopoietic stem-cell transplantation in such diseases show the significance of interleukin-10 signaling in immune cells as an immunoregulatory mechanism. Of interest, a missense variant in *IL10RA* increases the risk of adult-onset polygenic inflammatory bowel disease (IBD),³ and regulatory variants that boost interleukin-10 expression are associated with reduced IBD susceptibility.⁴ These data suggest an effect of interleukin-10 signaling in both early-onset and adult-onset IBD, but the possibility remains that a lack of interleukin-10 signaling in infancy has a more profound effect on gut immune homeostasis because of a developmental window of susceptibility.

The spectrum of inborn errors of immunity encompasses a wide array of genetic disorders, some of which can be mimicked by autoantibodies targeting the same pathways (phenocopies of inborn errors of immunity).^{5,6} Among these, neu-

Key observation

- Whole blood did not respond to IL-10
- Washed PBMCs recovered normal signaling
- Patient serum blocked IL-10 reporter assays

Clinical signal

- Infantile-onset IBD can mimic IL-10 pathway deficiency
- B-cell depletion lowered anti-IL-10 titer
- IBD therapy could later be withdrawn

Interpretation

Anti-IL-10 behaves like a soluble receptor defect: the receptor pathway is intact, but the cytokine is neutralized before signaling.

The 2026 cohort linked anti-IL-10 seropositivity to HLA-DRB1*01:03

ORIGINAL ARTICLE

Interleukin-10 Autoantibodies and HLA-DRB1*01:03 in Inflammatory Bowel Disease

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ABSTRACT

BACKGROUND

Neutralizing autoantibodies against interleukin-10 can result in a phenocopy of monogenic defects of interleukin-10 signaling in children and may be associated with inflammatory bowel disease (IBD). The allele HLA-DRB1*01:03 is the strongest genetic risk factor for ulcerative colitis.

METHODS

We used a cellular interleukin-10 reporter assay and a confirmatory competitive enzyme-linked immunosorbent assay to assess neutralizing interleukin-10 autoantibodies in serum samples obtained from patients with IBD in the Oxford and U.K. IBD BioResource cohorts and from persons without IBD (controls). An in vitro cytokine-release bioassay was performed in a subgroup of patients to assess interleukin-10, interleukin-23, interleukin-1 β , tumor necrosis factor, and interleukin-6. We performed HLA association analysis using imputation and high-resolution sequencing.

RESULTS

Interleukin-10–neutralizing autoantibodies were detected in 173 of 4909 patients with IBD (3.5%; 95% confidence interval [CI], 3.0 to 4.1) and in none of 1006 controls ($P<0.001$). High anti-interleukin-10 activity in serum was associated with a reduction in detectable interleukin-10 and with an exaggerated proinflammatory cytokine response, consistent with functional neutralization of interleukin-10 signaling. Anti-interleukin-10 seropositivity was strongly associated with HLA-DRB1*01:03 on the basis of imputed data from the Oxford cohort (odds ratio, 50.0; 95% CI, 16.4 to 152.3; $P=6.14\times10^{-12}$) and the U.K. IBD BioResource cohort (odds ratio, 24.7; 95% CI, 14.5 to 42.1; $P=6.20\times10^{-12}$) and in a high-resolution sequencing analysis of data from the Oxford cohort (odds ratio, 29.5; 95% CI, 12.2 to 71.1; $P=4.85\times10^{-14}$).

CONCLUSIONS

Neutralizing interleukin-10 autoantibodies were present in a subgroup of patients with IBD and were strongly associated with HLA-DRB1*01:03. (Funded by the National Institute for Health and Care Research and others.)

173 / 4909

IBD patients
positive

3.5%

Prevalence in
IBD

0 / 1006

Controls positive

HLA association

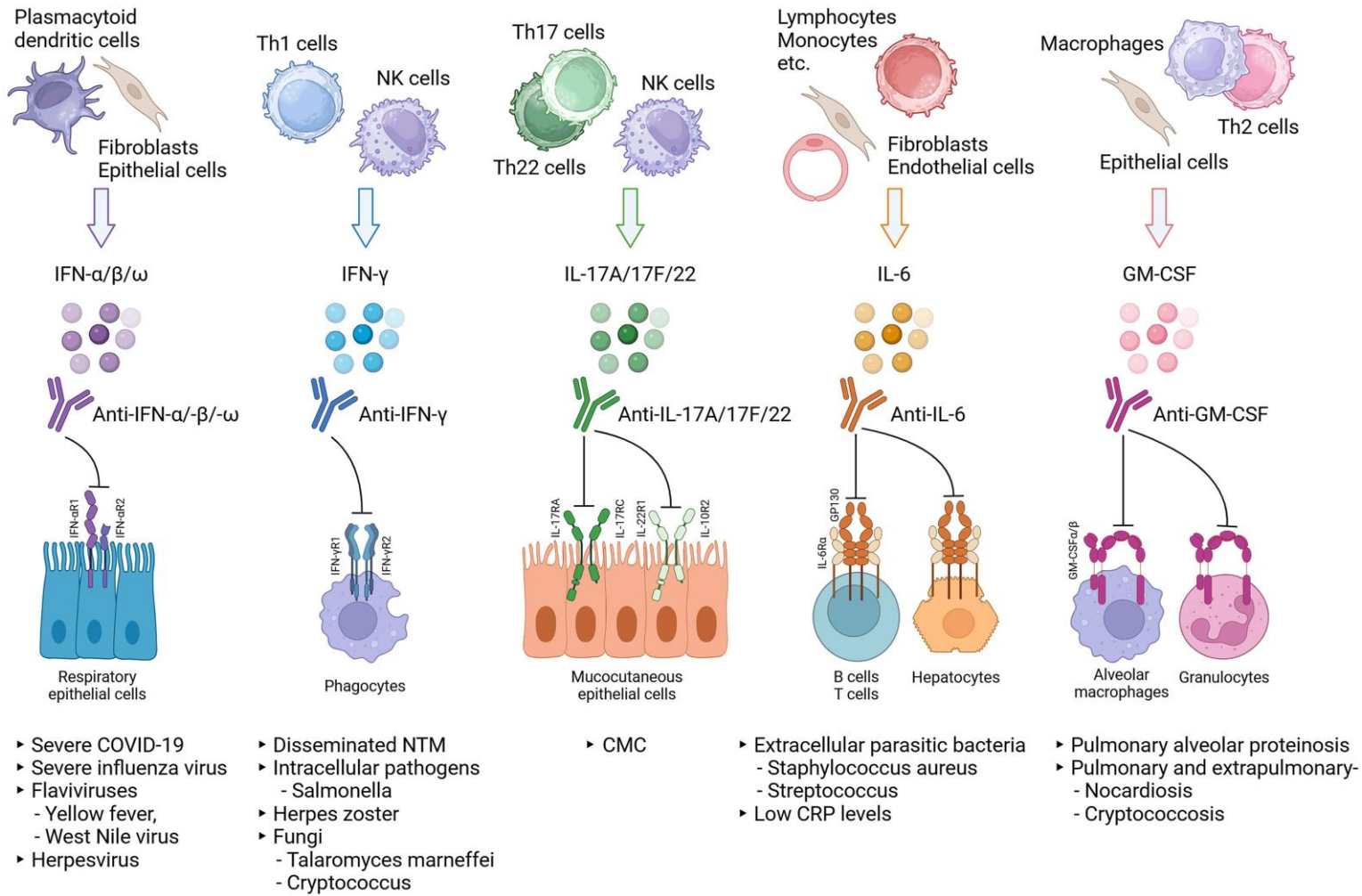
HLA-DRB1*01:03 showed very strong association with anti-IL-10 seropositivity.

Imputed odds ratios: 50.0 in Oxford; 24.7 in UK IBD BioResource.

Functional readout

- High anti-IL-10 activity reduced detectable IL-10
- Patient serum showed exaggerated proinflammatory cytokine release
- This supports functional neutralization, not only binding

Anticytokine autoantibodies: an emerge etiology for infectious diseases



Take Home Message

- In infectious diseases, the contribution of host factors are largely under-estimated.
- ACADs are emerging as an acquired cause of immune dysregulation, infectious susceptibility, and inflammatory disease, particularly in adults.
- Anti-type I IFN autoantibodies are relatively common in the general population, especially in older adults over 60 years, and markedly increase susceptibility to severe viral infections.
- Anti-IFN- γ autoantibodies, or AIGA, are enriched in Southeast Asia, including Taiwan, and explain many cases of severe nontuberculous mycobacterial infection.
- Anti-GM-CSF autoantibodies underlie autoimmune pulmonary alveolar proteinosis and are also associated with nocardiosis and CNS infection caused by *Cryptococcus gattii*.
- Anti-IL-10 autoantibodies define a subgroup of IBD, accounting for approximately 3.5% of total IBD cases in a recent cohort.
- Although ACADs are not classical genetic disorders, their development is strongly linked to genetic factors, including HLA alleles and defects in immune tolerance pathways such as AIRE.
- Low-titer autoantibodies are likely under-recognized and may contribute to a broad range of human diseases.