Autoimmune (and other) Cytopenias in PIDs

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Disclosures

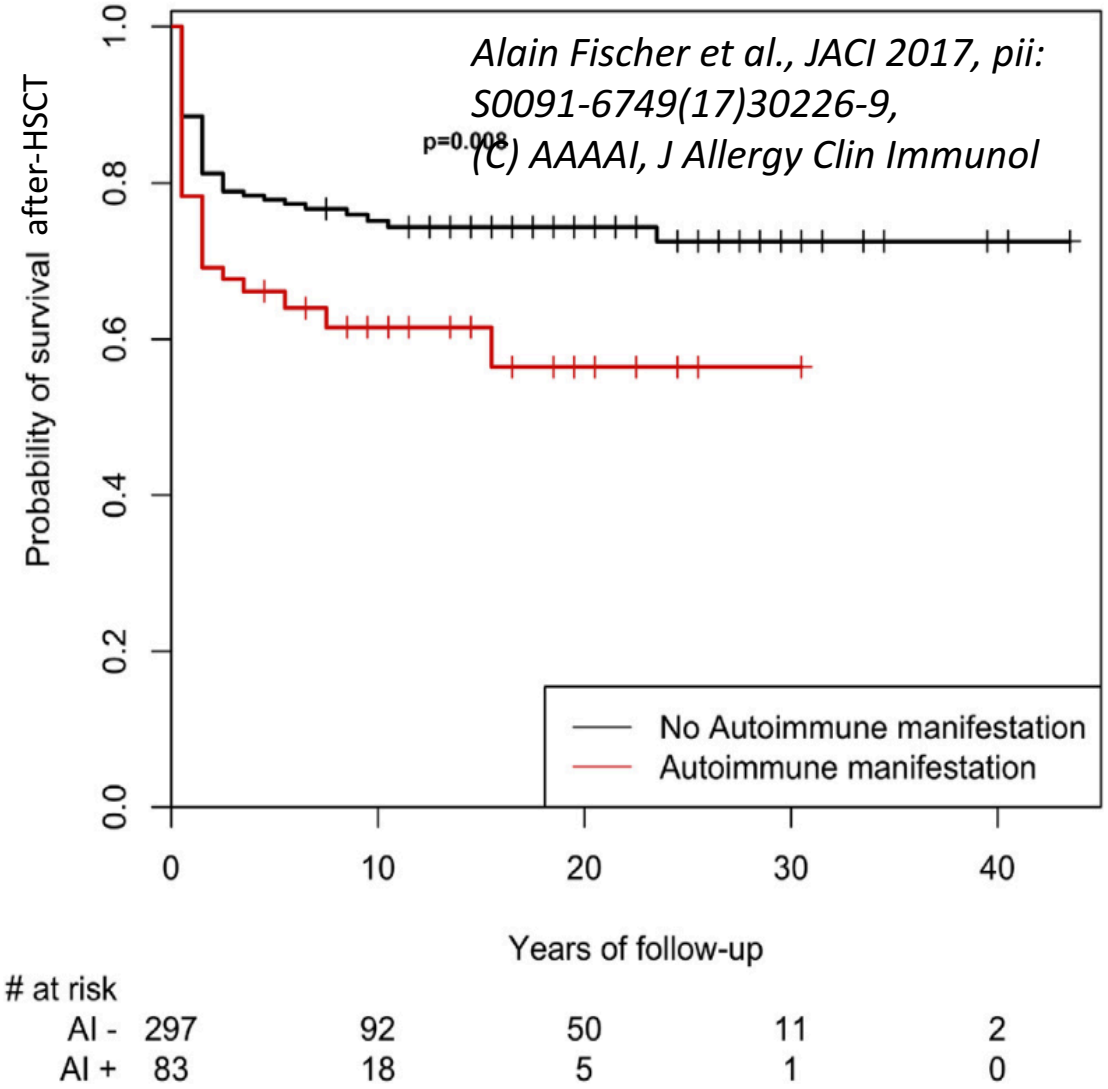
Consultancy fee (onetime) 2016: Baxalta [Ig, Hyaluronidase], Novartis [TRA]

Travel grants 2016: Jazz, Octapharma, Baxalta

Lecture honoraria 2016: CSL Behring

Cytopenias in primary immunodeficiency: notions and conundrums

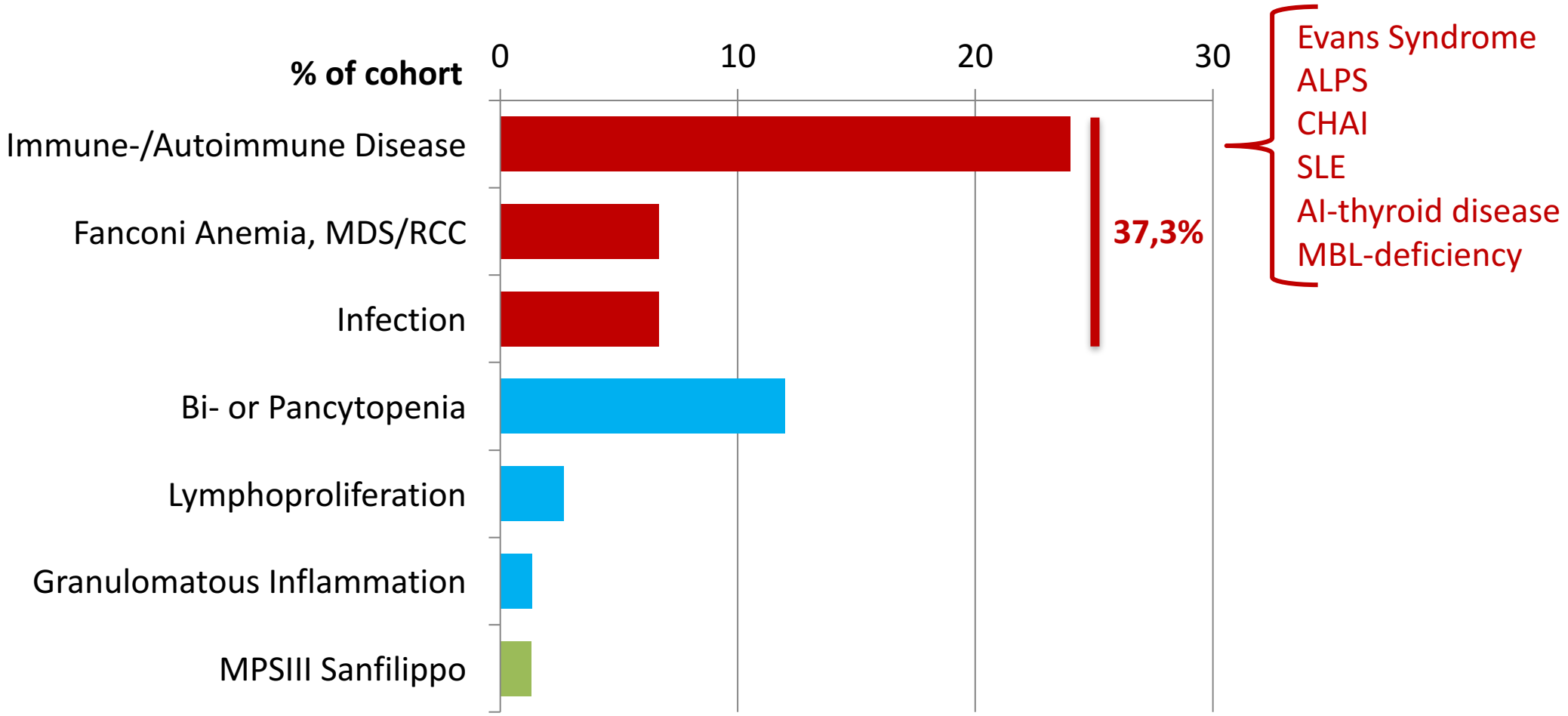
- French Cohort Study, 2183 PID patients (*Alain Fischer et al.*, JACI 2017):
  - 26% had autoimmunity or inflammation, occurs in all age groups
  - **relative risk to develop autoimmune cytopenia in PID is 120x, AIHA 830x**, ITP 60x
  - mostly B & T -PIDs
  - allergy is a risk factor, **outcome is worse**!
  - 15% of AI cytopenias in children are estimated to be based on a PID



- ➢ not all *cytopenias* are ALPS- or CVID-linked
- ➢ 85% are *not* linked to a known PID

Immune cytopenia from the hematologist‘s view: pediatric cITP Austria (n=81)

→ many additional or other diagnoses in children with chronic ITP

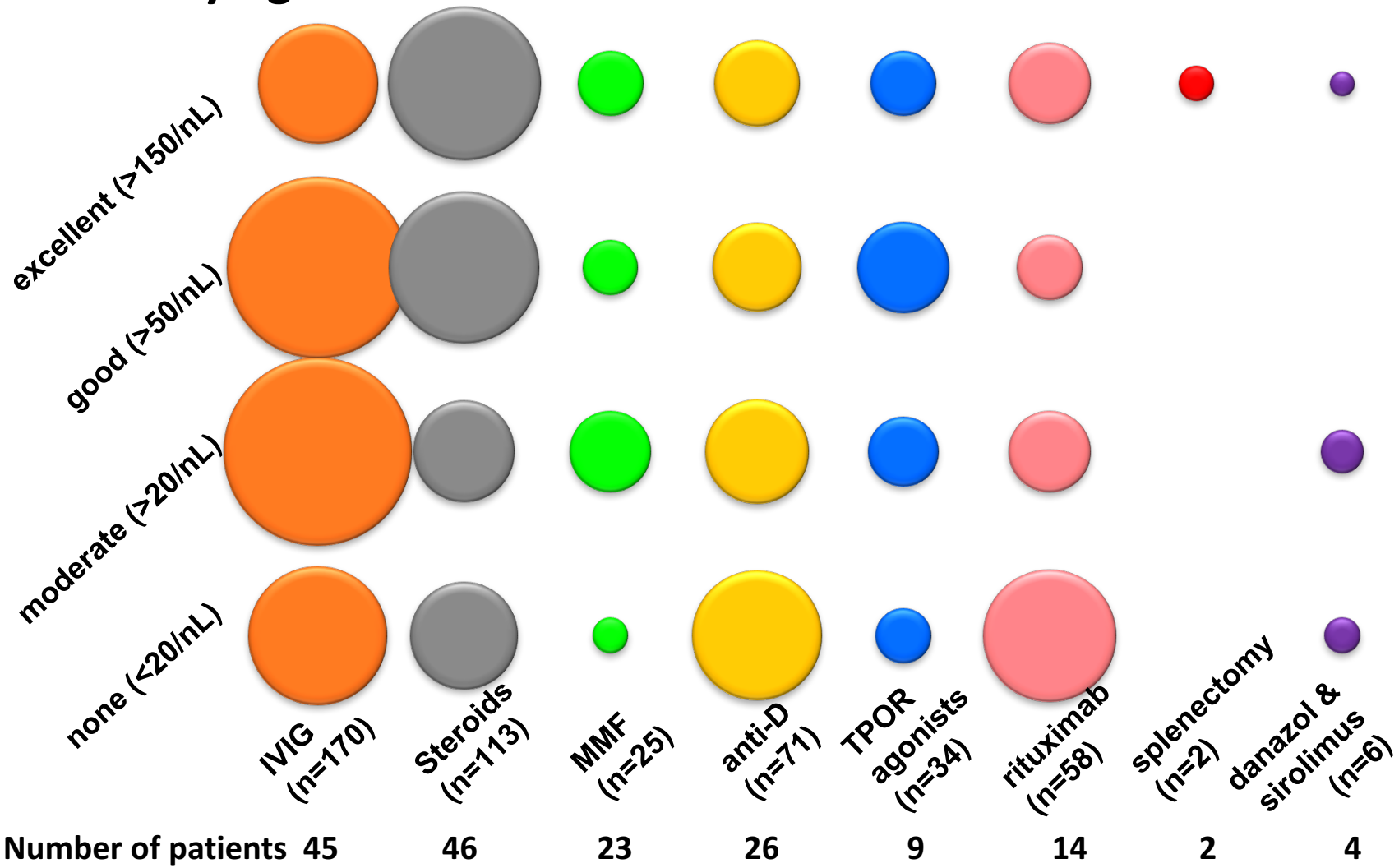


Sipurzynski et al., Semin. Hematol. 2016

Highly variable responses to multiple lines of treatment in pediatric cITP

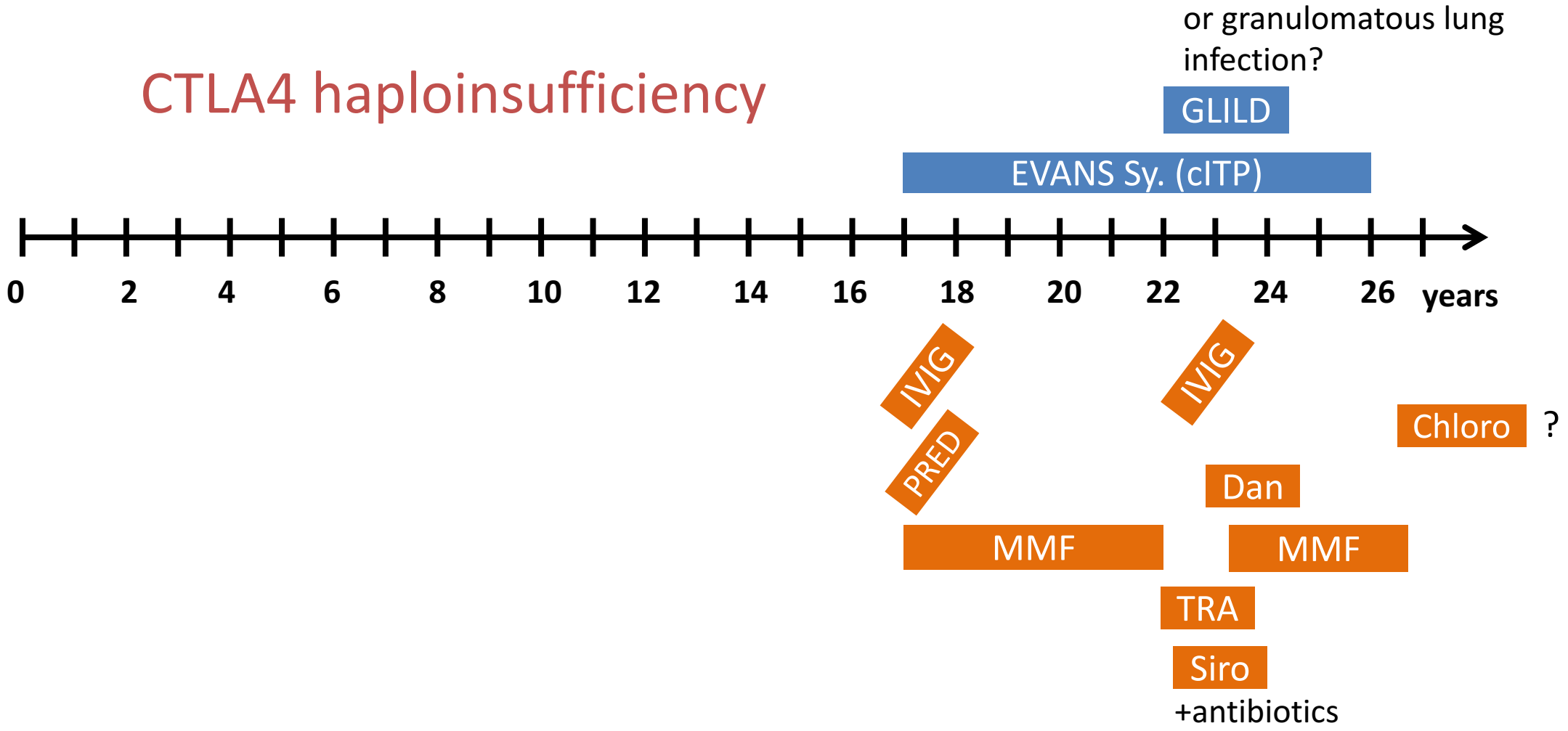
→ different underlying mechanisms?

479 interventions

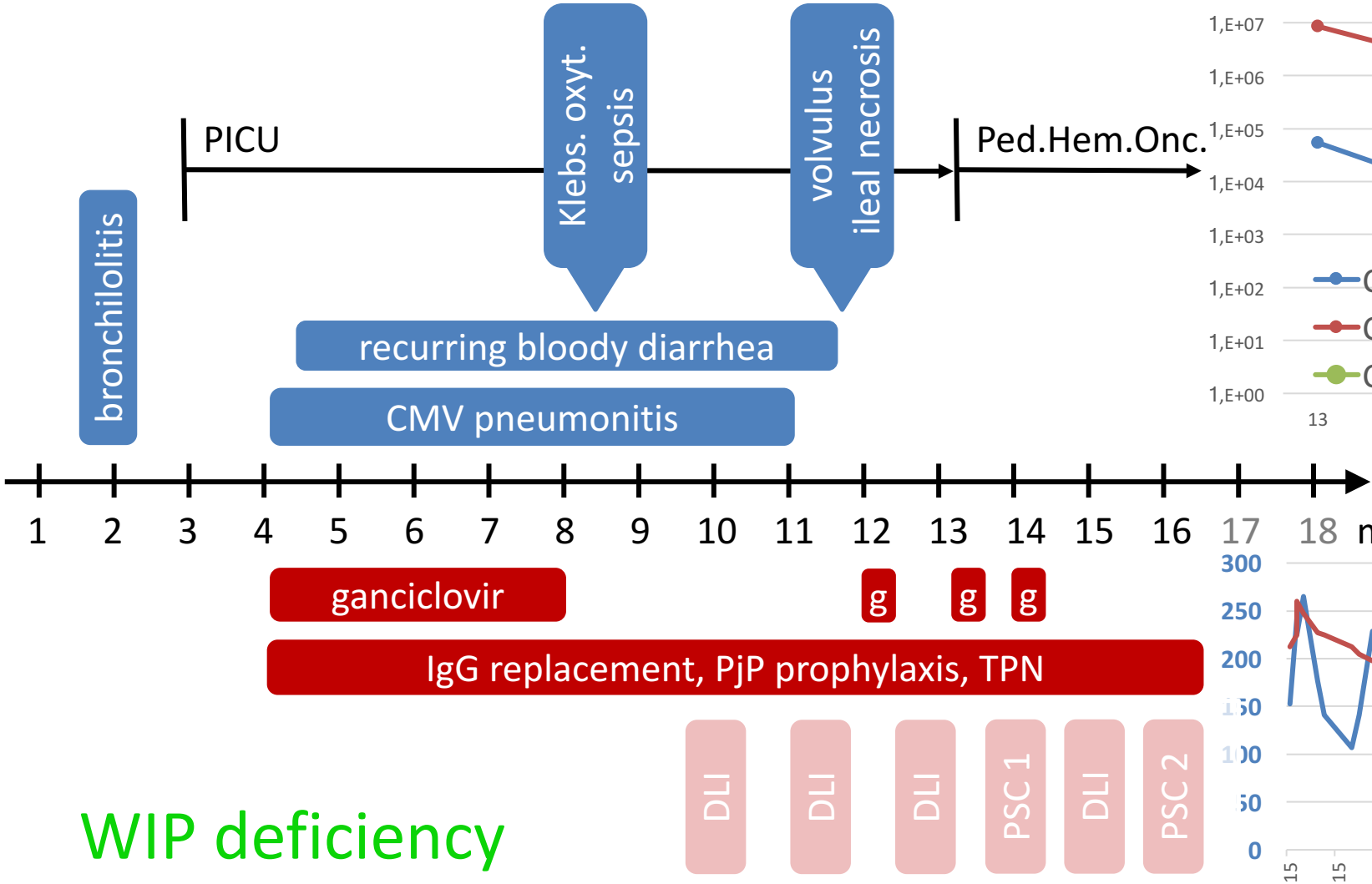


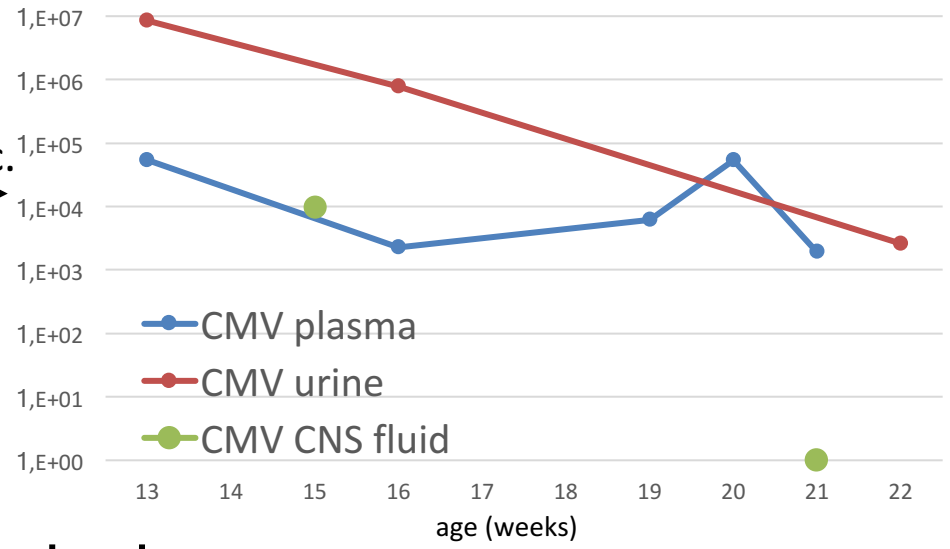
Sipurzynski et al., Semin. Hematol. 2016

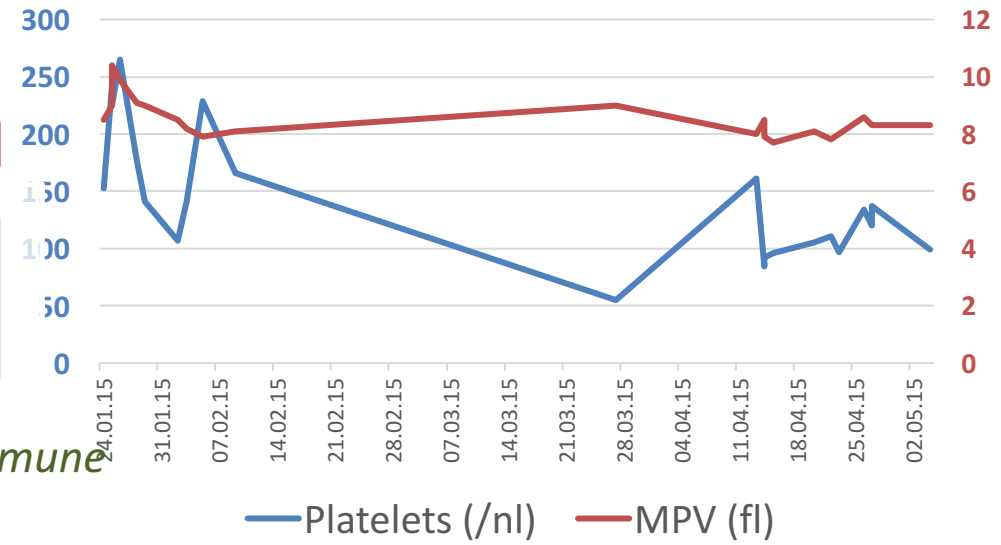
Adolescent with Evans Syndrome and GLILD



Infant with invasive CMV infection and many causes for thrombocytopenia...







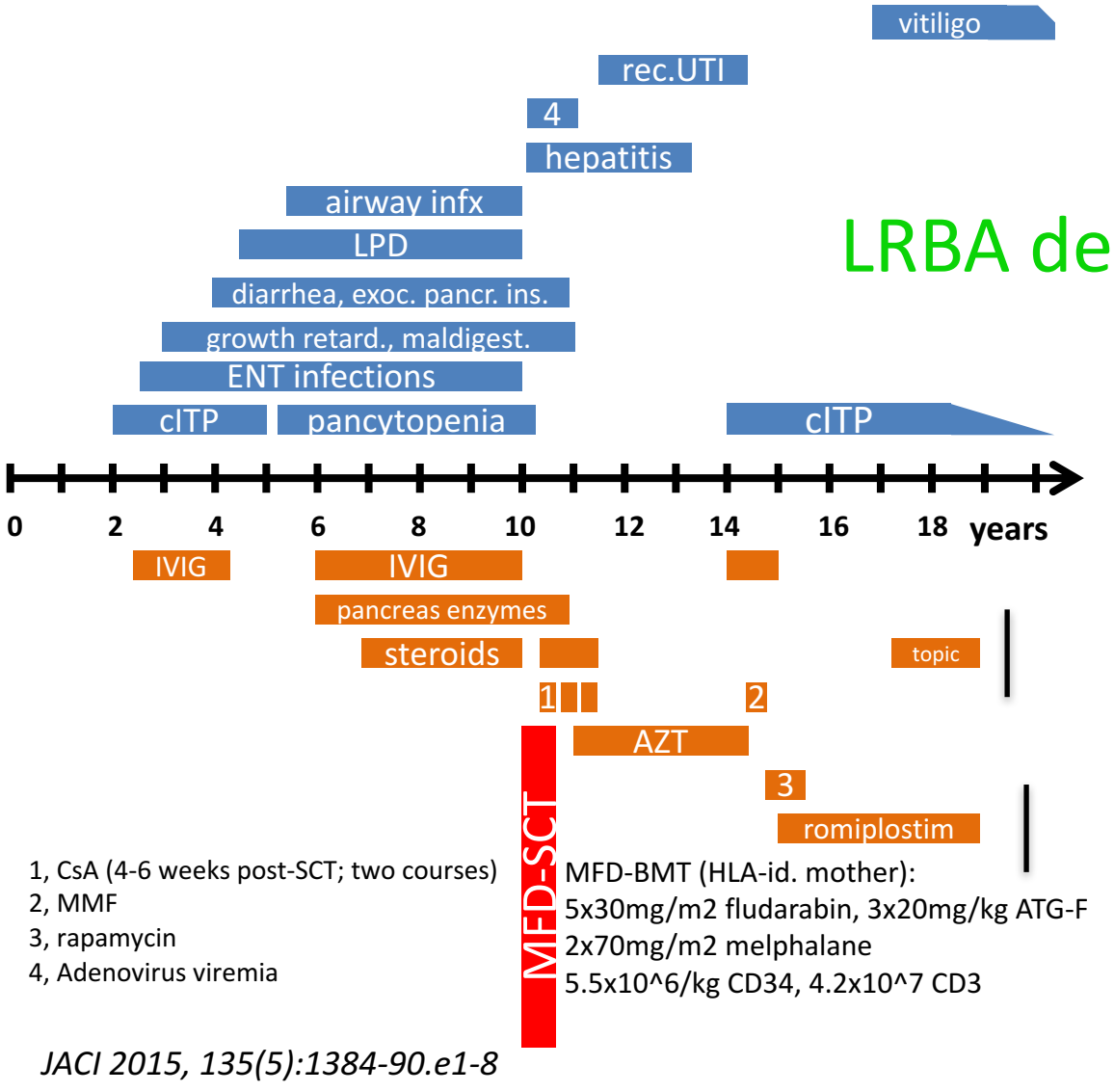
WIP deficiency

Pfajfer, Seidel et al., submitted

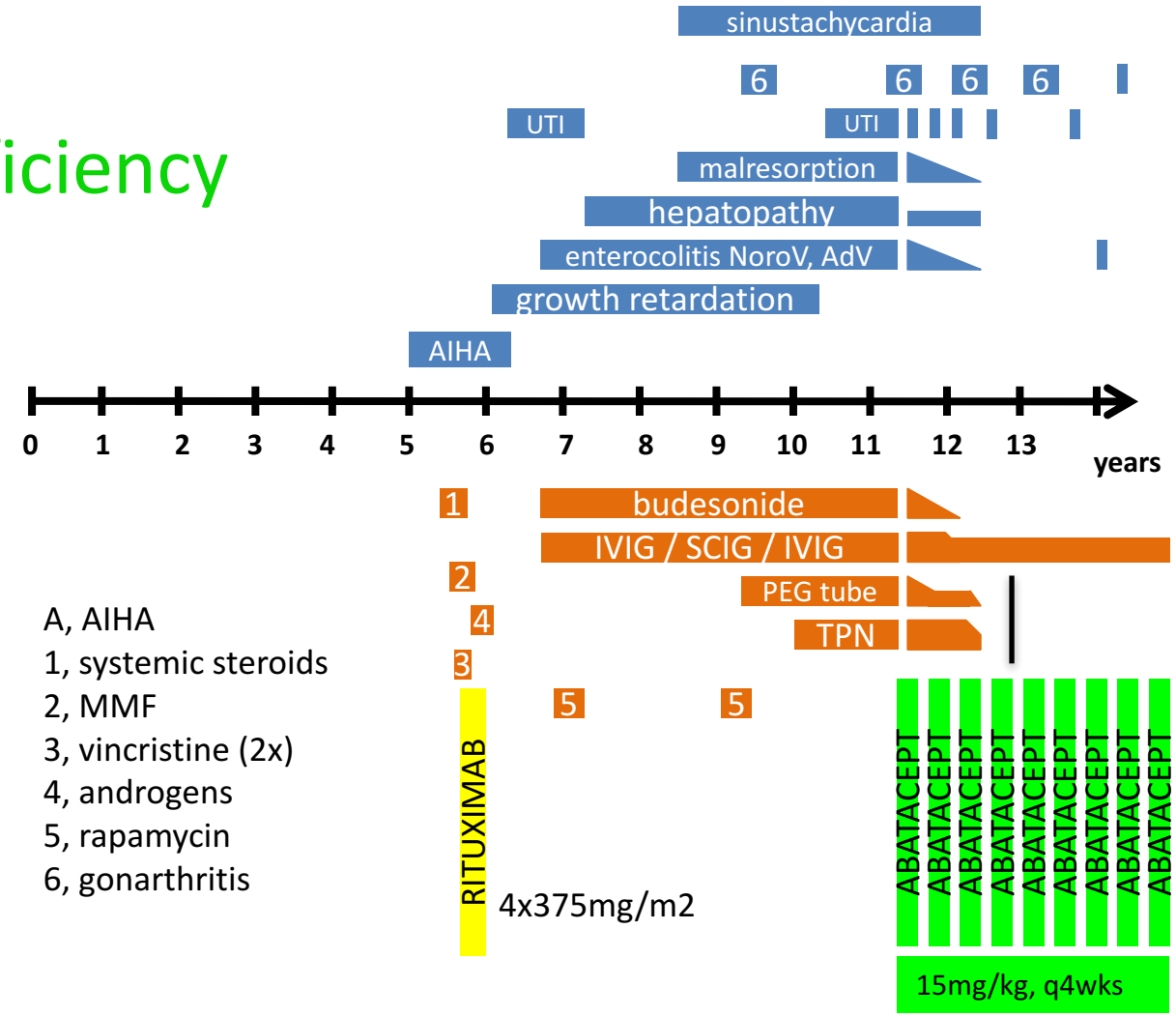
→ not all cytopenias in PID are *autoimmune*

Two sisters with cytopenias, multiorgan autoimmunity, and infections:
1x cured by HSCT (12yrs FU), 1x improved on abatacept (2yrs, ongoing)

LRBA deficiency



JACI 2015, 135(5):1384-90.e1-8



Different pathomechanisms require different treatments

- primary immunodeficiencies
  1. what causes the cytopenia?
  2. which PID is it?
  3. which pathway is involved (phenotype, functional, & genetics)?
  4. is a targeted treatment available?

  ➢ identify cytopenia-related common features: "biomarkers" within the immune phenotype, e.g. skewed lymphocyte subsets

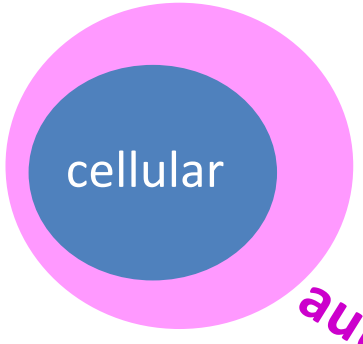
  ➢ discover epigenetic tolerance-impeding factors

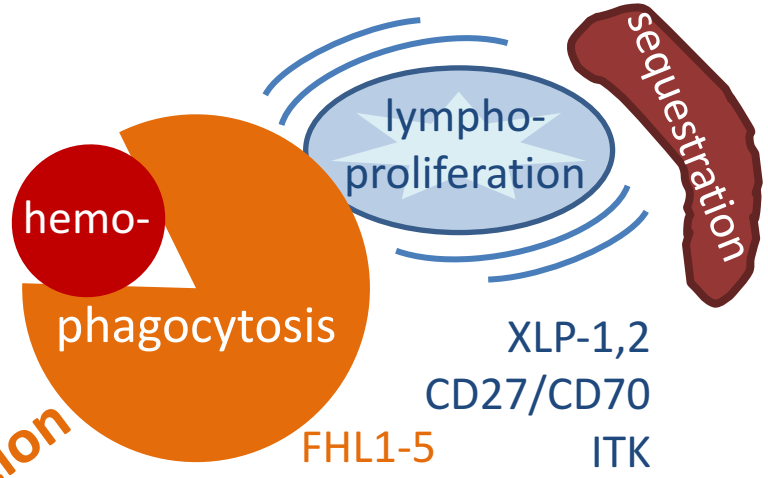
- parallels to GvHD?
  (among the worst immune cytopenias!)
  1. what can we learn from GvHD?
  2. what can we use from the treatment of multiple myeloma / CLL?

- "primary" immune cytopenias (85%)
  1. exclude underlying PID or hematological disease ASAP
  2. identify parallel patterns to PID

  ➢ **stratify** treatment modality to avoid prolonged phases of try-and-error and to **improve** therapy

Cytopenias in PID





autoimmunity

CID*
WAS, WIP [+ptl defect]
22q11
[SAA, MDS-RCC]

CVID
ALPS
SLE
CID* (LRBA, CTLA4, Pi3Kd)
Good
[ITP, AIHA, AIN, ES]

immune-dysregulation

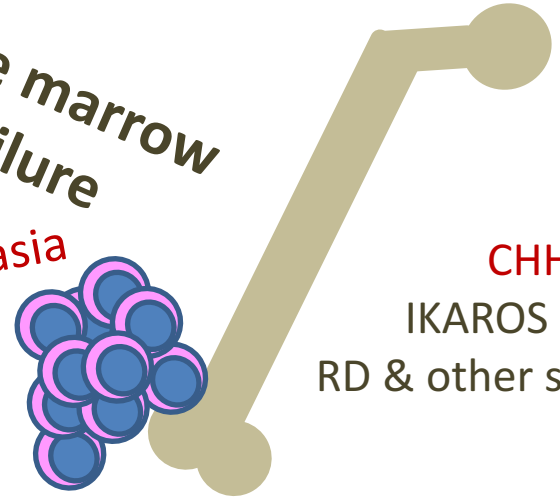
IPEX(-like)
FHL1-5
Griscelli-2
CHS, HPS-2
[secondary HLH]

XLP-1,2
CD27/CD70
ITK
ALPS

myelosuppression

(virus) infection-mediated
drug-induced; nutritional
malignoma
myelokathexis, WHIM

bone marrow failure



myelodysplasia

MonoMac/GATA2
SCN1
PNH/CD59

SDS, DKC
CHH, Schimke
IKAROS deficiency
RD & other syndromes

BLOOD. 2014 Oct 9;124(15):2337-2344

* incl. hypomorphic mutations in SCID genes, CD40, CD40L, etc.; # excl. primary defects of phagocyte number or function

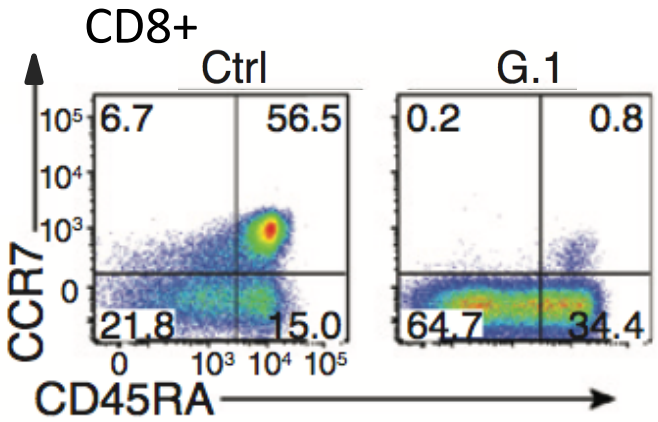
General: Mechanisms of Autoimmunity in Primary Immunodeficiencies

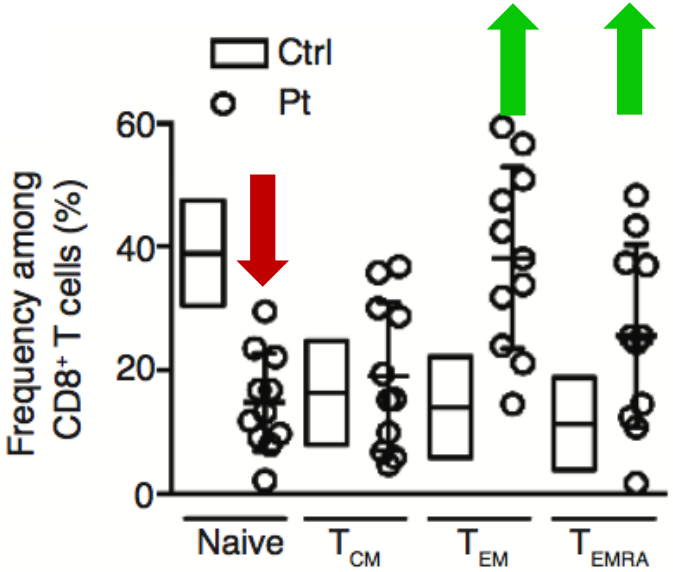
1. **Lymphopenia** (RAG1/2, Artemis...) expansion of T &B cells with autoreactive TCR/BCR
2. **Apoptosis defects**: ALPS, autoreactive T and B cells are not eliminated
3. Breakdown of **central tolerance** (DGS, APECED): impaired auto-Ag presentation, checkpoint editing, and defective negative selection
4. Breakdown of **peripheral tolerance**: lost Treg function (FoxP3, CD25, CTLA4, LRBA...)
5. **Increased type 1 Interferon** signature: STAT1 GOF, STAT3 GOF
6. **Defect of early complement components** (C1q, C1r/s, C2, C4) – with SAA and CRP strong opsonins for IC and apoptotic material, if lost → nuclear antigens induce IFNα in plasmacytoid dendritic cells and break self-tolerance in autoreactive T and B cells
7. **Impaired clearance of cell debris:** variants of FcγRII/III, CRP, or ITGAM (CD11b), deficiency of coatomer protein (COPA; ER stress), tripeptidyl peptidase II (TPPII; post-proteasome cytosolic protein modification, amino acid homeostasis)
8. **Hyperactivation of lymphocytes**: PI3Kδ GOF, PLCγ2, PKCδ
9. **Impairment of B-lymphocyte function/BCR production:** e.g. AID

Grimbacher et al., JACI 2016; 137(1):3-17
(C) AAAAI, J Allergy Clin Immunol

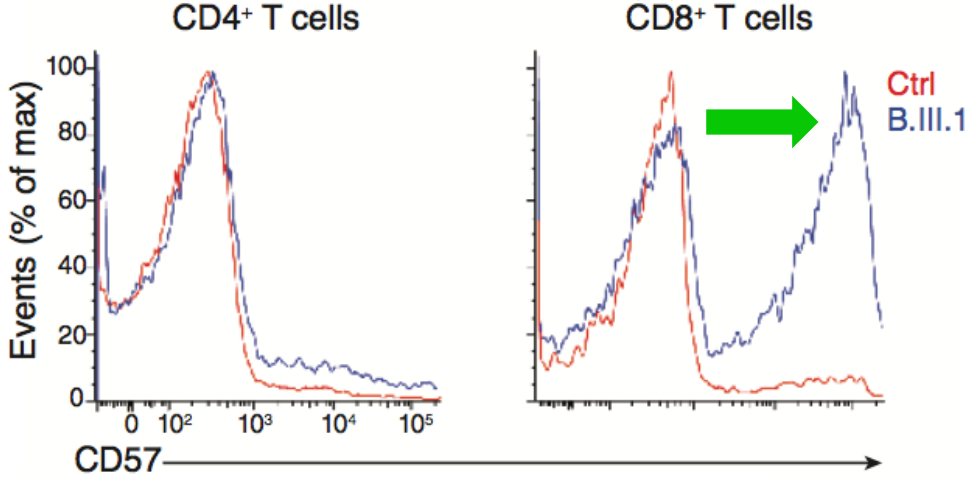
...*no such fool* like an *immunosenescent* fool...

APDS





Lucas et al., Nat Immun 2014; 15(1):88-97

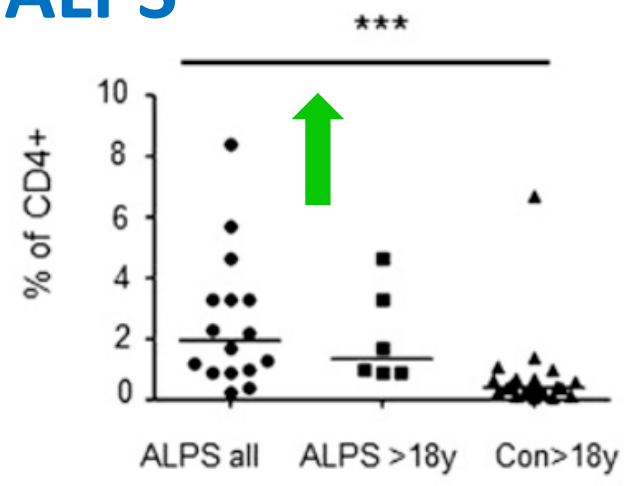


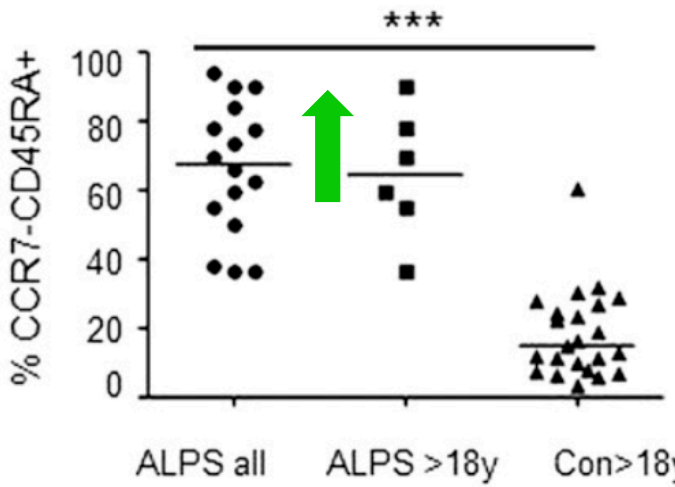
CD4+CCR7-CD45RA+

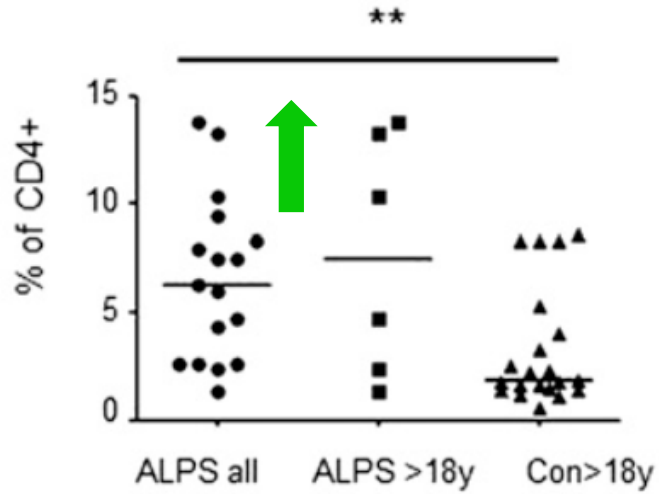
DNT TEMRA

CD4+CD57+

ALPS

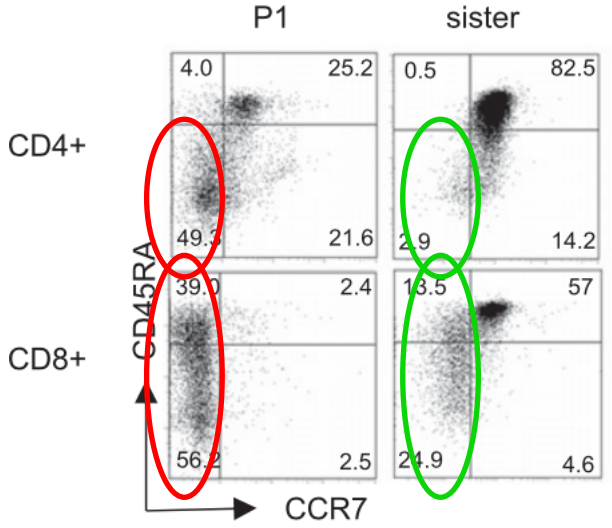


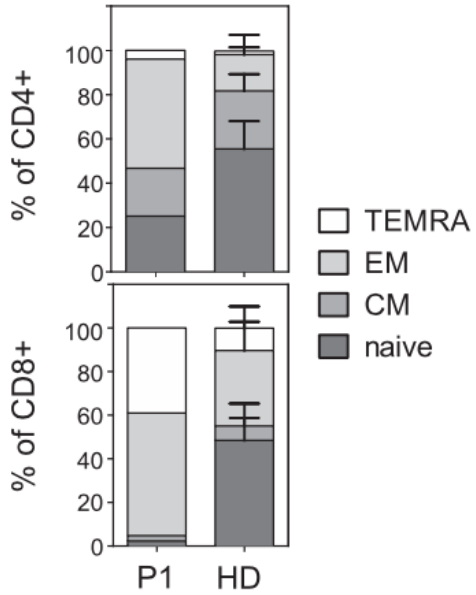


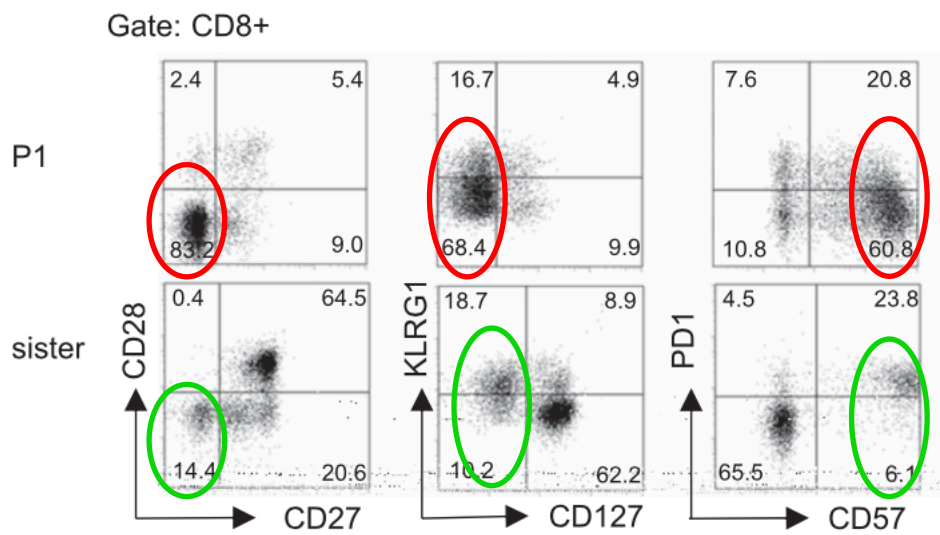


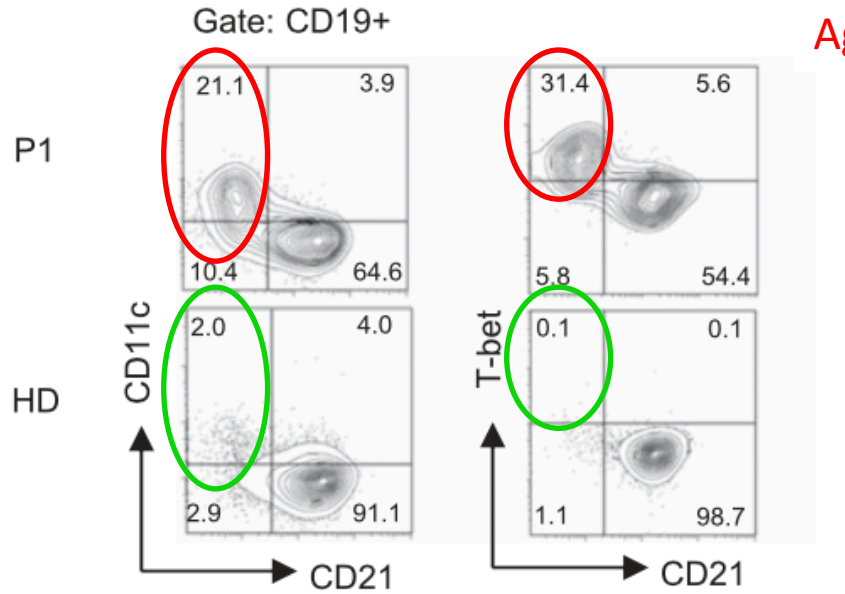
Rensing-Ehl et l., Blood. 2014;124(6):851-860)

e.g.: TEMRA & Senescence of CD8+ & B cells: **TPP2 deficiency**

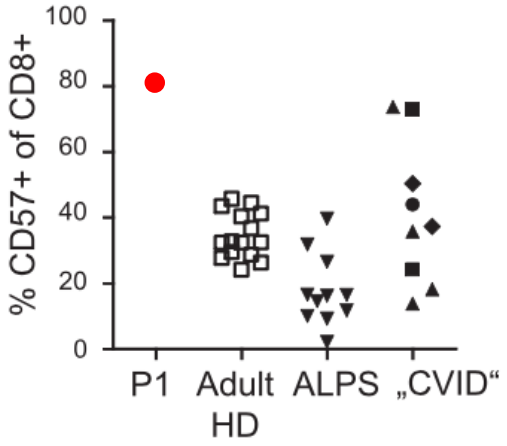




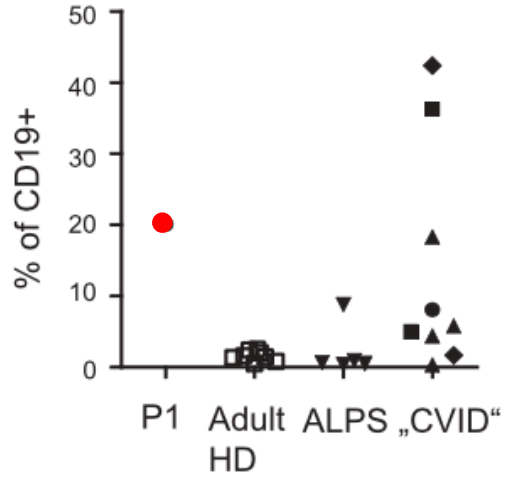




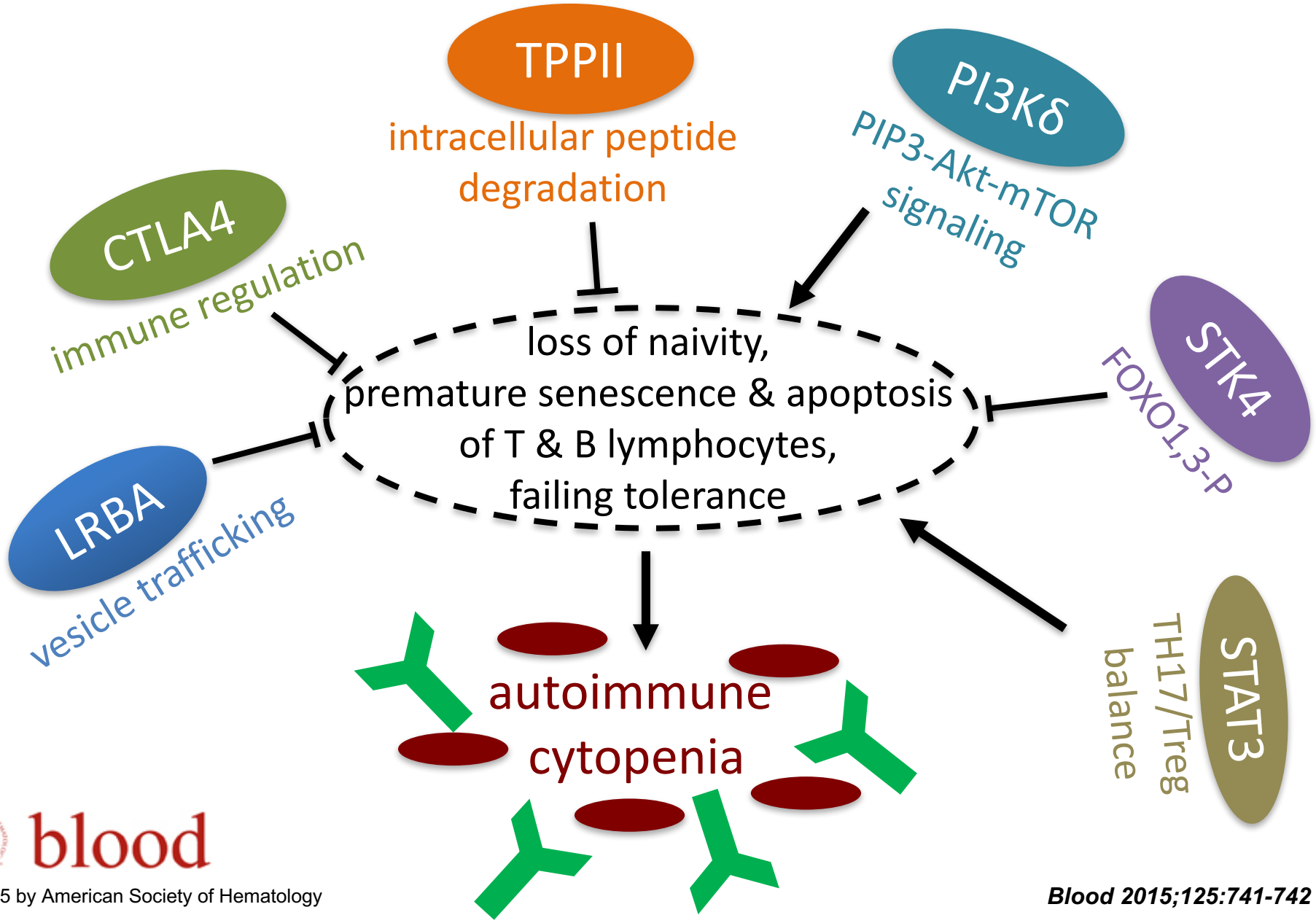
senescent CD8+ T cells



Age associated B cells (ABC)



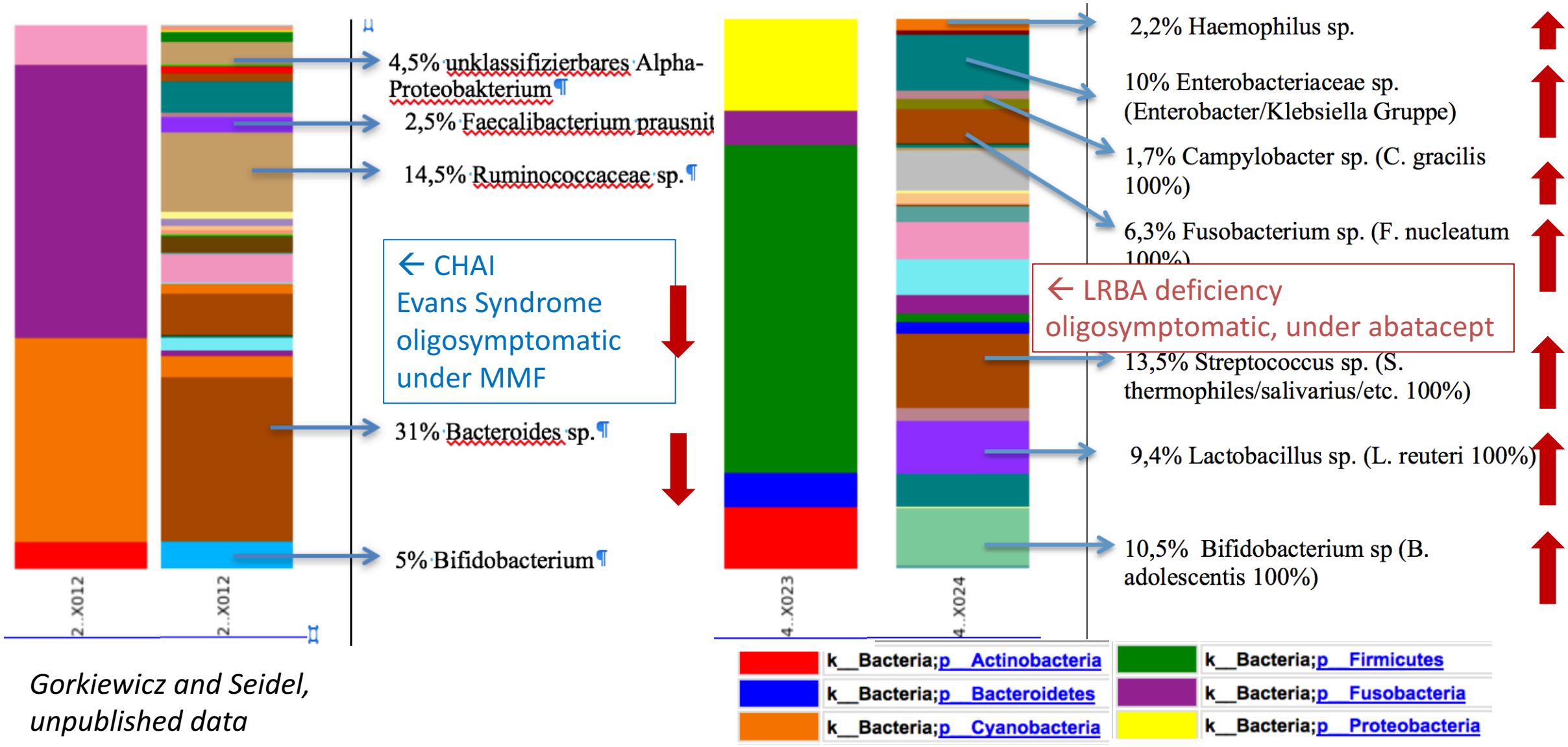
Stepensky et al., Blood 2015; 125(5):753-61



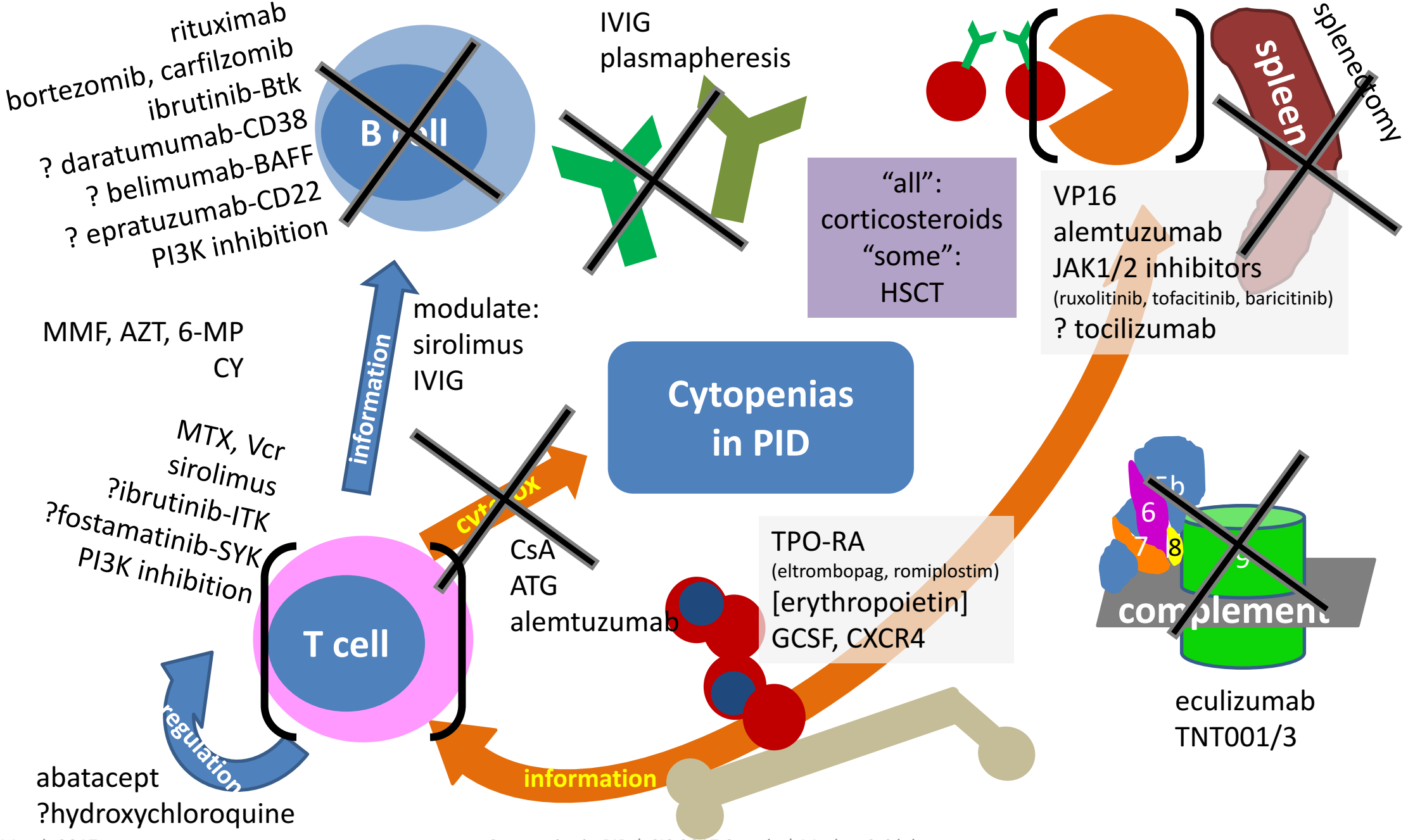
blood

Blood 2015;125:741-742

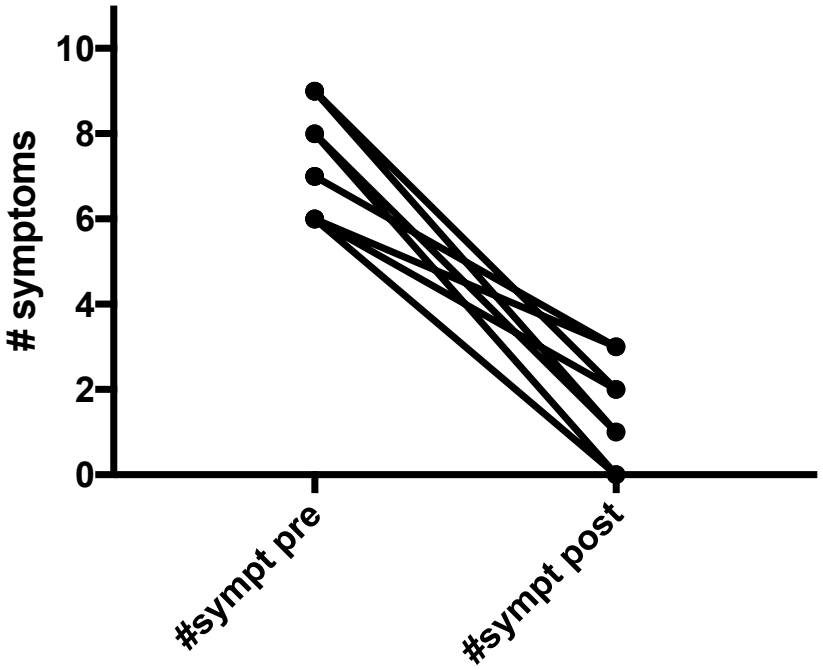
Epigenetic regulators: Microbiome & cytopenias? prospective studies warranted

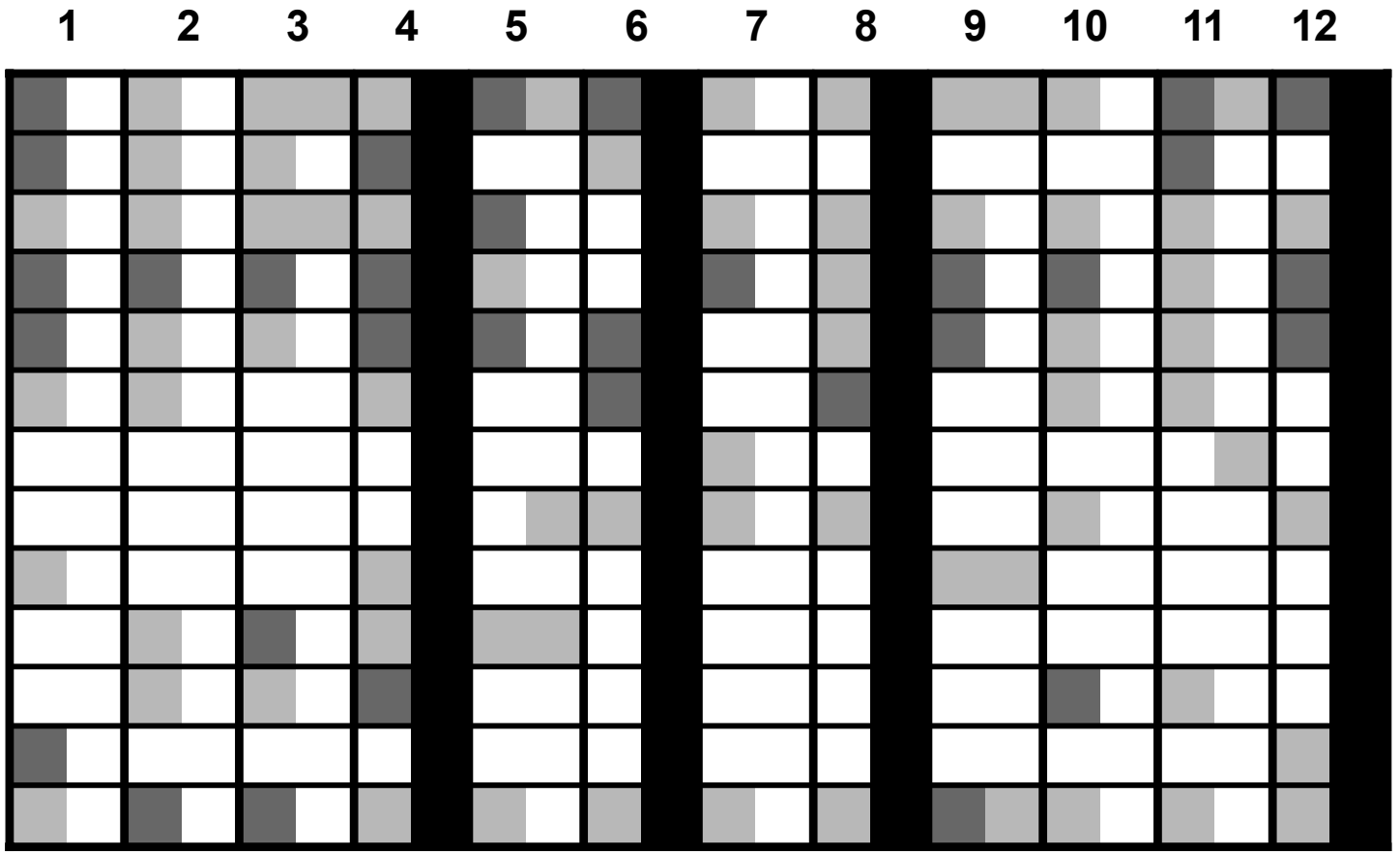


Gorkiewicz and Seidel, unpublished data


rituximab
bortezomib, carfilzomib
ibrutinib-Btk
? daratumumab-CD38
? belimumab-BAFF
? epratuzumab-CD22
PI3K inhibition
B cell
IVIG
plasmapheresis
"all":
corticosteroids
"some":
HSCT
spleen
splenectomy
VP16
alemtuzumab
JAK1/2 inhibitors
(ruxolitinib, tofacitinib, baricitinib)
? tocilizumab
MMF, AZT, 6-MP
CY
information
modulate:
sirolimus
IVIG
Cytopenias
in PID
MTX, Vcr
sirolimus
?ibrutinib-ITK
?fostamatinib-SYK
PI3K inhibition
cytotox
CsA
ATG
alemtuzumab
T cell
regulation
abatacept
?hydroxychloroquine
TPO-RA
(eltrombopag, romiplostim)
[erythropoietin]
GCSF, CXCR4
information
6
7
8
9
complement
eculizumab
TNT001/3

HSCT cures LRBA deficiency: symptoms before and after

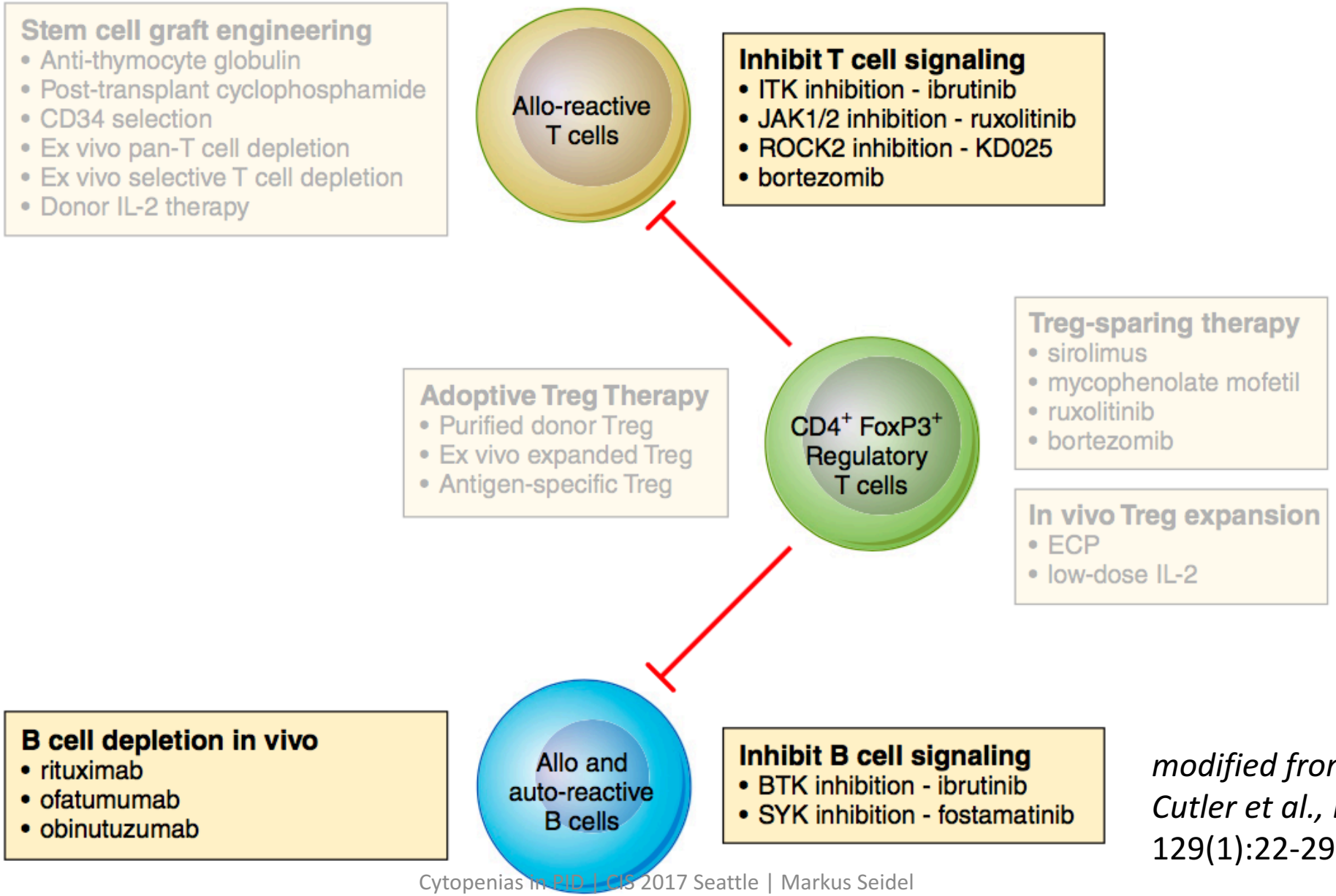




absent | mild-moderate | severe and HSCT indication | n.a./deceased

Seidel et al.-IEWP, revisions submitted

Graft-*versus*-Host Disease: anything to transfer to PIDs?



modified from:
Cutler et al., Blood 2017;
129(1):22-29

Different pathomechanisms require different treatments

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  (among the worst immune cytopenias!)
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  1. exclude underlying PID or hematological disease ASAP
  2. identify parallel patterns to PID

  ➢ **stratify** treatment modality to avoid prolonged phases of try-and-error and to **improve** therapy

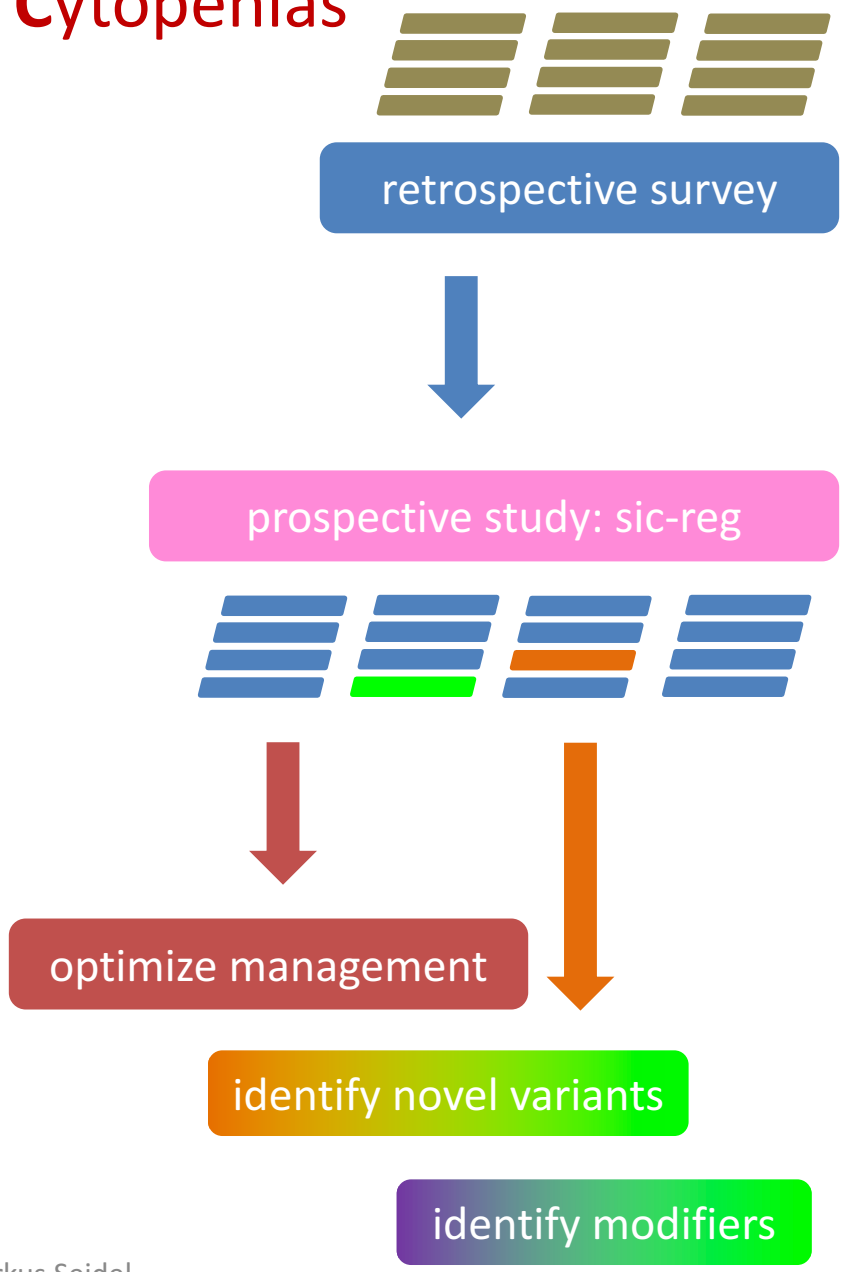
Proposal **SIC-reg**: **Reg**istry for **S**evere **I**mmune **C**ytopenias

prospective multicenter study including:

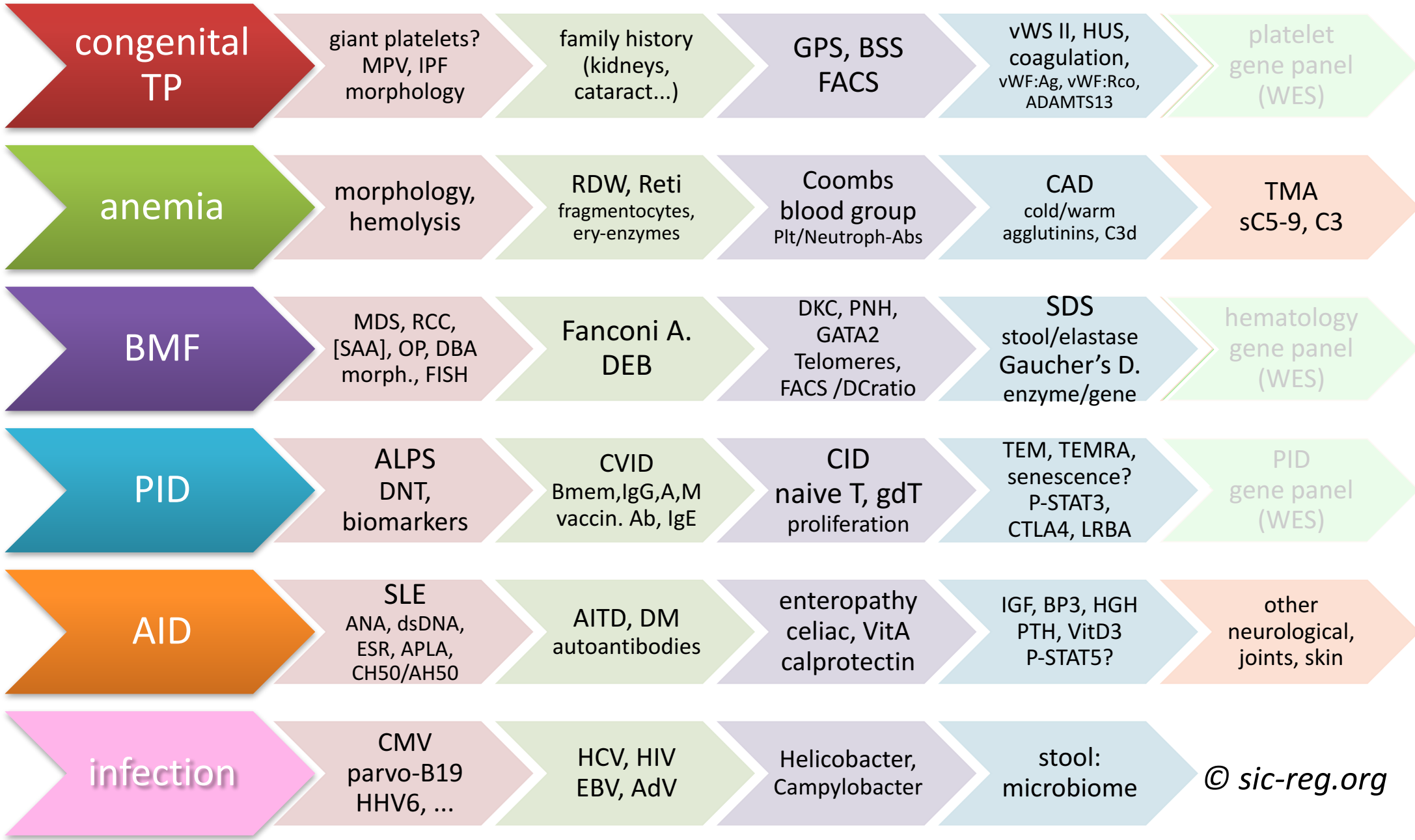
- persisting/chronic ITP [from 6 months duration]
- autoimmune hemolytic anemia [from start]
- Evans Syndrome [from start]
- ~~isolated Autoimmune neutropenia~~

Aims:

- **discover underlying diseases** early
- recommend and harmonize **diagnostic steps**
- recommend **stratified** first & second line **therapy**
- recommend **when to refer** to which centres
- **gather data** on epidemiology and use of modern (incl. off-label) drugs
- provide platform at the interface of hem-immun



- coming soon: www.sic-reg.org (under construction)


congenital TP
giant platelets? MPV, IPF morphology
family history (kidneys, cataract...)
GPS, BSS FACS
vWS II, HUS, coagulation, vWF:Ag, vWF:Rco, ADAMTS13
platelet gene panel (WES)
anemia
morphology, hemolysis
RDW, Reti fragmentocytes, ery-enzymes
Coombs blood group Plt/Neutroph-Abs
CAD cold/warm agglutinins, C3d
TMA sC5-9, C3
BMF
MDS, RCC, [SAA], OP, DBA morph., FISH
Fanconi A. DEB
DKC, PNH, GATA2 Telomeres, FACS /DCratio
SDS stool/elastase Gaucher's D. enzyme/gene
hematology gene panel (WES)
PID
ALPS DNT, biomarkers
CVID Bmem,IgG,A,M vaccin. Ab, IgE
CID naive T, gdT proliferation
TEM, TEMRA, senescence? P-STAT3, CTLA4, LRBA
PID gene panel (WES)
AID
SLE ANA, dsDNA, ESR, APLA, CH50/AH50
AITD, DM autoantibodies
enteropathy celiac, VitA calprotectin
IGF, BP3, HGH PTH, VitD3 P-STAT5?
other neurological, joints, skin
infection
CMV parvo-B19 HHV6, ...
HCV, HIV EBV, AdV
Helicobacter, Campylobacter
stool: microbiome
© sic-reg.org

preliminary treatment algorithms, derived from international guidelines/publications

AIHA, ES: goal = remission

first line:
Prednisolone 2-5mg/kg/d days 1-3, then 1-2mg/kg/day, wean off after 4 wks > 8wks…

second line#:
Pred + MMF 1200mg/m2/d
- if DNT ↑: Pred + sirolimus 1-2.8 mg/m2/d [trough level 5ng/mL]
- if signs of CID, consider targeted therapy*, HSCT
- wean off pred after 4 weeks
- wean off after 6-12 months over 3-6 months#

or methyl prednisolone 10-30mg/kg/d>4d (? dexa.)
+ rituximab 4x 375mg/m2 or 2x1g/m2 q2 wks (vaccin.)

third line#:
danazol, AZT, VCR, bortezomib, carfilzomib?, eculizumab (CAD, PNH), CY, CSA, [ibrutinib?, daratumumab?],... splenectomy, HSCT

cITP: goal = no risk of hemorrhage, QoL

first line -if treatment is needed (!?!):
IVIG 0.5-0.8 g/kg
- if Rh+: anti-D (25)50-75µg/kg s.c. or i.v.
dexamethasone 5-10(20)mg/m2/day>3-5 days

second line#:
MMF 1200mg/m2/d ± prednisolone
- if DNT ↑: sirolimus
- if signs of CID, consider targeted therapy*, HSCT

TPOR-Agonists: eltrombopag 25-50mg/d (0.8-1.2mg/kg <6yrs); romiplostim (>18yrs or eltr. non-responders) 100-250µg/m2/week
- wean off after 6-12 months over 3-6 months #

third line#:
rituximab, danazol, AZT, VCR, Dapson, (Retinoids?)
- adults: splenectomy (vaccinate!, OPSI-prophyl.)...

** or targeted therapies if underlying disease is identified (e.g. p110 inhib. in APDS-study, abatacept in LRBA-def. & CTLA4 haploins....)*

 # order depending on immune or phenotypical abnormality

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Tamam Bakchoul
Würzburg
Harald Schulze
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Vienna
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Tumor genetics
Vienna – CCRI
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Katrin Böhm
Oliver Kindler

Thank you for your attention!