16th Biennial Meeting of the
EUROPEAN SOCIETY FOR IMMUNODEFICIENCIES
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PID and Autoimmunity: Managing Autoimmunity and autoinflammation complications

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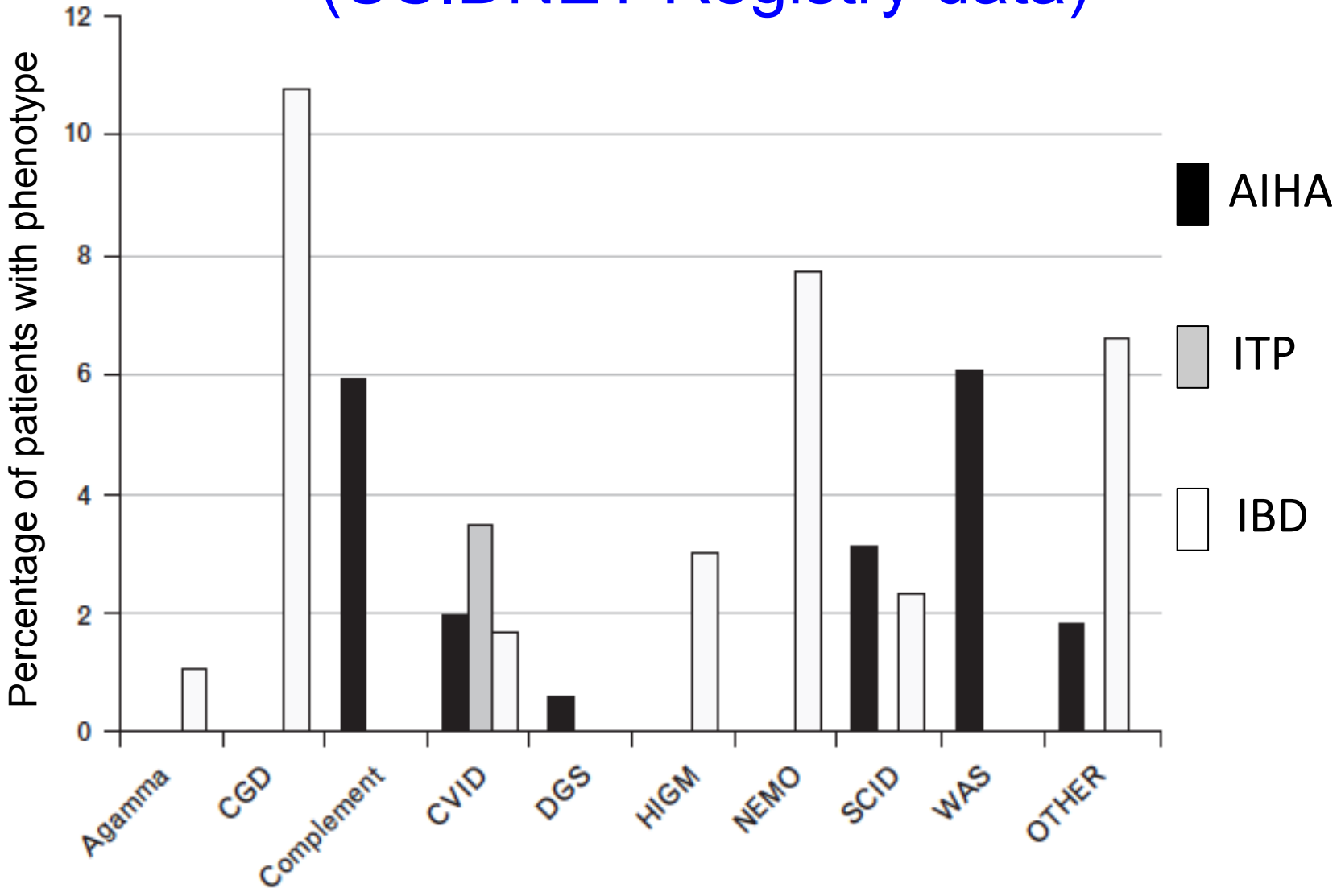
The seesaw model of immunological competence

Autoimmune disease types and frequency in PID (USIDNET Registry data)

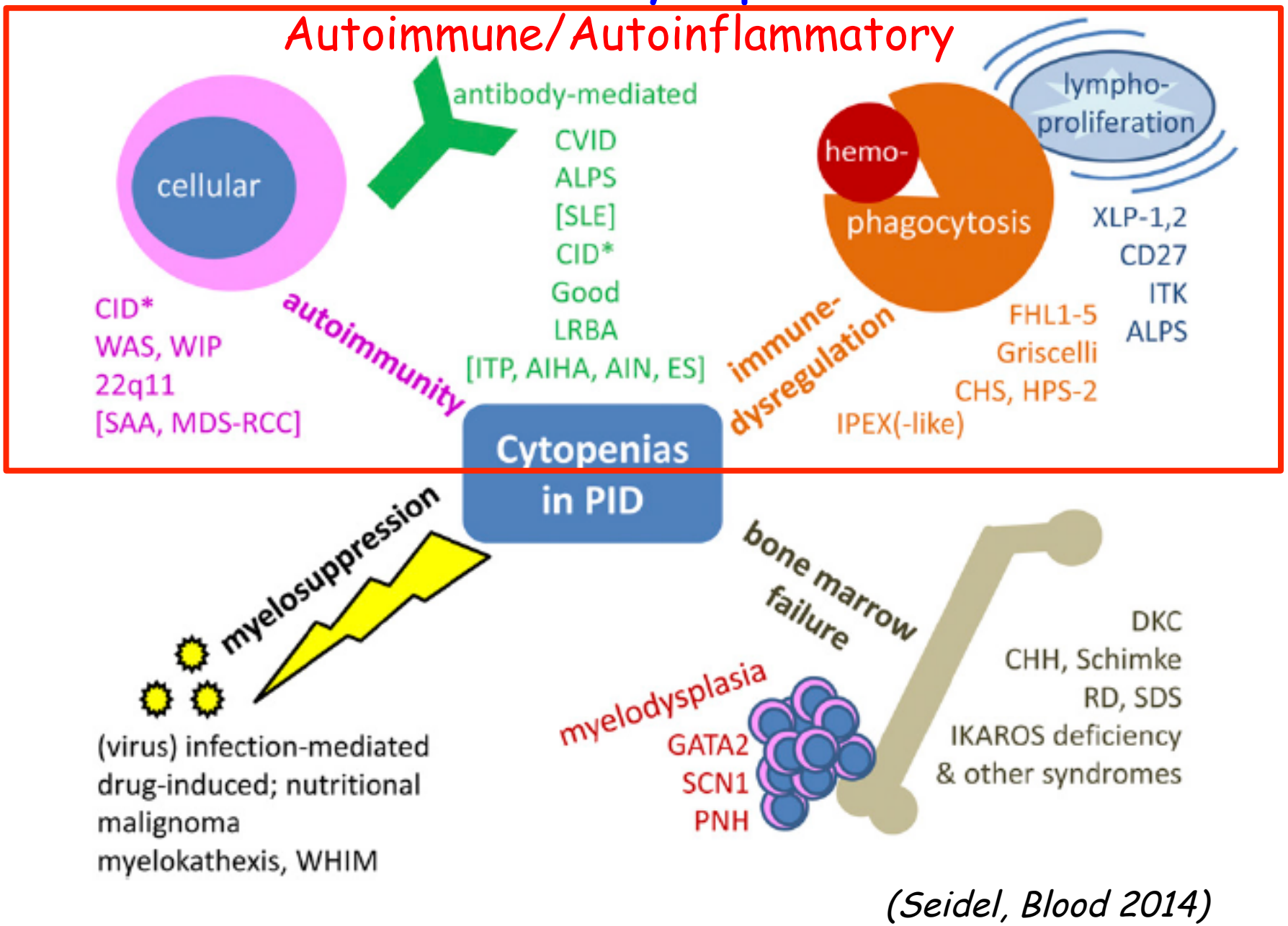


(Magadottir and Sullivan, Curr Opin Rheumatol 2014)

Frequency of autoimmune cytopenias in Primary Immunodeficiencies

	Primary Immunodeficiency	%
Autoimmune hemolytic anemia	Wiskott-Aldrich syndrome	36
	ALPS	29
	IPEX	20
	CVID	5
Autoimmune thrombocytopenia	ALPS	23
	IPEX	15
	CVID	6
	DiGeorge anomaly	4
Autoimmune neutropenia	WAS	25
	ALPS	19
	CD40LG deficiency	65 (?)

Mechanisms of cytopenias in PID

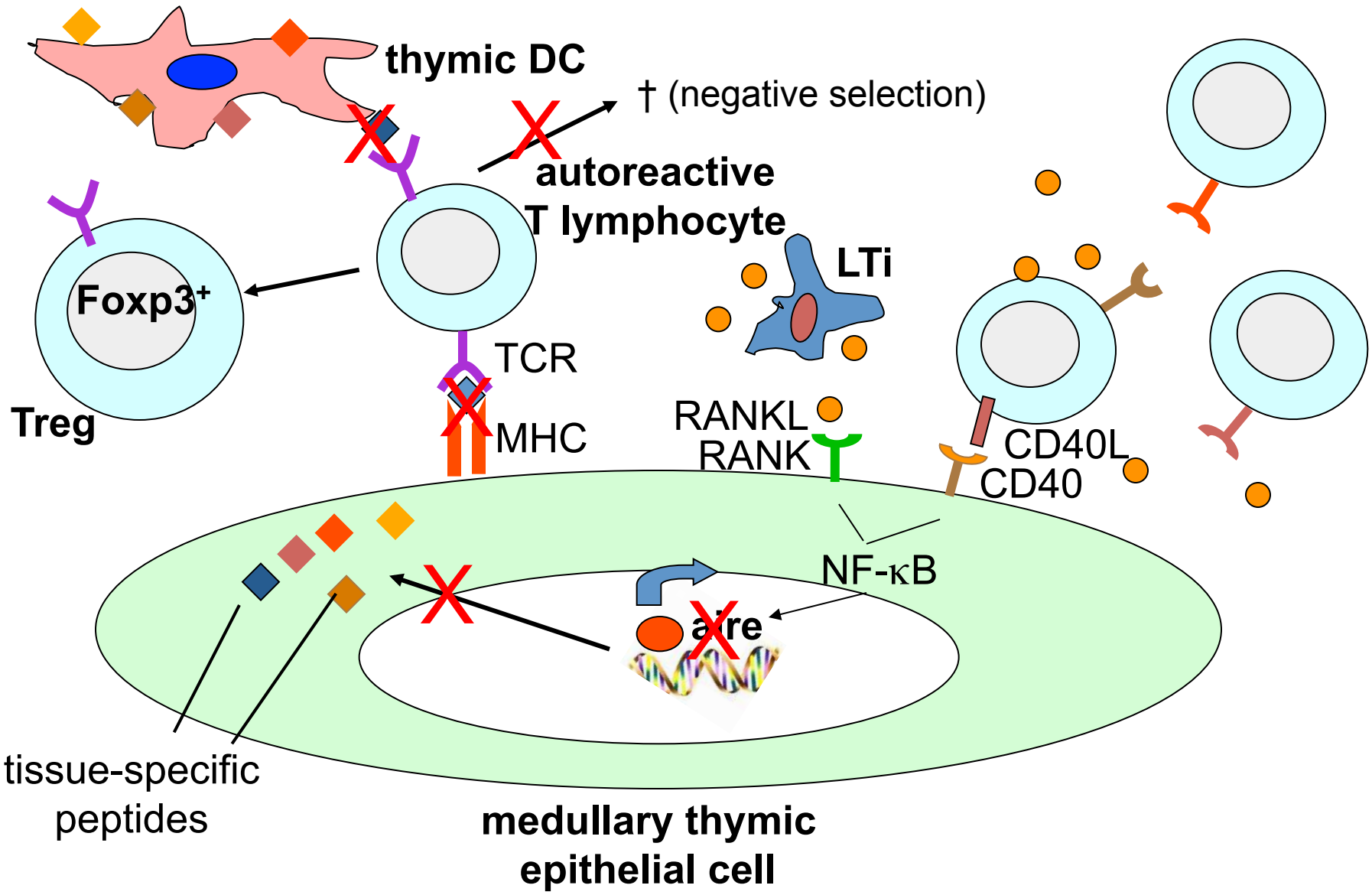


(Seidel, Blood 2014)

Mechanisms responsible for autoimmunity in PID

- defective negative selection of autoreactive T cells
- impaired generation/function of regulatory T cells
- impaired apoptosis of autoreactive lymphocytes
- homeostatic lymphocyte proliferation
- defective purging of self-reactive B cells (receptor editing, BAFF)
- increased load/decreased clearance of apoptotic cells
- defective clearance of immune complexes
- persistent infection/inflammation

AIRE: a key player of central tolerance



APECED: a disorder with organ-specific autoimmunity

Clinical feature	Frequency (%)						
	total n=185	Norway n=20	Finland n=68	N.Italy n=47	Iran n=23	USA n=16	S.Italy n=11
Chronic candidiasis	18-100	85	100	83	18	75	100
Hypoparathyroidism	79-100	85	79	89	96	100	100
Adrenal failure	22-93	80	72	77	22	93	82
Alopecia areata	13-72	40	72	40	13	50	nd
Gonadal failure	18-46	31	60	40	38	24	18
Chronic thyroiditis	4-36	10	4	10	4	31	36
Autoimm. hepatitis	5-31	5	12	19	nd	31	27
Vitiligo	0-25	25	13	15	nd	12	0
Pernicious anemia	0-15	0	13	15	9	nd	9
IDDM	0-12	0	12	4	4	nd	0
Keratopathy	12-35	10	35	12	0	nd	nd
Nail dystrophy	10-70	10	52	nd	>70	nd	nd
Tumors	1-7	nd	1	7	nd	nd	nd

Autoimmunity of APECED

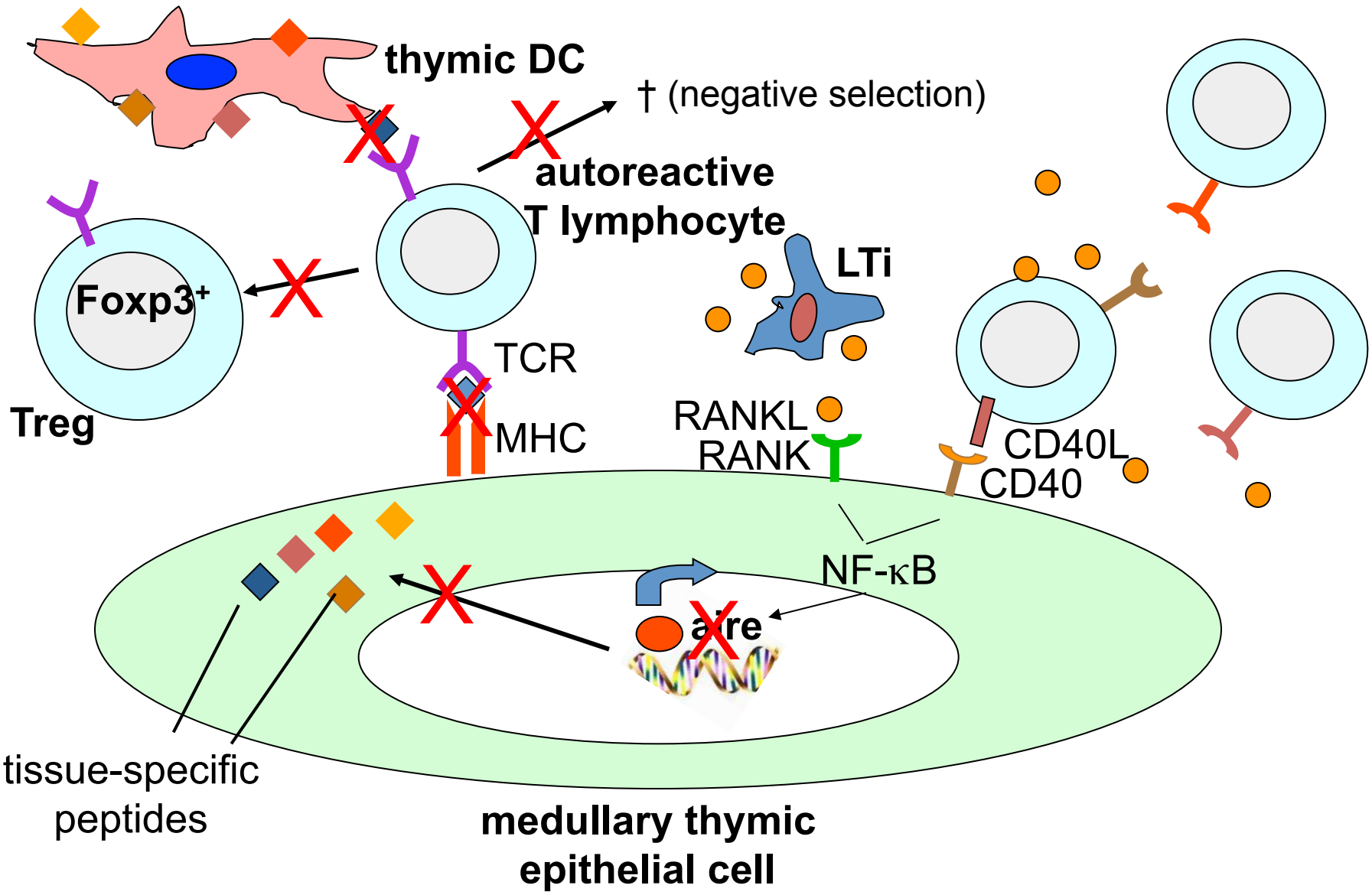
- Many of the self-antigens recognized by organ-specific autoAb encode for intracellular enzymes involved in hormone or neurotransmitter biosynthesis.

- AutoAb to these self-antigens have little disease-causing role in vivo. Their production is likely elicited by tissue damage induced by self-reactive T cell clones

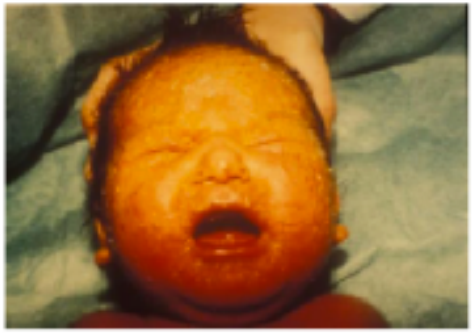
- By contrast, neutralizing anti-IL-17 and anti-IL-22 autoAb play a role in CMC of APECED. They inhibit IL-17-induced secretion of defensins and other antimicrobial peptides.

- Immunosuppression may be beneficial in APECED, in spite of infections (and apparent immunodeficiency)

Deletional and non deletional mechanisms of central tolerance are impaired in Omenn syndrome

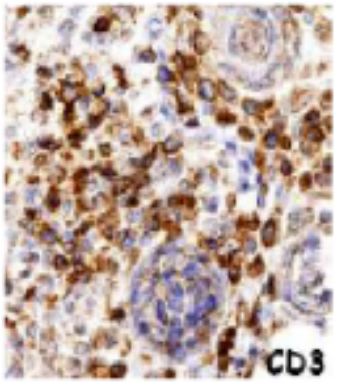


Omenn syndrome: immunodeficiency with immune dysregulation

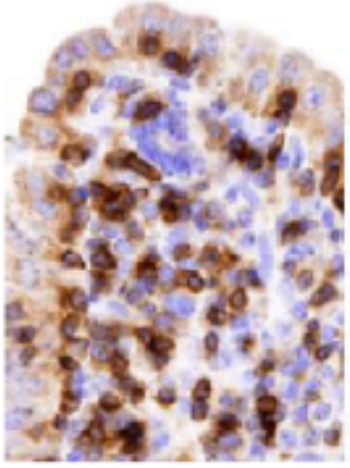


- early onset
- severe infections
- erythroderma
- lymphadenopathy
- liver/spleen enlarg.
- rapidly fatal, unless treated by HCT

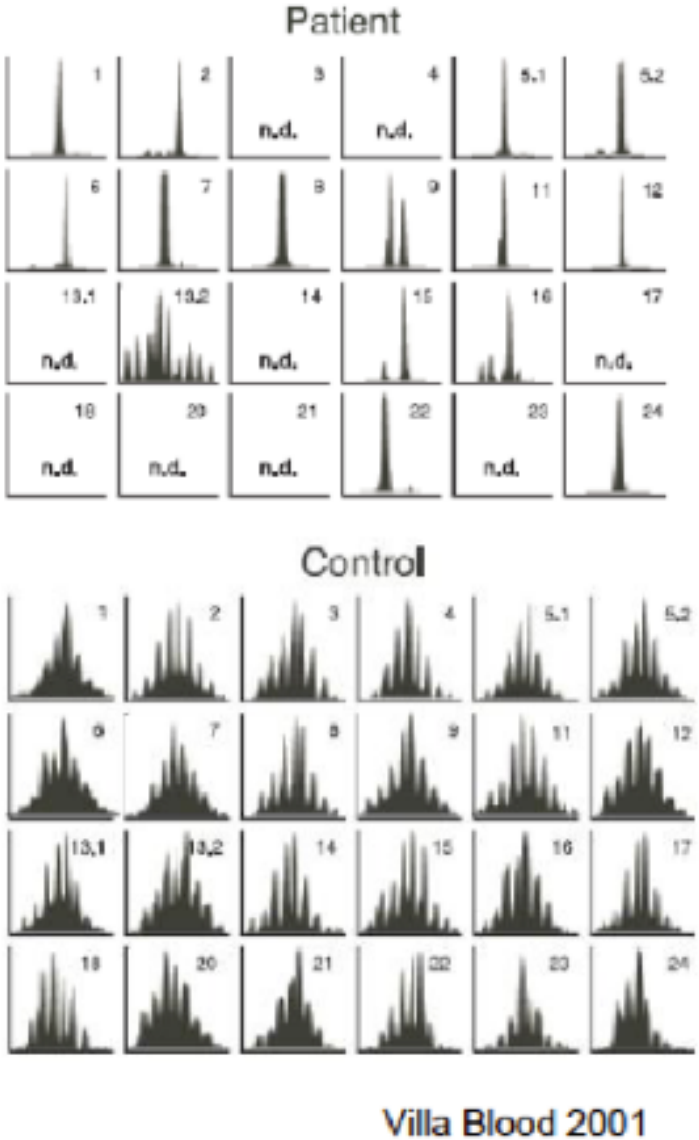
skin



gut

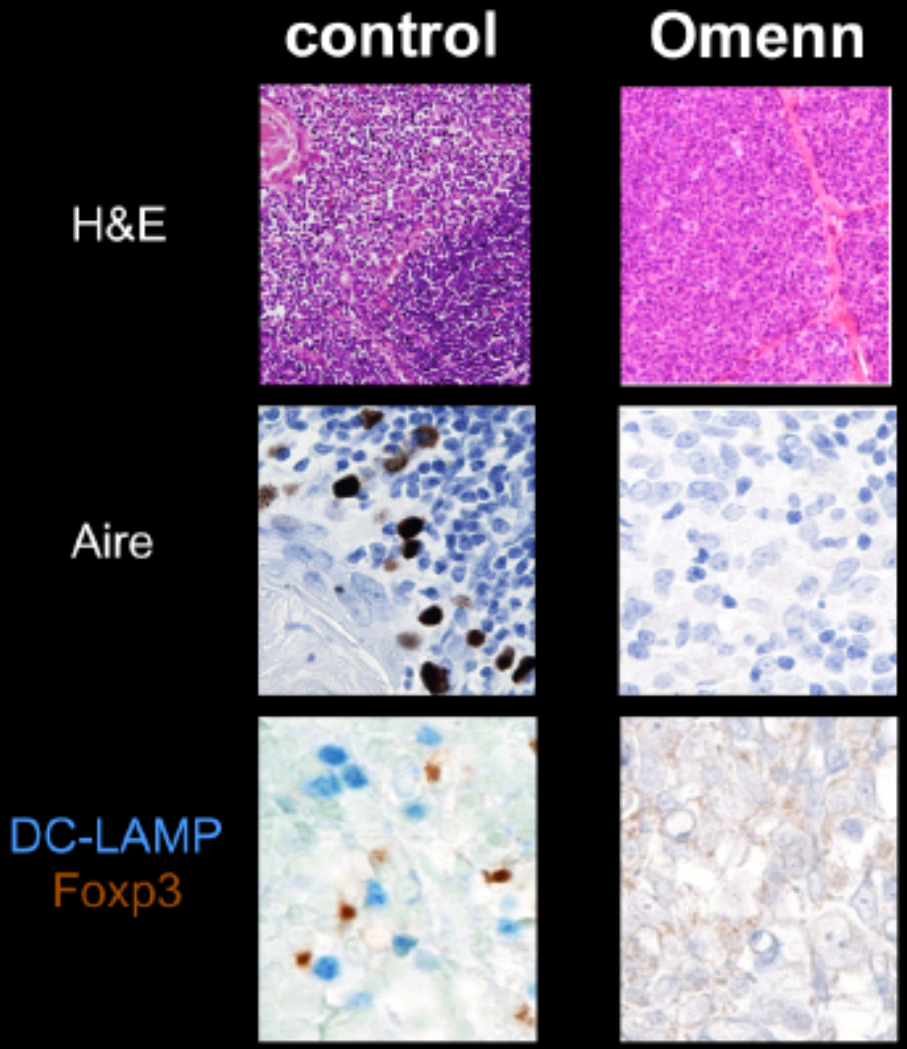


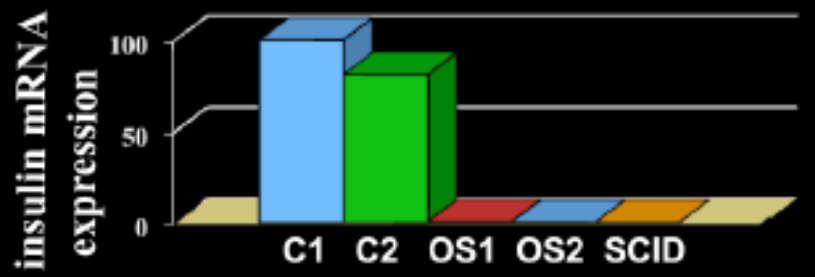
CD3

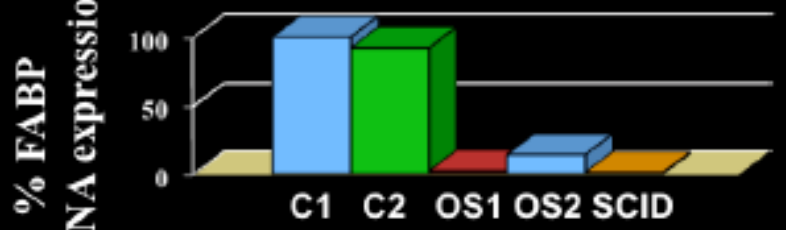


Villa Blood 2001

Abnormal thymic architecture and impairment of tolerance in patients with Omenn syndrome

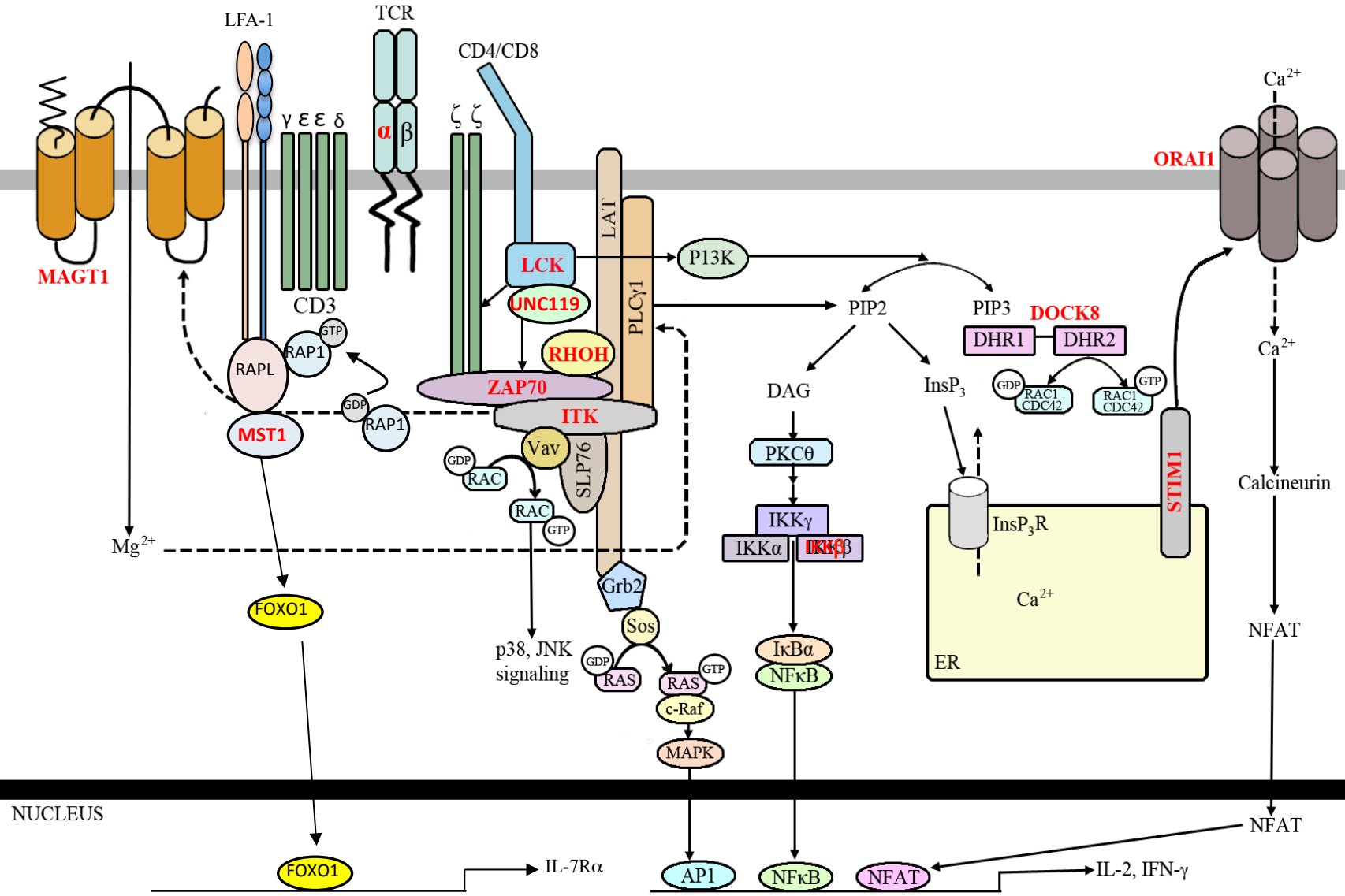






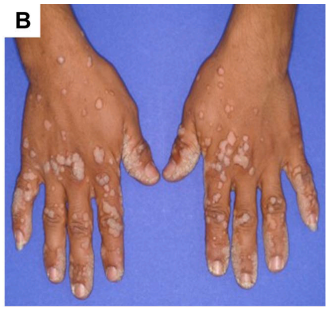
(Cavadini et al., J Clin Invest 2005)
(Poliani et al., Blood 2009)

Combined immunodeficiencies with dysfunctional T lymphocytes: molecular bases



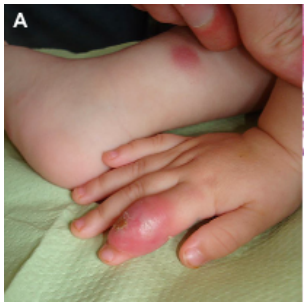
Combined immunodeficiencies with dysfunctional T lymphocytes: overlapping phenotype

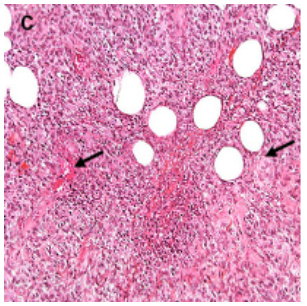
Clinical features



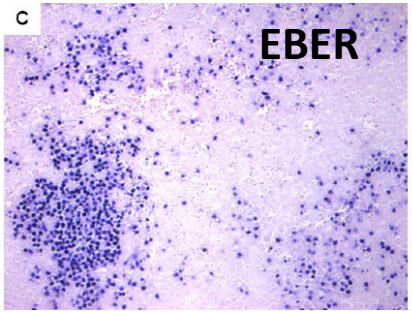
- Recurrent infections
  chronic viral infections (HPV, EBV, VZV)

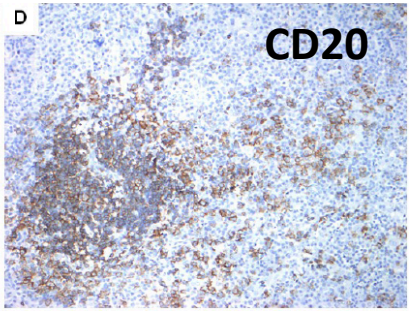
- Immune dysregulation
  granuloma, vasculitis, skin nodules
  autoimmune cytopenias





- Increased occurrence of EBV-related lymphoma

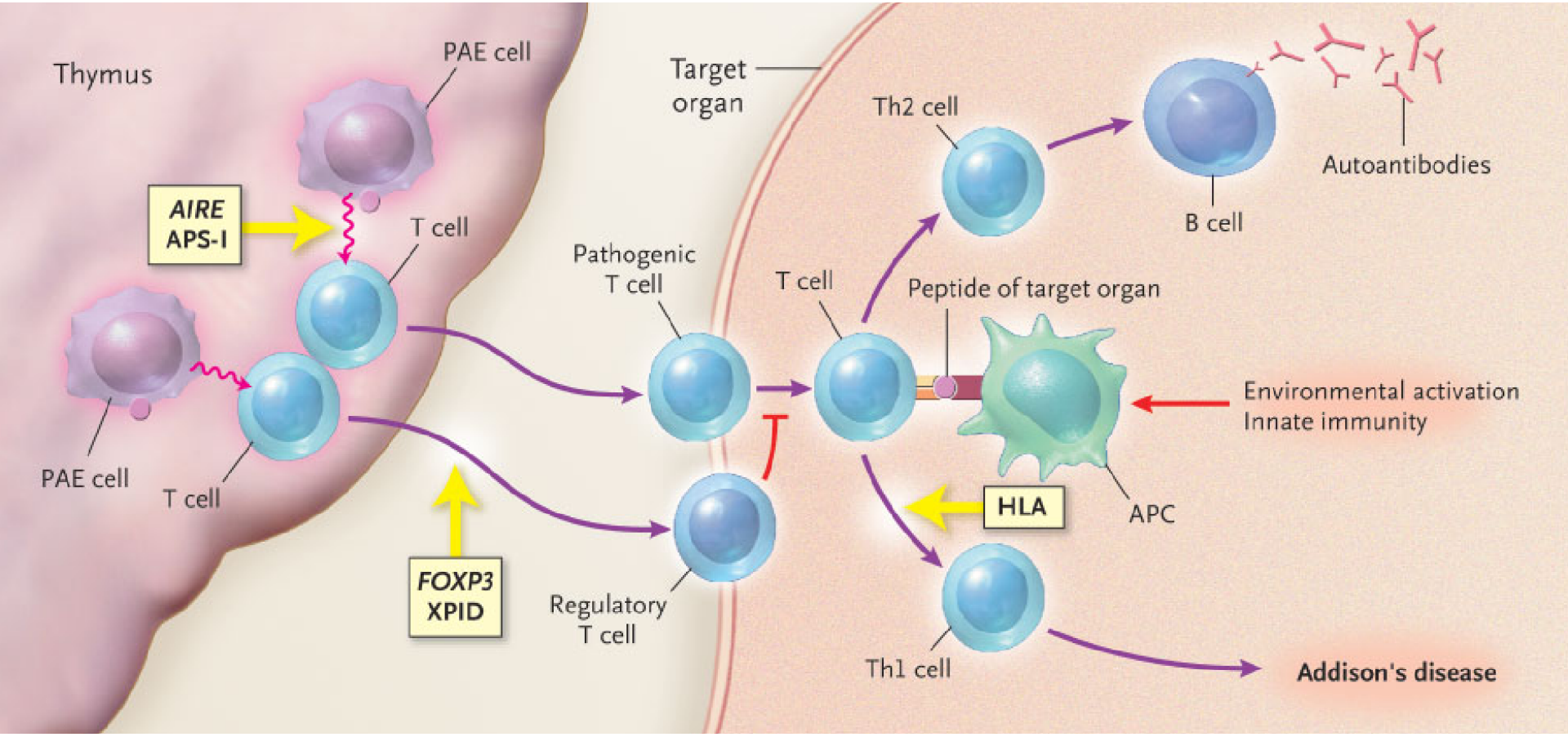




Dysfunctional T cell defects:
When immunodeficiency and autoimmunity go hand-in-hand

Reduced TCR signaling

- impaired thymopoiesis/survival
- reduced effector T cell function
- defective Treg function
- defective negative selection of self-reactive T cells
- impaired activation-induced cell death

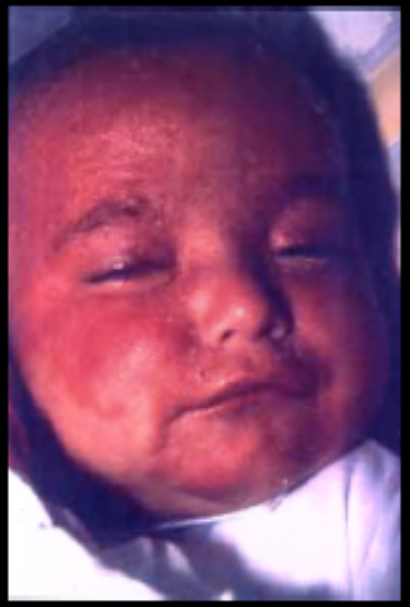

Thymus
PAE cell
AIRE
APS-I
T cell
PAE cell
T cell
FOXP3
XPID
Target
organ
Pathogenic
T cell
Regulatory
T cell
T cell
Th2 cell
B cell
Autoantibodies
Peptide of target organ
Environmental activation
Innate immunity
HLA
APC
Th1 cell
Addison's disease

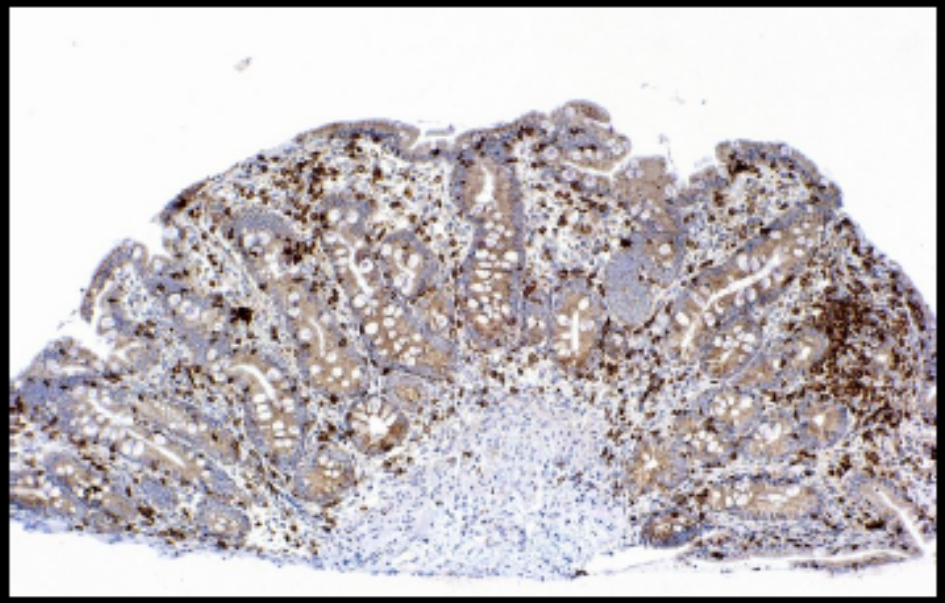
I Immune deficiency/dysregulation

P Polyendocrinopathy

E Enteropathy

X X-linked inheritance





IPEX: clinical and laboratory features

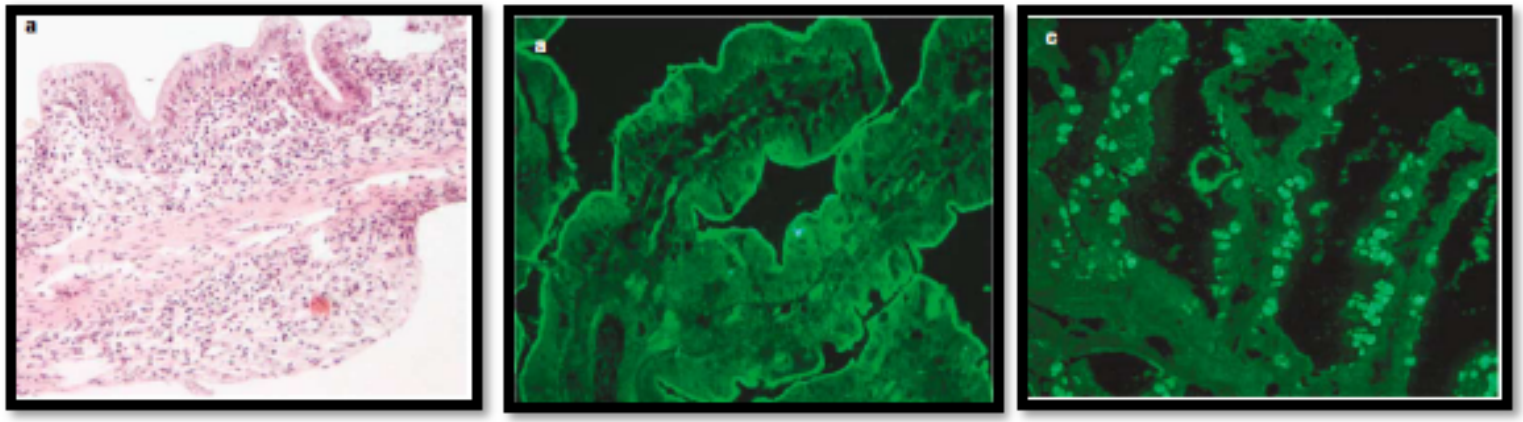
• enteropathy (diarrhea, villous atrophy)	100%
• skin disease	100%
• early-onset IDDM or hypothyroidism	80-90%
• glomerulonephritis	60%
• autoimmune cytopenia	50%
• growth failure	90%
• developmental delay/neurological problems	40%
• severe infections	50%

- elevated IgE
- lymphocytic infiltrates

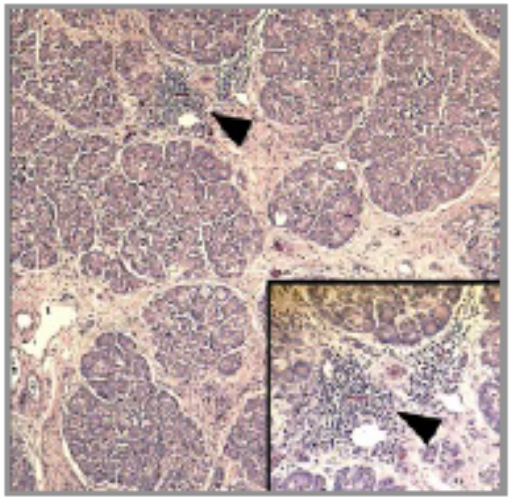
- in typical cases, death by 2 years, unless treated by HCT

Immune dysregulation of IPEX

gut

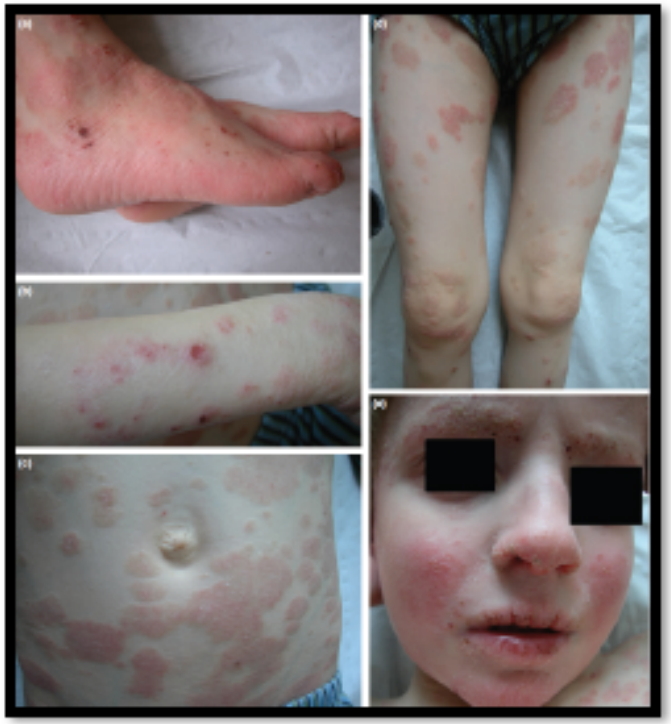


pancreas

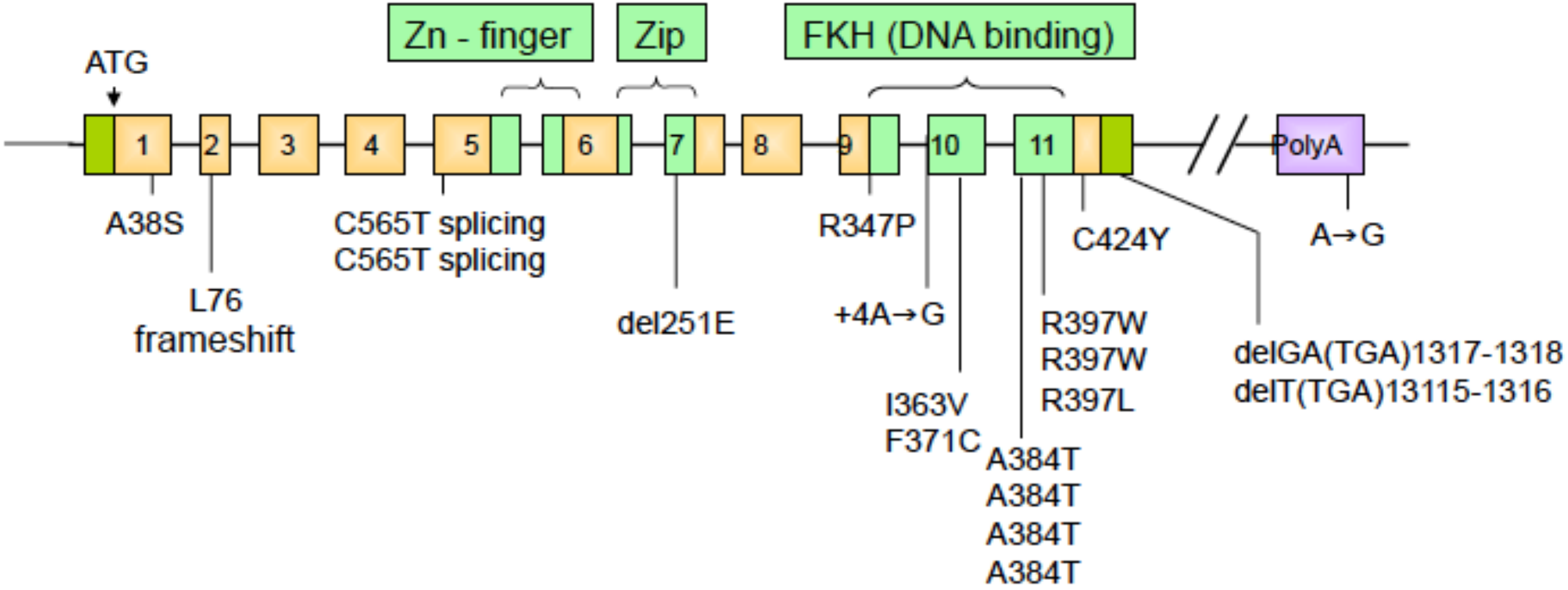


(Torgerson and Ochs. JACI (2007) 120: 774)

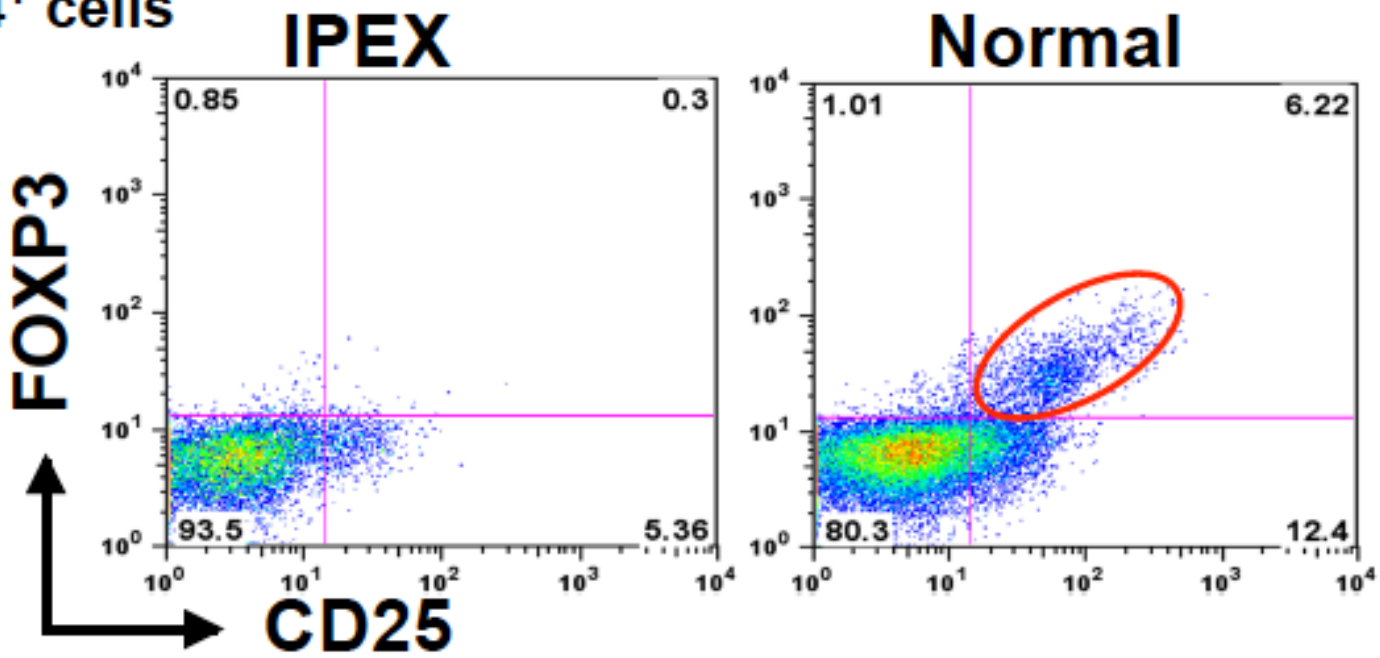
skin



(Halabi-Tawii et al. Br J Derm. (2008) 160: 645)

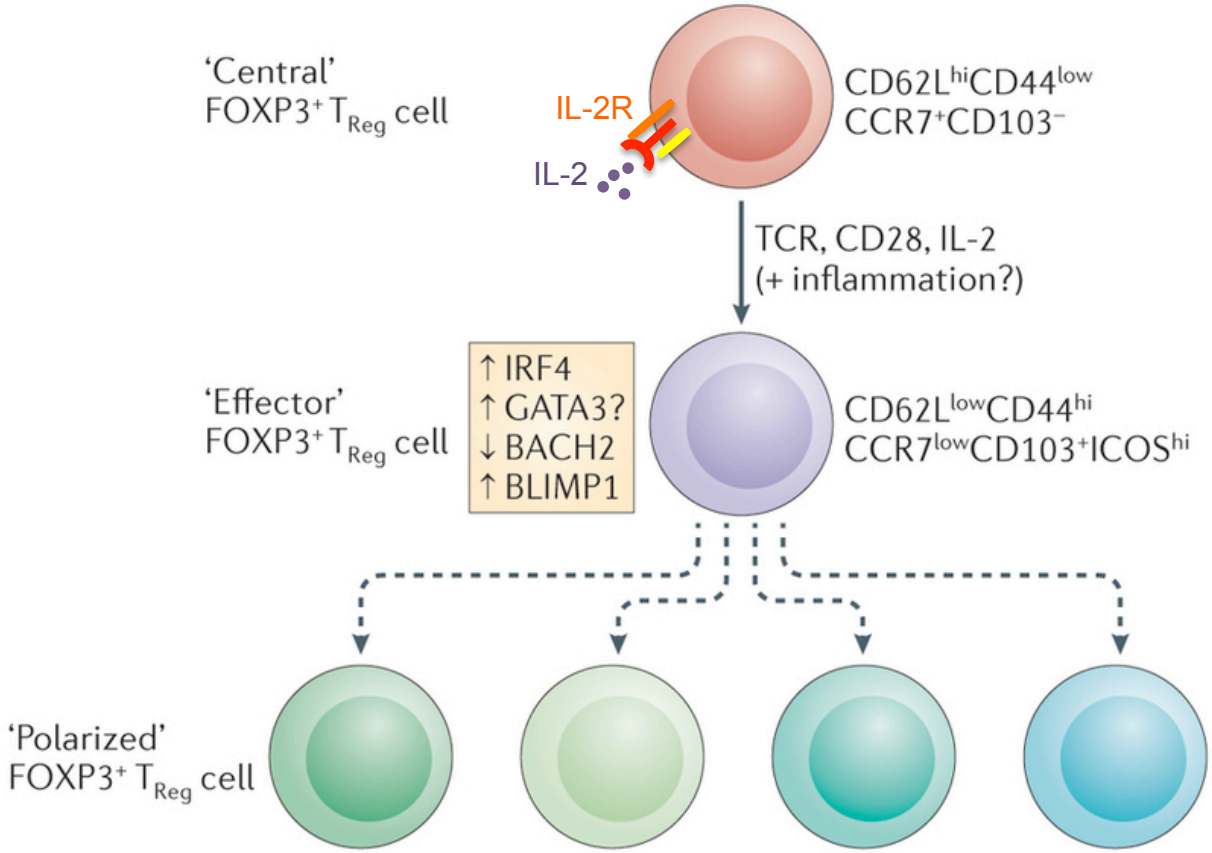


gated on CD4⁺ cells

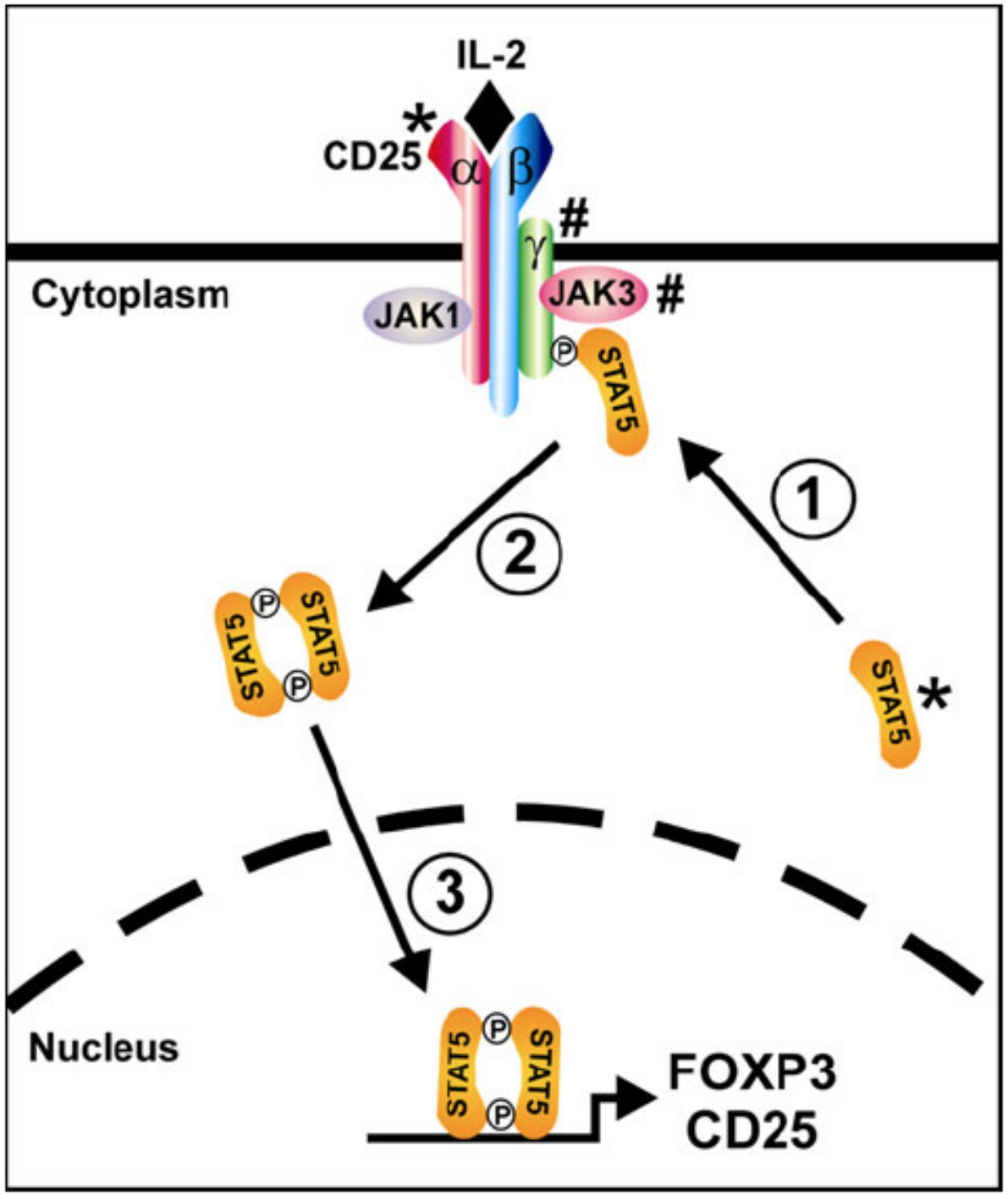


IPEX: Therapeutic Approach

- Immunosuppression
  - Corticosteroids
  - Tacrolimus
  - Sirolimus
  - Cyclosporin
  - T cell depletion
  - B cell depletion
- Immune reconstitution with HSCT
  - Best done prior to onset of endocrinopathy
- Health maintenance
  - Nutrition
  - Vaccine avoidance



Regulates	Skin and lung inflammation	Gut homeostasis	Germinal centres	Adipose metabolism
Transcription factors	FOXP3 T-bet	FOXP3 STAT3	FOXP3 BCL-6	FOXP3 PPARγ
Chemokine receptors	CXCR3 CCR4	CCR6	CXCR5	?
Homeostatic mediators	CD40L IFNγ IL-27 IL-7	SCFA IL-10 IL-6 IL-1	?	Lipids LCFA



IL2RA deficiency

Enteropathy
Recurrent/chronic viral inf.
Hematomegaly
Lymphadenopathy
Eczema
Candidiasis
Normal IgE
AR inheritance

STAT5B deficiency

Markedly short stature
Chronic lung disease
Eczema
Diarrhea
Autoimmune hepatitis
Autoimmune hypothyroidism
Recurrent viral infections
Normal GH, very low IGF-1
AR inheritance

Dominant gain-of-function *STAT1* mutations in *FOXP3* wild-type immune dysregulation–polyendocrinopathy–enteropathy–X-linked–like syndrome

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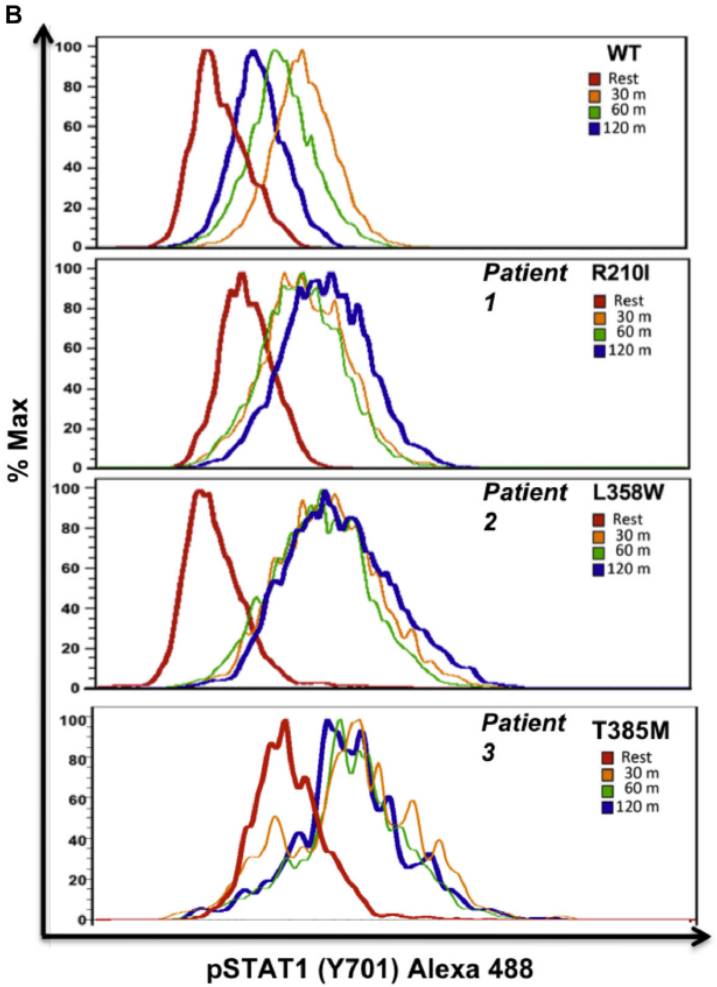
+ IFN-γ



- Chronic mucocutaneous candidiasis
- Severe and recurrent viral infections
- Bacterial infections
- Histoplasmosis
- Enteropathy
- Growth failure
- Autoimmunity (T1DM, Evans, hypothyroid)
- Aneurysms

- Progressive lymphopenia
- Loss of memory B cells
- Progressive hypogammaglobulinemia
- Normal Treg number and function

STAT1 GOF -> prolonged and enhanced response to IFN-α and IFN-γ

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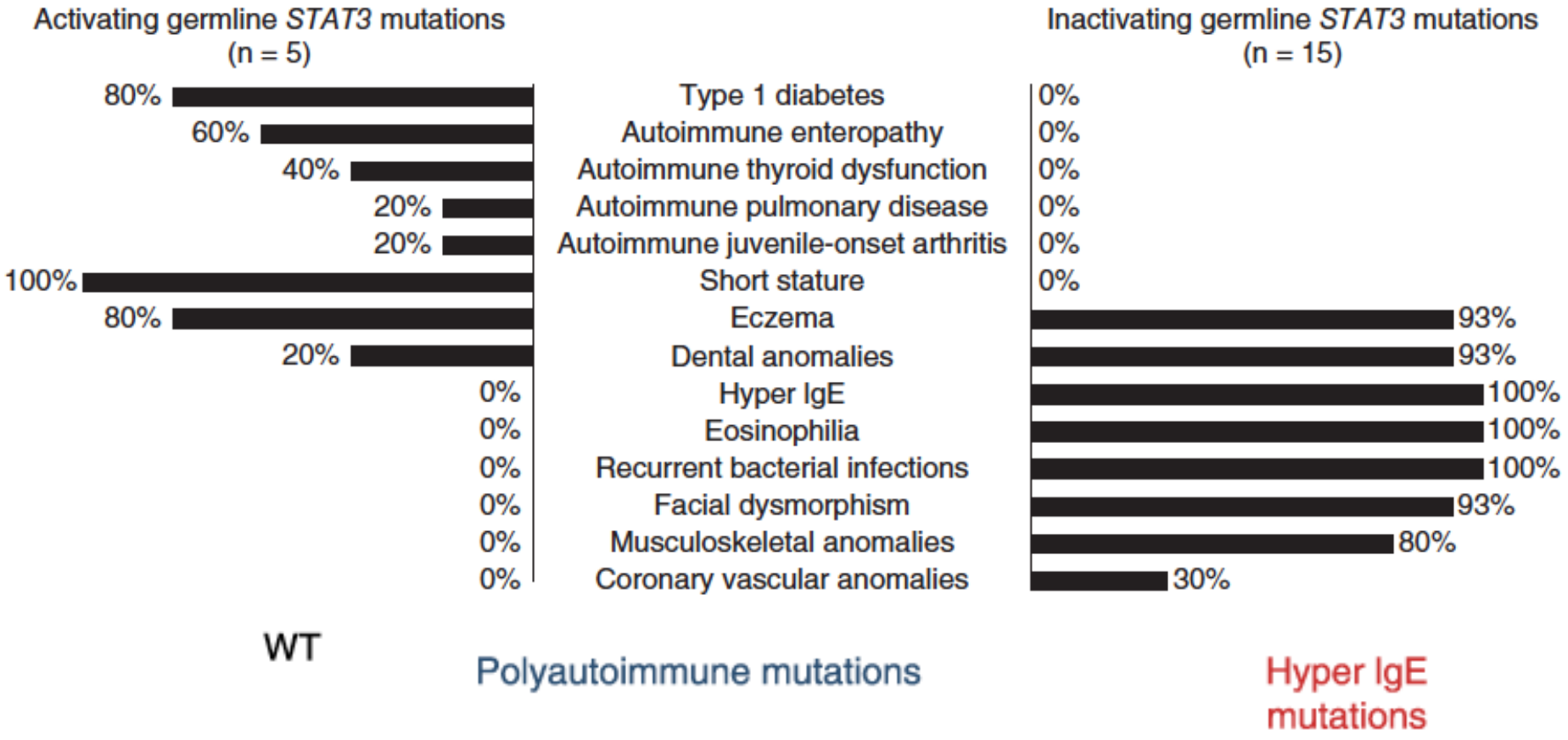
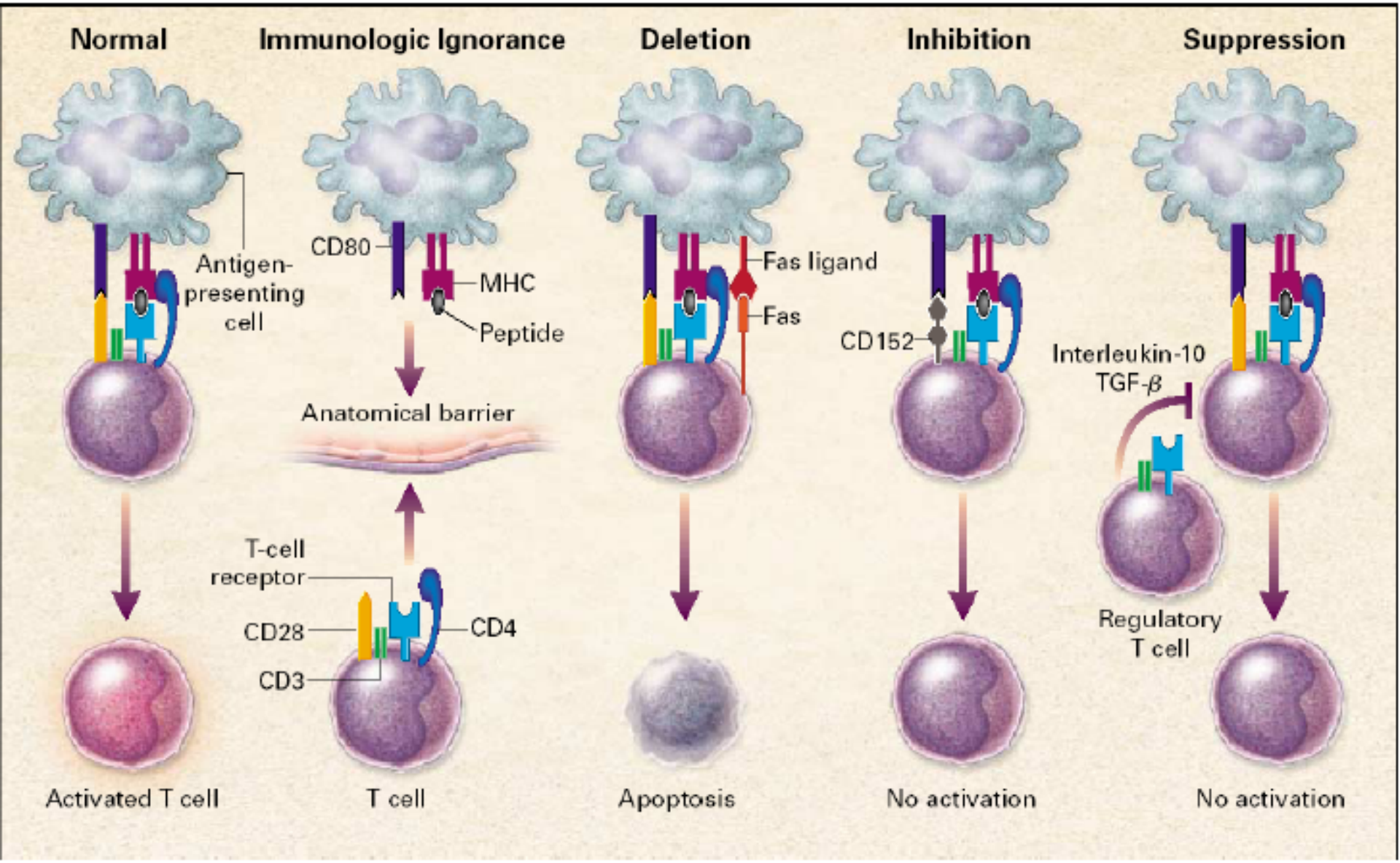
Activating germline mutations in *STAT3* cause early-onset multi-organ autoimmune disease

Sarah E Flanagan[1,16], Emma Haapaniemi[2,3,16], Mark A Russell[1,16], et al.

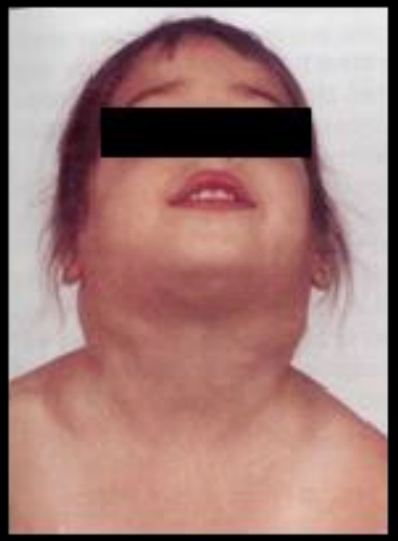



Normal
Immunologic Ignorance
Deletion
Inhibition
Suppression
Antigen-presenting cell
CD80
MHC
Peptide
Anatomical barrier
T-cell receptor
CD28
CD3
CD4
Fas ligand
Fas
CD152
Interleukin-10
TGF-β
Regulatory T cell
Activated T cell
T cell
Apoptosis
No activation
No activation

Autoimmune LymphoProliferative Syndrome (ALPS)

Clinical features

non malignant chronic lymphoproliferation
autoimmune cytopenias
increased risk of lymphoma (10%)

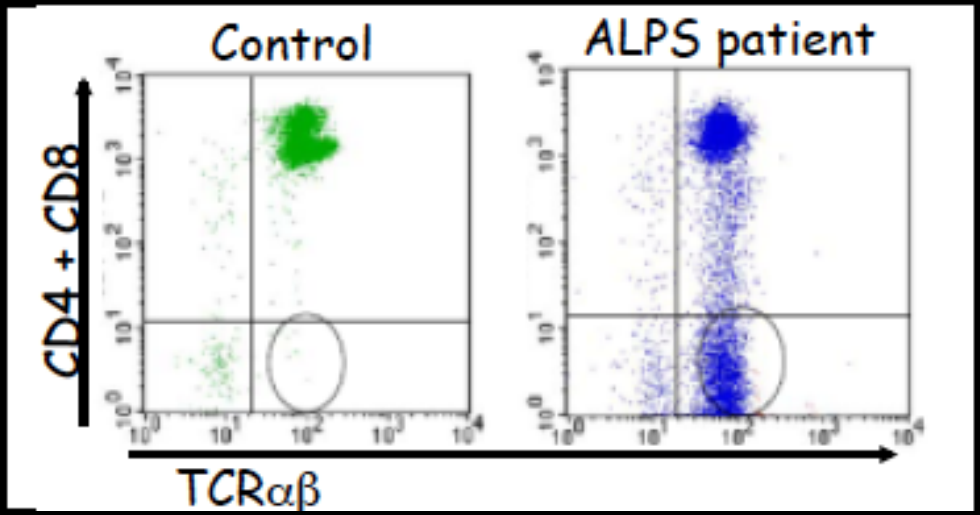


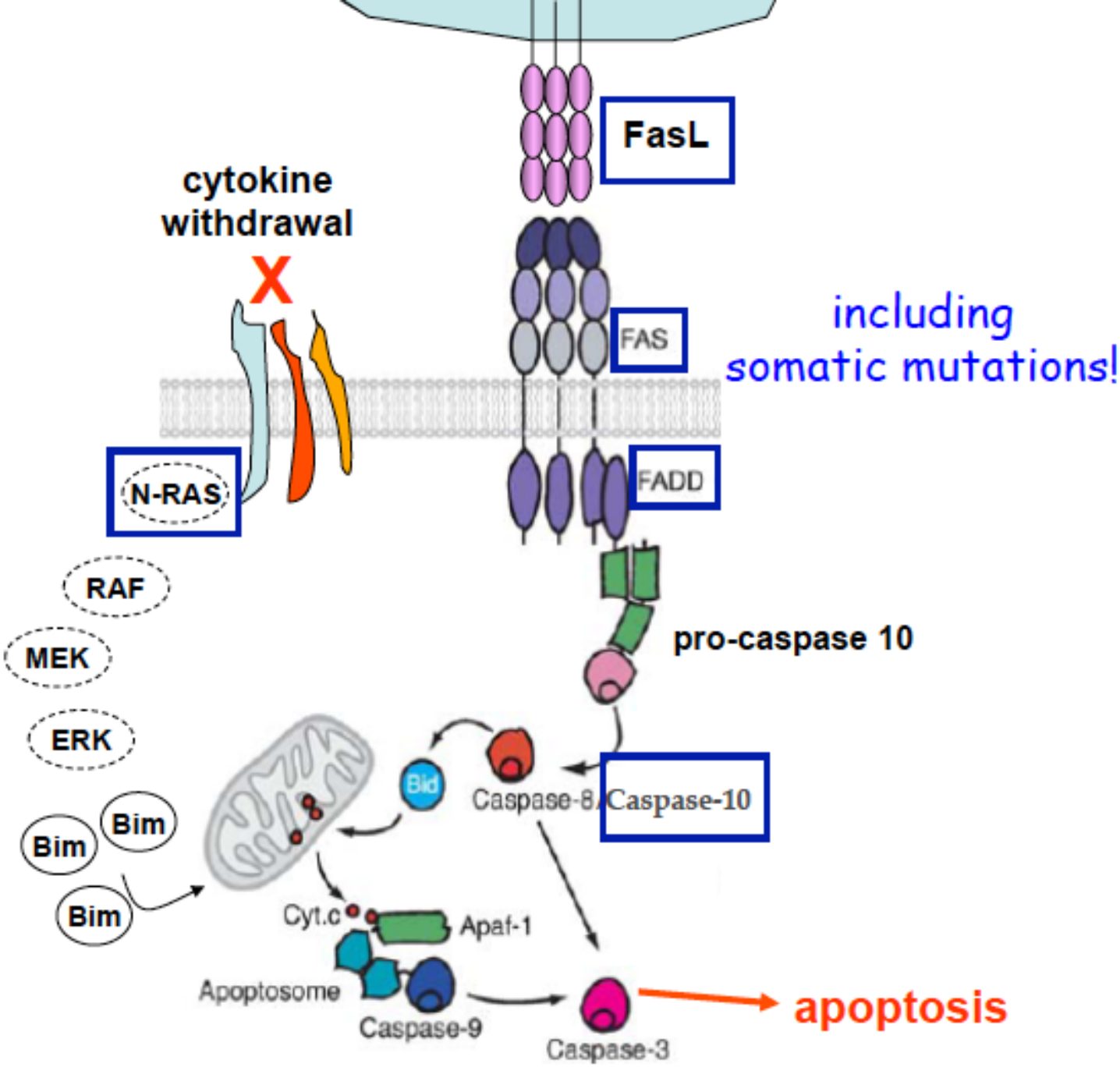
Laboratory features

↑ TCR$\alpha\beta^+$ $CD4^-$ $CD8^-$ (DN) T cells
impaired Fas-mediated apoptosis (most cases)
↑ FasL, ↑ IL-10
↑ vit. B12

Genetics

AD or sporadic
AR (more rare)
somatic mutations



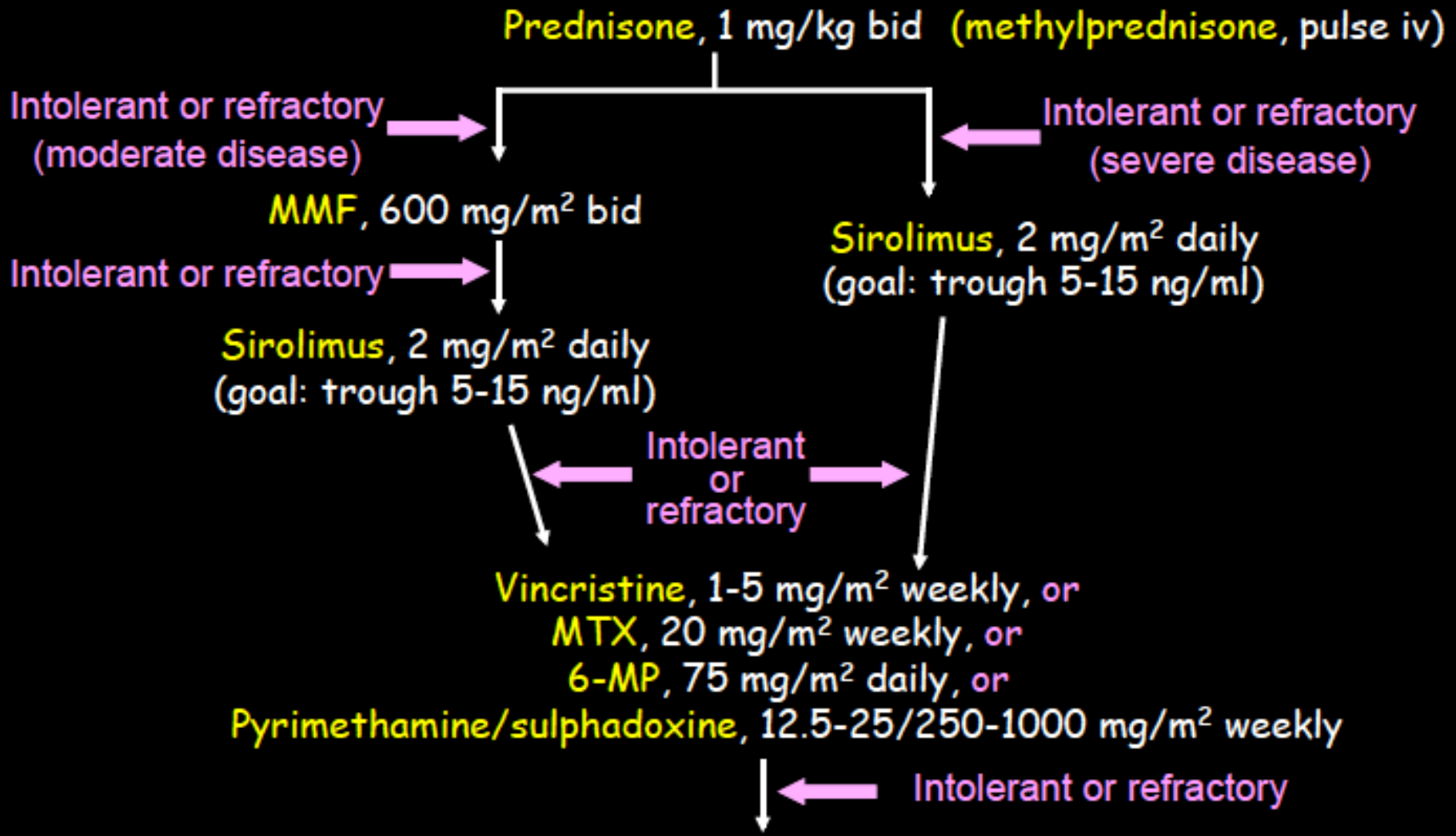

FasL
cytokine
withdrawal
X
FAS
including
somatic mutations!
N-RAS
FADD
RAF
pro-caspase 10
MEK
ERK
Bid
Caspase-8
Caspase-10
Bim
Bim
Bim
Cyt.c
Apaf-1
Apoptosome
Caspase-9
Caspase-3
apoptosis

Autoimmune cytopenias in ALPS

	AIHA (%)	ITP (%)	neutropenia (%)
Sneller et al., 1997 (n=9)	55	33	33
Infante et al., 1998 (n=11)	27	18	9
Carter et al., 2000 (n=11)	64	36	9
Stroncek et al., 2001 (n=34)	29	26	21
Kwon et al., 2003 (n=26)	38	31	27
Rieux-Laucat et al., 2003 (n=56)	39	34	18
Campagnoli et al., 2006 (n=8)	25	75	50
Rao et al., 2006 (n=79)	29	23	19

- autoimmune cytopenias may mark the onset of the disease
- multiple autoimmune cytopenias may be observed in the same pt.
- autoantibodies to RBCs, neutrophils and platelets in >75% of pts.

Management of autoimmune cytopenias in ALPS



(modified from Teachey et al, BJH 2009)

Common Variable Immunodeficiency (CVID)

Diagnostic criteria:

- four years of older
- IgG <4.5 g/l (adults) or <2.5th centile, usually with IgA (or IgM) < lower limit of normal for age
- lack of antibody response to protein antigens
- exclusion of all other known causes of failure of antibody production (IUIS PID classification)

Prevalence:

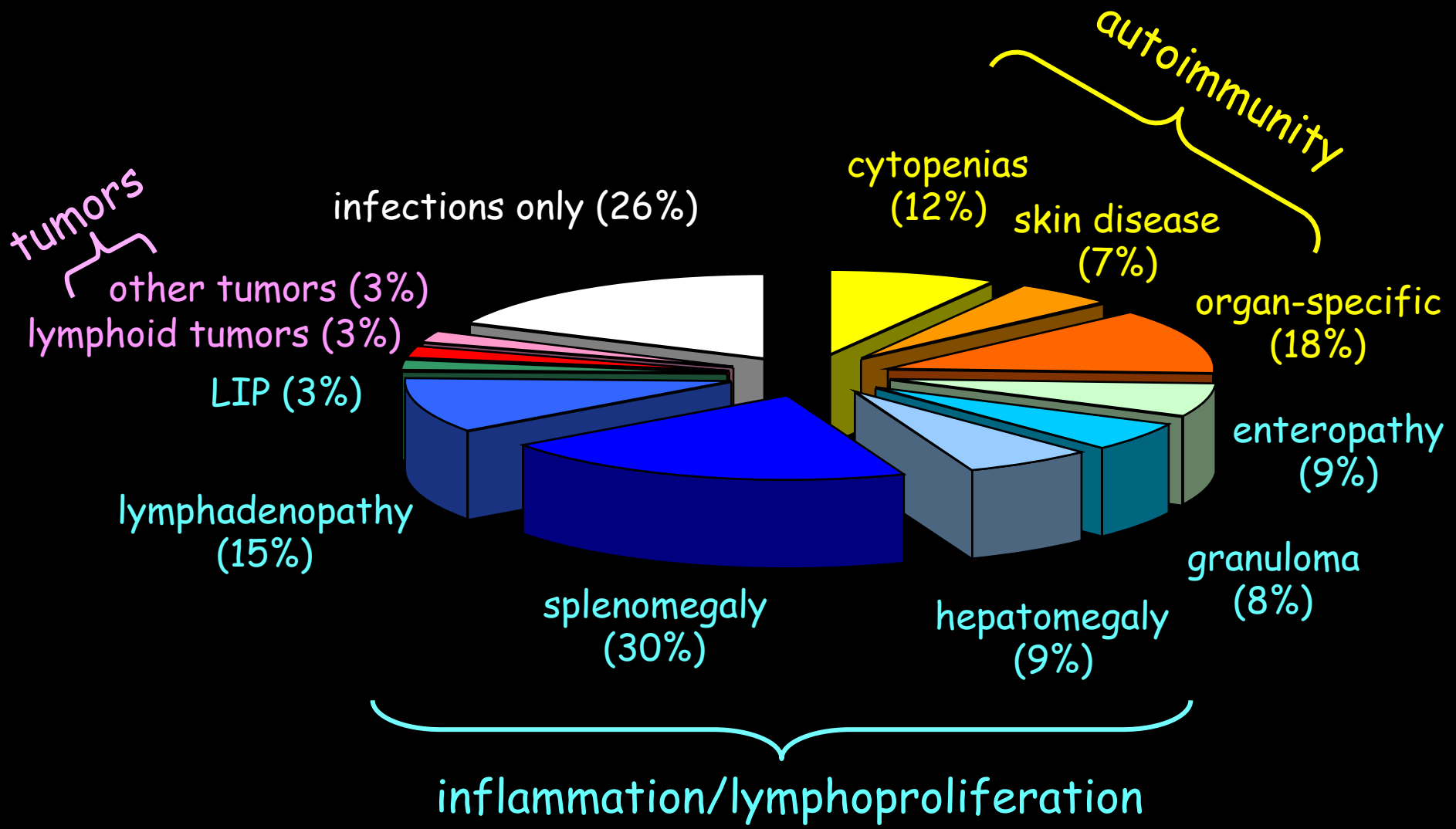
- 1/30,000 -1/160,000

Clinical features:

- recurrent infections (URTI, lungs, GI, UTI)
- autoimmune/inflammatory/lymphoproliferative
- lymphoid malignancies (2-8% develop NHL)

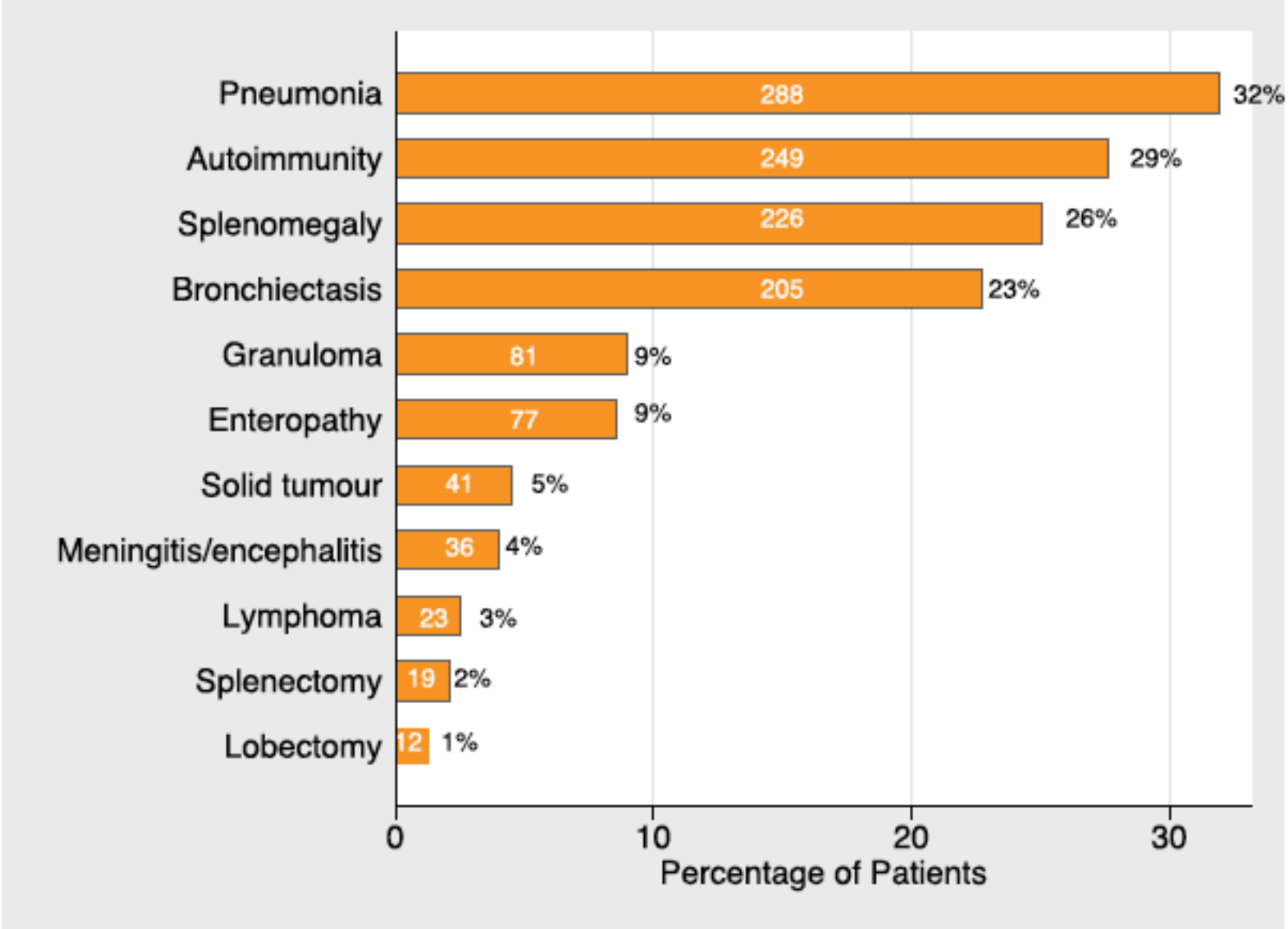
(Chapel and Cunningham-Rundles, BJH 2009)

Clinical phenotype in 334 patients with CVIDs



(Chapel et al., BLOOD 2008)

Clinical picture and treatment of 2212 patients with common variable immunodeficiency



(Gathmann et al., JACI 2014)

Autoimmune cytopenias in CVIDs

	AIHA (%)	ITP (%)	neutropenia (%)
Cunningham-Rundles et al., 1999 (n=248)	4.8	6.0	0.8
Michel et al., 2004 (n=105)	n.d.	20.0	n.d.
Wang et al., 2005 (n=326)	6.1	7.9	n.d.
Quinti et al., 2007 (n=224)	2.7	5.6	2.7
Wehr et al., 2007 (n=213)	5.1	10.2	n.d.
Sève et al., 2008 (n=252)	5.5	n.d.	n.d.
Chapel et al., 2008 (n=334)	3.9	6.9	0.9

Prevalence of autoimmune cytopenias in CVID:
100-1000x than in general population

Treatment of autoimmune cytopenias in CVIDs

- similar as for immune competent individuals. However:

- immunosuppression should be used with caution (shorter duration, avoid high dosage) to prevent opportunistic and/or severe infections

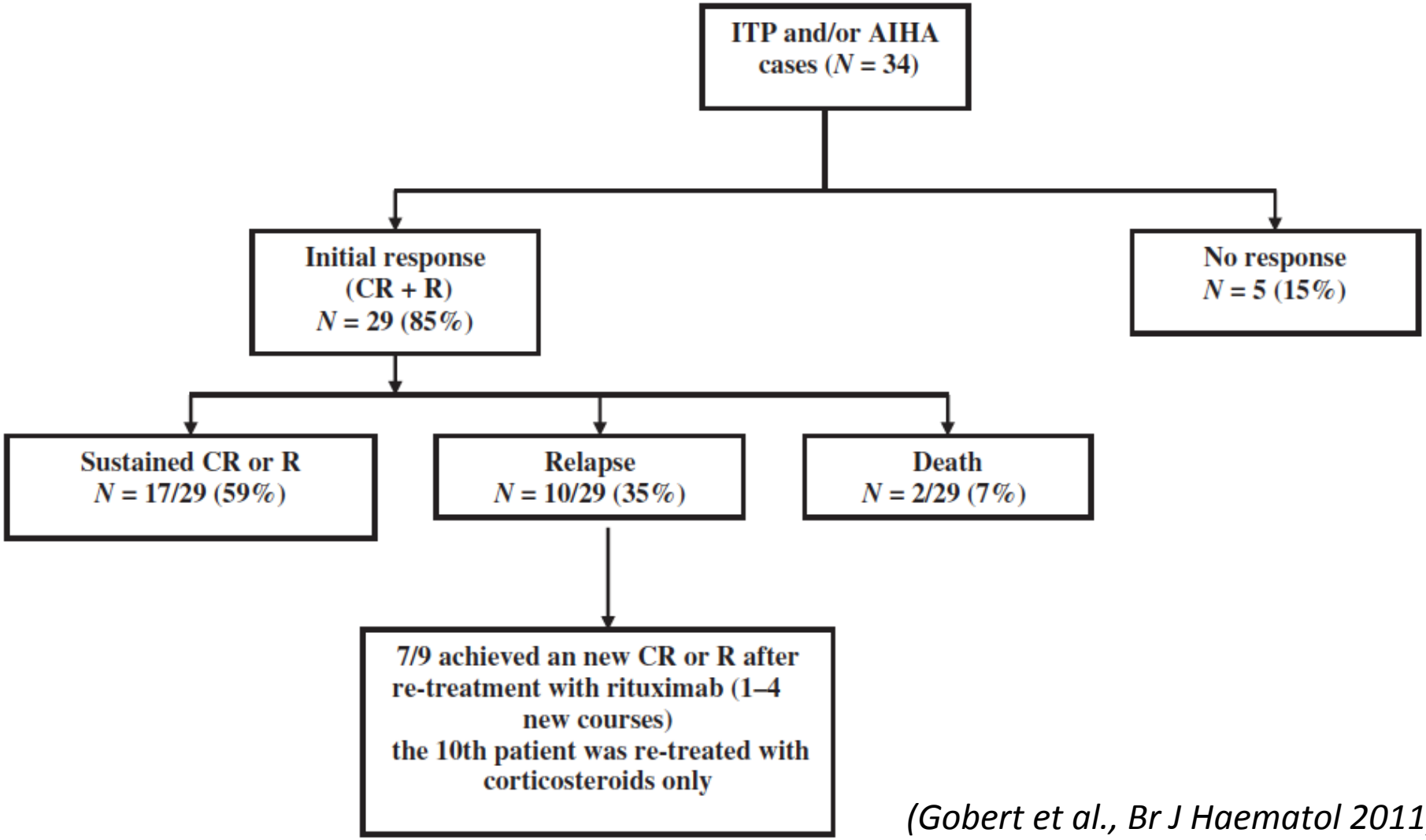
- high-dose IVIG may be beneficial. Among CVID pts with cytopenia,
  54% pts had ITP/AIHA before dx of CVID
  32% pts developed ITP/AIHA concurrent with dx of CVID
  14% pts developed ITP/AIHA after dx and while on IVIG
  (Wang et al., 2005)

- success with rituximab reported in CVIDs with ITP
  (Carbone et al., 2005; Gobert et al., 2011)

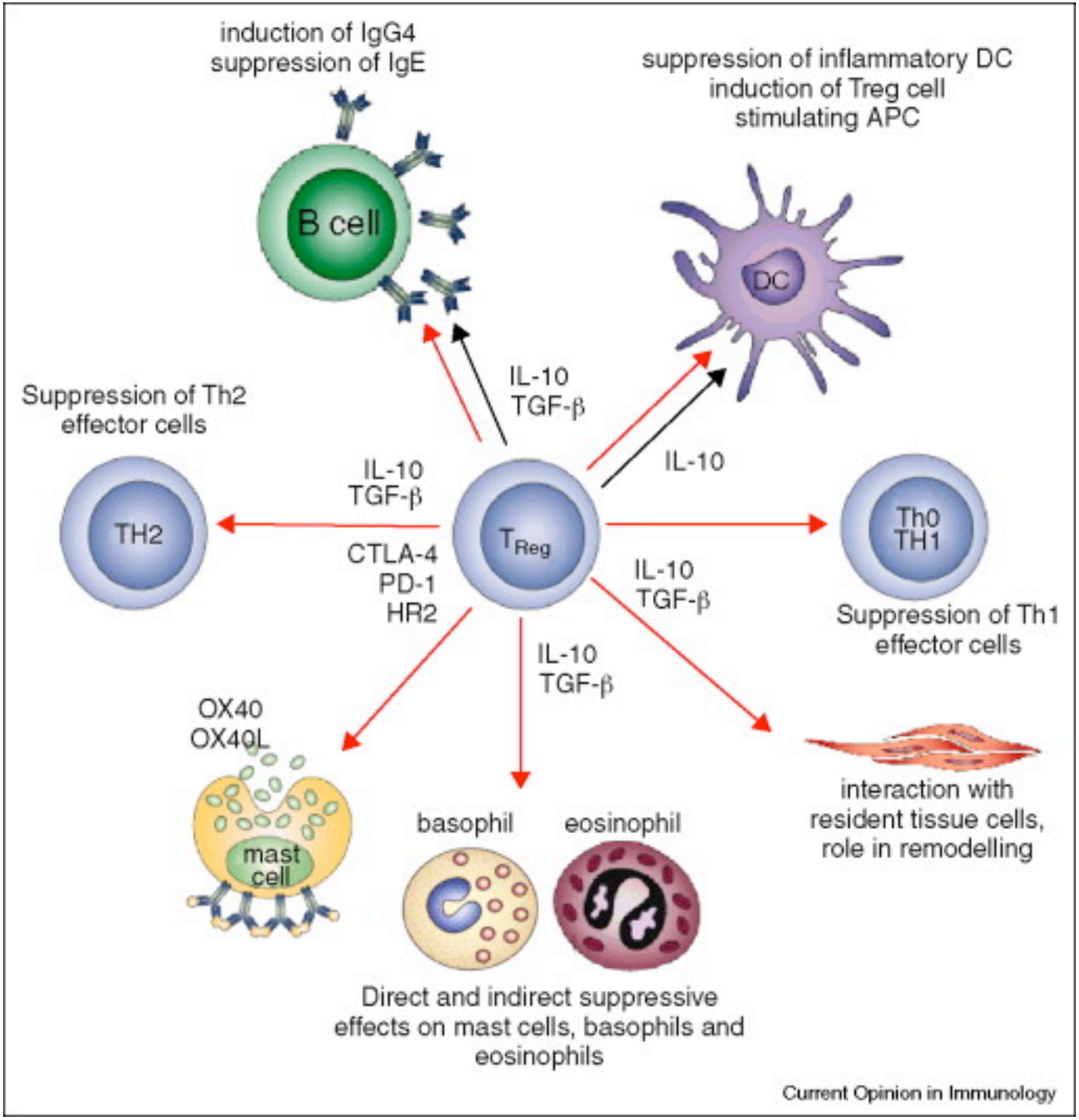
- risks/benefits of splenectomy in refractory cases remain unclear

bjh research paper

Efficacy and safety of rituximab in common variable immunodeficiency-associated immune cytopenias: a retrospective multicentre study on 33 patients



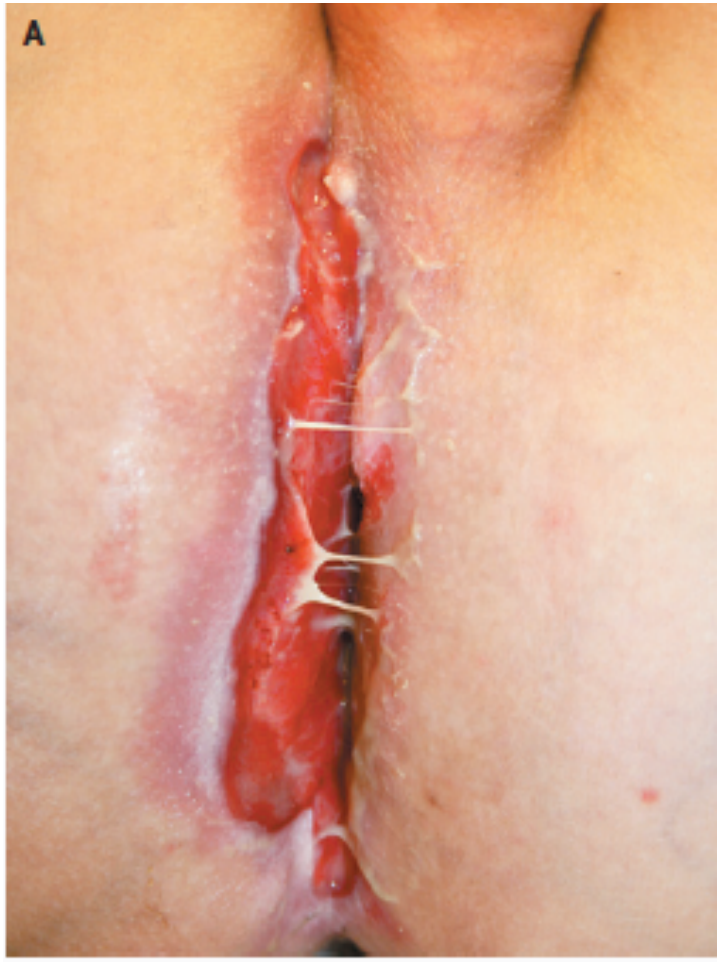
(Gobert et al., Br J Haematol 2011)

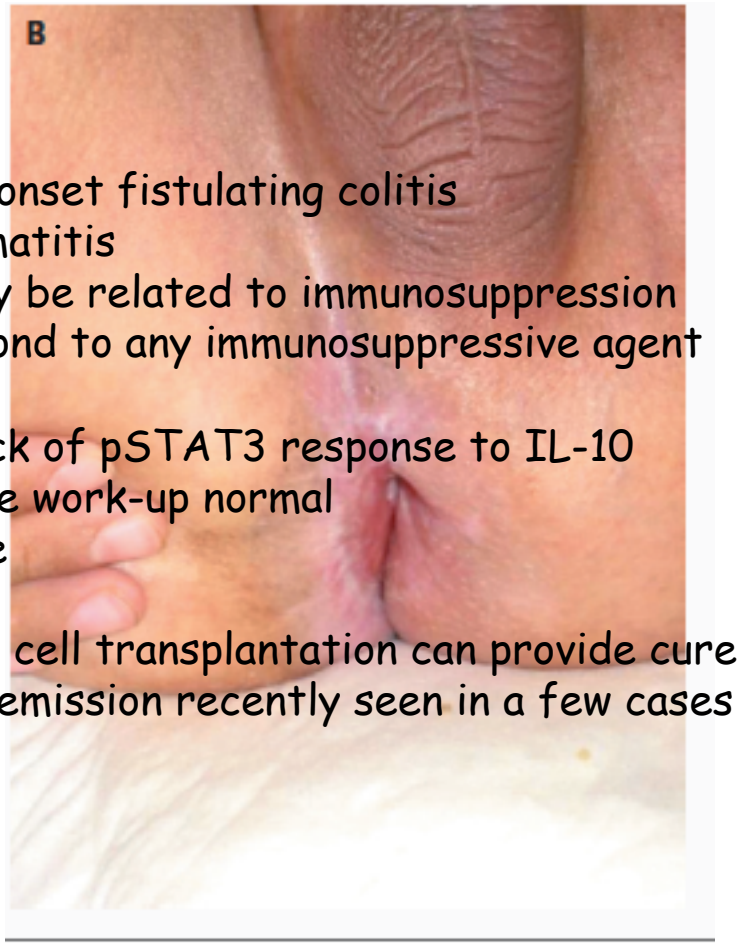

induction of IgG4
suppression of IgE
B cell
suppression of inflammatory DC
induction of Treg cell
stimulating APC
DC
IL-10
TGF-β
Suppression of Th2
effector cells
IL-10
TGF-β
IL-10
TH2
TReg
Th0
TH1
CTLA-4
PD-1
HR2
IL-10
TGF-β
Suppression of Th1
effector cells
IL-10
TGF-β
OX40
OX40L
mast
cell
basophil
eosinophil
interaction with
resident tissue cells,
role in remodelling
Direct and indirect suppressive
effects on mast cells, basophils and
eosinophils
Current Opinion in Immunology

N ENGL J MED 361;21 NEJM.ORG NOVEMBER 19, 2009

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.,





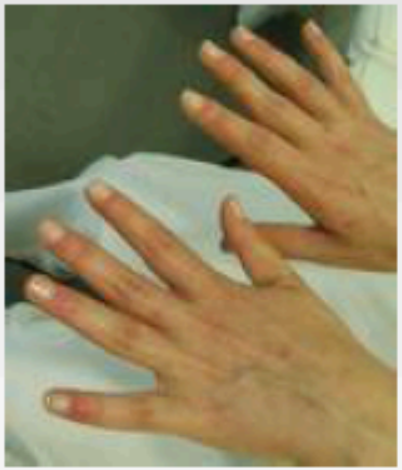
- Severe, early-onset fistulating colitis
- Follicular dermatitis
- Infections may be related to immunosuppression
- Does not respond to any immunosuppressive agent

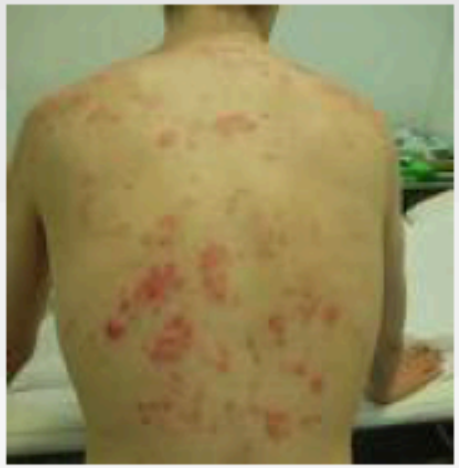
- IL10R def: Lack of pSTAT3 response to IL-10
- Rest of immune work-up normal
- AR inheritance

- Hematopoietic cell transplantation can provide cure
- Spontaneous remission recently seen in a few cases (?)

A- Inherited Classical Pathway Deficiencies

Complement Proteins	Defect	Diseases Associated
C1q, C1r, C1s, C4, C2	Impaired solubilization of immune complexes; poor immunoregulation	Autoimmune disease (SLE), may be severe; infections with encapsulated organisms





Immune modulators for autoimmune cytopenias

Corticosteroids – trafficking, cytokines, lymph. deplet.

Pros:

- most active for most patients
- fast acting
- ability to titrate dose to response
- lots of data available

Cons:

- short-term toxicities: mild (hypertension, hyperglycemia, weight gain, irritability)
- long-term: potentially severe (avascular necrosis, cataracts, growth delay, demineralization)

Infectious risk:

- single agent: low
- combination therapy: potentially high (consider TMP+SMX and antifungals)

(Teachey and Lambert, Pediatr Clin N Am, 2013)

Immune modulators for autoimmune cytopenias

IVIG – competition with pathogenic IgG for FcγR

Pros:

- active for most patients with ITP
- well tolerated
- fast-acting (48h)

Cons:

- short duration of activity
- patients with chronic ITP may need repeat Tx
- limited activity against AIHA or AIN
- aseptic meningitis, severe allergic reactions

Infectious risk:

- none (but hyperinflammatory responses in some patients with active infection)

(Teachey and Lambert, Pediatr Clin N Am, 2013)

Rituximab (anti-CD20 mAb) - B

Pros:

active in many cases of autoimmune cytopenias
does not require daily medications

Cons:

very long half-life (prolonged B lymphopenia!)

Infectious risk:

risk of viral reactivation
may require IVIG

Alemtuzumab (anti-CD52 mAb) – T, B, and NK

Pros:

active in many cases of autoimmune diseases

Cons:

long half-life (prolonged multilineage lymphopenia)

Infectious risk:

high! Viral and fungal. Prophylaxis!

(Teachey and Lambert, Pediatr Clin N Am, 2013)

ATG, ALG – T (other cells?)

Pros:

active in many autoimmune diseases

Cons:

limited data in childhood cytopenias

Infectious risk:

high! Long half life – Prophylaxis

infusional toxicities

6MP, Azathioprine, Thioguanine, Fludarabine – purines

Pros:

well tolerated, can be combined with others

Cons:

may take few months for response

TPMT polymorphisms -> increased toxicity (liver, BM)

Infectious risk:

low

(Teachey and Lambert, Pediatr Clin N Am, 2013)

Methotrexate– (folate, purines/pyrimidines) [T>B]

Pros:

active in many autoimmune rheum. diseases

can be combined with others

Cons:

myelosuppression; liver/CNS/renal toxicity

Infectious risk:

low when dosed for autoimmune diseases

MMF – purines [T, B, NK]

Pros:

well tolerated

Cons:

partial responses; diarrhea and neutropenia

Infectious risk:

low, but PML [FDA]; risk to fetuses

(Teachey and Lambert, Pediatr Clin N Am, 2013)

Tacrolimus, CsA– calcineurin inhibitors [T cell act.]

Pros:

well tolerated

Cons:

microangiopathic hemolytic anemia;

CsA-> renal toxicity, seizures (drug monitorng)

Infectious risk:

rather low

Sirolimus, Everolimus – mTOR inhibitor [B, T]

Pros:

spare Treg, well tolerated, very active in ALPS

not associated with risk of PML

Cons:

increased risk of MAH if combined with CsA/tacro

mucositis, hyperlipidemia

Infectious risk: low

(Teachey and Lambert, Pediatr Clin N Am, 2013)

Cyclophosphamide – (DNA alkylator) [T, Treg, B, NK]

Pros:

active in many autoimmune rheum. Diseases

Cons:

short-term toxicity: BM, GI, alopecia

long-term: MDS/AML, infertility in males

Infectious risk:

dose-dependent (high if high doses)

Vincristine/vinblastine – mitotic inhibitors [T, B, NK]

Pros:

large experience, good efficacy

Cons:

vincristine: neuropathy, constipation

vinblastine: toxicity on BM, GI, alopecia

Infectious risk:

low unless combined with others

(Teachey and Lambert, Pediatr Clin N Am, 2013)

Splenectomy – removes site of destruction and Ab prod.

Pros:

active especially in ITP

Cons:

high risk of OPSI (immunize!!!! AB prophylaxis)

portal hypertension, pulmonary arterial hypertension

Romiplostim, eltrombopag– TPO mimetics

Pros:

good efficacy in thrombocytopenic adults

Cons:

limited experience in children

discontinuation may cause rebound thrombocytopenia

BM fibrosis, venous thromboembolism

eltrombopag: liver toxicity

Infectious risk:

none

(Teachey and Lambert, Pediatr Clin N Am, 2013)

Plasmapheresis – removes (auto)Ab

Pros:

effect is rapid, good for IgG-mediated disease

Cons:

improvement is often short-lived

relapses are common

requires CVL in children -> risk of infections

limited efficacy against IgM-mediated disease

hypotension, hypoglycemia

removes also good antibodies and other drugs

(Teachey and Lambert, Pediatr Clin N Am, 2013)

Immunosuppressive agents used for childhood autoimmune cytopenias and association with progressive multifocal leukoencephalopathy (PML)

Drugs associated with PML	Drugs **not** associated with PML
Azathioprine	Everolimus
Cyclosporine	Methotrexate
Cyclophosphamide	Sirolimus
MMF	
Rituximab	
Tacrolimus	

(Teachey and Lambert, Pediatr Clin N Am, 2013)

What is new?

Bortezomib	proteasome inhibitor (targets plasma cells) systemic autoimmunity
Belimumab	anti-BAFF (prevents B cell activation) SLE
Tocilizumab	anti-IL-6R (blocks IL-6-mediated inflamm.) adult rheumatoid arthritis, systemic JA
Epratuzumab	anti-IL-22 (targets B cells) SLE
Abatacept	CTLA4-Fc (blocks second signal in T cells) rheumatoid arthritis