IPOPI 5TH REGIONAL ASIAN PID MEETING

24-25 MARCH 2024

TOKYO, **JAPAN**

an **IPOPI** event

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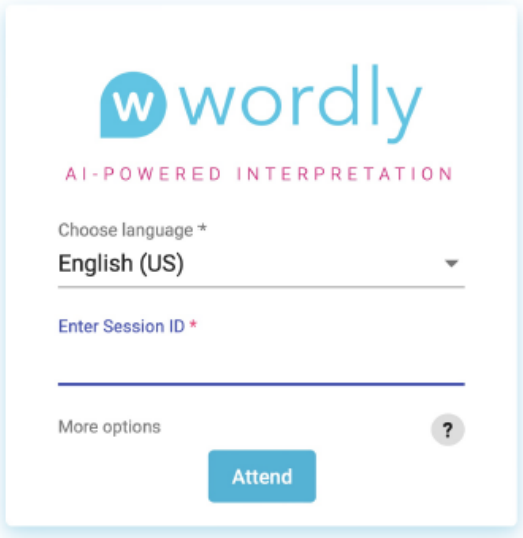

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Step 3

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SESSION 1 | The fast-evolving field of immunodeficiency

Moderators:

Dr Nizar Mahlaoui (France)

Prof Kohsuke Imai (Japan)

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The role of auto-inflammation in primary immunodeficiency

Prof Ryuta Nishikomori | *Japan*

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The role of auto-inflammation in primary immunodeficiency

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COI disclosure: Yes

The author has no COI to disclose concerning the presentation

What is an autoinflammatory disease?

Proposed by Dr. Kastner (NIAMS/NIH) in 1999.

Primarily caused by **dysregulation of innate immune response**, as opposed to "autoimmune" diseases, caused by defective regulation of acquired immune response.

Clinically characterized by **periodic fever**.

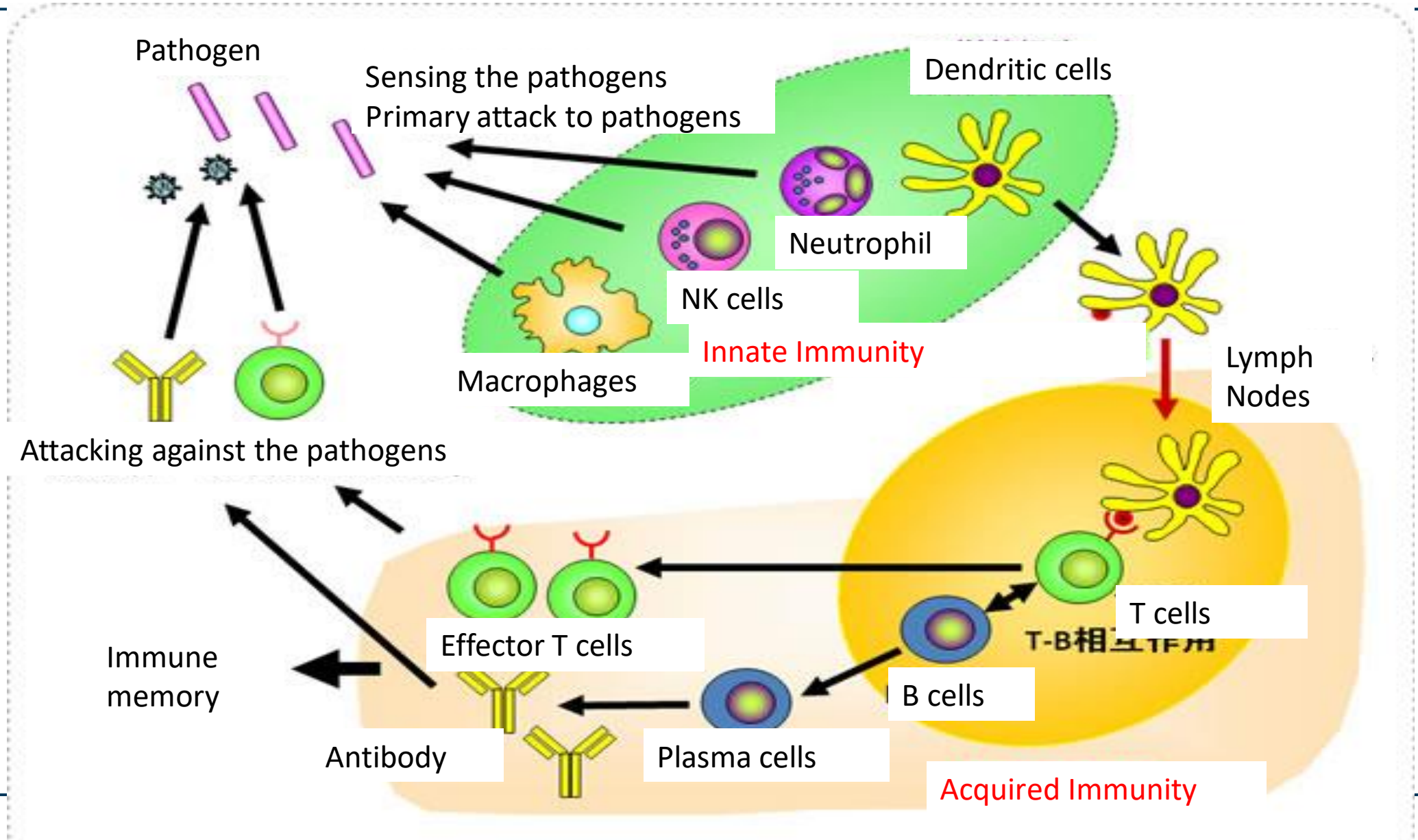
Other common symptoms: **rash, arthritis/arthralgia, abdominal pain**.

Usually **hereditary diseases**.

Dr. Kastner (NIAMS/NIH)

Created by RN

Innate immunity and acquired immunity



Innate immunity sensors: Pattern Recognition Receptors

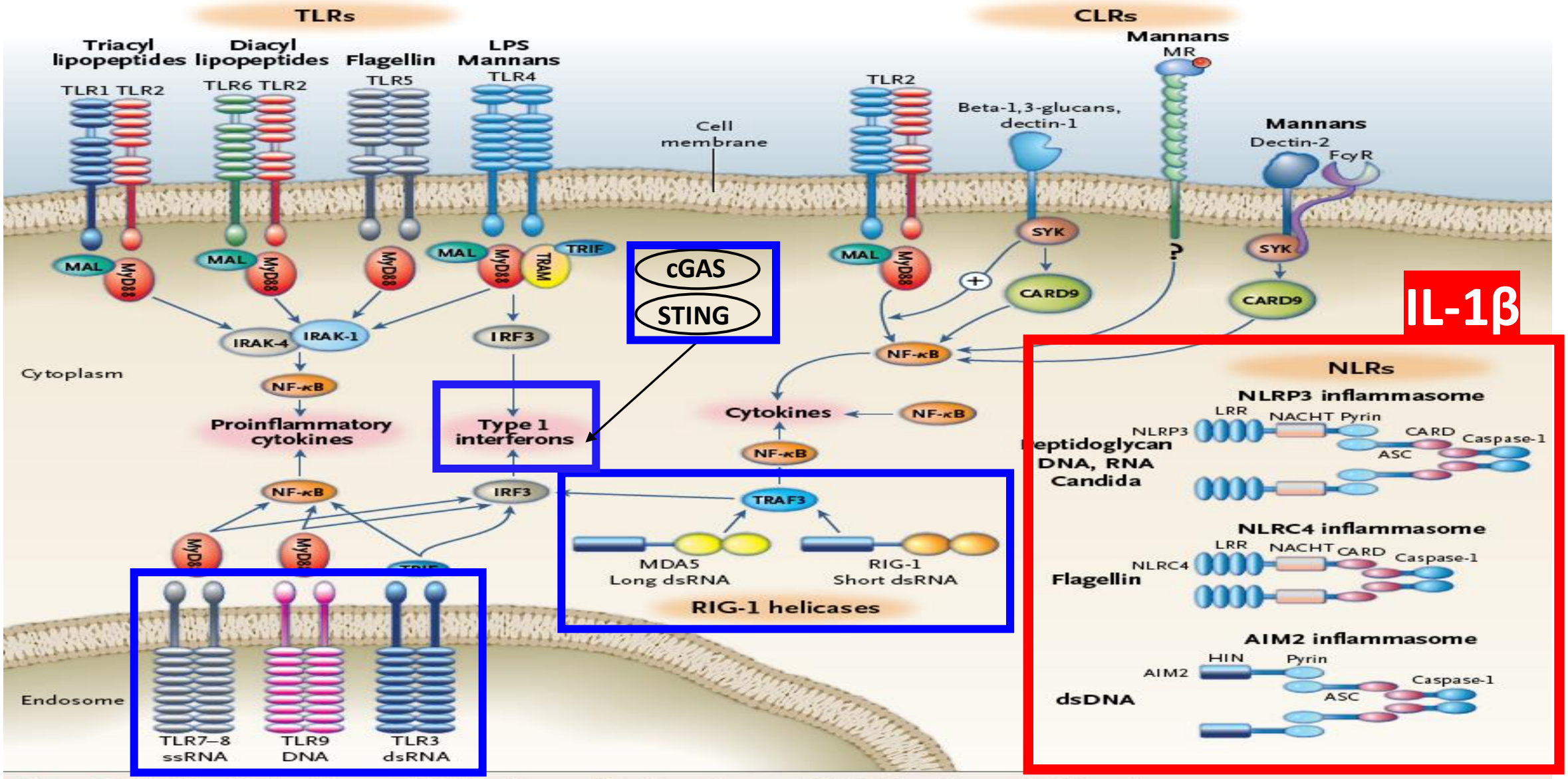


Figure 1. The Four Major Classes of Pattern-Recognition Receptors and Their Most Important Ligands.

N Engl J Med 2011;364:60-70を改変

Classification of Autoinflammatory diseases

A)Genetically defined autoinflammatory diseases

- Cryopyrin-associated periodic syndrome (CAPS)
- Mevalonate kinase deficiency (MKD)
- Familial Mediterranean Fever
- PAAND
- NLRC4-associated autoinflammatory syndrome
- CDC42 c-terminus syndrome
- Majeed syndrome
- Deficiency of the IL-1 receptor antagonist
- TNF receptor-associated periodic syndrome (TRAPS)
- P A P A syndrome
- Nakajo-Nishimura syndrome (PRAAS)
- A i cardi-Goutières syndrome
- ADA2 deficiency
- COPA syndrome
- STING-associated vasculopathy with onset in infancy (SAVI)
- Blau syndrome
- A20 haploinsufficiency
- OTULIN deficiency
- CARD14
- VEXAS syndrome

B) Non-genetic autoinflammatory diseases

- Systemic JIA
- PFAPA
- Adult Still' s disease
- Gout
- Pseudogout
- Schnitzler syndrome
- Type II diabetes mellitus
- Behçet's disease
- CNO/CRMO
- MIS-C

IL-1β・inflammasome-related
Type I interferonopathy
NF-κB-related

- More than 50 genes have been discovered
- Rare to ultrarare diseases

Created by RN

Epidemiology of autoinflammatory diseases in Japan

Diseases	FMF	C A P S	T R A P S	DADA2	PRAAS	SAVI	Blau
Patients number	~1000	100～	50～	~10	10~20	10	50

Research group for the autoinflammatory diseases funded by Research on Measures for Intractable Diseases, MLHW (2020-2022)

Autoinflammatory diseases which have PID features

Deficiency of ADA2

Proteasome-associated autoinflammatory syndrome
- CANDLE syndrome
  - Nakajo-Nishimura syndrome
- PSMB9 syndrome
  - Autoinflammatory features with T cells/B cells, or T cells/NK cells deficiency
  - HCT worked for 1 patient

STING –associated vasculopathy with onset in infancy

PLCG2- associated immune dysregulation
- APLAID

Causing HLH
- Mevalonate kinase deficiency
- CDC42 C terminus syndrome
- NLRC4

DADA2 (ADA2 deficiency)

DADA2 is a rare, monogenic recessively inherited autoinflammatory disease

Systemic inflammation, vasculitis, early-onset stroke, immunodeficiency, and bone marrow failure.

Approximately 25% of patients are diagnosed before one year of age and 77% by 10 years of age.

Patients with DADA2 who have bone marrow failure tend to present during early infancy, whereas delayed presentation is common in patients with vasculitis affecting medium- and small-sized vessels and systemic inflammation.

Early diagnosis is critical to minimize systemic organ damage. The best treatments today are TNF inhibitors for the autoinflammatory aspects of the disease.

For those with critical bone marrow failure, a bone marrow transplant may be necessary.

The clinical spectrum of DADA2 is broad, and manifestations can vary even among family members with the same genotype.

The DADA2 Foundation

DADA2：aspects of immunodeficiency

Humoral Immunodeficiency

• Decrease in immune system function due to a decrease in the number of B−cells that make antibodies

Lymphoproliferation

• Lymphoproliferative disorders are a group of diseases characterized by the uncontrolled production of white blood cells called lymphocytes. Lymphoproliferative disorders develop due to immune system dysfunction.

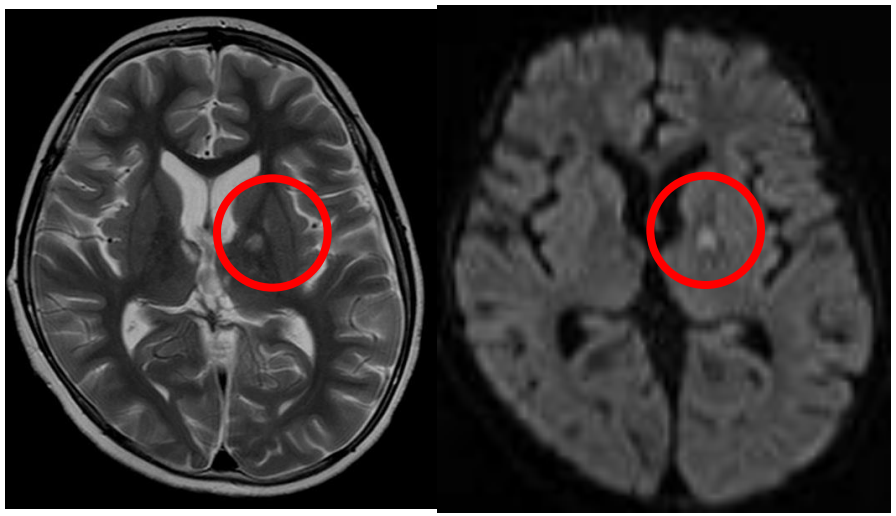
Recurrent Viral or Bacterial Infections

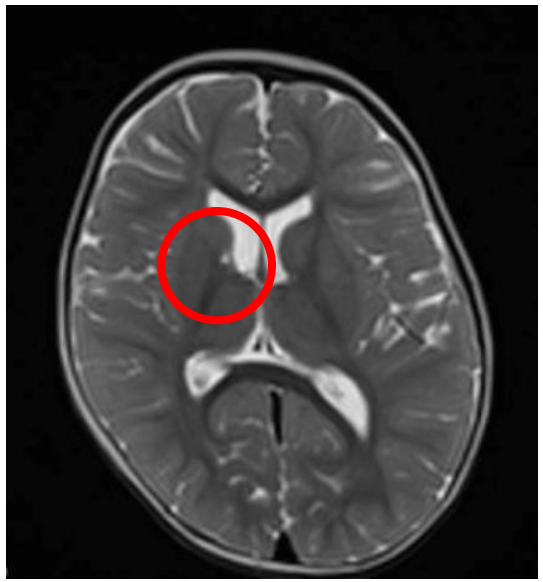
• When infections occur more frequently, are often more severe, and have a greater risk of complications, due to immunodeficiency.

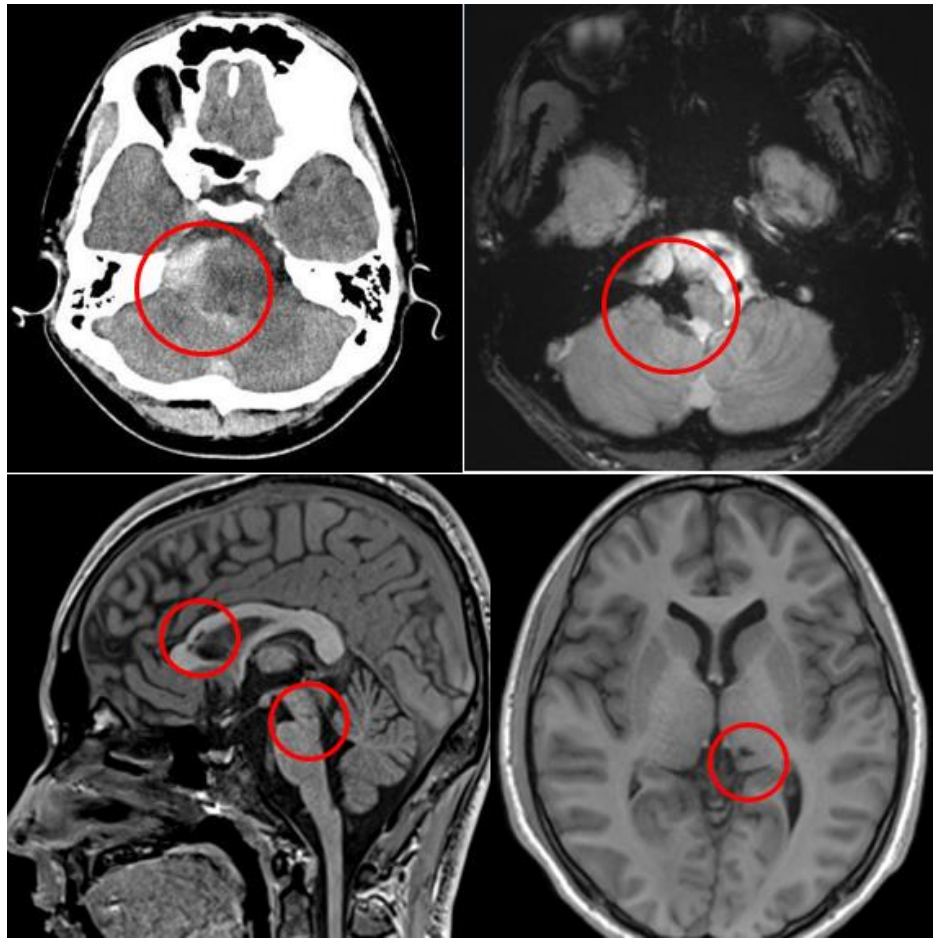
Patient No. (Family No.)	Sex	Age			Mutation	Symptoms	Previous		Current Treatment	
		Onset	Diagnosis	Current			therapy	Treatment efficacy	therapy	efficacy
P1(F1)	M	9y	17y	20y	• p.Tyr227Cys (c.680A>G) • p.Gly358Arg (c.1072G>A)	• intracranial hemorrhage • rash (livedo racemose) • fever • renal infarction	• tocilizumab • IVCY • plasma transfusion	PR (recurrent cerebral infarction)	• anti-TNF-α agent (ADA)	CR
P2(F2)	M	10y	22y	25y	• p.Glu328Lys (c.982G>A) • unknown	• intracranial hemorrhage • cerebral infarction • rash (livedo racemose) • frostbite • fever • splenomegaly • renal infarction	• high dose steroids • IVIG	PR (recurrent cerebral infarction)	• anti-TNF-α agent (IFX) • SCIg	CR
P3(F2)	M	12y	18y	22y	• p.Glu328Lys (c.982G>A) • unknown	• diplopia • memory disturbance • rash (livedo racemose) • frostbite • renal infarction	• None	NA	• anti-TNF-α agent (IFX) • SCIg	CR
P4(F3)*	F	3m	6m	4y	• p.Glu328Asp (c.984G>C) • p.Tyr236del (c.706_708TACdel)	• small lacunar infarction (asymptomatic) • rash (livedo racemose) • fever • splenomegaly	• high dose steroids • tocilizumab	PR (steroid dependent)	• low dose steroids • anti-TNF-α agent (IFX→ADA)	CR (switch IFX to ADA due to anti-IFX antibody)
P5(F3)	M	2m	1m	2y	• p.Glu328Asp (c.984G>C) • p.Tyr236del (c.706_708TACdel)	• red cell aplasia • rash	• None	PD (recover from anemia without any specific treatment, relapse with fever not with anemia)	• anti-TNF-α agent (ADA)	CR
P6(F4)	F	5y	17y	21y	• p.Arg49Alafs*13 (c.143-144insG) • p.Leu92Val(c.274C>G) • p.Phe355Leu (c.1065C>A)	• intracranial hemorrhage • cerebral infarction • rash (livedo racemose) • renal infarction • splenic infarction	• high dose steroids • IVCY • rituximab • colchicine • CsA • Tac	PR (recurrent cerebral infarction)	• low dose steroids • anti-TNF-α agent (IFX→ETN)	CR (switch IFX to ETN due to resistance to IFX)
P7(F5)**	F	13y	17y	20y	• p.Arg248Serfs (c.744delG) • p.Ile93Thr (c.278T>C)	• red cell aplasia • rash (livedo racemose)	• CsA	PR (relapse when CsA is tapered)	• CsA • anti-TNF-α agent (ETN)	CR
P8(F6)	F	12y	12y	15y	• p.Pro251Pro (c.753G>A) • p.Pro251Leu (c.752C>T)	• rash (livedo racemosa) • fever • myositis • renal hypertention	• None	NA	• anti-TNF-α agent (ADA)	CR

5 patients had central nervous system manifestations

- 4 had cerebral infarction
- 3 had intracranial hemorrhage

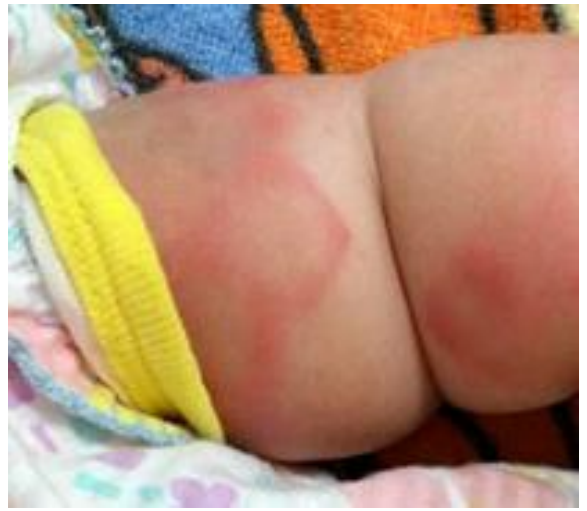


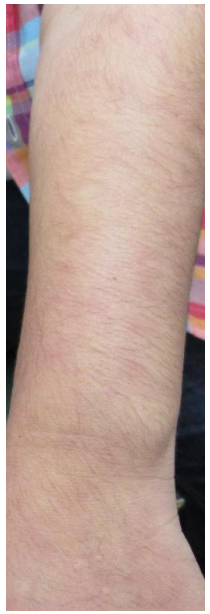


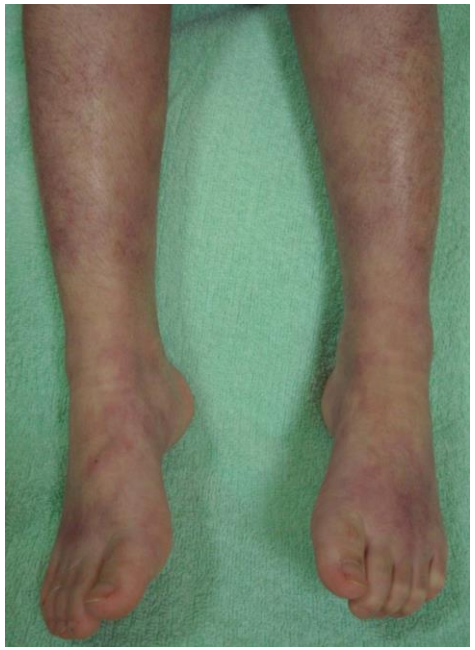


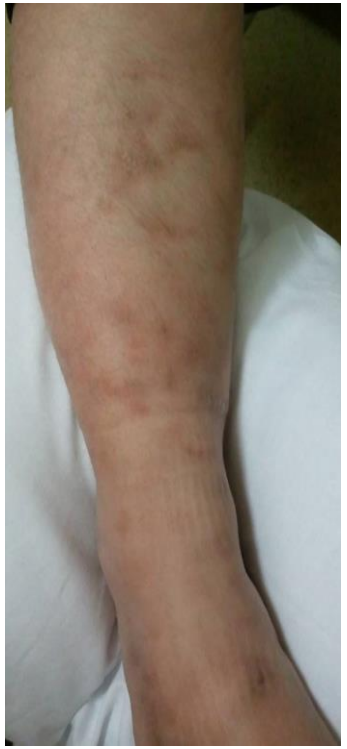
8 patients had cutaneous manifestations

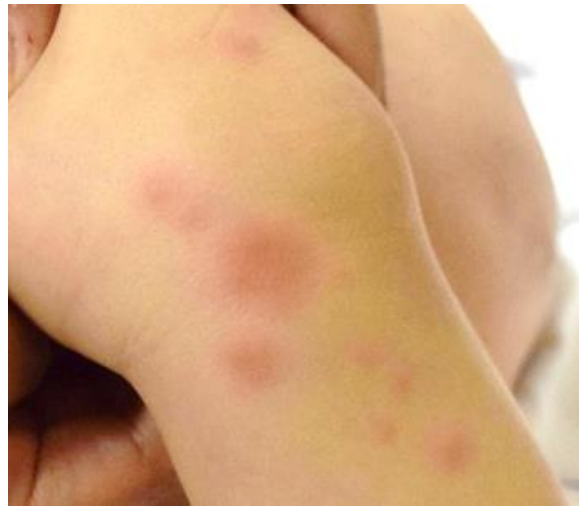
- **7 had livedo racemosa.**
- **4 had non-specific rashes**
- **3 had Raynaud phenomenon.**











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		Onset	Diagnosis	Current			therapy	Treatment efficacy	therapy	efficacy
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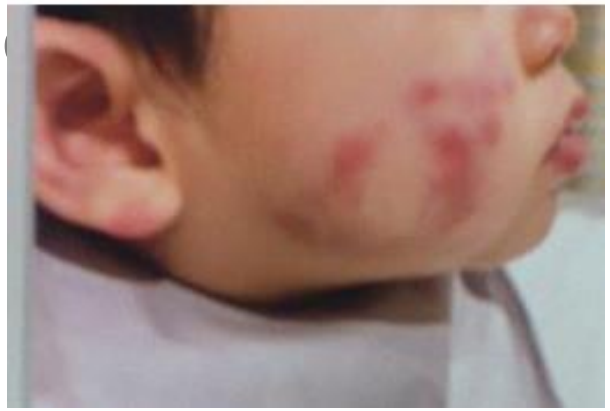
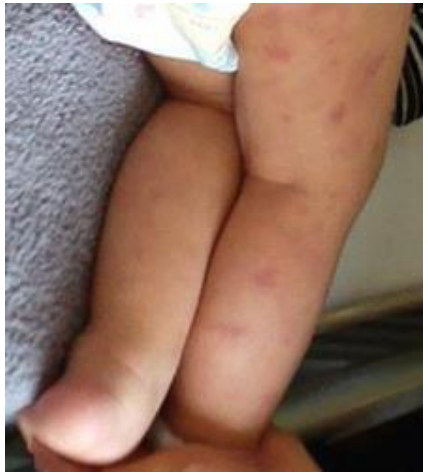
CANDLE syndrome

7 months Erythematous rash

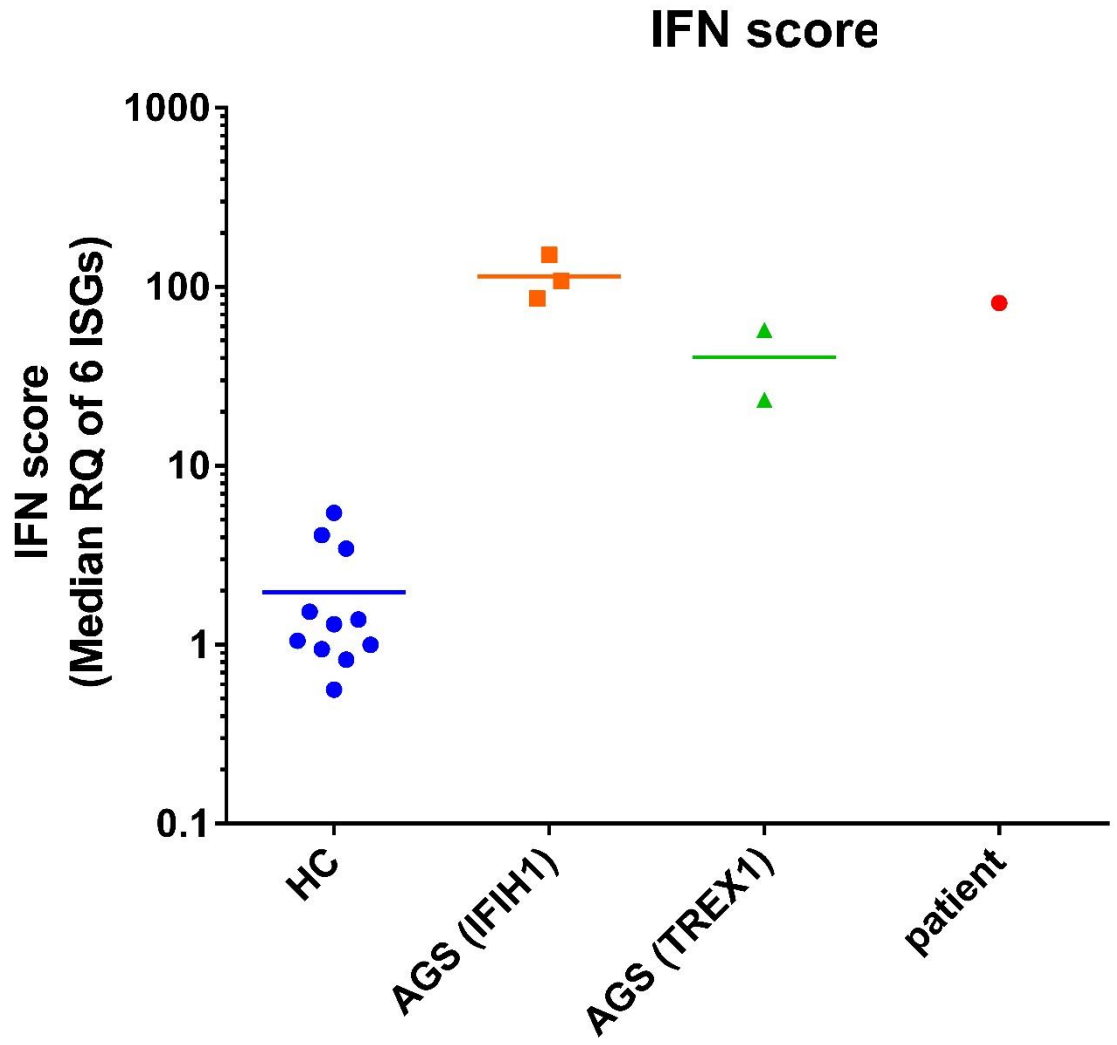
10 months Chilblain-like rash on both fingers, spreading to cheeks and thighs.

1 year and 2 months Fever continued for 1 week and the patient was admitted to th





High IFN score



IFN score
= median fold change of the 6 ISG.
Cutoff：5.04
（mean IFN score of HC +2SD）

CANDLE syndrome

PSMB8 gene　compound heterozygous

- C.602G>T hetero,　G201V
- c.389delT hetero, p.129R+27*　（frameshift deletion）

CANDLE syndrome

(Nakajo-Nishimura syndrome)

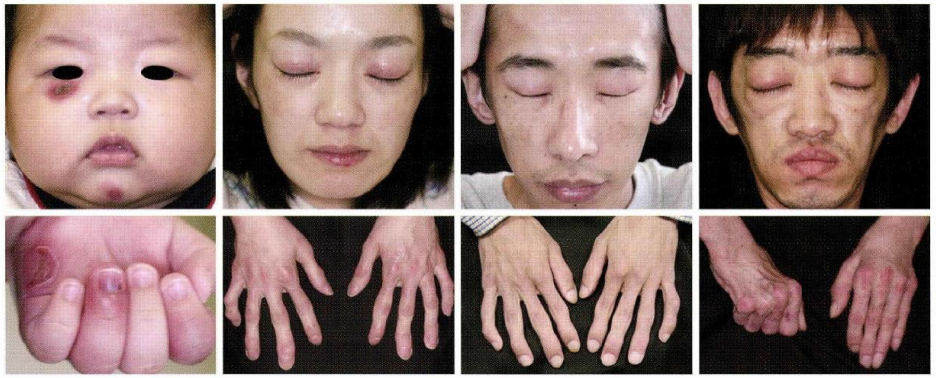
CANDLE

Responsible gene：*PSMB8 gene etc.*

Autosomal recessive

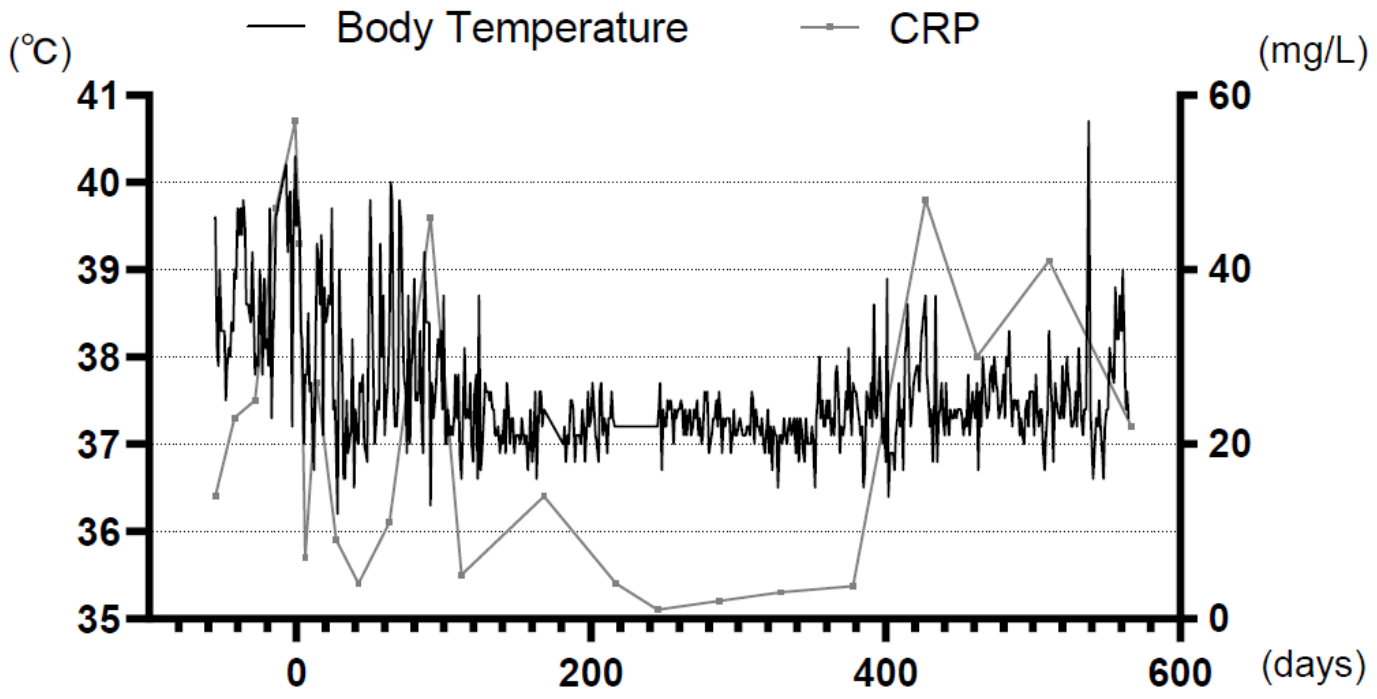
Symptoms

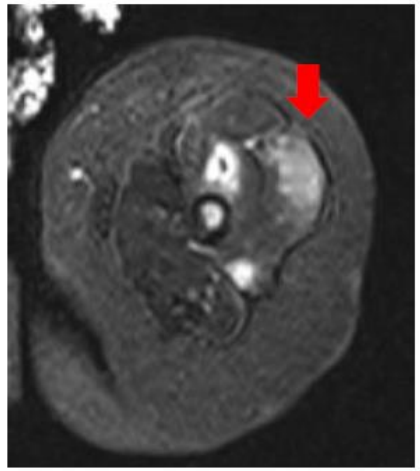
- Chilblain-like skin rash in childhood
- Fever
- Skinny upper body, mainly on the face and upper extremities
- Long, knobby digits with contractures
- Lack of immunodeficiency



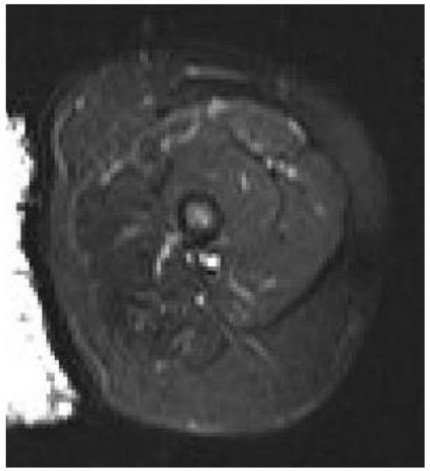
新薬と臨床2016

Treatment: JAK inhibitor

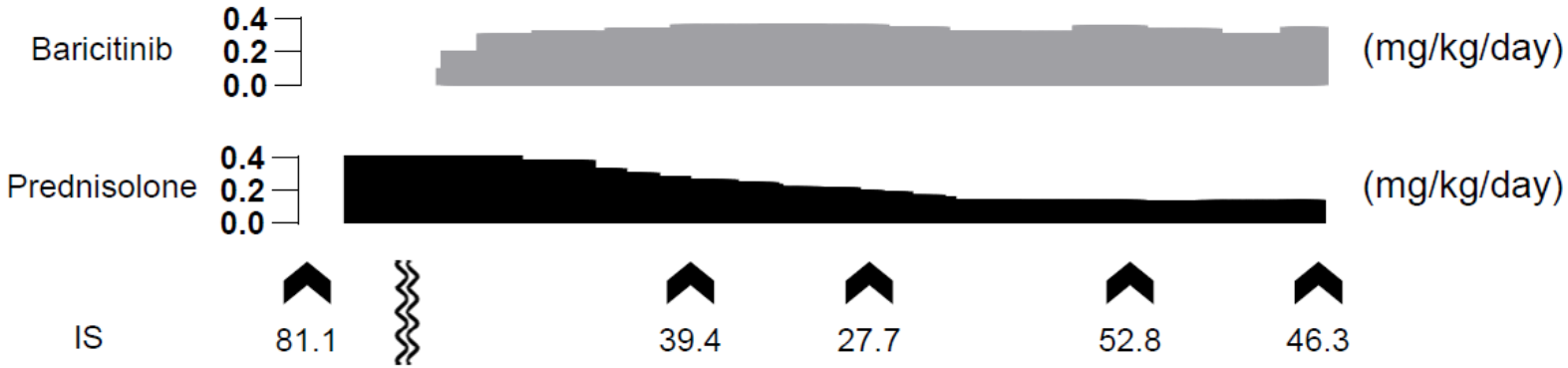




Pre-treatment



Post-treatment
Day 428



STING-associated vasculopathy with onset in infancy: SAVI

Gain-of-function mutations in *STING1* gene

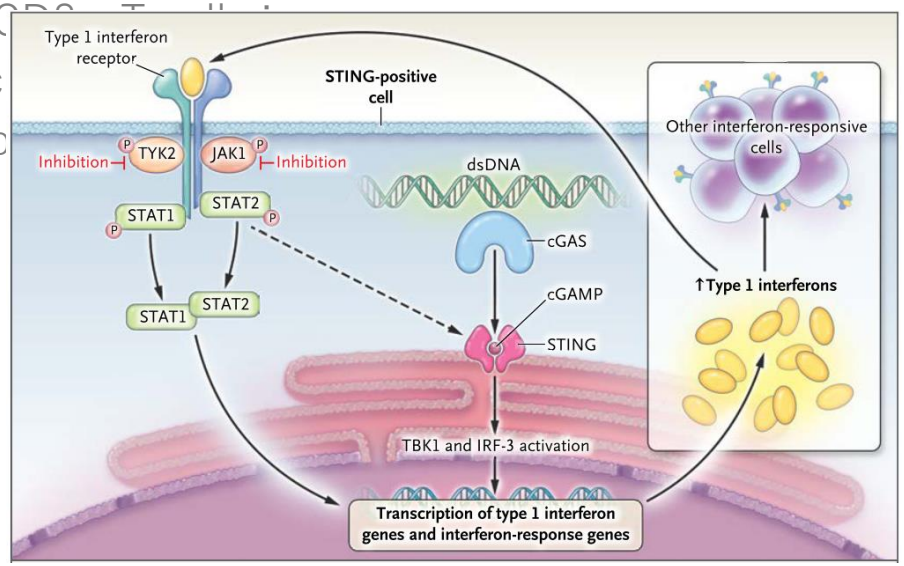
Autosomal dominant

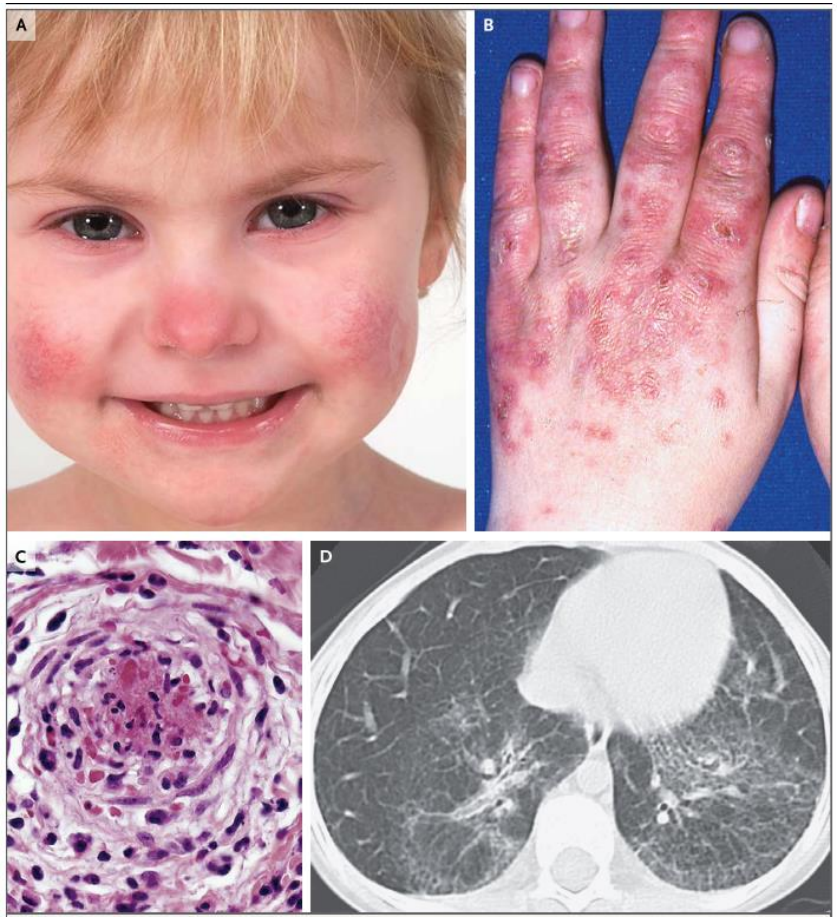
Type I interferonopathy

Treatment: JAK inhibitors, steroid

Immunodeficient features

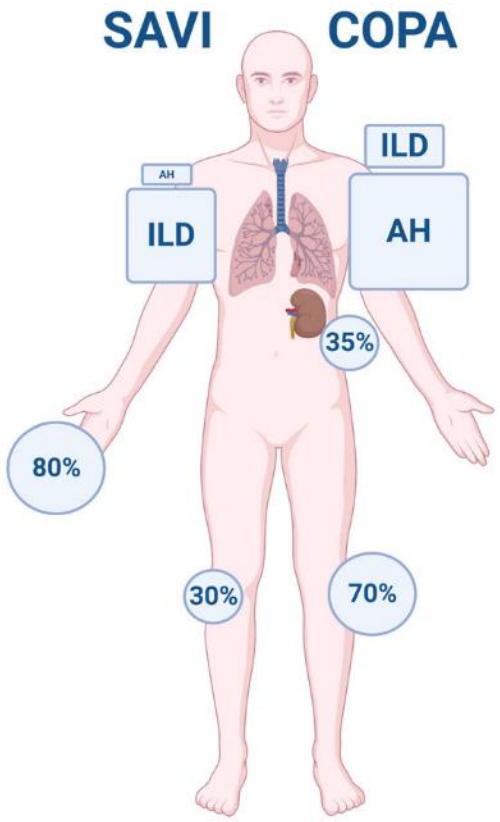
- Naïve CD4+ and C
- Memory CD8+ T c
- Combined immunc

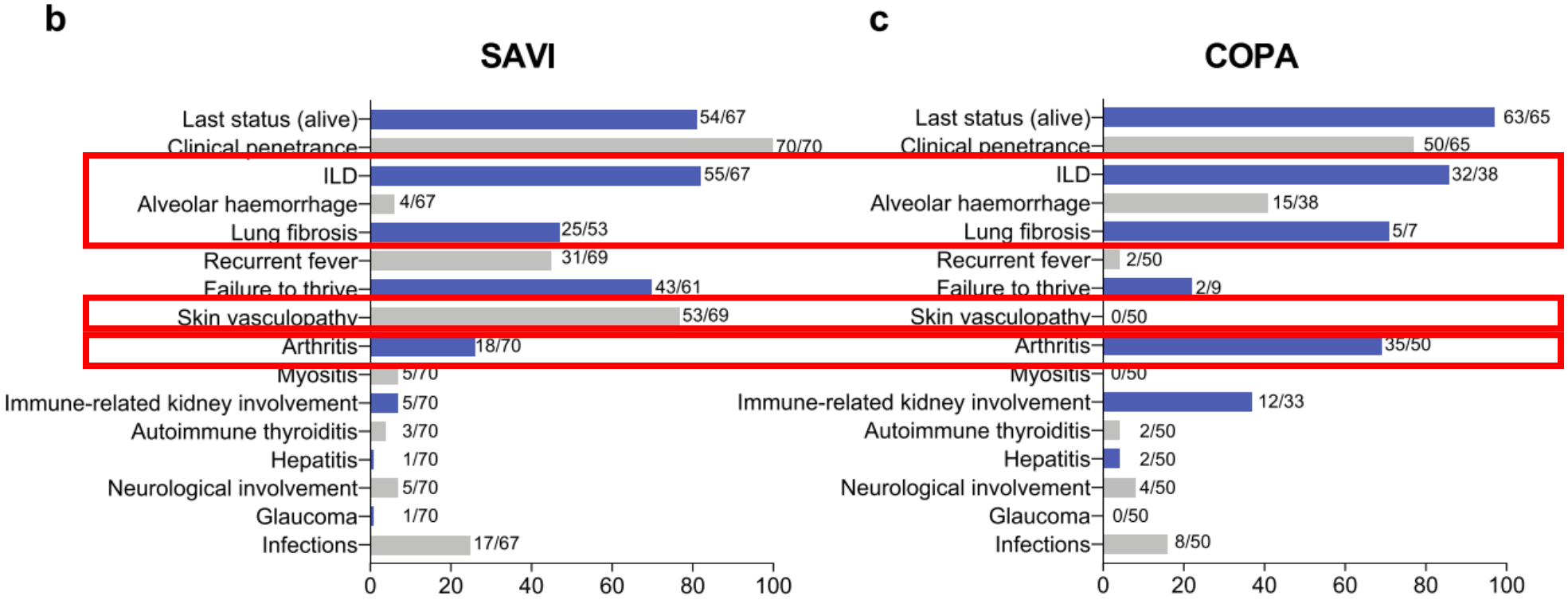




Liu Y, et al. N Engl J Med. 2014

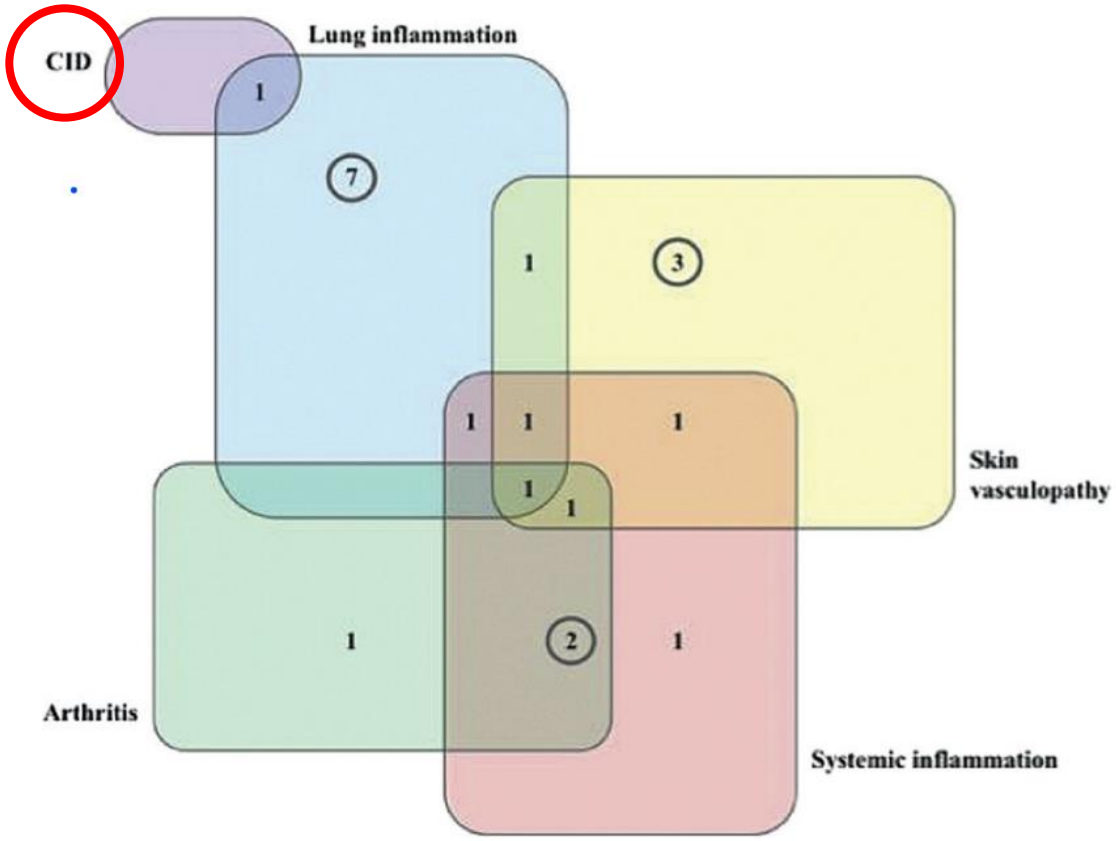
SAVI

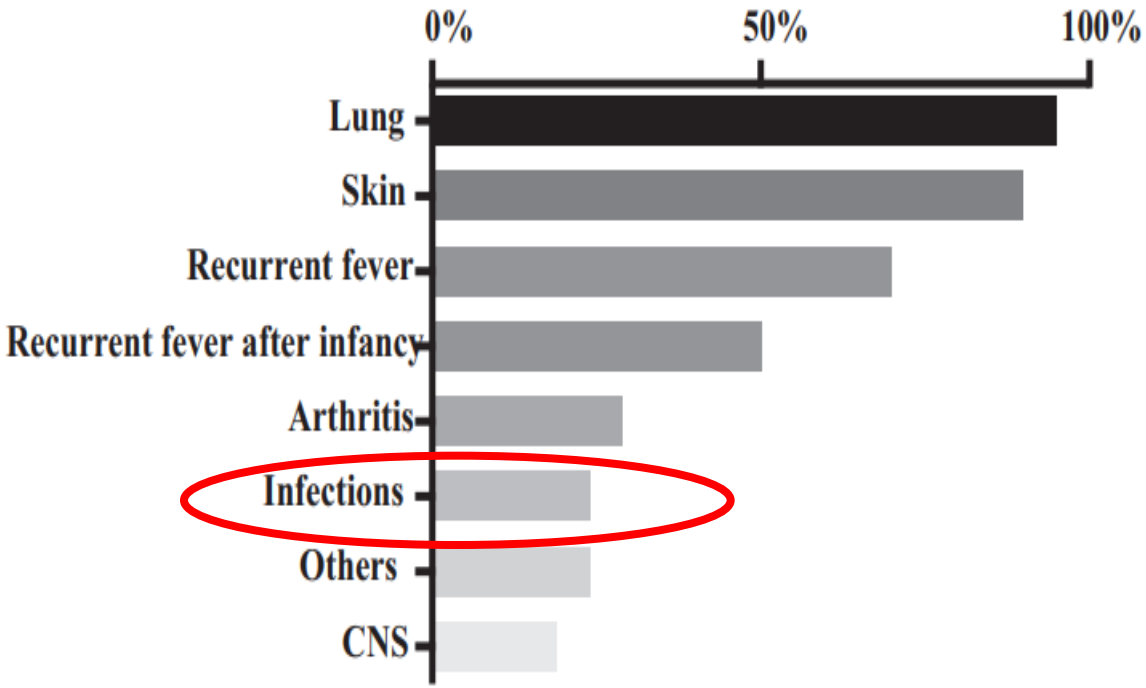




Frémond, J Clin Immunol 2021

Out of 21 patients of SAVI





CID:combined immunodeficiency

Frémond, J Allergy Clin Immunol Pract, 2021

TABLE II. Treatment with ruxolitinib in the cohort

	Age at initiation (y)	Follow-up (mo)	Initial dosing (mg/kg/d)	Dosing at last follow-up (mg/kg/d)	Concomitant treatments at JAKi initiation	IVIg	Time to discontinuation of steroids (mo)	Time to discontinuation of DMARDs (mo)	Time to discontinuation of biologics (mo)	Infectious adverse effects	Other adverse side effects
P1	4	52 (switch tofacitinib)	0.48	1	Steroids (0.5)	Yes	9	–	–	No	Papillary edema[26] Rebound effect
P5	12	30 (switch baricitinib)	0.38	0.45	Steroids (0.2) HCQ	No	1	No (still on HCQ)	–	Zona, BK viremia (nonquantifiable)	Rebound effect
P7	14.2	2.5 (transplant)	0.32	0.28	Steroids (0.16)	No	Steroids (0.16 each 2 days)	–	–	Rhinovirus	No
P8	8.4	50	0.26	1.11	Steroids (0.6)	No	8	–	–	Zona, cutaneous infection (*Staphylococcus aureus*)	No
P9	7.8	41	0.31	1.10	Steroids (0.625)	Yes	29 (pulse of steroids at M37 for arthritis)	–	–	H1N1 influenza Upper respiratory tract infections (4 episodes, no identified organism)	No
P12	12.5	17 (transplant)	0.2	0.2	Steroids (1.5) and monthly steroid pulse	Yes	7 (stop pulses at initiation of JAKi)	0 (MMF)	–	Pneumonia (no identified organism) Aspergilloma (diagnosed by histological analysis of her native lung)	No
P14	8	18	0.44	0.83	Steroids (0.22) Monthly steroid pulse Etanercept	No	3	–	No (decrease of dosing of etanercept)	No	No
P16	0.6	24	0.83	1	–	Yes	–	–	–	No	No

DMARD, Disease-modifying antirheumatic drug; *HCQ*, hydroxychloroquine; *IVIg*, intravenous immunoglobulins; *JAKi*, JAK inhibitor; *MMF*, mycophenolate mofetil; *mo*, month; *y*, year.

Frémond, J Allergy Clin Immunol Pract . 2021

Summary

What is autoinflammatory diseases?

- Definition
- Innate immune sensors: pattern recognition receptors
  - Key molecules for AIDs
- Classification of AIDs
- Epidemiology on AIDs in Japan

Focusing on the AIDs with PID features

- Deficiency of ADA2 gene
- PRAAS (CANDLE syndrome, Nakajo-Nishimura syndrome)
- STING-associated vasculopathy with onset in infancy (SAVI)

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Yushiro Yamashita

Kurume Univ, Dermatology
Eri Katayama
Takekuni Nakama

Kurume Univ, Ophthalmology
Masatoshi Haruta
Shigeo Yoshida

St. Maria Hosp.
Tsuyoshi Kawano
Toyojiro Matsuyoshi

Karatsu Red Cross Hp.
Katsuya Tashiro

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Eitaro Hiejima
Kazushi Izawa
Tomonari Awaya
Takahiro Yasumi
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I have appreciated the patients and doctors in charge for providing us the opportunity to work on the autoinflammatory diseases

厚生労働省 Ministry of Health, Labour and Welfare
文部科学省 MINISTRY OF EDUCATION, CULTURE, SPORTS, SCIENCE AND TECHNOLOGY-JAPAN
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The crossover between primary and secondary immunodeficiencies

Prof Martin Van Hagen | *The Netherlands*

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The crossover between PIDs and SIDs

Prof. dr. Martin van Hagen, internist-immunologist

Department of Internal Medicine, Section Clinical Immunology, Erasmus MC and Eye Hospital Rotterdam, The Netherlands, Chulalongkorn University, Bangkok Thailand and medical advisory board IPOPI

IPOPI/ASOD, March 25th, 2024

Disclosure of speaker's interests

(Potential) conflict of interest	None/See below
Potentially relevant company relationships in connection with event	Company names
• Sponsorship or research funding • Fee or other (financial) payment • Other relationship, i.e. …	• Jeffrey Model Foundation, Behring CSL, Pharming clinical trial, NWO • Peervoice, CSL Behring sponsering chairing workshop IPIC 2023 lecture • Takeda, fee lecture Masterclass 2023 and "nascholing PID". • Visiting Professor (honorary), Chlalongkorn University Bangkok • Vice-chair IPOPI medical board • Member "werkgroep horizonscan immunologie"

PIDs and SIDs

Introduction

Immunodeficiencies

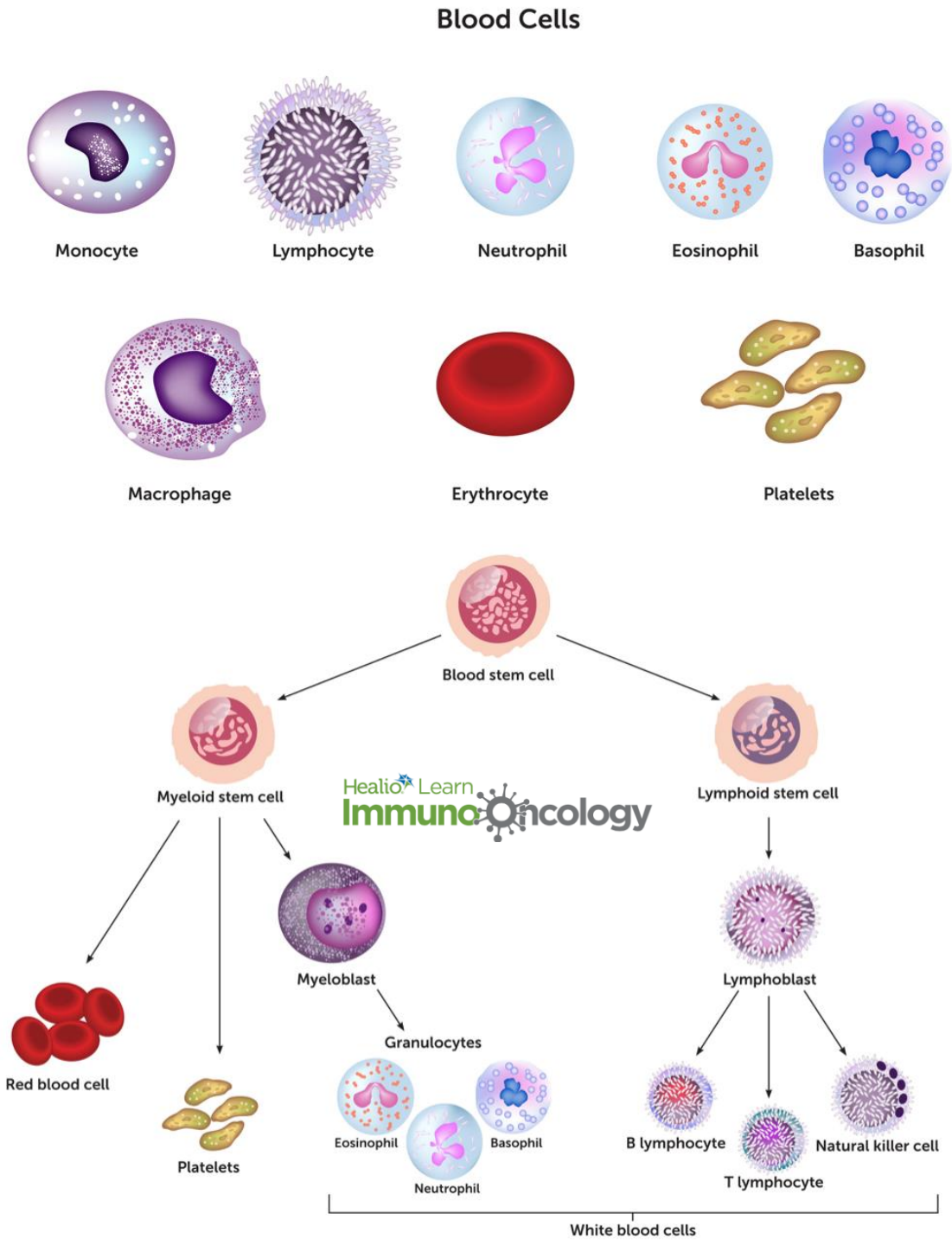
- PADs and SADs
- SADs in new therapies
  - BTK inhibitors
  - CD19+ CAR T cells
  - BCMA CAR T cells
  - Anti-FcRn approaches

Conclusions

Introduction

SID or SAD?

As with PIDs, all parts of the immune system can be secondary involved



PIDs and SIDs

Introduction

Immunodeficiencies
- PADs and SADs
- SADs in new therapies

Conclusions

Secondary antibody deficiencies

Secondary antibody deficiencies (SADs) occurs when the antibody production is weakened by another treatment or illness

Differential Diagnosis of Hypogammaglobulinemia

Neoplasms

Immunodeficiency with Thymoma
B cell malignancies

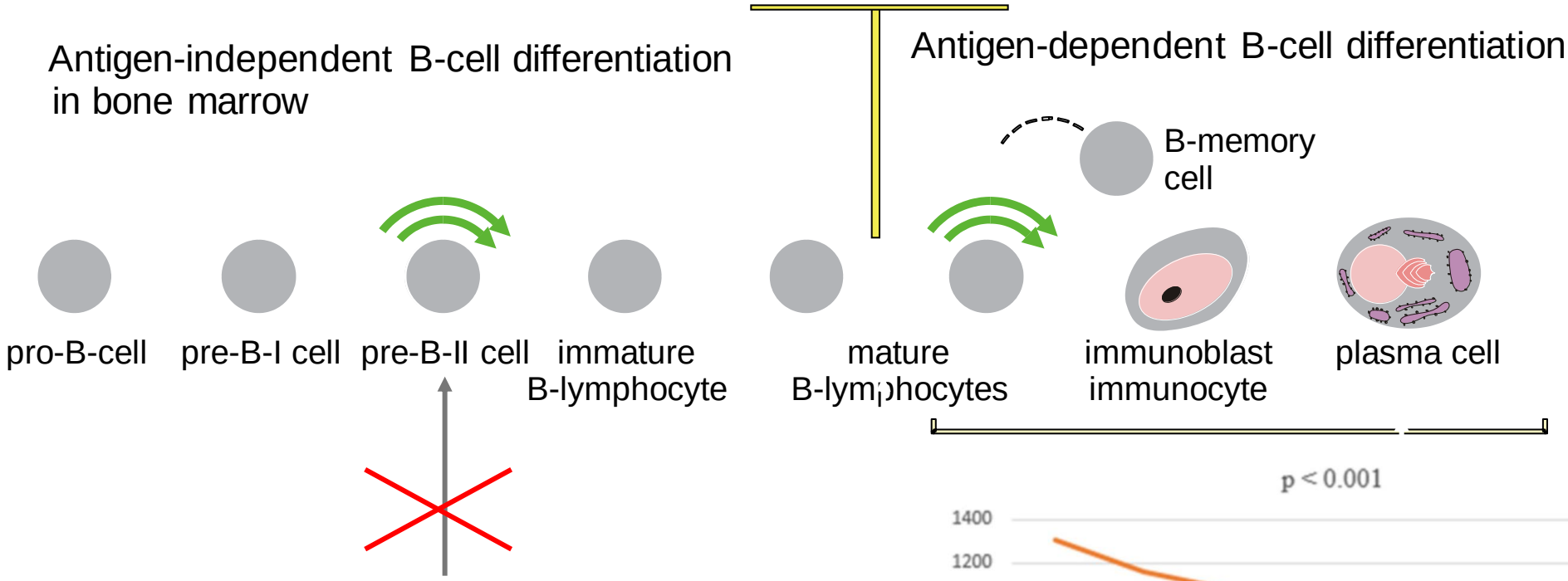
Systemic Disorders

Immunodeficiency caused by excessive loss of immunoglobulins (nephrosis, severe burns, lymphangiectasia, severe diarrhea)
Measure albumin!!!

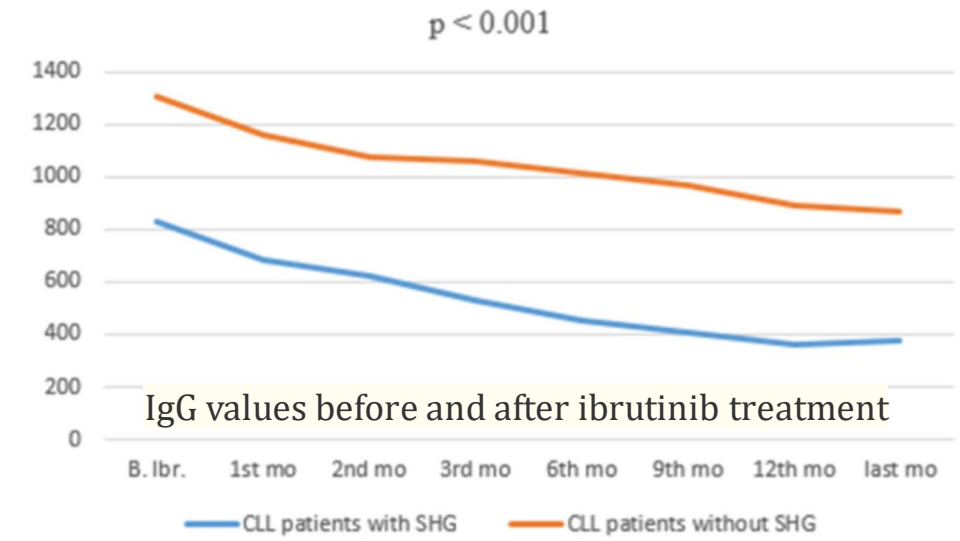
Drug Induced

Anti-epileptics
Penicillamine
Immunosuppressives
Glucocorticosteroids
B-cell ablative therapies
IgG catabolism

Defects in human B-cell differentiation



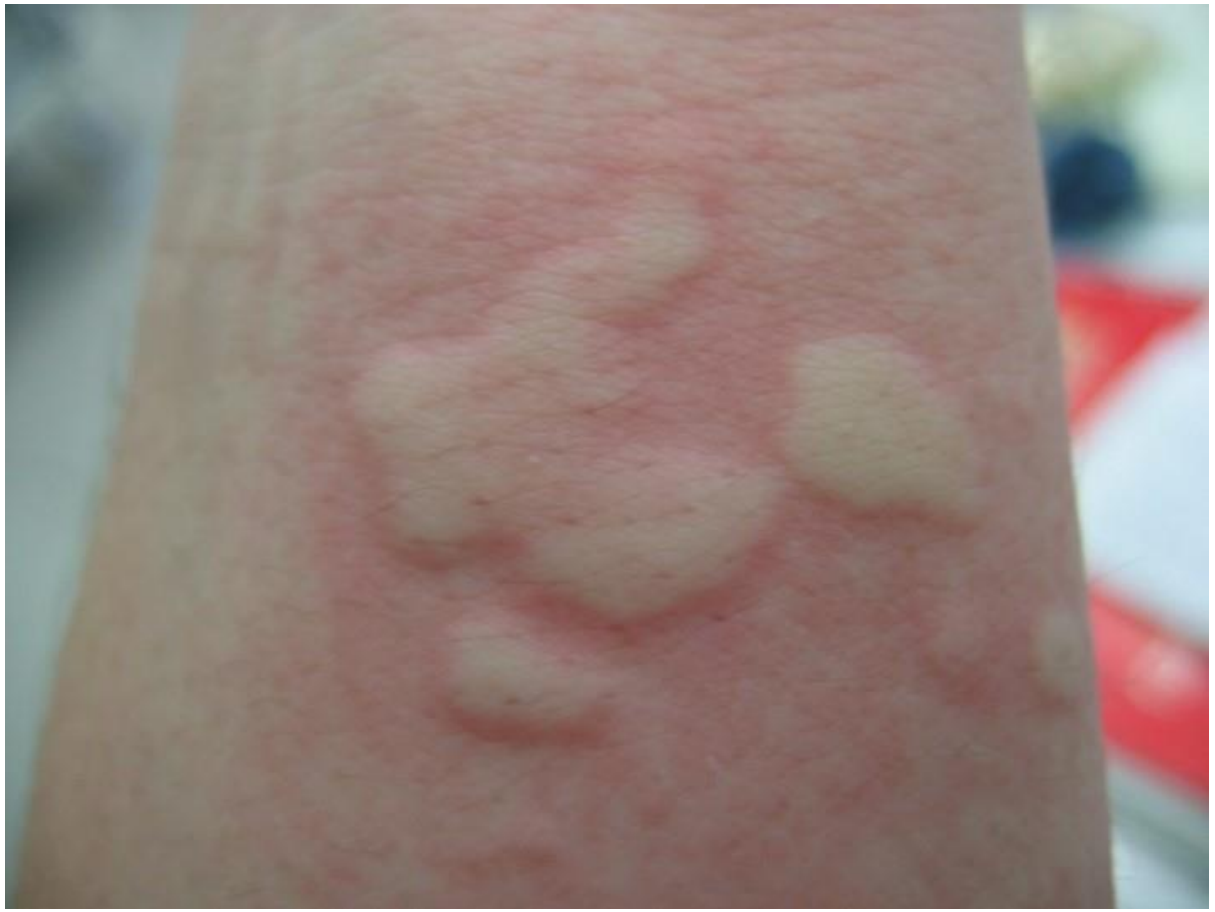
Ibrutinib' is a small molecule drug that inhibits B-cell proliferation and survival by irreversibly binding the protein Bruton's tyrosine kinase (BTK)
- NHL, CLL, Waldenstrom

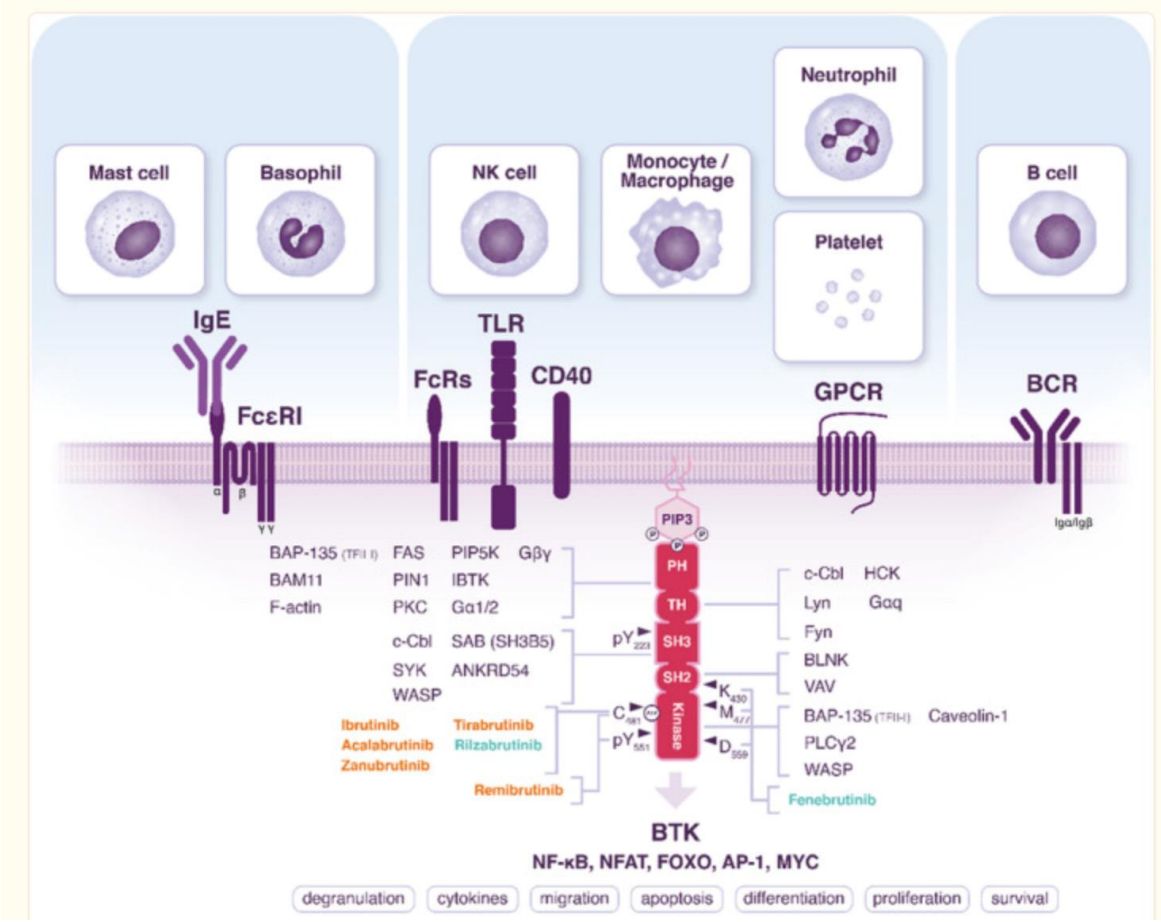


IgG values before and after ibrutinib treatment

Celik et al, Indian J Haemaol Blood Trans, 2022

Chronic spontaneous urticaria

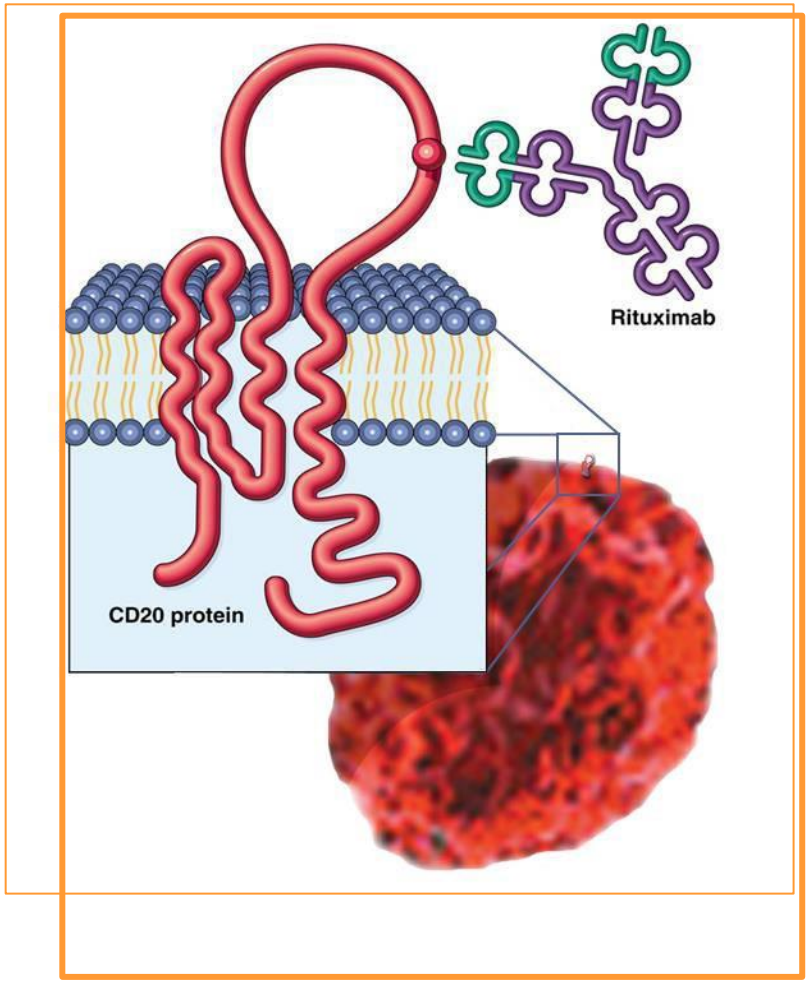




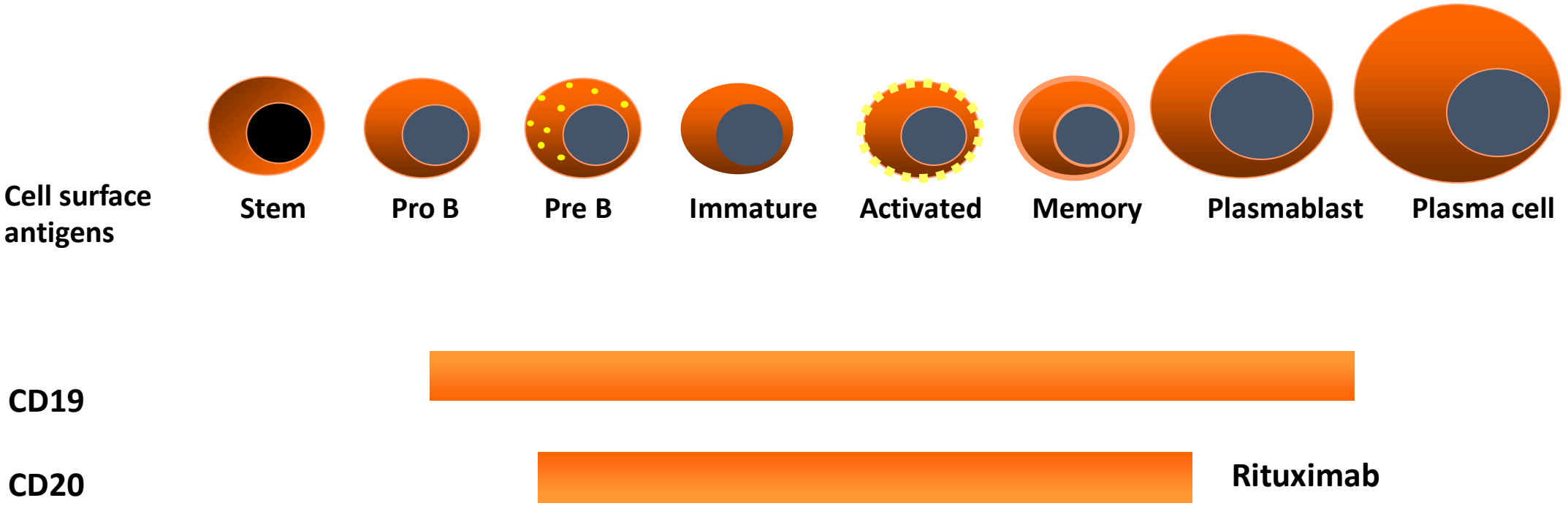
Mendes-Bastos et al, allergy, 2022

Rituximab (MabThera®, Rituxan®):

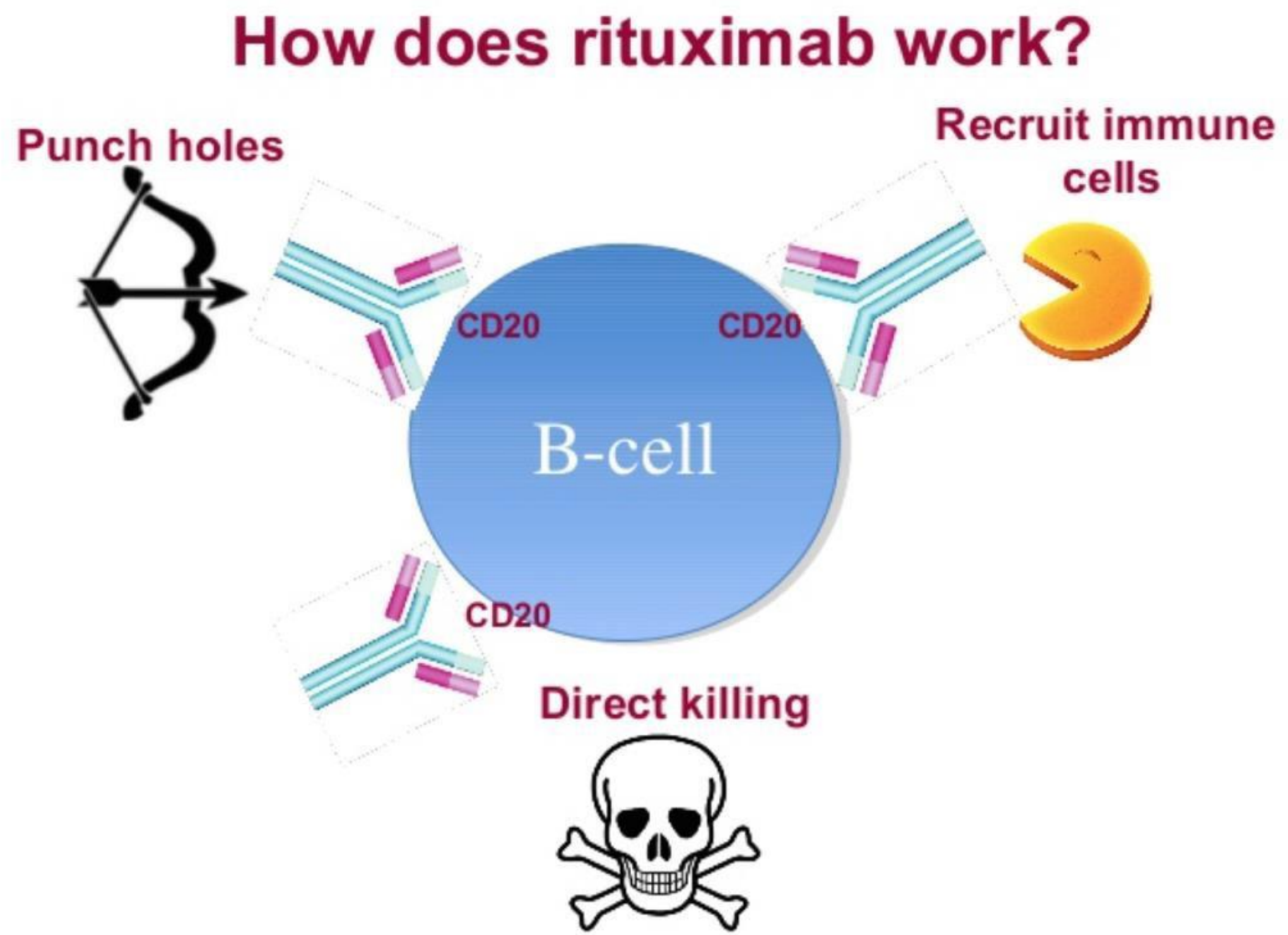
- Rituximab is a genetically engineered anti-CD20 therapeutic monoclonal antibody that *selectively* depletes CD20+ B cells



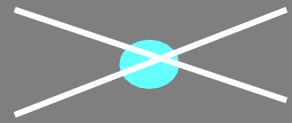
Steps in the Maturation of B Cells



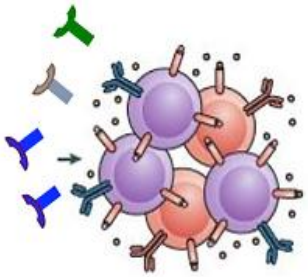
Malignant lymphoma



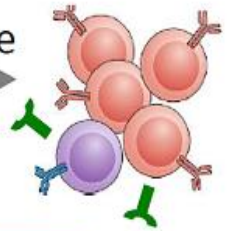
Rituximab: positive effects reported in the literature

	Case reports	Case series	Open label trials	Controlled trials
Rheumatoid arthritis				
SLE				
ANCA associated Vasculitis **(Including scleritis uncontrolled)**				
Idiopathische thrombocytopenia				
IgG4 associated disease				
Dermatomyositis/pemphigus				

Anti-CD20 therapy



Hyperimmune → Hypoimmune



Rituximab or other B cell depleting therapies

Clinical state	Autoimmune disease → Risk of infections		
Immune phenotype	Normal B cell counts Normal IgG level	Increased risk* →	B cell lymphopenia Hypogammaglobulinemia
Risk assessment	• Clinical and family Hx • Immunizations • Basic immune evaluation		• IgRT, antibiotic therapy • Genetic evaluation for PID • Mechanism-based tx

*Patients at risk for PH, infections and refractory AI
Pediatric age
AIHA / Evans syndrome
Underlying PID

Clinical improvement

Engel ER, Walter JE. Hematol Am Soc Hematol Educ Program 2020

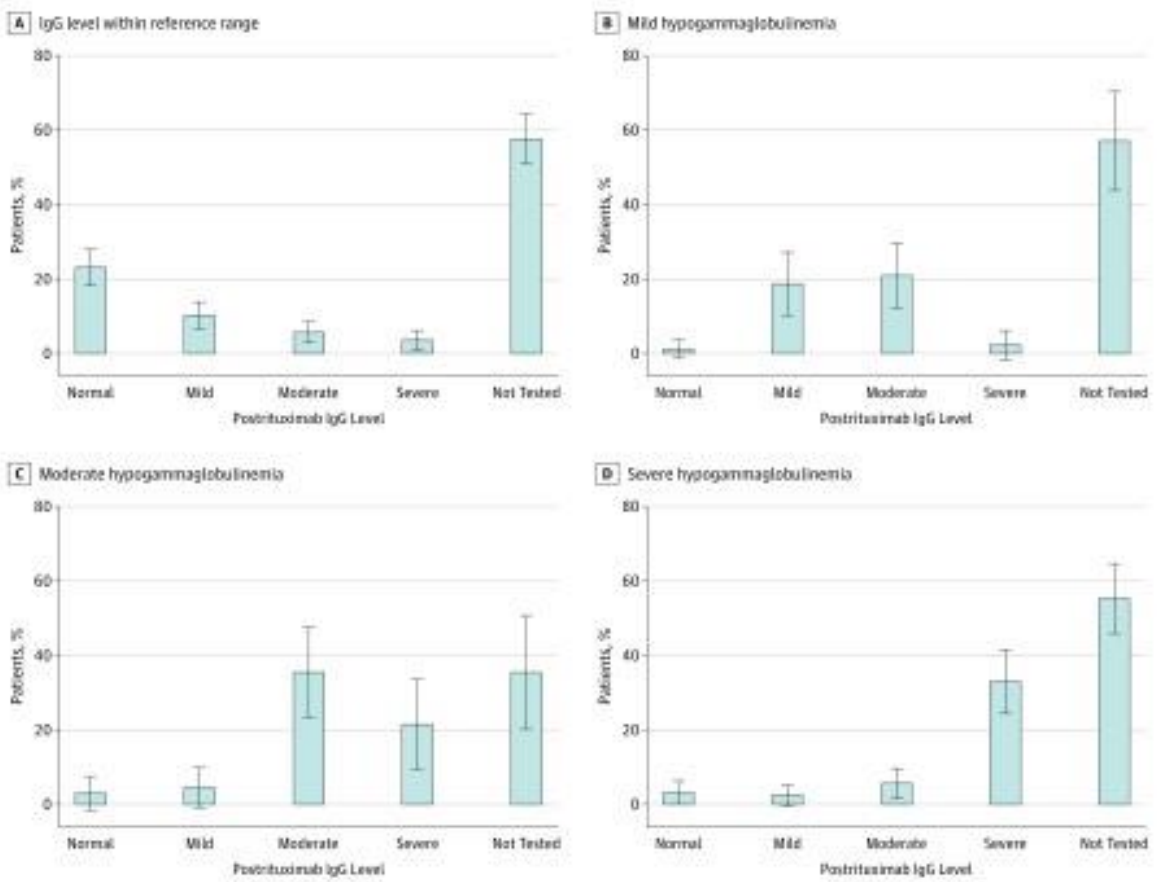
Hypogammaglobulinaemia after Rituximab

The incidence of new hypogammaglobulinemia after treatment with rituximab is not precisely known

Measurement of serum immunoglobulin levels prior to treatment has not been standard-of-care in many of the specialties that use rituximab extensively

RTX in 4479 patients

- Pre IgG levels measurement; hypo-Ig was noted in 313 (47.8%)
- Significant increase in the proportion of patients who experienced severe infections following rituximab use in the overall study cohort (from 17.2% to 21.7%; $P < .001$)
- Cancer patients (from 19.1% to 25.1%; $P < .001$)
- Total of 201 patients (4.5%) received Ig therapy higher dose decreased risk



Barmettler et al, JAMA open, 2018

Possible risk factors hypogamma after RTX

Repeated courses of rituximab

Cancer

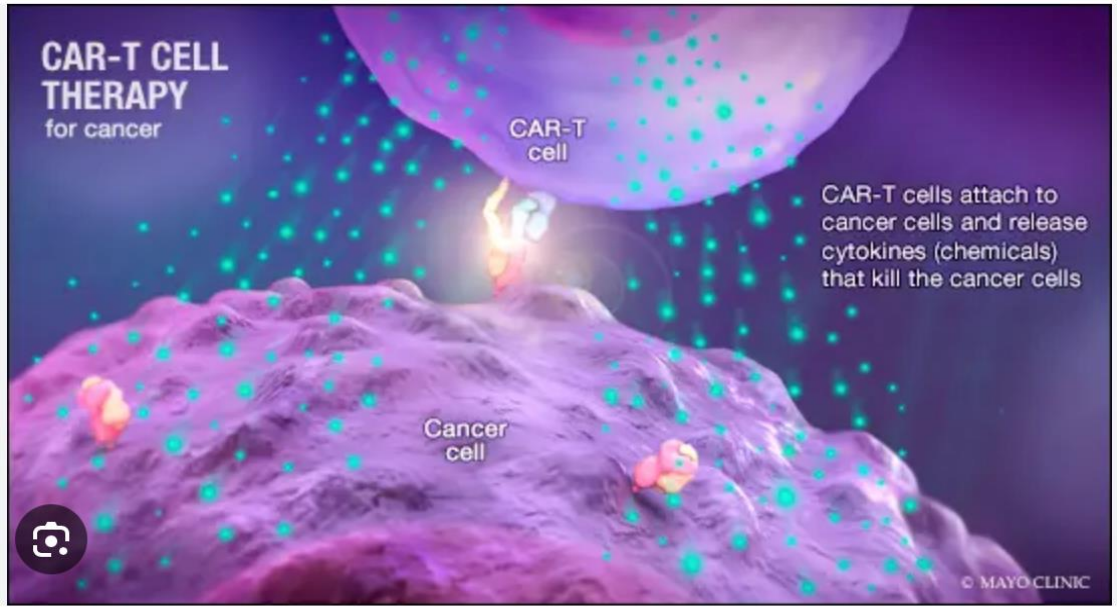
Rituximab treatment in combination with chemotherapy

Older age

Pre-existing hypogammaglobulinemia

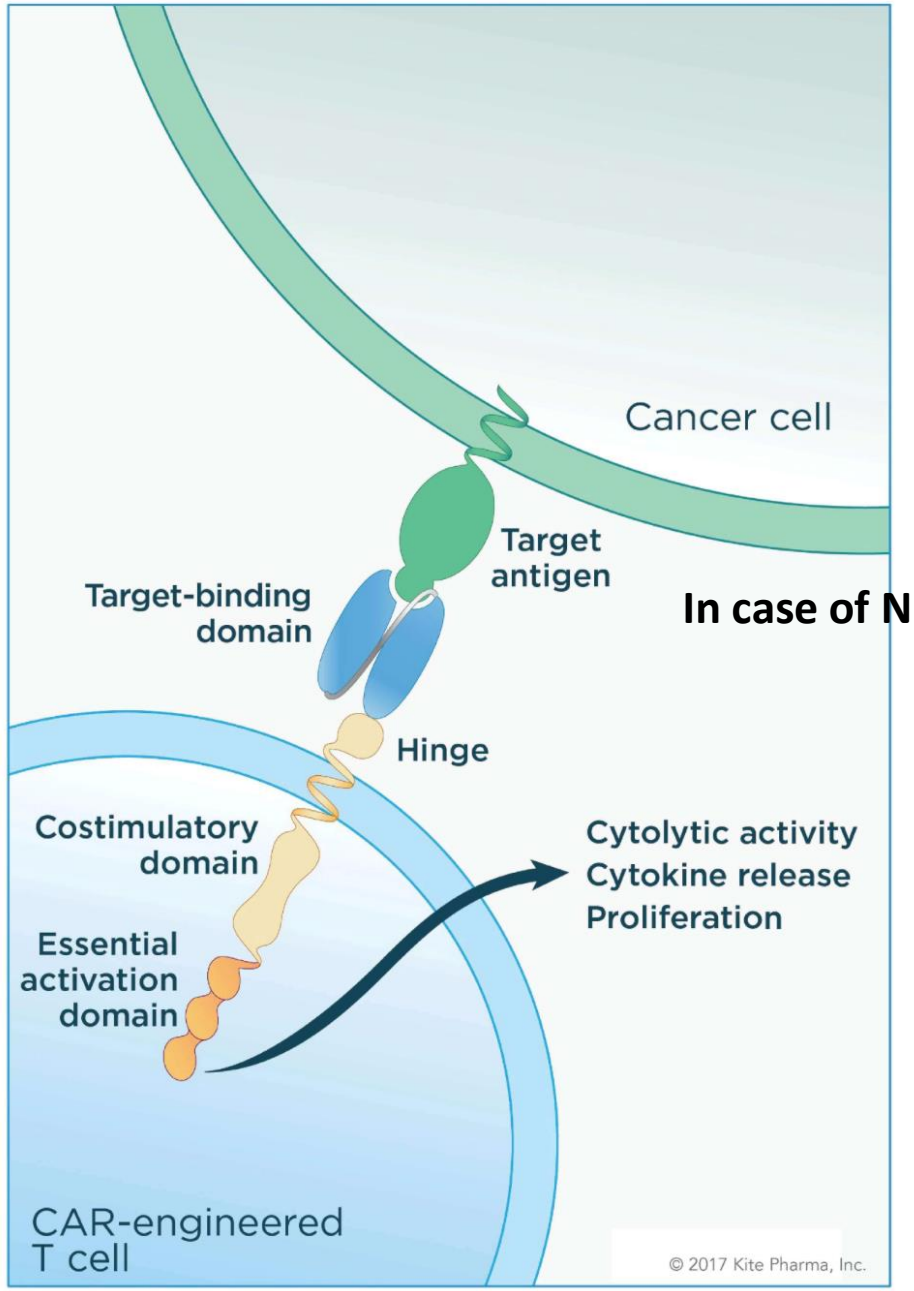
CAR-T cell therapy

CAR = chimeric antigen receptor



Mayo Clinic Q and A: Treating blood cancers with CAR-T cell therapy - Mayo Clinic News Network

CHIMERIC ANTIGEN RECEPTOR (CAR)



In case of NHL, mostly CD19

CAR-T cell therapy

Multicentre trials that followed, complete response (CR) rates of 40–54%, 67% and 69–74% in aggressive B cell lymphomas, mantle cell lymphoma and indolent B cell lymphomas respectively

CAR-T cells have also generated CR rates of 71–81% in multicentre clinical trials involving patients with R/R B cell acute lymphoblastic leukaemia (B-ALL), who have limited treatment options

Neelapu, S. S. et al. *N. Engl. J. Med.* 2017
Abramson, J. S. et al. refractory. *Lancet.* 2020
Schuster, S. J. et al. *N. Engl. J. Med.* 2019
Maude, S. L. et al. *N. Engl. J. Med.* 2018
Shah, B. D. et al. *Lancet.* 2021

CAR T-cells

The most prominent long-term toxicities after CAR T cell therapy include cytopenias and hypogammaglobulinaemia

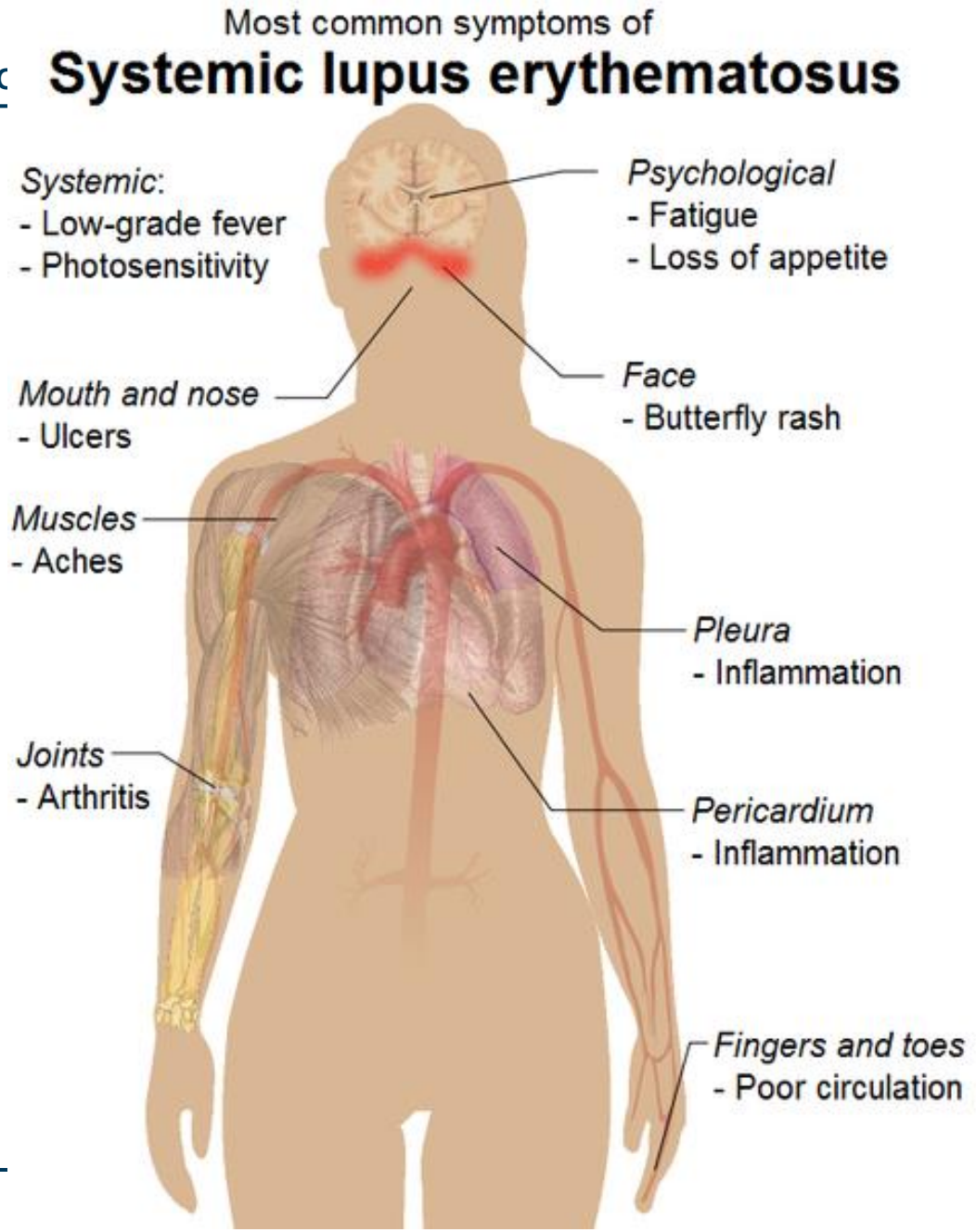
- Severe infections >1 month after CAR T cell therapy is low compared to infections seen in the acute period immediately after cell infusion

IgG depletion persisting several years after cell infusion in 18–74% of patients who received CD19-targeted CAR T cells

Persistent B cell depletion in 25–38% of patients even several years after CAR T cell infusion

An impaired response to vaccines is an important effect of B cell depletion and hypogammaglobulinaemia in patients receiving CAR T-cells

Cappell, K. M. et al. *J. Clin. Oncol.* 2020
Chong, E. A et al. *N. Engl. J. Med.* 2021
Cordeiro, A. et al. *Biol. Blood Marrow Transpl.* 2020
Locke, F. L. et al. *N. Engl. J. Med.* 2022
Chong, E. A., et al. *N. Engl. J. Med.* 2021
Locke, F. L. et al. *Lancet Oncol.* 2019



Systemic autoimmune diseases:

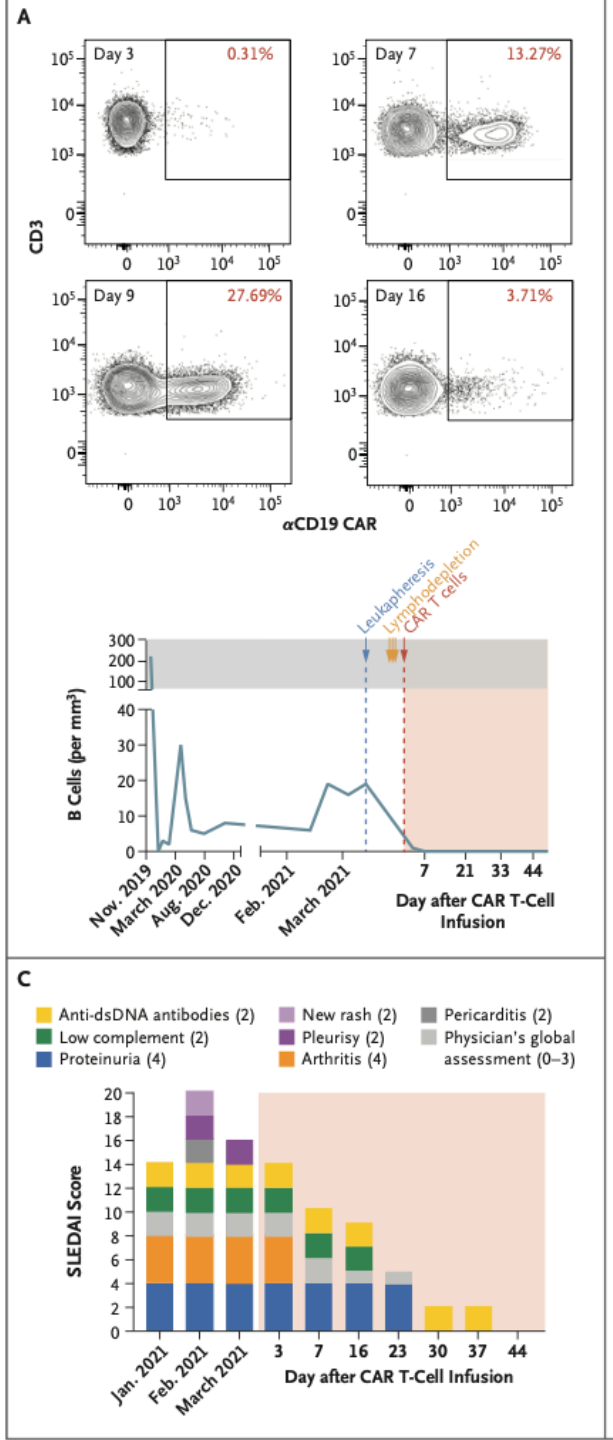
Several organs involved

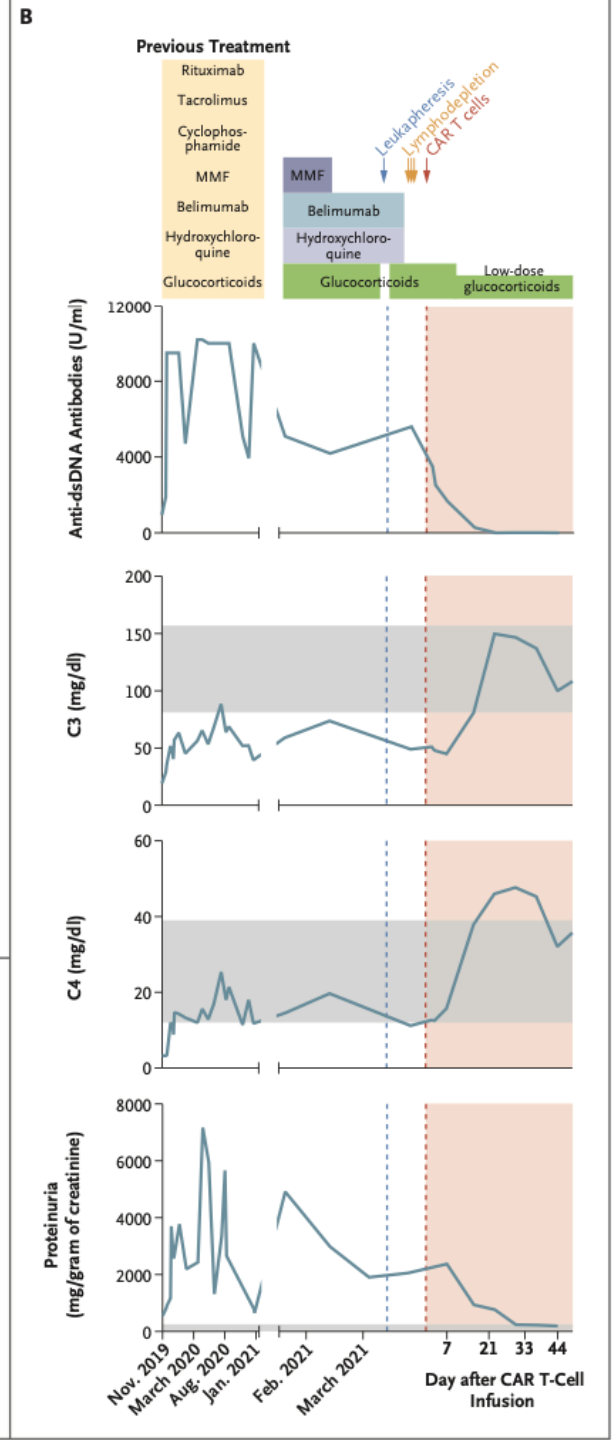
The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

2021

CD19-Targeted CAR T Cells in Refractory Systemic Lupus Erythematosus





Systemic lupus erythematosus (SLE) is a life-threatening autoimmune disease characterized by adaptive immune system activation, formation of double-stranded DNA autoantibodies and organ inflammation.

Refractory to several immunosuppressive drug treatments were enrolled in a compassionate-use chimeric antigen receptor (CAR) T cell program.

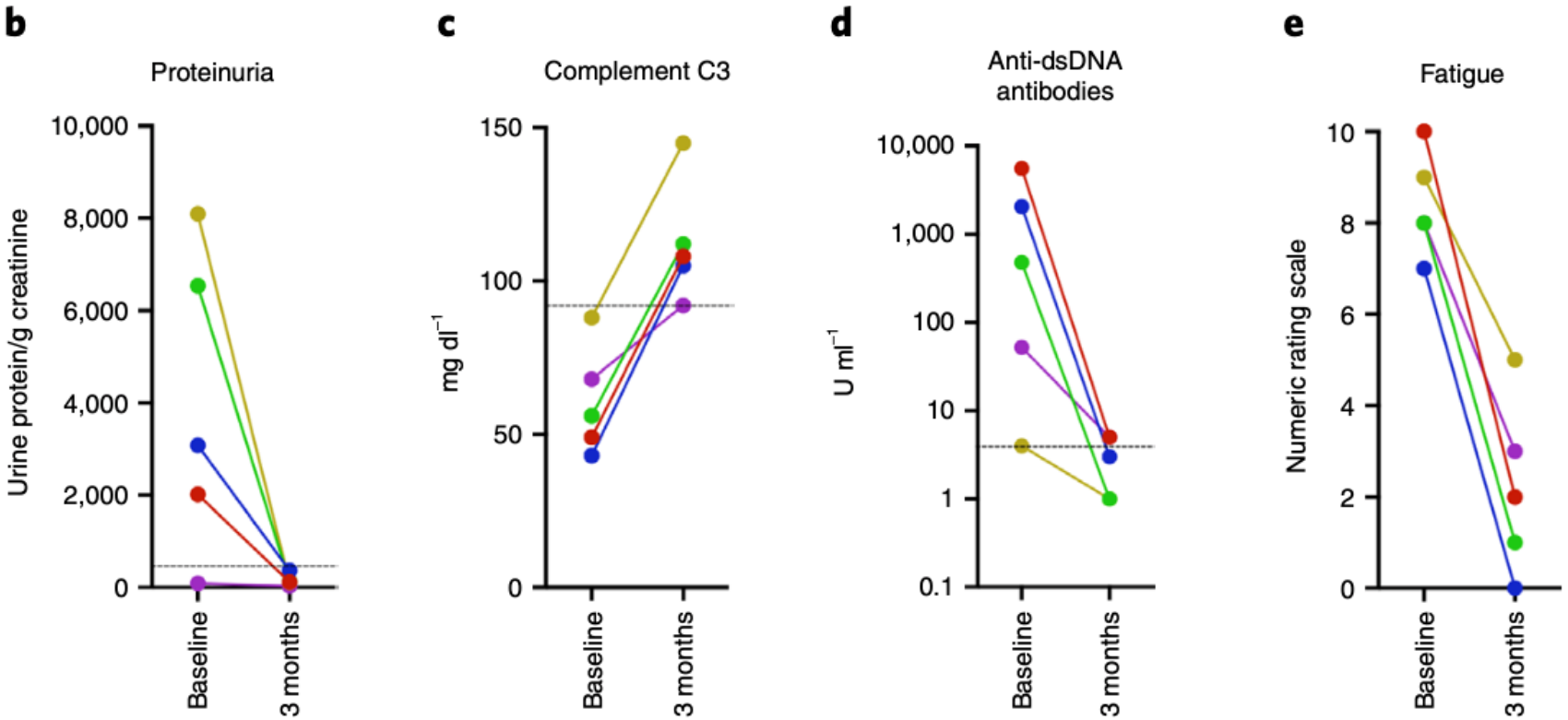
Autologous T cells from patients with SLE were transduced with a lentiviral anti-CD19 CAR vector, expanded and reinfused at a dose of 1 × 10E6 CAR T cells per kg body weight into the patients after lymphodepletion with fludarabine and cyclophosphamide.

ARTICLES
https://doi.org/10.1038/s41591-022-02017-5
nature medicine
Check for updates

Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen[1,2,8], Fabian Müller[1,2,8], Dimitrios Mougiakakos[1,2,3,8], Sebastian Böltz[2,4], Artur Wilhelm[2,4], Michael Aigner[1,2], Simon Völkl[1,2], David Simon[2,4], Arnd Kleyer[2,4], Luis Munoz[2,4], Sascha Kretschmann[1,2], Soraya Kharboutli[1,2], Regina Gary[1,2], Hannah Reimann[1,2], Wolf Rösler[1,2], Stefan Uderhardt[2,4], Holger Bang[5], Martin Herrmann[2,4], Arif Bülent Ekici[6], Christian Buettner[6], Katharina Marie Habenicht[7], Thomas H. Winkler[7], Gerhard Krönke[2,4,8] and Georg Schett[2,4,8] ✉

CAR T-cell therapy in SLE



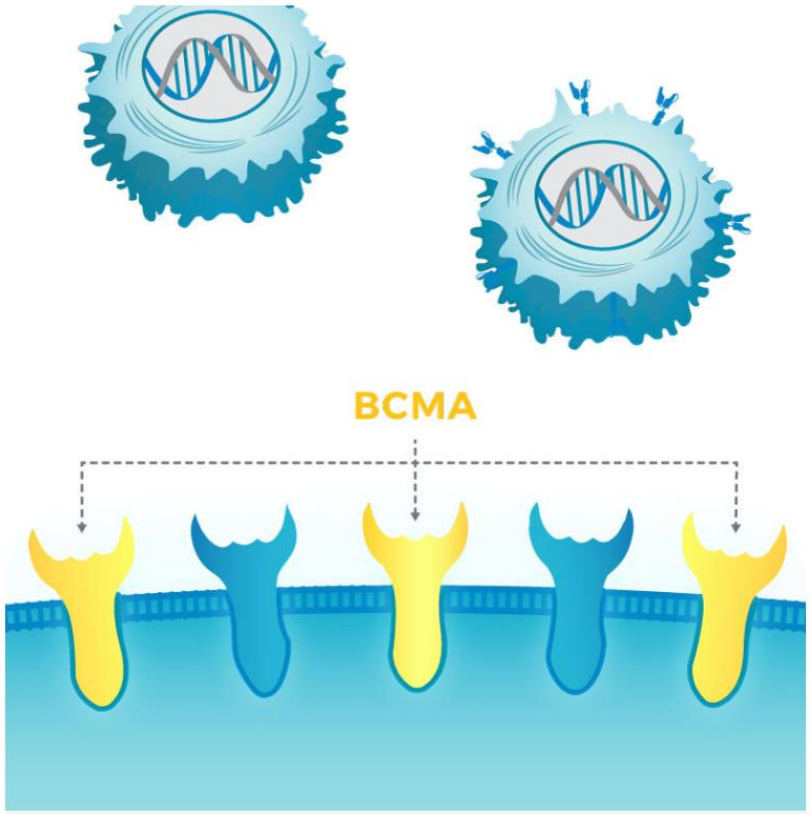
Mackensen et al. Nat Medicine, 2022

CD19 CAR T-Cell Therapy in Autoimmune Disease — A Case Series of 15 patients with Follow-up

- **Lupus 8 patients, 3 Idiopathc inflammatory myositis, 4 systemic sclerosis**
- Median follow-up was 15 months (range, 4 to 29). M
- Mean (±SD) duration of B-cell aplasia was 112±47 days.
- All the patients with SLE had DORIS remission, all the patients with myositis had an ACR–EULAR major clinical response, and all the patients with systemic sclerosis had a decrease in the score on the EUSTAR activity index
- Immunosuppressive therapy was completely stopped in all the patients.
- Toxicity; Grade 1 cytokine release syndrome occurred in 10 patients.
- One patient each had grade 2 cytokine release syndrome, grade 1 immune effector cell–associated neurotoxicity syndrome, and pneumonia that resulted in hospitalization.

Muller et al, NEJM, 22 february, 2024

Multiple myeloma; B-cell maturation antigen



Increasing the expression of the BCMA protein on the surface of multiple myeloma cells may improve the efficacy of BCMA-targeted CAR T-cell therapy, results from a new study suggest.

Credit: National Cancer Institute

- The recovery of immunoglobulin (Ig) was investigatedin the patients who achieved ≥ PR.
- The median time to recovery was 30 months for serum IgG, > 24 months for IgA, and > 9 months for IgM

1.J. Hematol. Oncol. 15, 86 (2022)

New candidates?? Antibody mediated autoimmune diseases, plasma cell targeting??

Graves' Disease

Auto-immune thyroiditis

Addison's disease

IDDM

Myasthenia Gravis

Auto-immune encephalopaties

Autoimmune hemolytic anaemia

Autoimmune thrombocytopenia

Scleroderma

Systemic lupus erythematosus???

Anti-synthetase syndromes (JO-1)

Anti-phospholipid syndromes

ANCA-associated vasculitis

Goodpasture syndrome

Celiac disease

Pemphigus

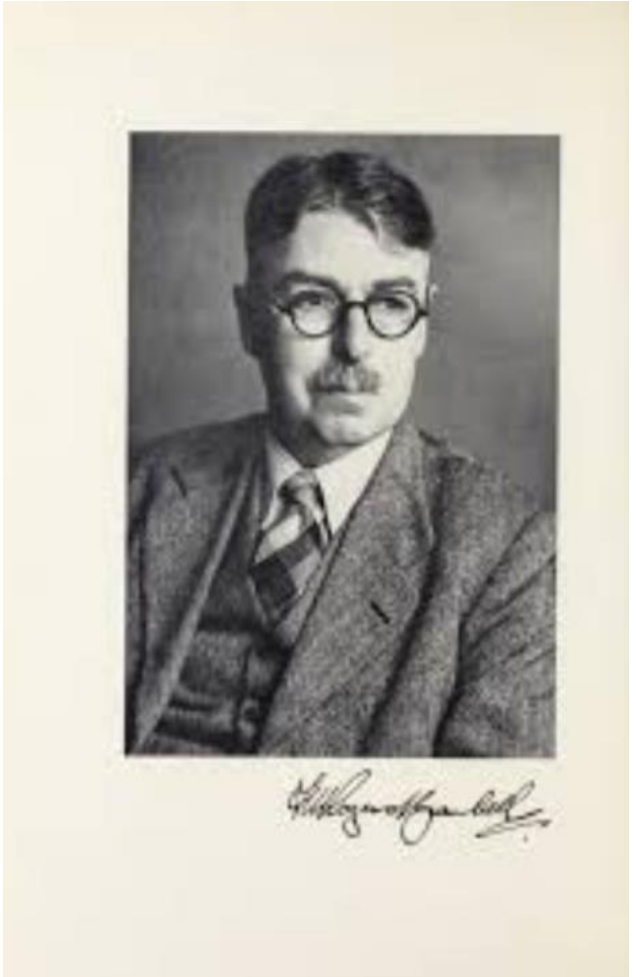
Anti-cytokine disease, anti-interferon-γ

Neonatal Fc receptor (FcRn) regulates IgG $t_{1/2}$

"A singular receptor may control both the transport of IgG during early life and the protection of IgG from catabolism in later life."

- F.W. Brambell

PRIFYSGOL BANGOR UNIVERSITY



Brambell FWR (1966) The transmission of immunity from mother to young and catabolism of immunoglobulins. Lancet ii: 1087–1093.

The protection receptor for IgG catabolism : The Brambell theory (Nature, 1964)

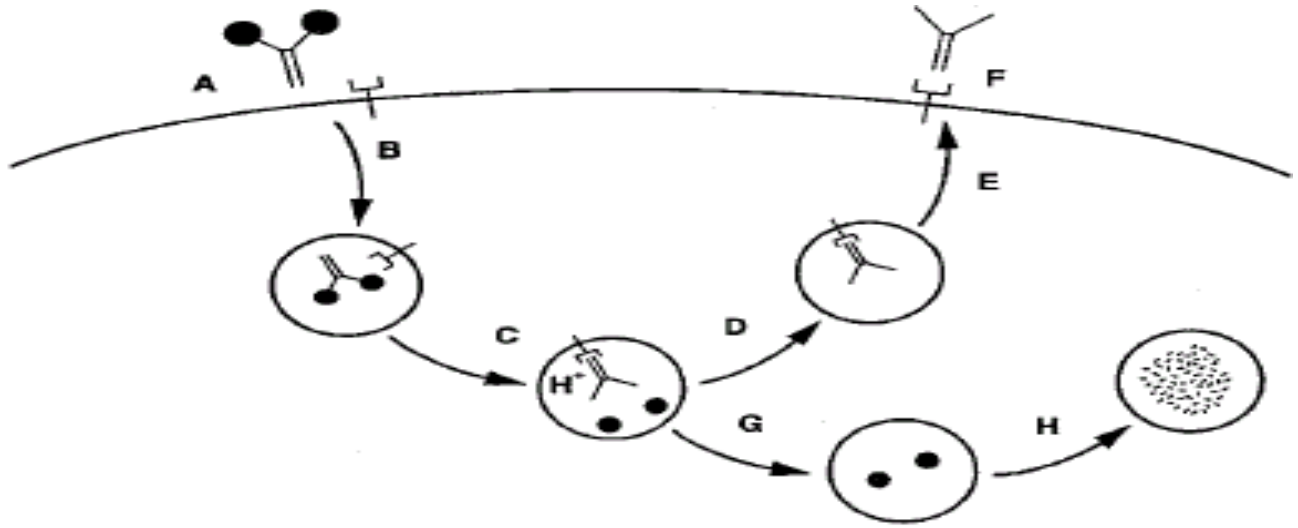


FIG. 4. Differential catabolism model incorporating Brambell receptor function. Circulating monomeric IgG plus antigen (*A*) is internalized into endosomes passively (*B*), without prior FcRp binding. In the low pH of the endosome (*C*), antigen dissociates from antibody, whereas binding of IgG to FcRp is promoted. The endosome then divides into two pathways. (*D–F*) Antibody retained by the FcRp is recycled to the cell surface and dissociates in the neutral pH of the extracellular fluid, returning IgG to circulation, free of antigen. (*G* and *H*) Unbound antigen is shunted with the endosomal contents to the lysosomes for degradation. When the Brambell receptor is deleted, the antigen and antibody pass together to lysosomal catabolism.

RP Jurghans & CL Anderson, PNAS 1996, 93:5512

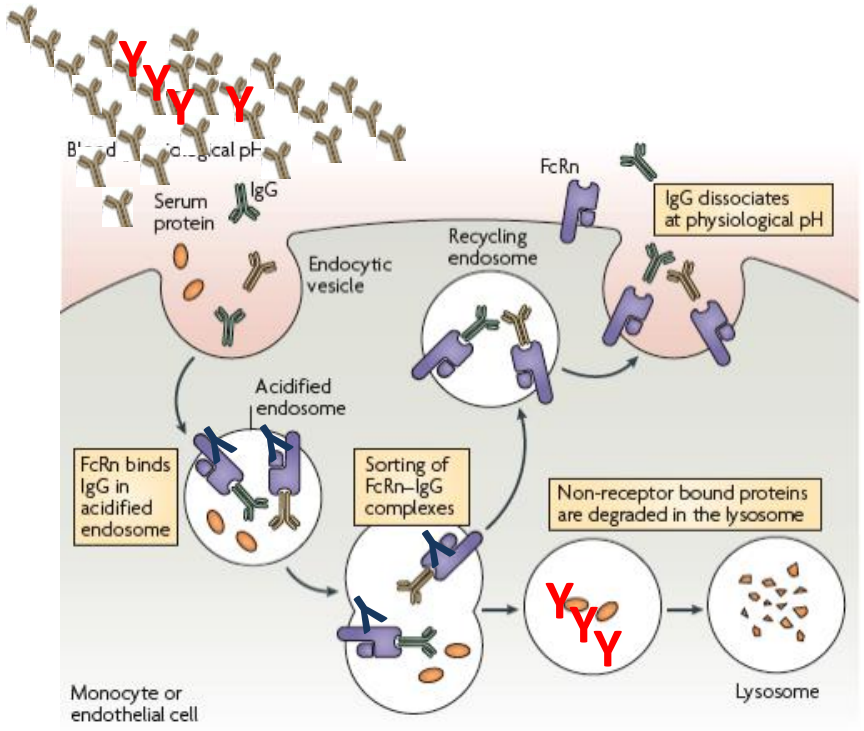
Is FcRn a target for therapy?

Yes!

High dose IVIG in autoimmune diseases increases competition of FcRn binding

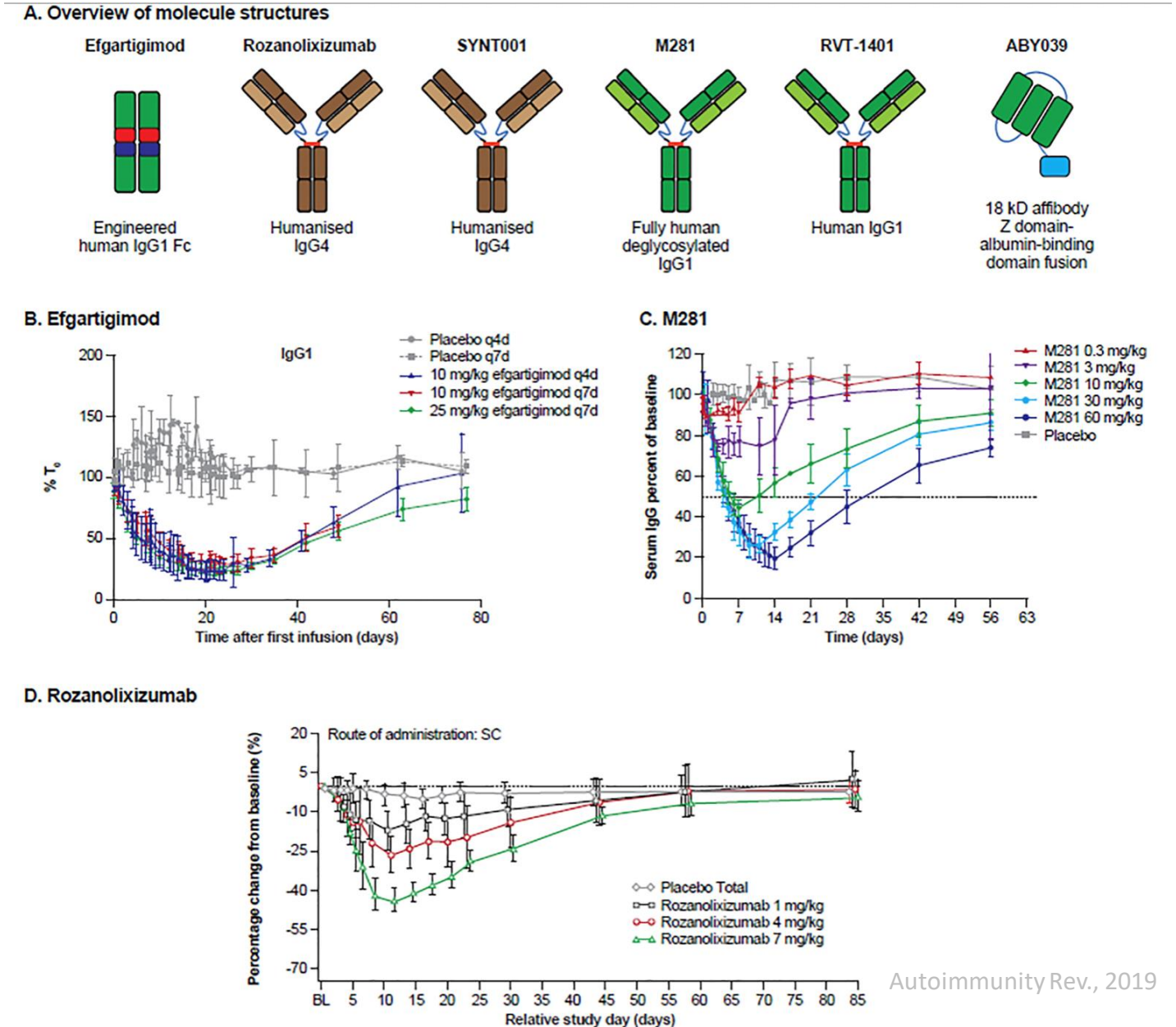
Anti-FcRn receptor biologics in for:

- ITP
- Myasthenia gravis



Roopenian, Nature Reviews, 2007

FcRn targeting therapeutics



Autoimmunity Rev., 2019

FCRN inhibitors

Efgartigimod, was approved by the United States Food and Drug Administration (FDA) for the treatment of generalized myasthenia gravis (gMG)

UCB announces U.S. FDA approval of RYSTIGGO[®] (rozanolixizumab-noli) for the treatment of adults with generalized myasthenia gravis

In diverse trials; about 43-74% reduction of serum total serum IgG

Pyzik et al, Nat Rev Immunology, 2023

PIDs and SIDs

Introduction

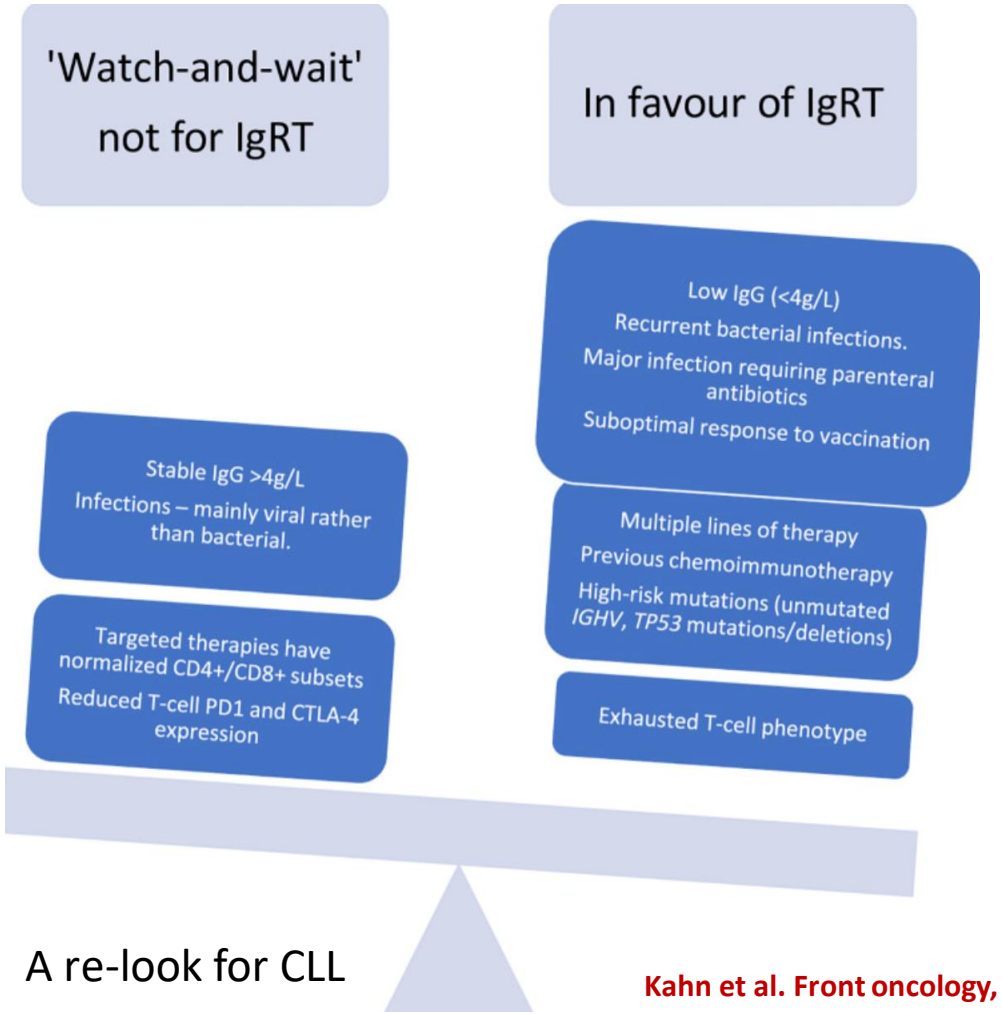
Immunodeficiencies
- PADs and SADs

SADs in new therapies
- BTK inhibitors
- CD19+ CAR T cells
- BMCsA CAR T cells
- Anti-FcRn approaches

Conclusions

In secondary immunodeficiency, immunoglobulin replacement therapy (IgRT) is recommended by guidelines (GL) for patients with IgG level<4 g/l and more than 3 infections or a severe infection. IgRT may be appropriate if IgG level < 4 g/l and/or 1–3 less severe infections (≤ grade 2)

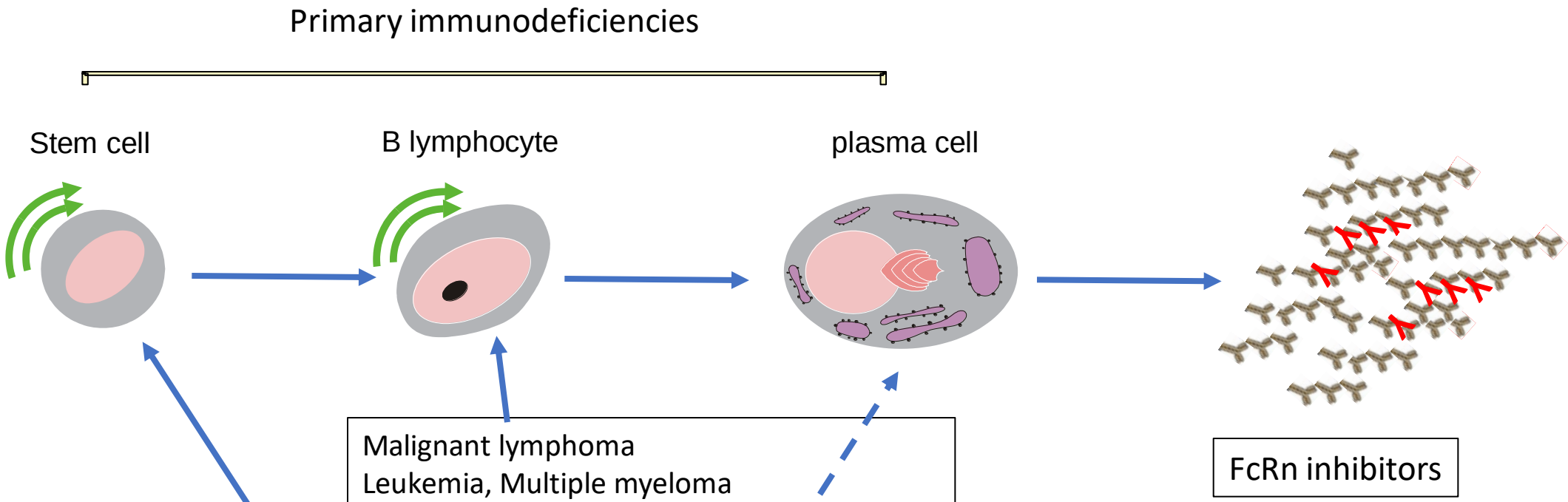
In the new era with targeted drugs; ibrutinib?



A re-look for CLL

Kahn et al. Front oncology, 2023

Secondary antibody deficiencies



Immunodeficiency Centre Rotterdam

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J van Laar
P van Biezen
N Suratanon
R La Distia Nora
Menno van Zelm
Pieter de Fraaij
Annemarie van Rossum
Barbara Barendregt
Samer Kahn
Hanna IJspeert

Marianne van der Ent
Prof. Peter van der Spek
Sigrid Swagermakers
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Sandra de Bruin
Ton Langerak
Iris Hollink
Astrid
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Infection/Immunology

Internal Medicine
Clinical Immunology

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Q&A

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TOKYO, JAPAN
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Challenging clinical cases (APSID+SEAPID)

APDS diagnostics | Prof Intan Hakimah *(Malaysia)*

HSCT in congenital neutropenia | Dr Jia Hou *(China)*

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ASIAN PID MEETING
24-25 MARCH 2024
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Challenging Clinical Cases (APSID+SEAPID): APDS Diagnostics

IPOPI Regional Asian PID Patients and Doctors' Meeting
25th March 2024

Intan Hakimah Ismail, MD, MMed Paeds, PhD
Clinical Immunologist & Allergist
Advanced Medical Research in Allergy and Clinical Immunology (AMRAC)
Universiti Putra Malaysia (UPM)

Patient Profile

HA, Malay girl

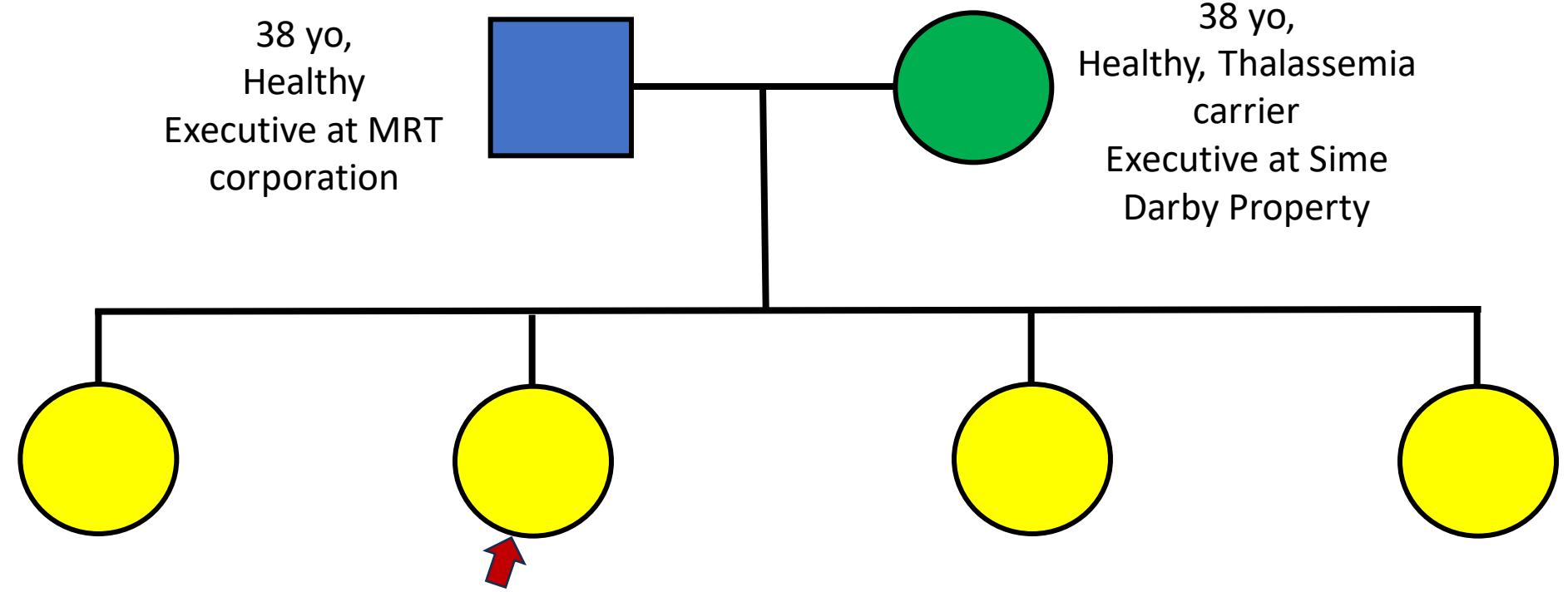
Currently 10 years 2 months old

2nd of 4 siblings

Parents are non-consanguineous

Attending Year 4 , primary school

Family Pedigree



No family history of:

Primary immunodeficiency

Autoimmunity

Malignancy

A case of 10 years old Malay girl with recurrent respiratory tract infection and recurrent bloody stool

8 months old

- Loose stools with blood streak stool
- Treated as dysentery

- Platelet 114 x 10^9/L
- Platelet on discharge 250 x 10^9/L

9 mo–15 mo old

Recurrent blood streak stool – total 6 episodes, increasing
Suspected ITP

- Platelet: 24 - 127
- Serial FBC: low ALC
- FBP: Leukoerythro-blastic picture with bicytopenia, IDA

- CXR: bilateral extensive pneumonia. No effusion
- CTAP: consolidation left UL
- LP: normal

16 months old

Referred for colonoscopy:
- Mucosal lymphoid hyperplasia 2° to infection
- Granulomatous reaction +
- No evidence of fungal or TB infection

BMAT: normal marrow with adequate megakaryopoeisis. Thrombocytopenia most likely immune mediated

TB workup:
- Mantoux test positive >20 mm
- Stain for fungi and AFB: -VE
- Biopsy TB C&S: -VE
- TB PCR, TB QuantiFERON: -VE

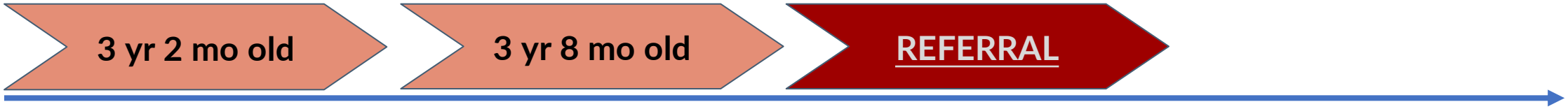
22 months old

No more episodes of bloody stool upon anti-TB completion.

Repeated colonoscopy (after intensive phase anti-TB):
- no crypt distortion, cryptitis or crypt abscess
- No giant cell and caseating necrosis
- histological evidence suggestive of infective colitis

Treated as "TB colitis" (2M EHRZ, 4M HR)
?Possible proctocolitis

A case of 10 years old Malay girl with recurrent respiratory tract infection and recurrent bloody stool



- Left neck swelling
- No fever
- Splenomegaly
- Conservative mx

Left neck swelling increased in size past 3/12 (submandibular LN 4x4.5cm)
Persistent splenomegaly (5-6 cm)

US neck: left submandibular nodule, multiple anterior cervical LN possibly reactive in nature

Hb 12.3 g/L
WBC 7.3 $x10^9$/L (ANC 4.5, ALC 2.0)
PLT 148 $x10^9$/L
ESR 15
US neck: persistent suspicion of pathological submandibular LN

A case of 10 years old Malay girl with recurrent respiratory tract infection and recurrent bloody stool

REFERRAL
3 yr 9 mo old

- Recurrent respiratory tract infection since age 6 months
- Treated as early onset bronchial asthma
- No family h/o allergy or asthma
- No eczema
- Attacks about every 2 months - required nebulization at least for 3-5 days, triggered by viral illnesses
- Required MDI Ventolin every 2 weeks
- Eosinophils always <4%
- Dust induced cough +
  Cold induced cough +
  No exercise induced symptoms
- No daytime symptoms
  No nocturnal symptoms

Examination
- Left submandibular LN 4x3cm
- Right shotty cervical LN
- Hepatosplenomegaly (liver 3cm, spleen 6cm)

- Treated with antibiotics for 2 weeks – not improved
- Referred to ENT surgeon for LN biopsy

	IgGAM
IgG	8.7 (4.3-13.4)
IgA	3.85 (0.19-2.2)
IgM	1.6 (0.21-1.8)

TBNK	
T cells	64% (1281) N
B cells	15% (298) L
CD4	25% (492) L
CD8	38% (753) L
NK cells	18% (361) N

A case of 10 years old Malay girl with recurrent respiratory tract infection and recurrent bloody stool

3 yr 2 mo old

- Left neck swelling
- No fever
- Splenomegaly
- Conservative mx

US neck: left submandibular nodule, multiple anterior cervical LN possibly reactive in nature

3 yr 8 mo old

Left neck swelling increased in size past 3/12 (submandibular LN 4x4.5cm)
Persistent splenomegaly (5-6 cm)

Hb 12.3 g/L
WBC 7.3 x10^9/L (ANC 4.5, ALC 2.0)
PLT 148 x10^9/L
ESR 15
US neck: persistent suspicion of pathological submandibular LN

REFERRAL

Left submandibular LN excisional biopsy

Lymph node biopsy HPE
→ Features suggestive of paediatric nodal marginal zone lymphoma
→ Suggest genetic profile in view of rare entity occurring in childhood
Tissue C&S: Salmonella sp.

3 yr 11 mo old

Immunostaining:
The neoplastic cells positive for CD20, negatives for CD3, CD5, CD10, BCL 6 and Tdt. A few cells positive for BCL2

Diagnosed as **nodal marginal zone lymphoma**

A case of 10 years old Malay girl with recurrent respiratory tract infection and recurrent bloody stool

4 years old

Diagnosed as **nodal marginal zone lymphoma**, no need chemotherapy
Prognosis is excellent

CT Neck, TAP:
Prominent lymph node at left submental region
No other significant lymphadenopathy in the neck, chest, abdomen or pelvis

LOST TO F/UP 4-7 years old

- Monthly URTI
- Recurrent fever, cough
- 2x per year ward admission - required O2 therapy and nebulization
- Positive influenza, RSV, adenovirus pneumonia
- Hepatosplenomegaly

US abdomen:
- Mild to moderate hepatomegaly 10cm with gross splenomegaly 12cm
- No focal lesion

8-9 years old

- Viral warts multiple fingers. Treated with laser + cryotherapy, recurred, 9-10 small isolated warts over finger pulps, no other areas involved
- Persistent bilateral ears discharge → conductive hearing loss

- ANA : negative
- RF : negative
- C4 : 0.22
- C3 : 1.05
- Direct Coomb test: -VE
- Infective screening: -VE

REFERRAL 10 years old

- Recurrent chronic cough
- Intercurrent respiratory infections
- Pneumonia
- Nasal allergies
- Hyperreactive airway
- Hepatosplenomegaly

HRCT thorax: Diffuse airway wall thickening with bilateral patchy tree in bud changes a/w right hilar lymphadenopathy. Middle lobe collapse, suspicious of PTB/NTM or other atypical infection

Examination

Not dysmorphic, cheerful

Weight 24.6 kg → 27 kg

Height: 127.5 cm → 130.5 cm

Fingers and toes clubbing grade 3

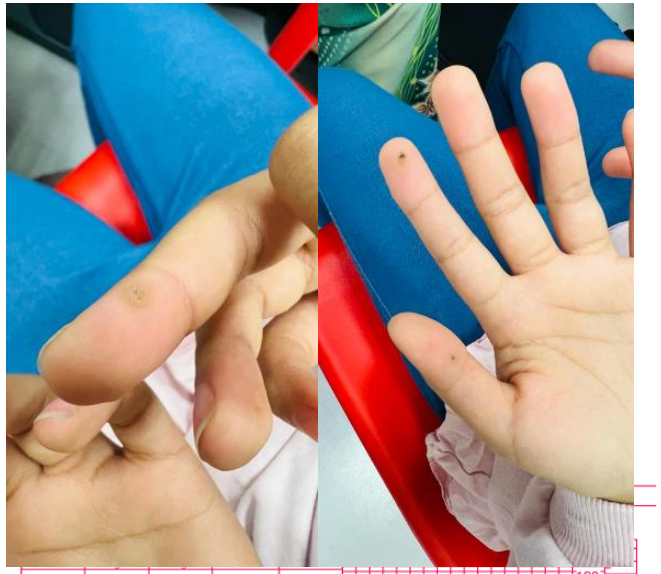
Multiple warts over bilateral tip of finger

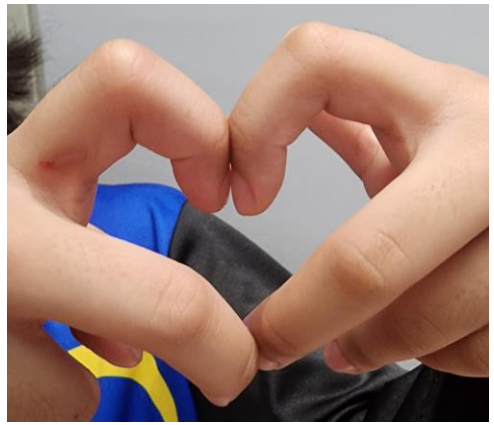
Throat : not injected, tonsils present

Inferior turbinate enlarged

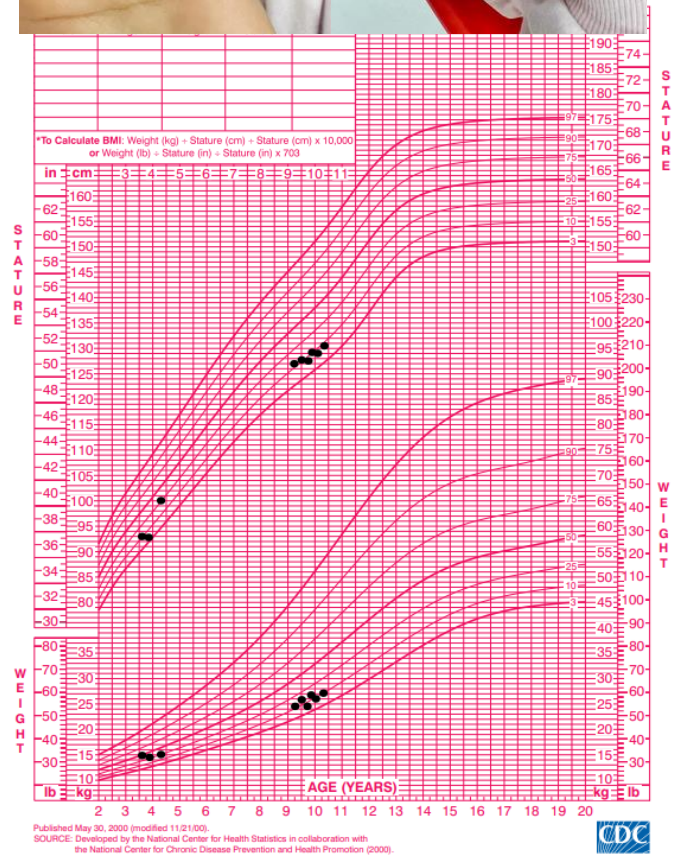
Otoscopy : right - ear wax, left tympanic membrane present, cone of light present

Tuning fork test : Rinne test positive on right side

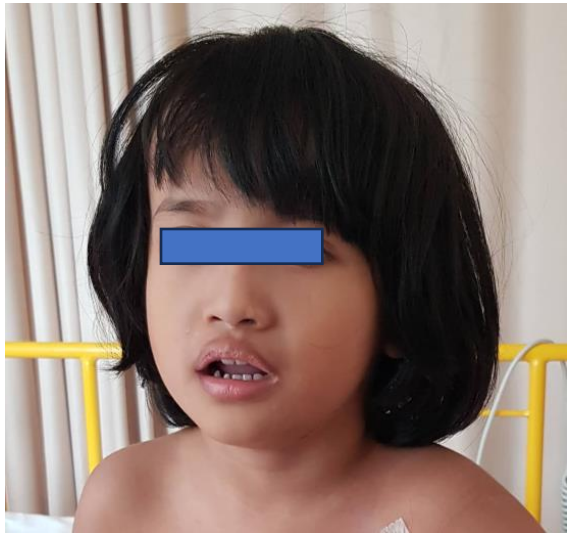


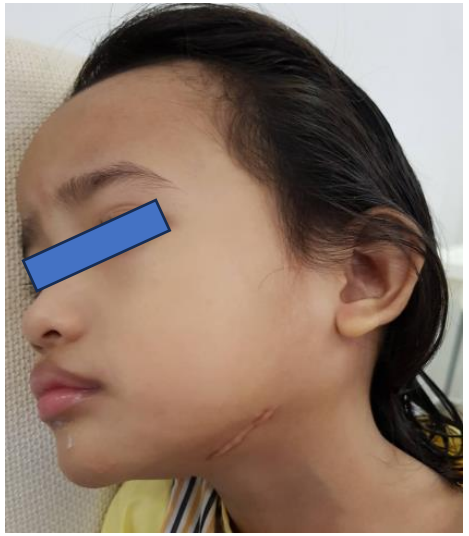


Informed consent obtained



Examination





LN biopsy scar at left submandibular region

Left cervical LN 1x1cm, mobile, not tender

Lungs:

- Hyperinflated chest, Harrison sulci seen
- Trachea not deviated, chest expansion equal
- Increase vocal resonance, bronchial breathing on right side and, bibasal fine crepitation

CVS: apex beat no deviated, DRNM, no loud P2

Abdomen: soft, not distended

- Liver 5cm → 5.5cm → 3cm → 2cm → 4cm → 2cm
- Spleen 7cm → 7cm → 6.5cm → 4cm → 6cm → 4cm

Informed consent obtained

Blood investigations – FBC

FBC	21/9/19	11/11/19	17/01/20	21/1/20	6/7/20	25/11/21	28/11/21	17/12/02	25/3/23	4/4/23
Hb	11.1	10.5	11.4	12	12.1	13.5	13	12.7	12.3	12.3
HCT	32	30	35	35	36	40	29	40	38	37.8
PLT	95	162	163	17	106	297	258	212	201	166
TWC	4.9	13.6	12.9	6.3	6.3	15.6	10.1	10.1	10.9	7.7
ANC	3.41	10.8	9.81	5.26	3.69	13.1	7.27	7.17	7.96	5.19
ALC	1.12	2.03	2.19	0.97	1.93	1.56	1.82	2.02	2.07	1.76
AMC	0.31	0.62	0.75	0.05	0.50	0.62	0.71	0.61	0.55	0.43

Immunoglobulins and Complements

DATE	OCT 2017 (4y)	JUL 2020 (7y)	APR 2023 (10y)
IgG (g/L)	8.7 (4.3-13.4)	13.31 (5.2-15.6)	16.13 (5.2-15.6)
IgA (g/L)	3.85 (0.19-2.2)	1.39 (0.54-3.6)	6.69 (0.54-3.6)
IgM (g/L)	1.6 (0.21-1.8)	1.81 (0.13-2.4)	2.15 (0.13-2.4)
IgE (ku/L)			< 25.0
C3 (g/L)	0.89		
C4 (g/L)	0.15		

T cell, B cell and NK cell enumeration

Age	7/4/2015 (1y 4m)	11/10/17 (3y 10m)	6/7/2020 (6y 7m)	25/3/23 (9y 3m)	4/4/2023 (9y 4m)
T cells	26% (833) L	64% (1281) N	56% (1222) N	56% (1363) N	57% (1156) N
B cells	50% (1765) H	15% (298) L	14% (311) L	20% (469) N	20% (416) N
CD4+	16% (464) L	25% (492) L	17% (381) L	22% (556) L	23% (481) L
CD8+	10% (291) L	38% (753) L	36% (787) L	34% (830) N	30% (621) N
NK cells	22% (779) H	18% (361) N	28% (613) H	24% (584) N	21% (429) N

Lymphocyte activation test

- Interpretation: Increased IFN-gamma expressing cells detected in stimulated patient samples as compared to unstimulated samples
- Note: Increased IFN-gamma expressing cells: Normal response or function of lymphocytes

	Unstimulated (SFU per million cells)	**Anti-CD3 stimulated (SFU per million cells)**	**PHA stimulated (SFU per million cells)**
Control	10	13940	7720
Patient	80	19060	9630

Specific antibody response test

- Interpretation: Increased IFN-gamma expressing cells detected in stimulated patient samples as compared to unstimulated samples

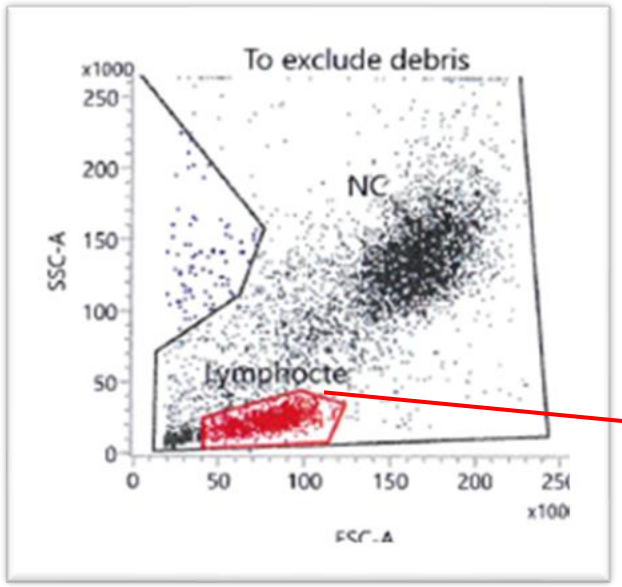
	Pre vaccine	**Post vaccine**
Tetanus	0.26 IU/mL	0.34 IU/mL (LOW)
Pneumococcal (PCP)	11.07 mg/L	10.39 mg/L (LOW)

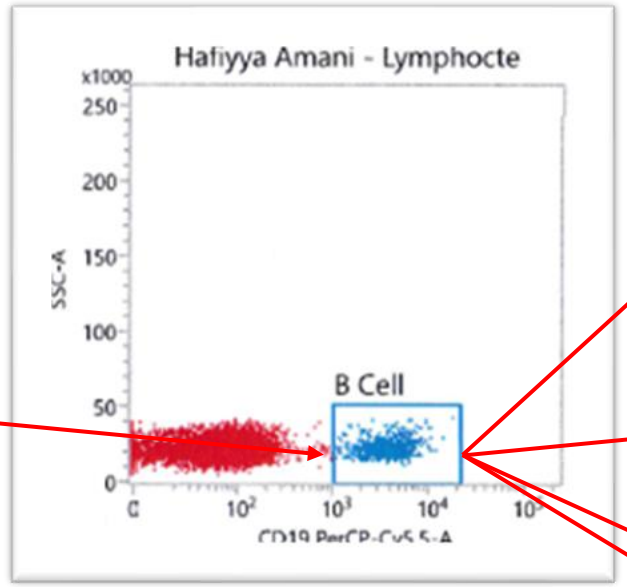
B cell panel

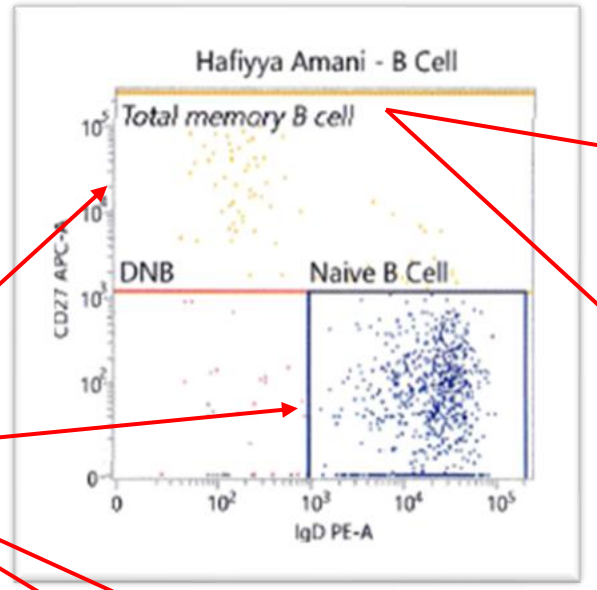
- This patient has reduced numbers of total B cells, and this is reflected on the lower numbers of memory B cells, switched and non-switched memory B cells, when compared to the reference range for age. This finding may support B-cell dysregulation.

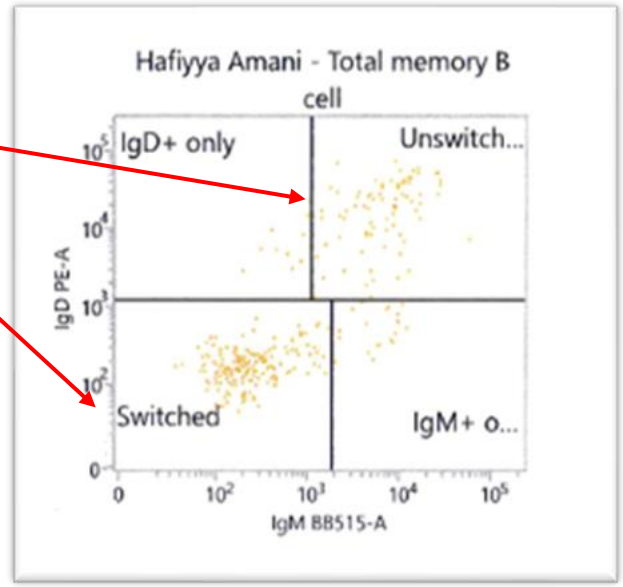
	Patient (9Y 8M)		Control (5Y 4M)	
	%	X 10^6/L	%	X 10^6/L
Total Lymphocytes	10.90	980.0	22.70	1510.0
Total B Cells	14.20	214.42	38.49	377.20
Transitional B Cells	81.00	173.68	13.03	49.15
Naïve B Cells	90.11	193.21	71.88	271.13
Total Memory B Cells	7.10	15.22	24.66	93.02
Non-switched Memory B Cells	2.04	4.37	15.86	59.82
Class switched Memory B Cells	4.31	9.24	7.34	27.69
Plasmablast	4.26	9.13	0.31	1.17

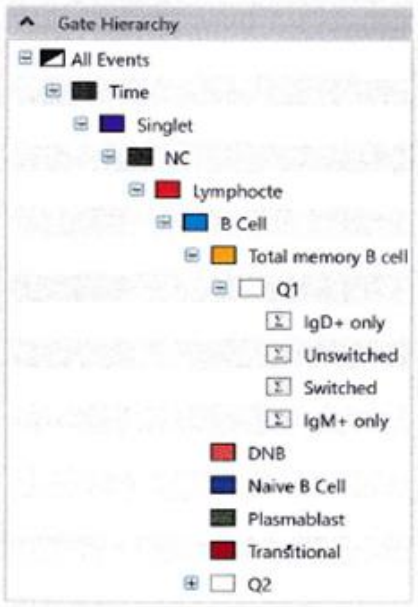
Gating strategy of class-switched memory B cells





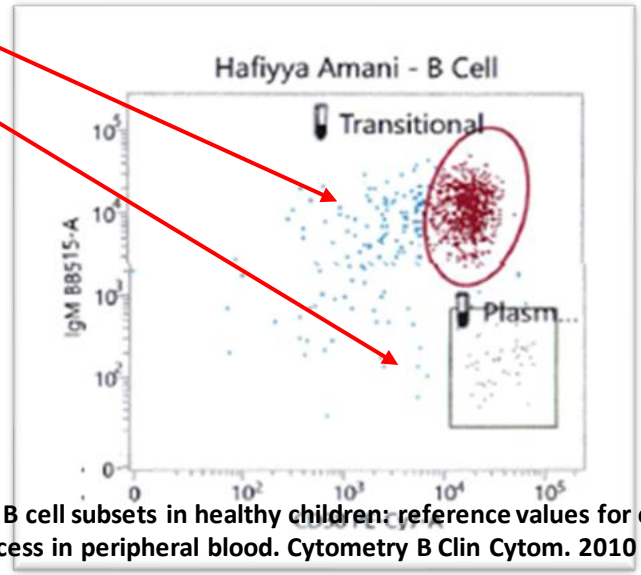






Hafiyya Amani RunPointerStatistics

Name	Events	% Grandparent	% Parent
All Events	133,859	***	***
NC	126,802	94.73	98.74
Lymphocte	29,758	23.17	23.47
B Cell	4,226	3.33	14.20
Total memory B cell	300	1.01	7.10
IgD+ only	10	0.24	3.33
Unswitched	86	2.04	28.67
Switched	182	4.31	60.67
IgM+ only	22	0.52	7.33
DNB	121	0.41	2.86
Naive B Cell	3,808	12.80	90.11
Plasmablast	180	0.60	4.26
Transitional	3,423	11.50	81.00



Piątosa B, et al. B cell subsets in healthy children: reference values for evaluation of B cell maturation process in peripheral blood. Cytometry B Clin Cytom. 2010 Nov;78(6):372-81.

Genetic testing

	Gene	Variant	Zygosity	Variant classification
Patient	P1K3CD	c.3061G>A (p.Glu1021Lys)	Heterozygous	Pathogenic
Mother	P1K3CD gene mutation not detected			
Father	P1K3CD gene mutation not detected			
11 yo sister	P1K3CD gene mutation not detected			
5 yo sister	P1K3CD gene mutation not detected			
3 yo sister	P1K3CD gene mutation not detected			

Current diagnosis:

1. Activated P13K Delta Syndrome (APDS)
2. Nodal marginal zone lymphoma
3. Bronchiectasis
4. Allergic rhinitis
5. Mild to moderate conductive hearing loss
6. Hand warts
7. Heterozygous HbE-Beta thalassemia carrier

Management

Multidisciplinary follow-up: immunologist, general paediatrician, ped ID, ped pulmonologist and ENT

Discussed about HSCT – but parents are undecided

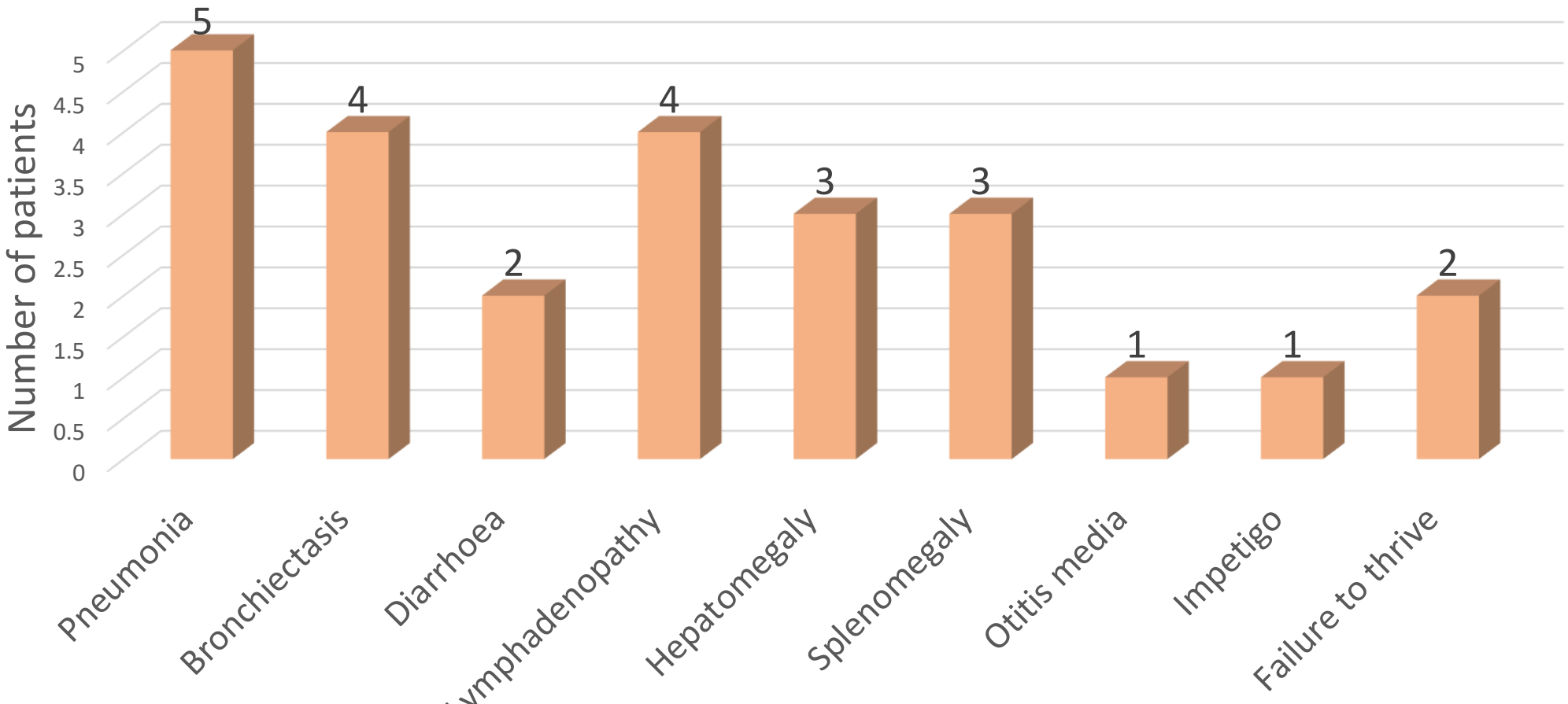
Medications

1. Sirolimus 1mg OD
2. Immunoglobin replacement therapy every 4 weeks
3. Salbutamol MDI 200 mcg PRN
4. Symbicort respihaler 45/160 mcg 1p BD
5. Azithromycin 250 mg 3x/ week
6. Avamys nasal spray 1p BD
7. T. Bilastine 10 mg ON

Number of APDS patients diagnosed in Hospital Sultan Abdul Aziz Shah (HSAAS), Universiti Putra Malaysia (UPM) from 2017 – 2024

Year diagnosed	Number of APDS patients
2017	1
2018	0
2019	0
2020	1
2021	1
2022	1
2023	1
Total	5

Clinical features of APDS patients



Clinical and immunological features of the APDS patients

Age, gender	11 y, F	12 y, F	8 y, F	13 y, F	20 y, M
Race	Malay	Malay	Malay	Malay	Chinese
Age of onset	6 m	2 y	1 y	1 y 6m	3 y
Sinopulmonary bacterial infections	+	+	+	+	+
Other infections	Otitis media	-	-	Otitis media	-
Bronchiectasis	+	+	+	+	+
Digital clubbing	+	+	+	-	+
Lymphadenopathy	+	+	+	-	+
Hepatomegaly	+	+	+	-	+
Splenomegaly	+	+	+	-	+
Impetigo	-	-	-	+	-
Failure to thrive	-	-	-	+	+
Short stature	-	+	-	-	+
Autoimmune disease	-	-	-	-	Autoimmune atrophic gastritis
Malignancy	Nodal marginal zone lymphoma				

Clinical and immunological features of the APDS patients

Age, gender	11 y, F	12 y, F	8 y, F	13 y, F	20 y, M
Other clinical findings	• HbE Beta thalassemia carrier • Mild to moderate conductive hearing loss • Hand warts	• Slow learner with soft dysmorphism	• Right Hydronephrosis • Anemia secondary to IDA and HbE trait • Incidental finding of thyroid lesion	-	• Chronic diarrhea with protein losing enteropathy • Thrombocytopenia and anemia possible secondary to hypersplenism
T cells	T cells: normal CD4: low CD8: normal	T cells: low CD4: low CD8: high	T cells: high CD4: low CD8: high	T cells: low CD4: low CD8: low	T cells: high CD4: high CD8: low
B cells	Normal	Low	Normal	Low	Normal
NK cells	Normal	High	Normal	Low	-
Iso-hemagglutinin	-	Normal	Reduced titre	-	-
SAR test	Poor response	No antibody response	Poor response	Poor response	-
LAT/LPT	Normal	Normal	-	Reduced lymphocyte proliferation	Reduced lymphocyte proliferation
Phagocytic function test	Reduced respiratory burst activity	Normal	-	Normal	Normal
Genetic study	PIK3CD gene	PIK3CD gene	PIK3CD gene	PIK3CD gene	-

F, female; *M,* male; *y,* year; *m,* month; *NK,* natural killer; *SAR,* specific antibody response; *LAT,* lymphocyte activation test; *LPT,* lymphocyte proliferation test.

Activated PI3Kδ syndrome (APDS)

Is a rare inborn errors of immunity (IEI)

First described in 2013/14 in a small group of patients with PID of unknown etiology

It may be caused by point mutations or deletions in one of the 2 genes encoding the two phosphoinositide 3-kinase δ (PI3Kδ) subunits

Both gain-of-function (GOF) in *PIK3CD* and loss-of-function (LOF) in *PIK3R1* contribute to the clinical phenotypes → APDS1 (*PIK3CD* gene) and APDS2 (*PIK3R1* gene)

Often manifests early in life with frequent infections, lymphoproliferation and autoimmunity, and later in life with deteriorating lung function or lymphoma

Due to the rarity of the disease and the heterogeneous clinical picture, many patients are not diagnosed until years after symptom onset

Activated PI3Kδ syndrome (APDS)

Treatment

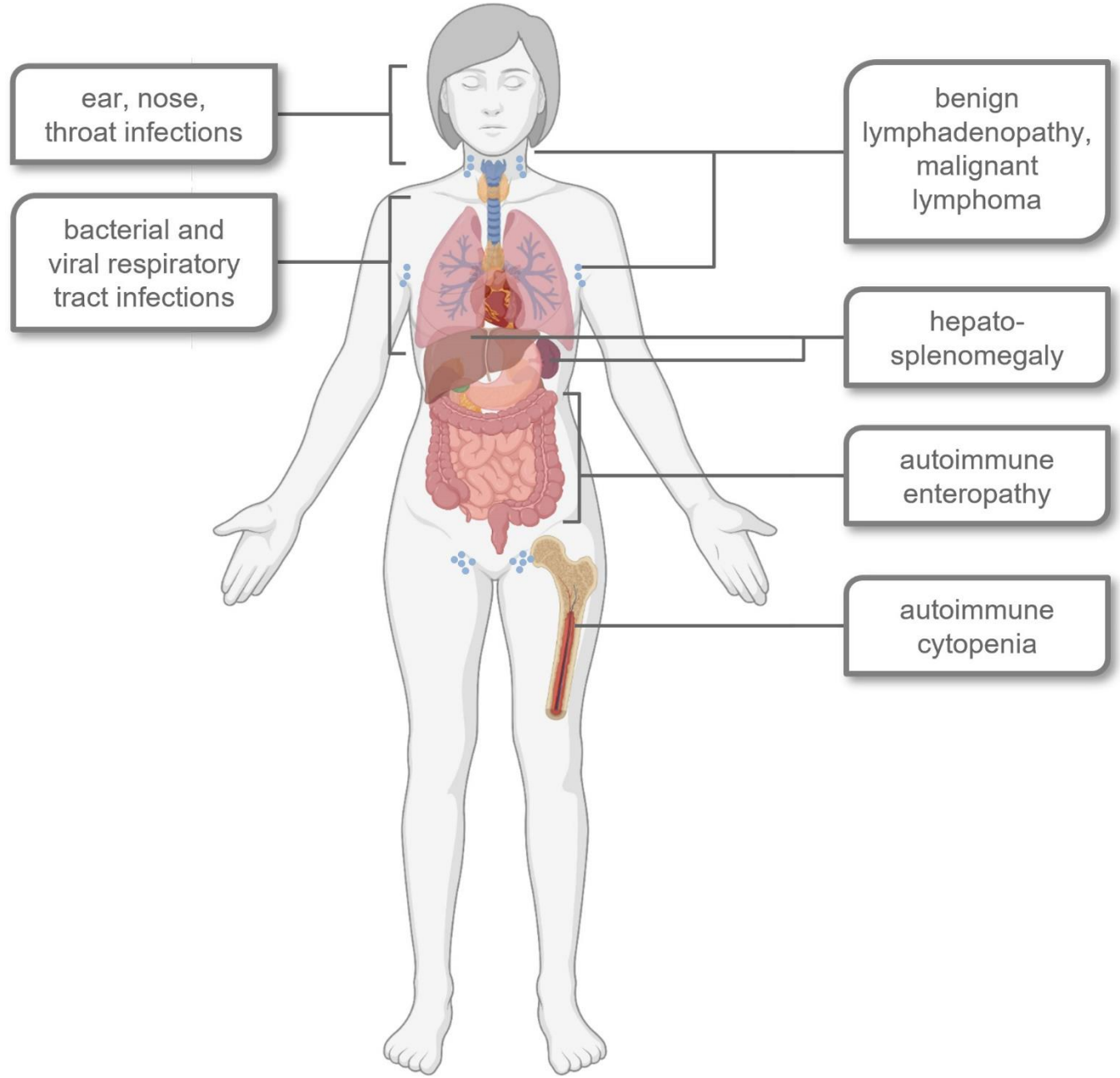
Symptom-oriented with immunoglobulin replacement therapy, immunosuppressive therapies and antibiotic or antiviral prophylaxes

Allogeneic stem cell transplantation

New targeted therapies

May improve patients' quality of life and life expectancy

Clinical course of the disease is difficult to predict which complicates the choice of appropriate therapies


ear, nose, throat infections
bacterial and viral respiratory tract infections
benign lymphadenopathy, malignant lymphoma
hepato-splenomegaly
autoimmune enteropathy
autoimmune cytopenia

AMRAC team

Advanced Medical Research in Allergy and Clinical Immunology

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Farah Hanim Roslan
Nur Nabilah Tan

THANK YOU

ADVANCED MEDICAL RESEARCH IN ALLERGY & CLINICAL IMMUNOLOGY
AMRAC

UPM
UNIVERSITI PUTRA MALAYSIA
BERILMU BERBAKTI

IPOPI.org

A cohort of congenital neutropenia from Children's Hospital of Fudan University China

Presenter

Dr Jia Hou

Department of Clinical Immunology

Children's Hospital of Fudan University

National Children's Medical Center

IPOPI
5TH REGIONAL
ASIAN PID MEETING
24-25 MARCH 2024
TOKYO, JAPAN
an IPOPI event

COLLABORATION

SUPPORTED BY

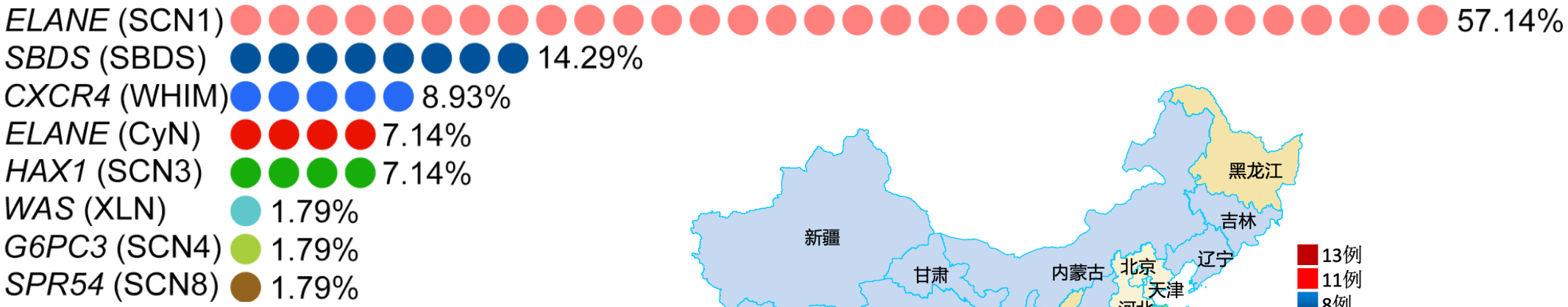
congenital neutropenia cohort

Department of Clinical Immunology ,Children's Hospital, Fudan University

2014-2021

Causative genes

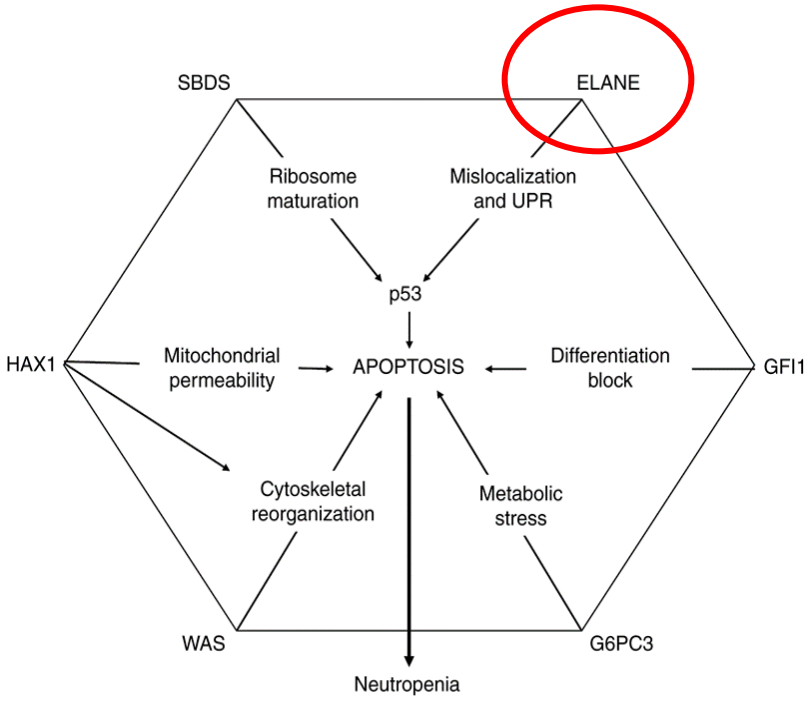
total 56 cases



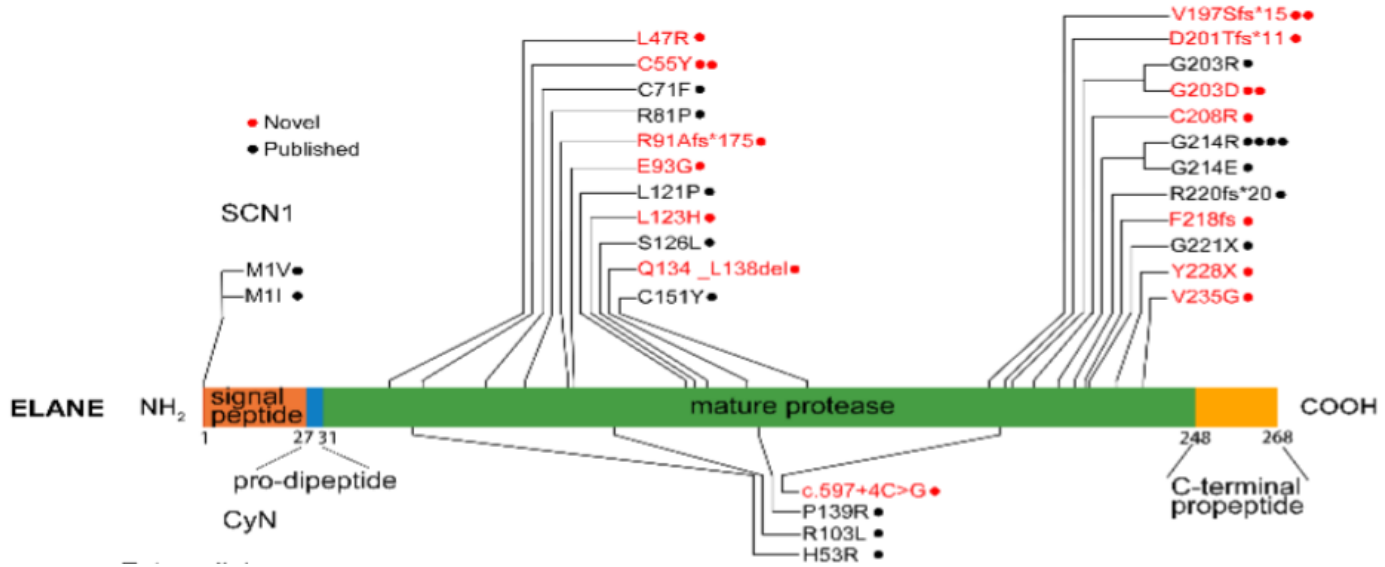
Distribution of the cohort

congenital neutropenia cohort

36（64.3%）



ELANE mutations



De novo mutation，87%

Case

First admission in Clinical Immunology department
2021-10-9

- M, 50d, DOB: 2021-8-19
- First admission: 2021-10-9
- "Be found to have leukopenia for more than 1 month and fever for 1 day"

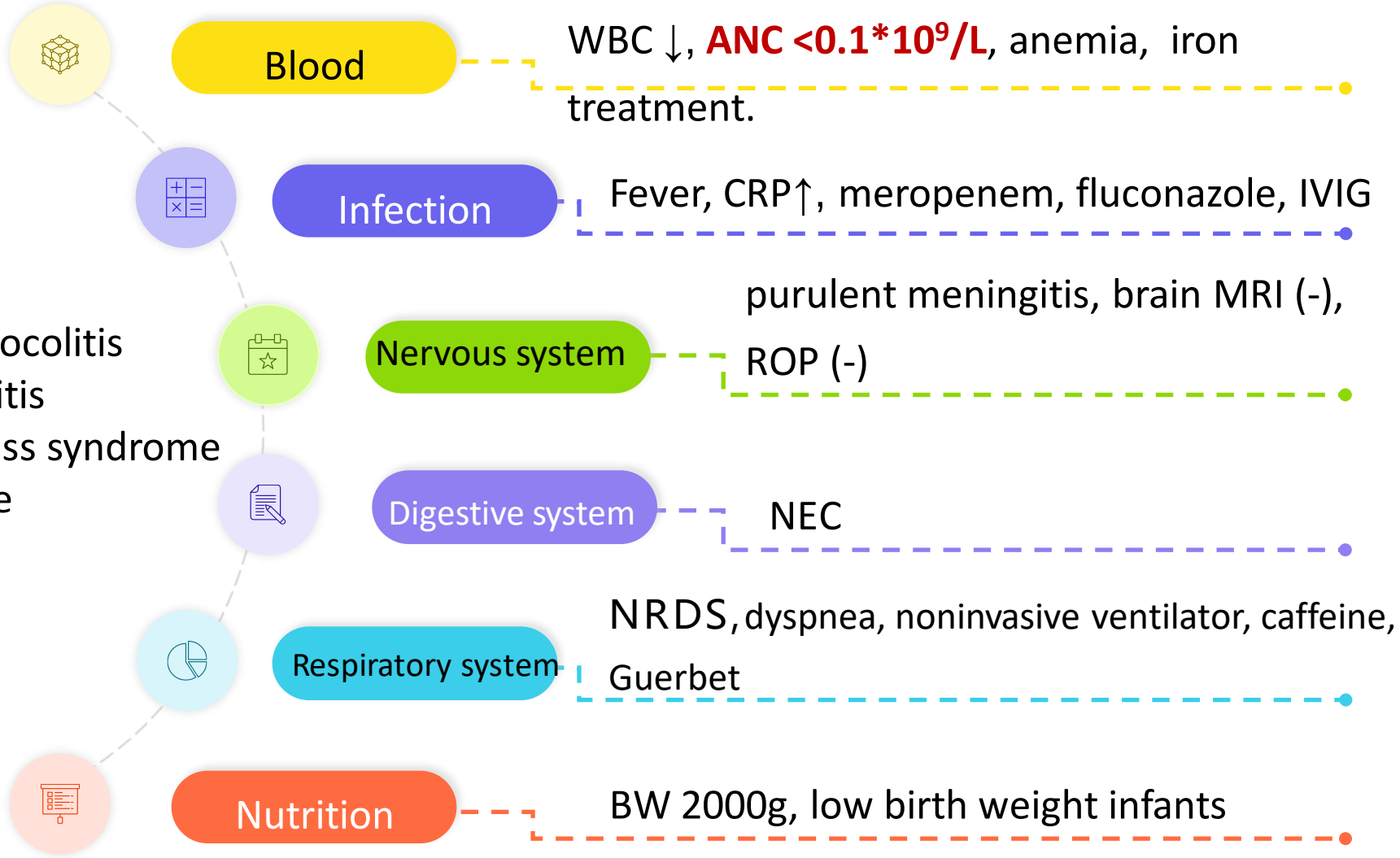
- Birth history: G5P2, preterm cesarean delivery, GA 32^{+1}W, BW 2000g(P50-75),Apgar 8-9'
- Family history: (-)

Case in Neonatal department for 58 days

2021.8.19-10.8

Diagnosis

- ☐ premature infant
- ☐ low birth weight infant
- ☐ neonatal sepsis
- ☐ neonatal necrotizing enterocolitis
- ☐ neonatal purulent meningitis
- ☐ neonatal respiratory distress syndrome
- ☐ neonatal respiratory failure
- ☐ **neutropenia**
- ☐ anemia
- ☐ neonatal jaundice



Case

Neonatal department

2021.8.19-10.8

1d

onset age

- sepsis
- NEC
- purulent meningitis
- NRDS
- respiratory failure
- **neutropenia**
- anemia
- jaundice

1m20d

2021-10-9

- neutropenia
- sepsis
- pneumonia产气克雷伯菌
- anemia
- growth retardation
- PDA, ASD
- BM
- gene detection

3m26d

2021-12-15

diagnostic age

- congenital neutropenia
- pneumonia
- anemia
- antibiotics, IVIG
- G-CSF 5-20ug/kg
- HSCT preparation

8m23d

HSCT

2022.5.12-7.9

- SCN (ELANE)
- HSCT

11m

2022.7.21-2023.1.11

follow up

- regular IVIG

3y7m

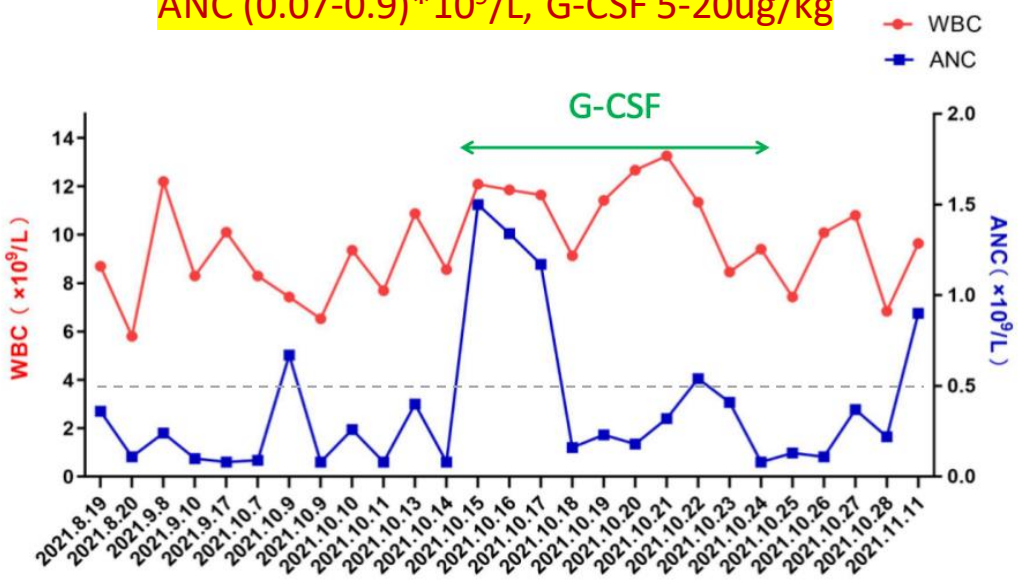
follow up

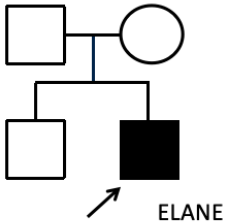
severe congenital neutropenia,

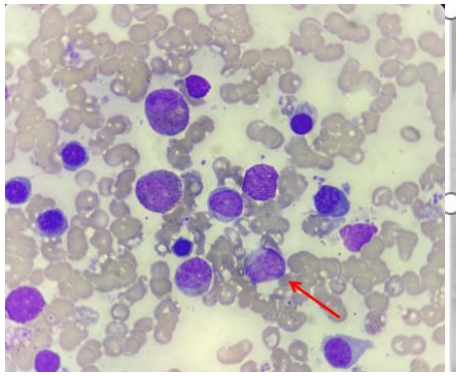
ELANE exon5 c.704T>G, p.V235G, De novo

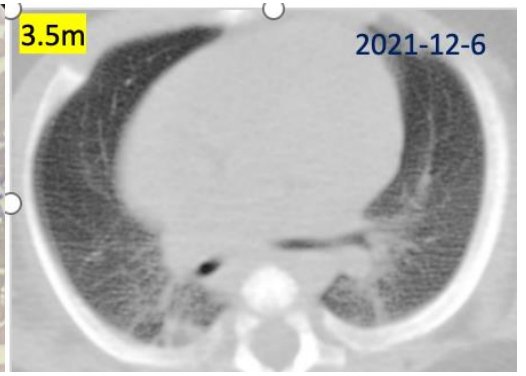
Case

ANC (0.07-0.9)*10^9/L, G-CSF 5-20ug/kg









	2021-10-11	2022-11-10	2023-10-4
IgA	0.03 ↓	0.17	0.88↑
IgG	7.5	10.8	17.0↑
IgM	0.28	0.43↓	1.24
IgE	13.35	<2	94.16
总补体	47		39
C3	0.99		1.00
C4	0.25		0.26

	2021-10-11	2022-11-10	2023-10-4
CD4+/CD8+	4.02	0.23	1.63
CD16+CD56+	5.7%(265)	9.6%(115)	6.4%(205)
CD19+	14.5%(672)	0.9%(11)	19.6%(629)
CD3+	78.9%(3653)	88.4%(1054)	72.2%(2313)
CD4+	62.5%(2899)	14.8%(176)	40.9%(1312)
CD8+	15.5%(721)	65.5%(781)	25.1%(805)
CD45+	4627	1191	3204

Case

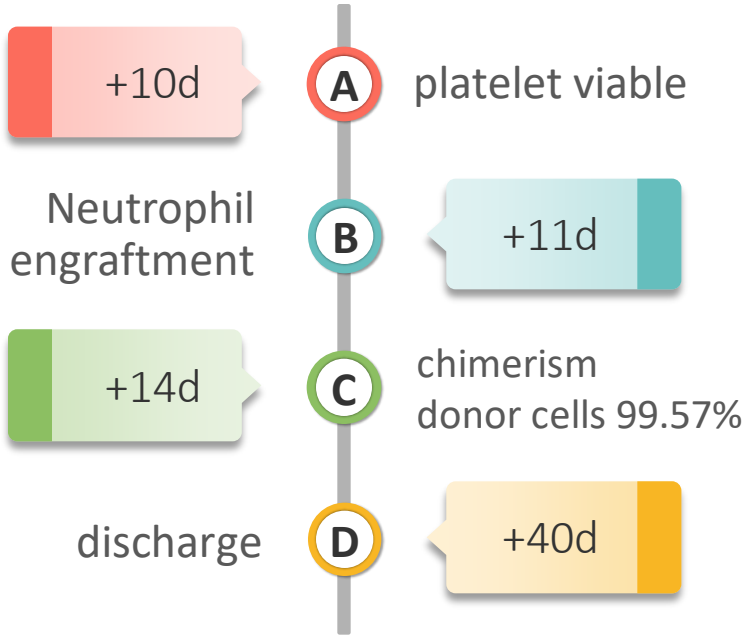
Successful HSCT

Pre-transplantation 2022-5-21

- ☐ Chemotherapy: busulfan + fludarabine + ATG
- ☐ Prevent VOD: alprostadil, ursodeoxycholic acid
- ☐ Anti fungi: caspofungin
- ☐ Anti viral infection: Ganciclovir, Aciclovir
- ☐ Prevent rejection: cyclosporine, secukinumab, +MTX
- ☐ Prevent serum disease: methylprednisolone
- ☐ Antiemetic: Pudendal
- ☐ Sedation: phenobarbital

transfusion 2022-5-30

Non-parental peripheral blood stem cell (10/10)



Complications

- 5.31 Fever, anti-infection, vancomycin + meropenem
- 6.5-6.11, G-CSF
- 6.6 Internal jugular vein thrombosis, anticoagulation: Heparin, Warfarin
- Gastrointestinal bleeding, diarrhea, hemostasis: etamsylate, batroxobin
- 6.10 Rash, skin GVHD, methylprednisolone
- RBC, platelet support
- Abnormal coagulation function: fibrinogen, plasma
- 7.7-7.12 mucositis, IV nutrition

Case

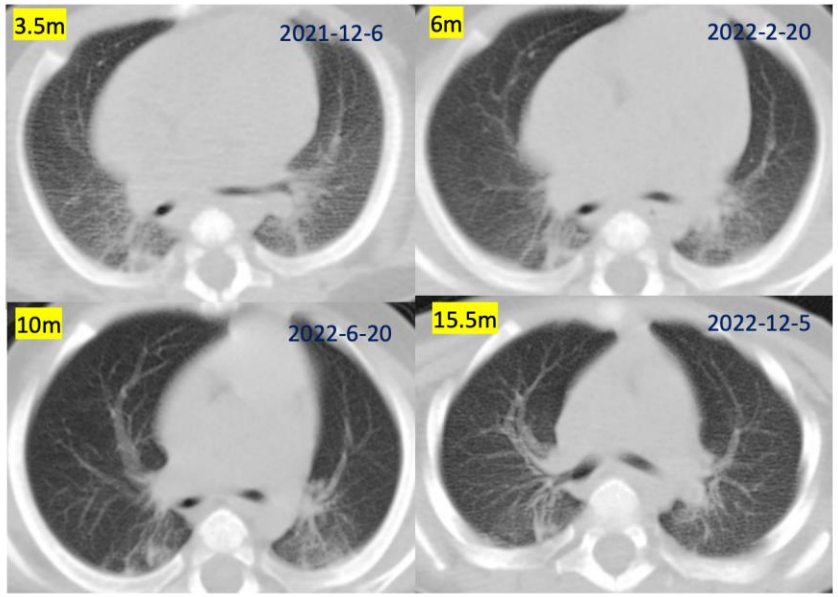
post HSCT

- Anti-rejection therapy: Secukinumab (Mycophenolate mofetil), cyclosporine, methylprednisolone
- Anti-infection: SMZ, voriconazole, acyclovir
- IVIG support

Follow-up

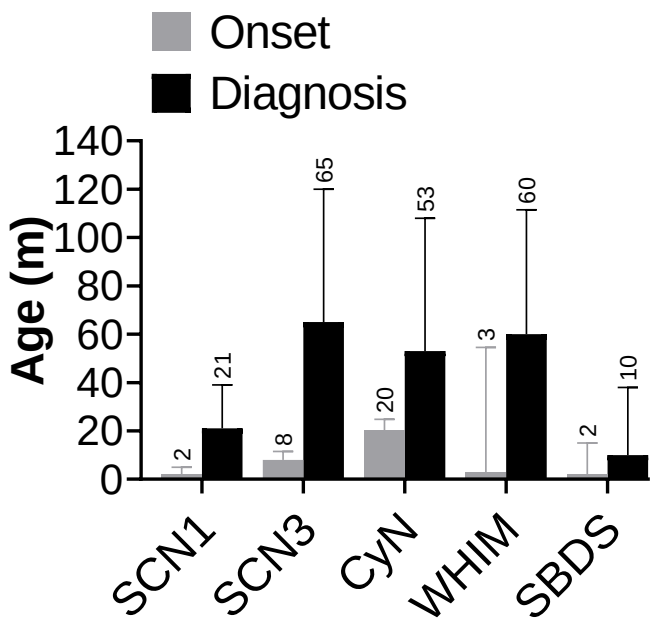
normal neutrophil count after HSCT

ANC (1.2-2.9)*10^9/L

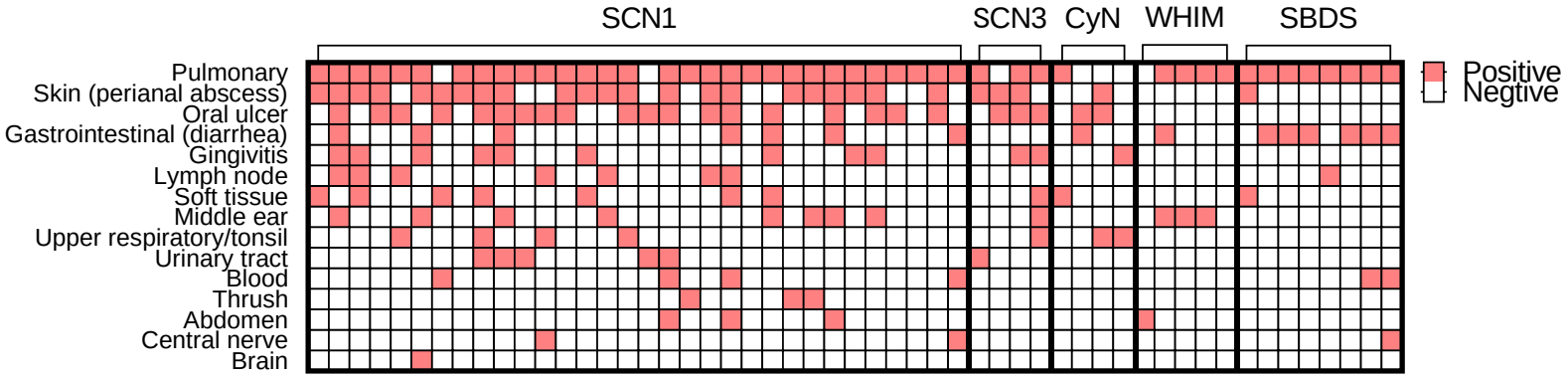


clinical characters of CN

The onset age and diagnosis age of different groups



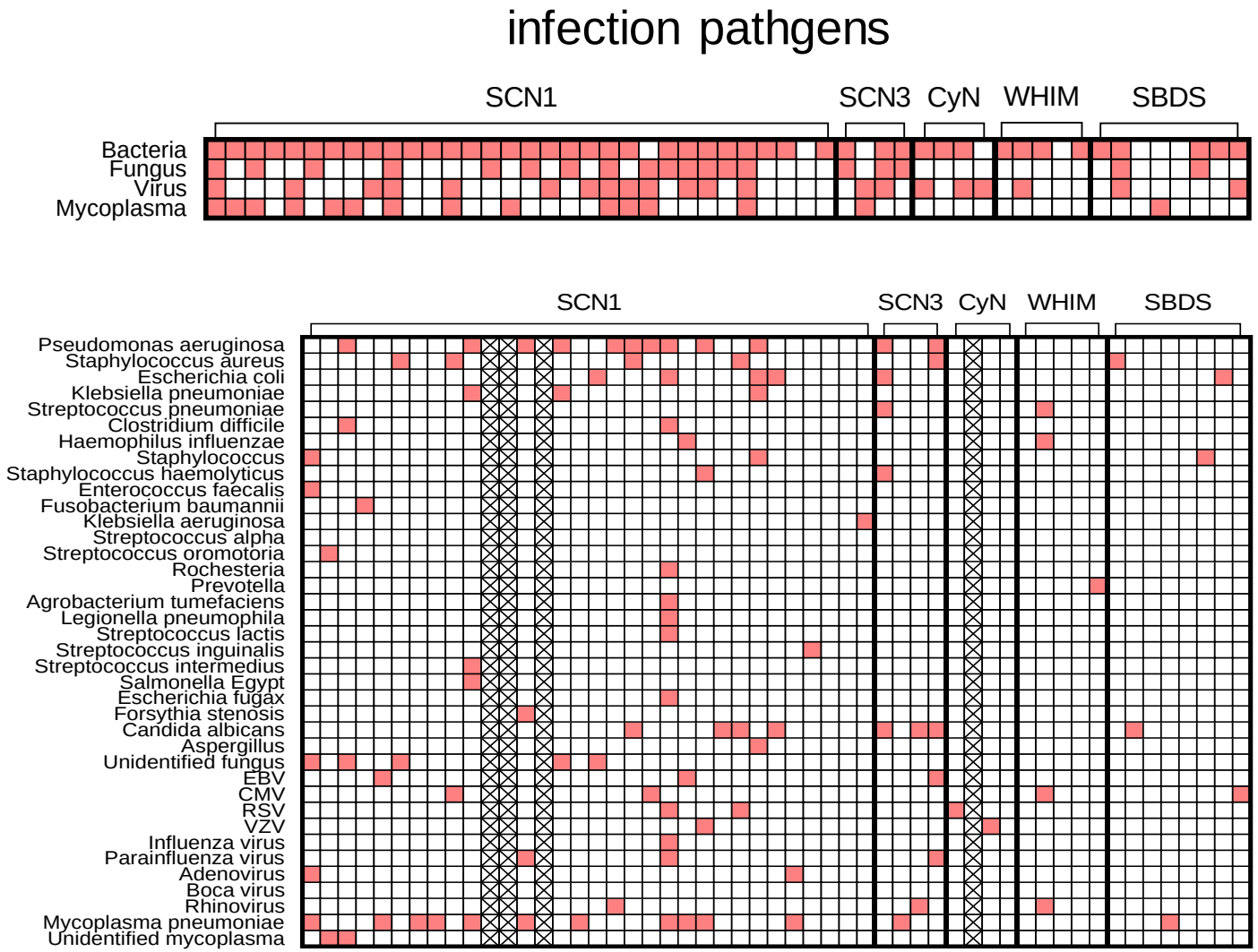
Infected organs/tissues



Repeated and multiple infections

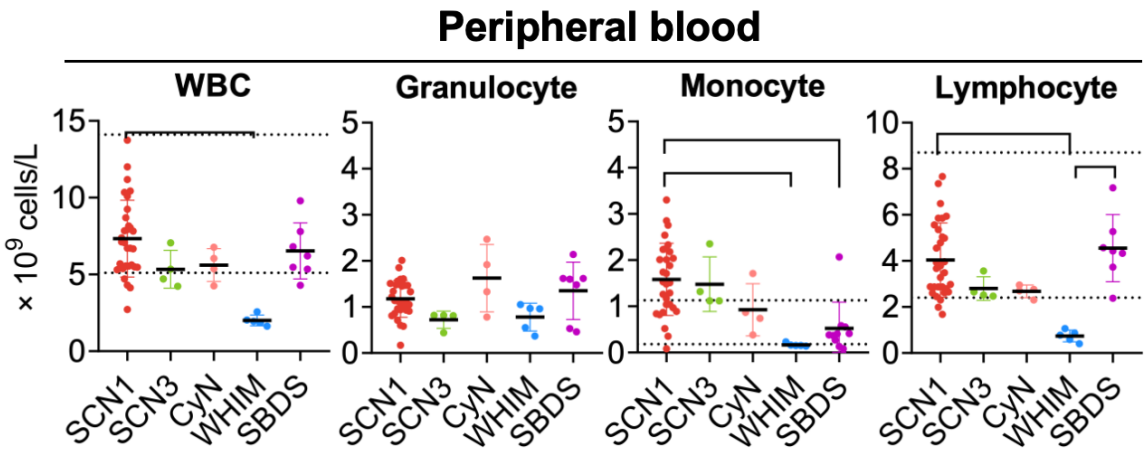
- SCN1, SCN3, CyN groups: more skin infection, oral ulcer
- SBDS group: more GI infection
- WHIM group: more Otitis media

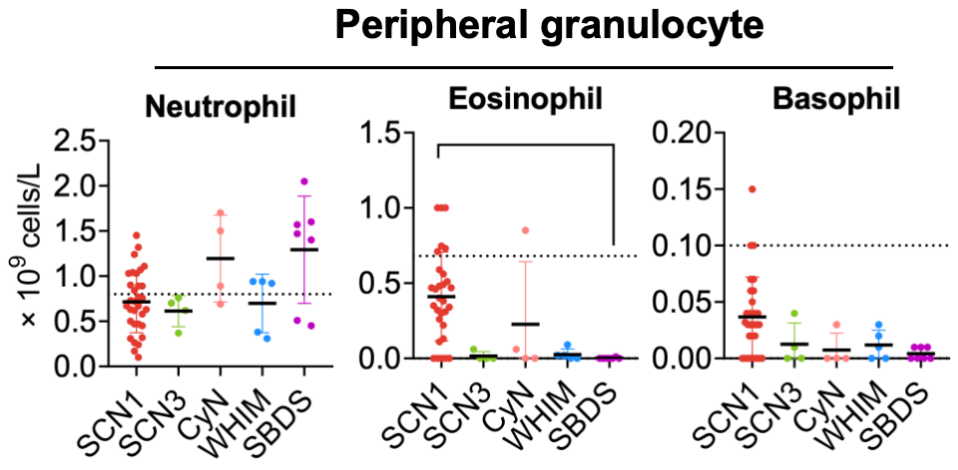
clinical characters of CN

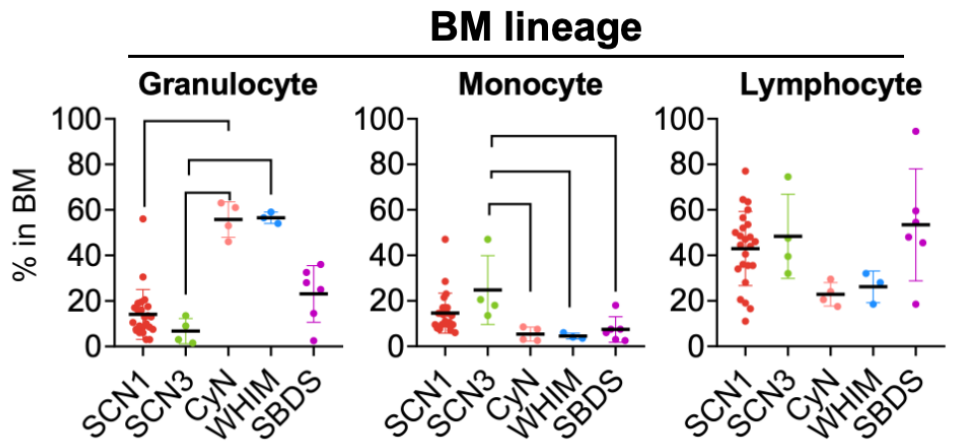


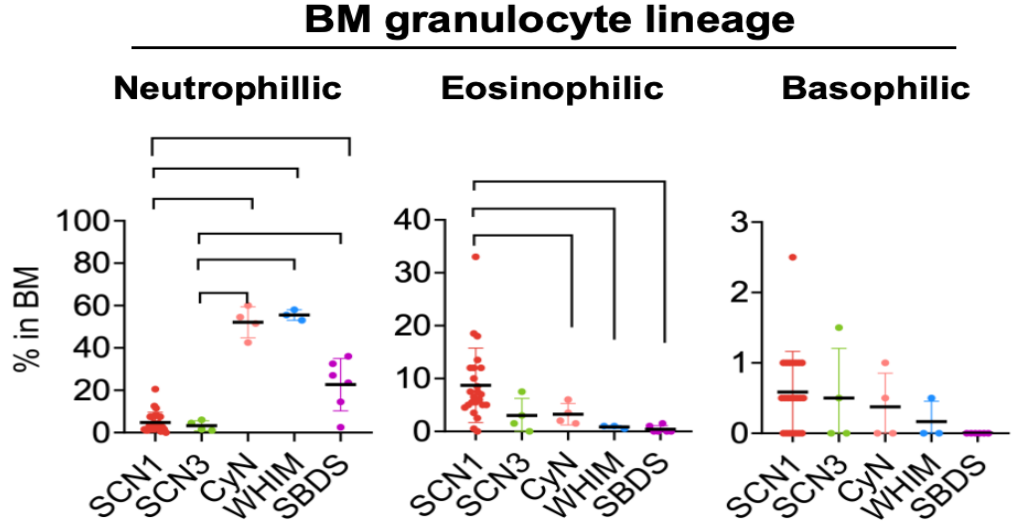
- bacteria: Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli
- fungus: candida albicans
- mycoplasma:Mycoplasma pneumoniae

BM or peripheral blood immune cell subsets

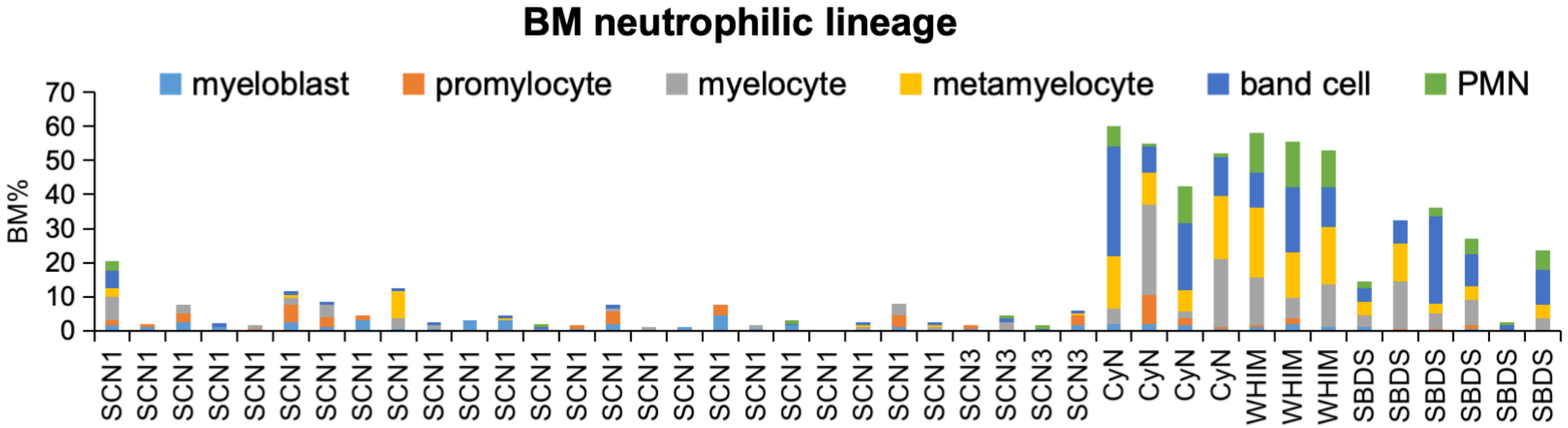






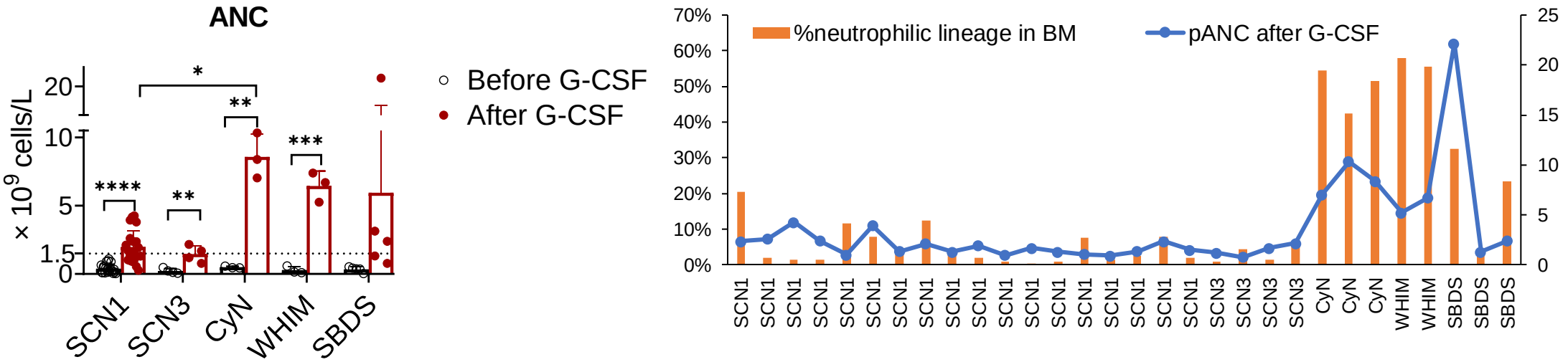


BM neutrophil development



- SCN1, SCN3: severe developmental abnormalities
- CyN: relatively normal, PMNs moderately decrease
- SBDS: intermediate between these two states
- WHIM: neutrophils from promyelocytes to segmented nuclei

BM neutrophil lineage development and G-CSF responsiveness



- The pANC of the CyN, WHIM, and SBDS groups were higher and had better response to G-CSF
- Only half of SCN1 and SCN3 pANC increase to more than 1.5×10^9/L

Treatment HSCT

- **IVIG**

For patients with frequent infection

- **HSCT**

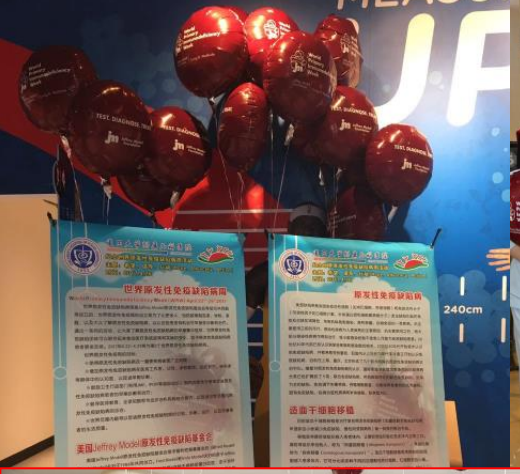
Indication: not respond to G-CSF (>50ug/kg/d → >15ug/kg/d);

myelodysplastic syndrome/leukemia;

ELANE Gly185Arg mutation

Efficacy: post HSCT 5-year survival rate was 87.5%

Bone Marrow Transplantation (2020) 55:1614–1622


240cm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Thank you


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World PI Week
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全球原发性免疫缺陷病关爱日
Turning real-world data into knowledge for better Primary Immunodeficiency (PID) care
DATA SAVES LIVES
时间：2023年4月25日
地点：5号楼一楼报告厅
国家儿童医学中心
复旦大学附属儿科医院临床免疫过敏科

Panel: Case discussion

Prof Martin Van Hagen *(The Netherlands)*

Prof Hirokazu Kanegane (Japan)

Ewen Munro (Pharming)

Dr Van Anh (Vietnam)

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