Inborn errors of immunity and other causes of **secondary ITP**: First interim results of the prospective Severe Immune Cytopenia Registry (www.sic-reg.org)

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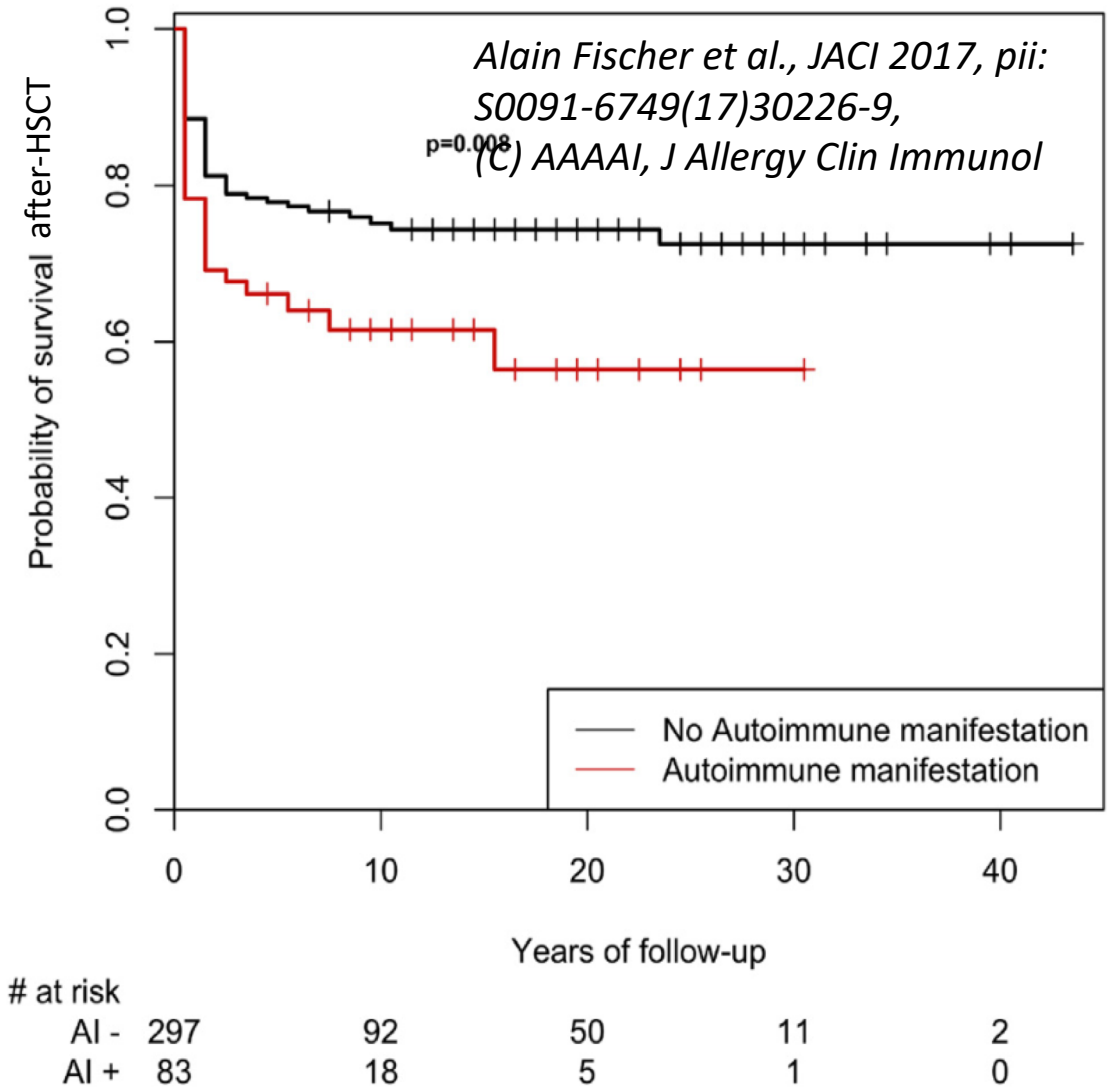
Sept. 2019, Locarno, CH

Autoimmunity in Primary Immunodeficiencies

- 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

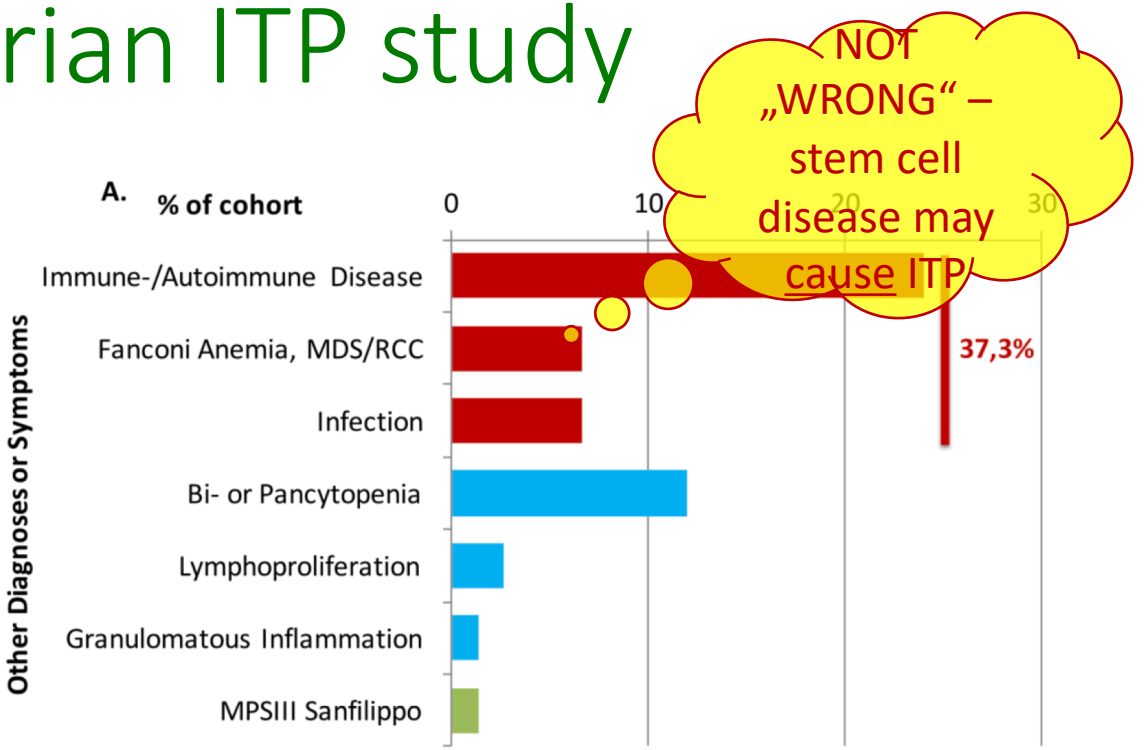


➢ not all *cytopenias* are ALPS- or CVID-linked

➢ 85% are *not* linked to a known PID

Own observations – Austrian ITP study

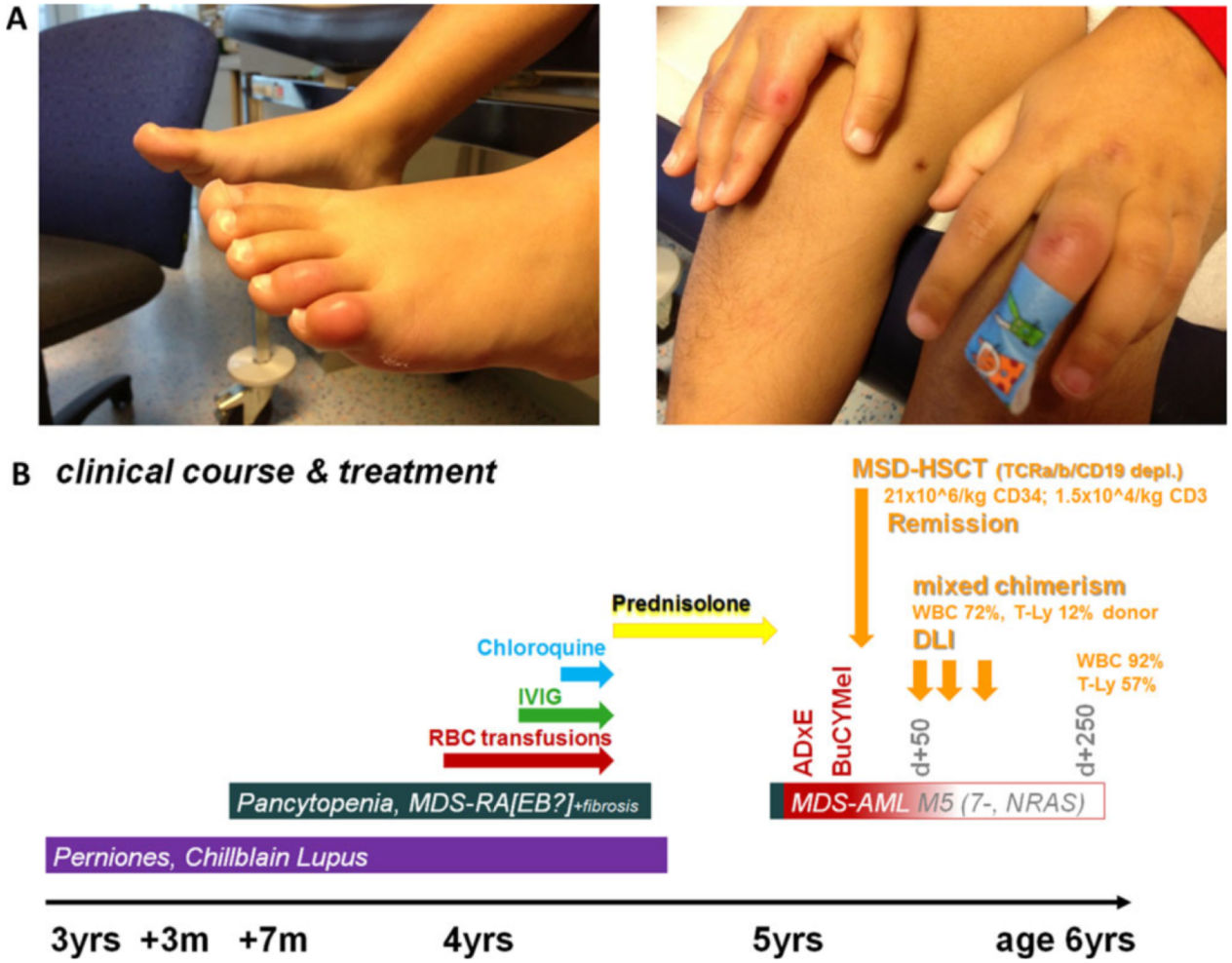
- Nationwide, retrospective study
- 81 patients with chronic ITP
  - Median age 8.57 years (1-17)
- Many (> 1/3) had other or additional diagnoses:
  - LRBA, CHAI, ALPS…, SLE
  - Fanconi anemia, RCC, MDS
  - Congenital thrombocytopenias…
  - (chronic) infections
- International guidelines for diagnosis & treatment were <u>not</u> adhered to



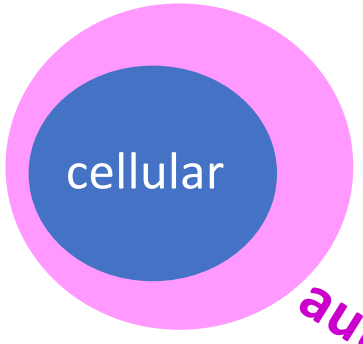
Sipurzynski et al., Semin. Hematol. 2016

MDS-linked ITP/Evans preceding AML in RASopathy

- Chilblain lupus in 3-yo boy „histiocytic Sweet syndrome“
- ANA, APLA, Coombs borderline positive
- Pancytopenia developed after 7 months
- Only responsive to prednisolone
- But.. AML developed after tapering of prednisolone
- RASopathy (RALD) was diagnosed and treated
- Remission 5 years after HSCT



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



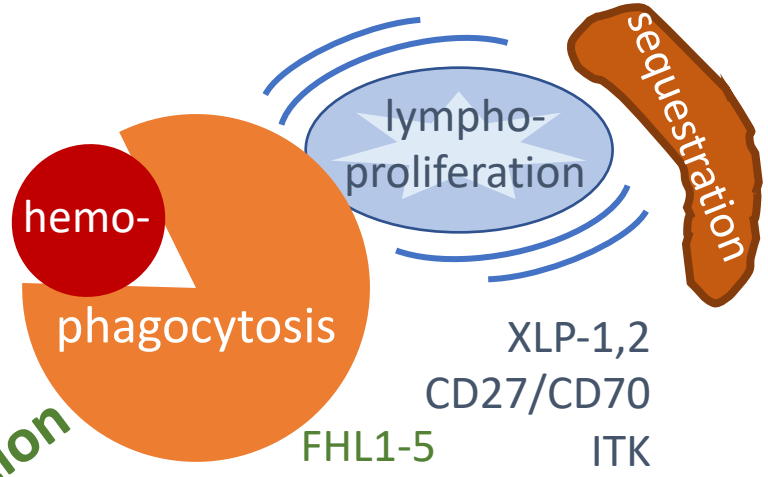
CID*
WAS, WIP [+ptl defect]
22q11
[SAA, MDS-RCC]

autoimmunity

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

Cytopenias in PID

immune-dysregulation



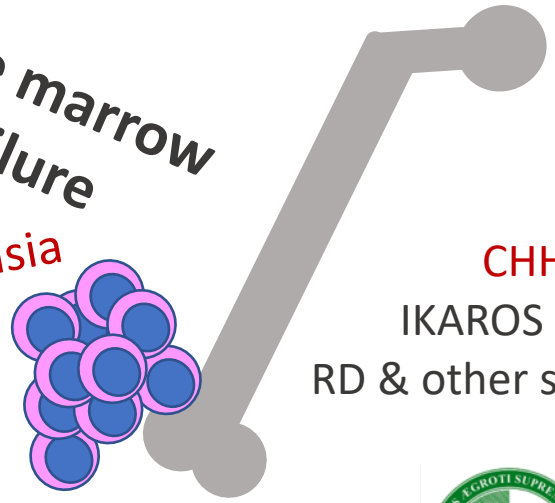
IPEX(-like)
FHL1-5
Griscelli-2
CHS, HPS-2
[secondary HLH]

XLP-1,2
CD27/CD70
ITK
ALPS

myelosuppression

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

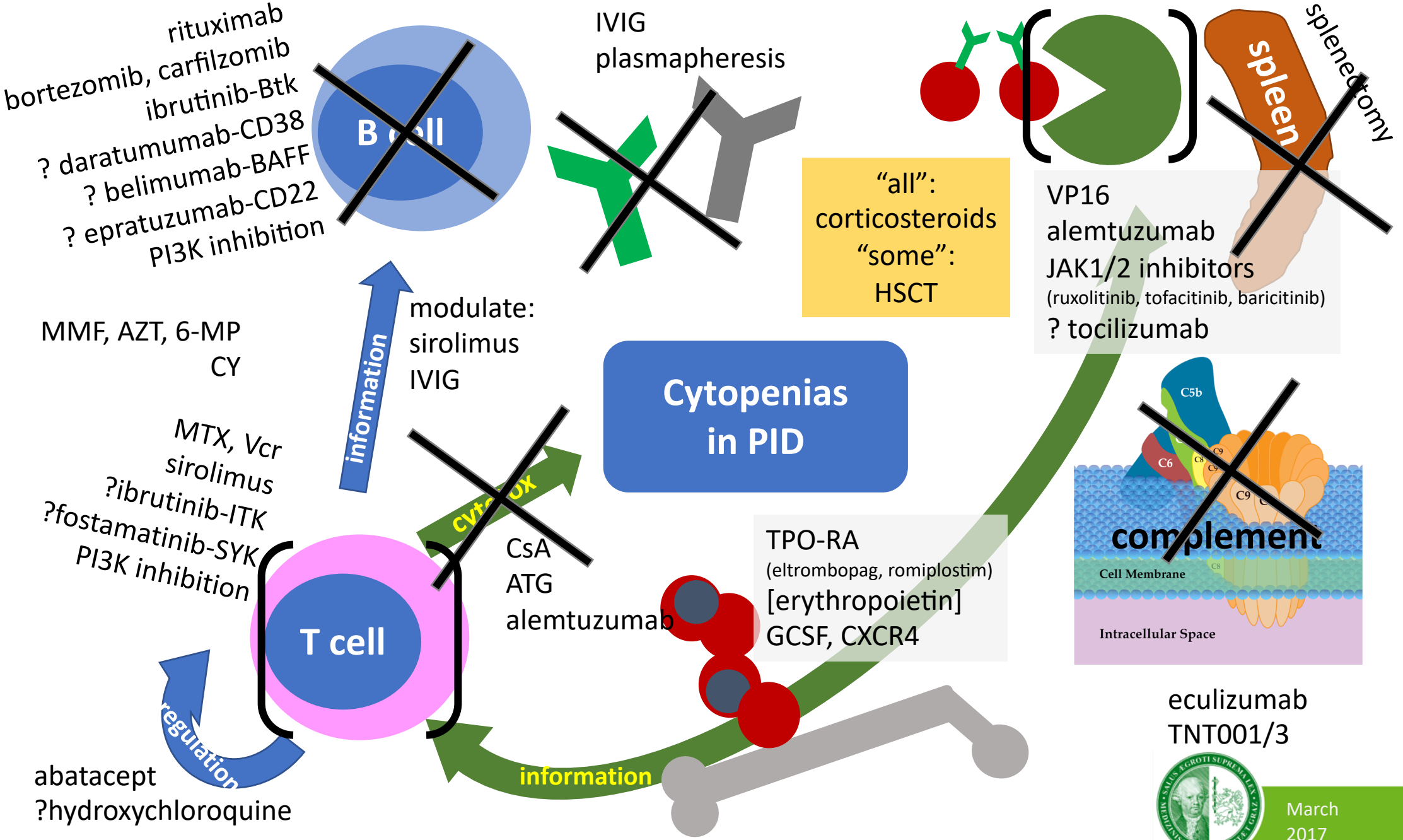
bone marrow failure



myelodysplasia
MonoMac/GATA2
SCN1
PNH/CD59

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

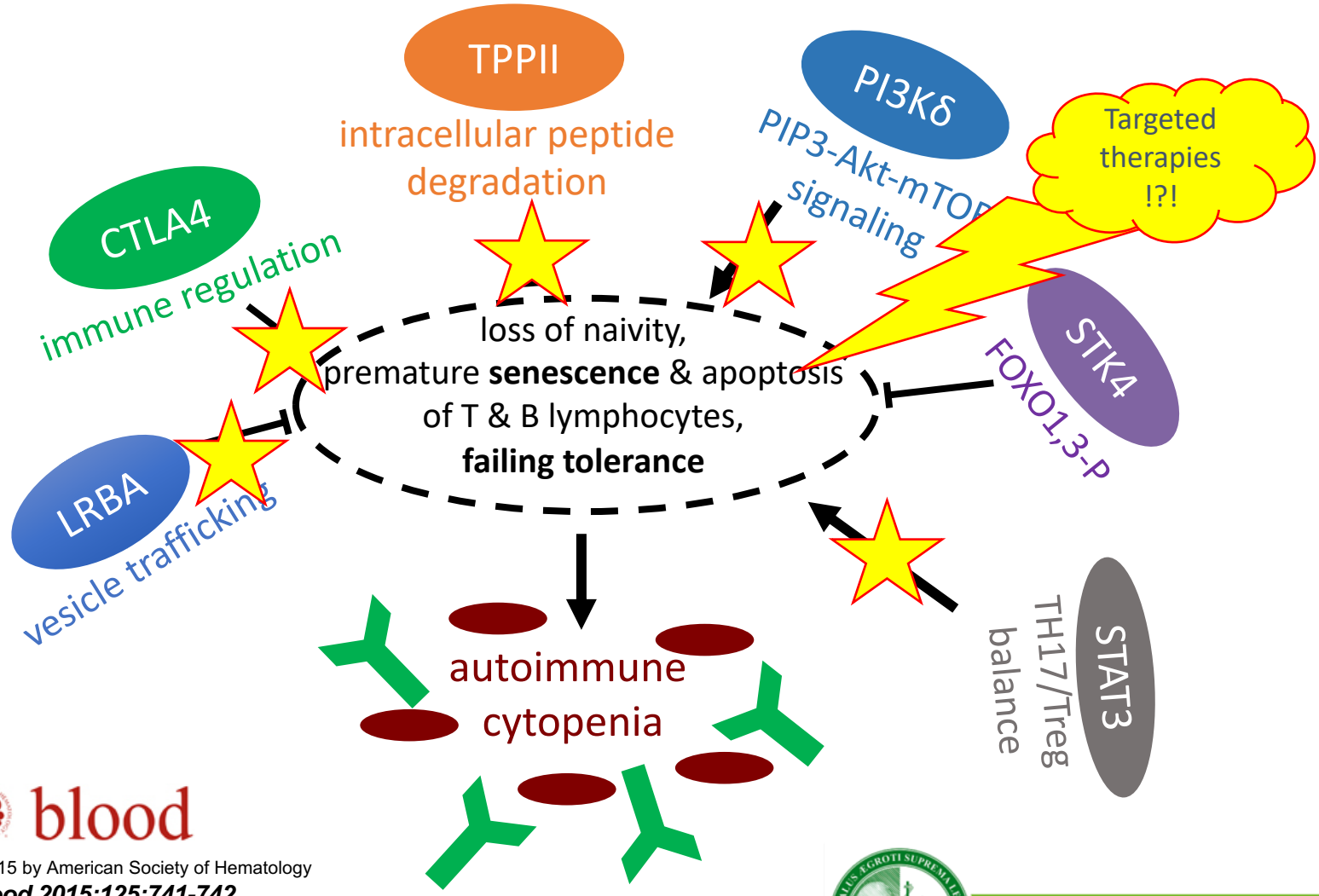
* incl. hypomorphic mutations in SCID genes, CD40, CD40L, etc.; # excl. primary defects of phagocyte number or function


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
T cell
CsA
ATG
alemtuzumab
TPO-RA
(eltrombopag, romiplostim)
[erythropoietin]
GCSF, CXCR4
C5b
C6
C9
complement
Cell Membrane
Intracellular Space
eculizumab
TNT001/3
regulation
abatacept
?hydroxychloroquine
information

Deviations of the immune system: a common theme?

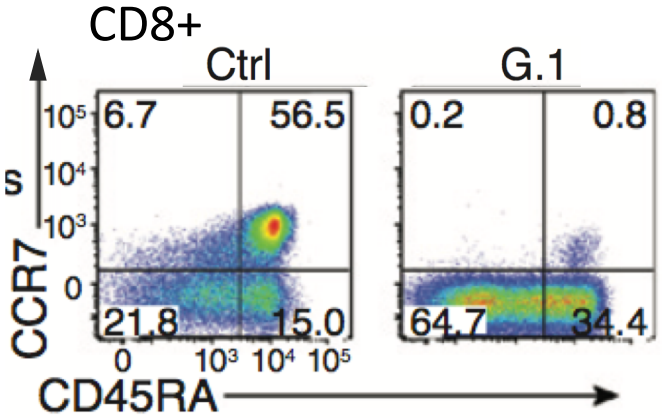
- Expansion of self-reactive T and B cells
- Signs of exhaustion and senescence
- Epigenetic modifiers?
  - infections
  - Intestinal microbiome

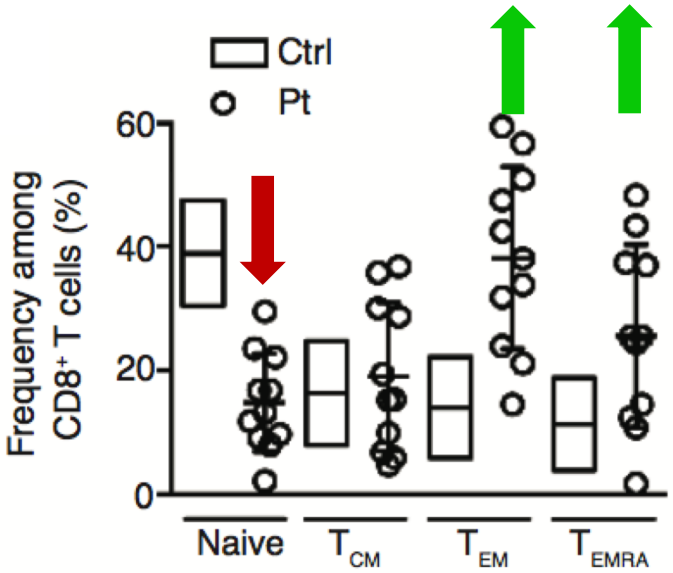
→ Diagnostic or treatment-stratifying biomarkers?



blood
©2015 by American Society of Hematology
Blood 2015;125:741-742

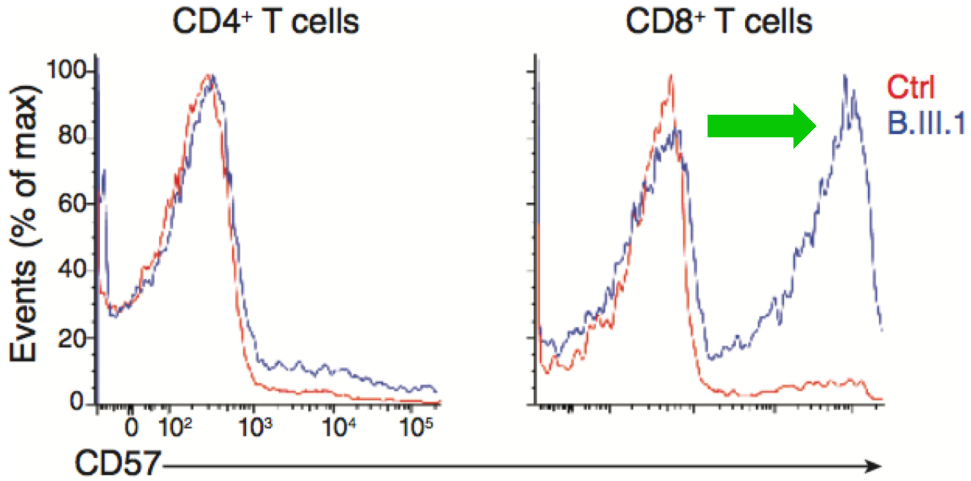
APDS/PI3Kd-GOF





DNT TEMRA

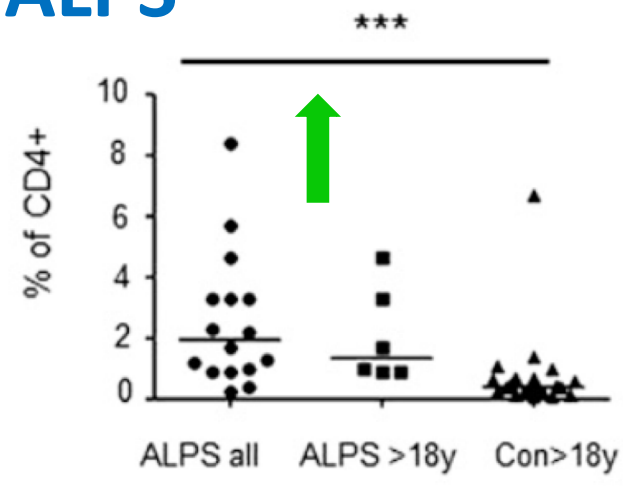
Lucas et al., Nat Immun 2014; 15(1):88-97

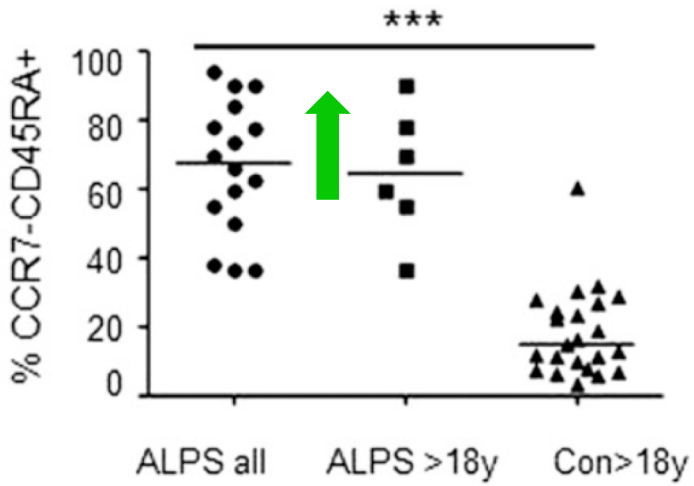


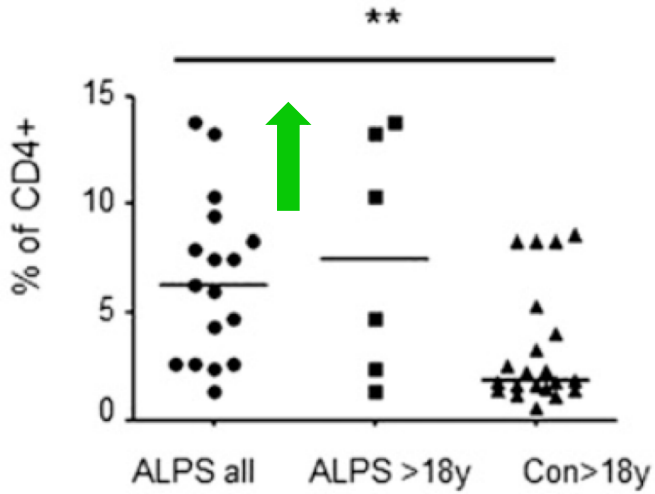
CD4+CD57+

ALPS

CD4+CCR7-CD45RA+

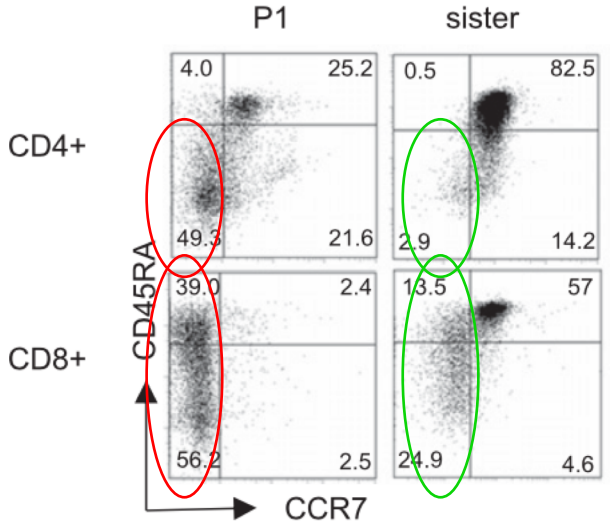


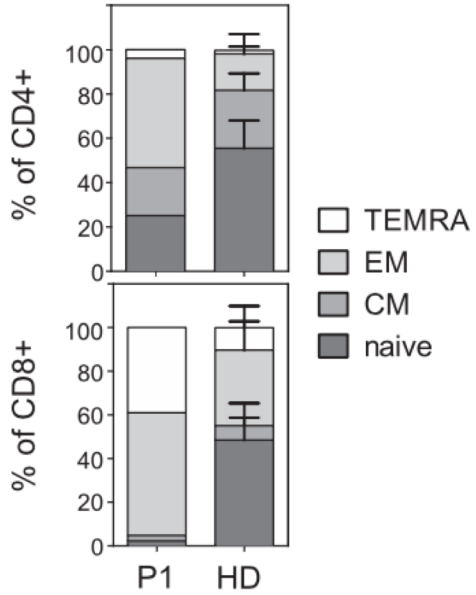


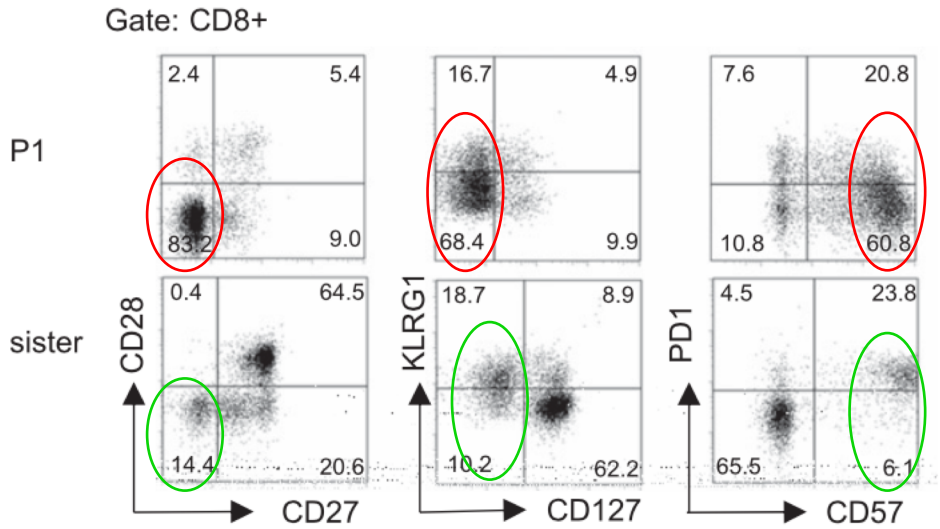


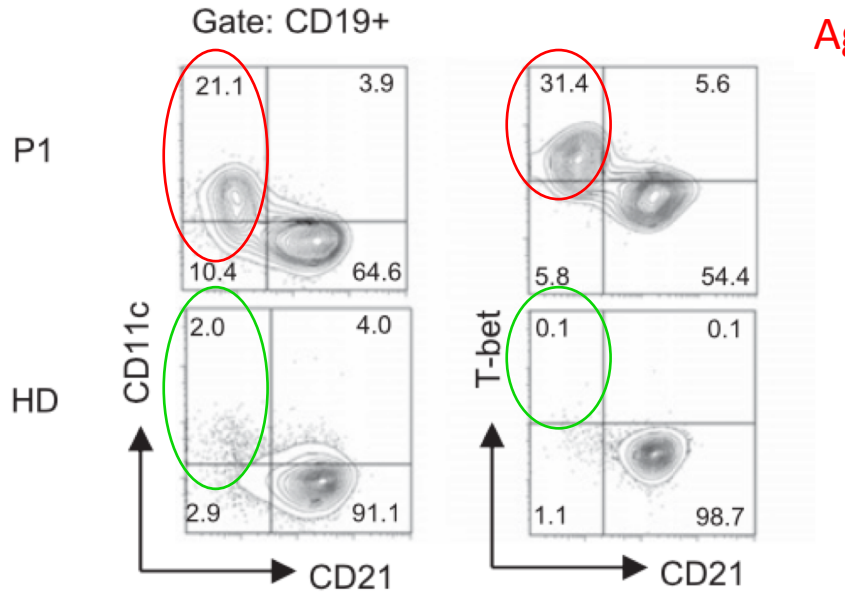
Rensing-Ehl I., Blood. 2014;124(6):851-860)

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

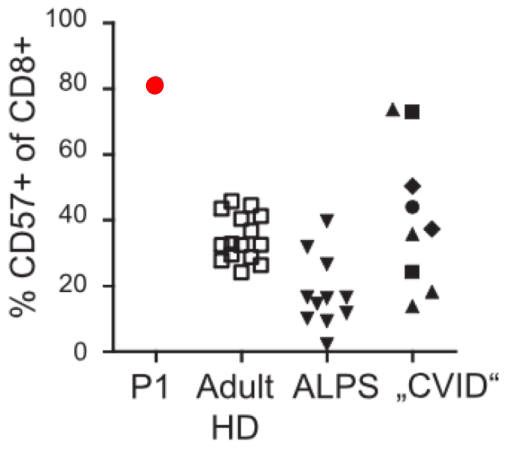




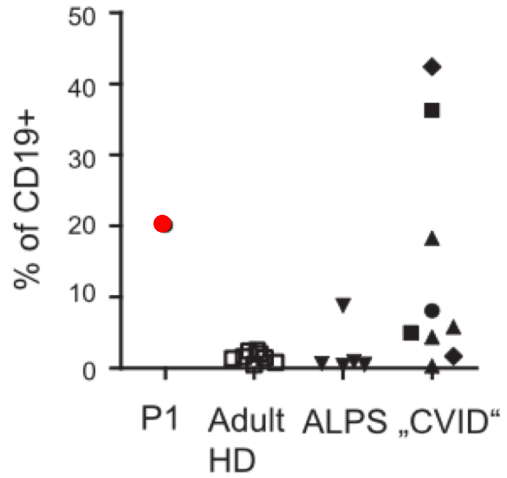




senescent CD8+ T cells



Age associated B cells (ABC)



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

e.g.: TEMRA & Senescence: GATA2 mutations

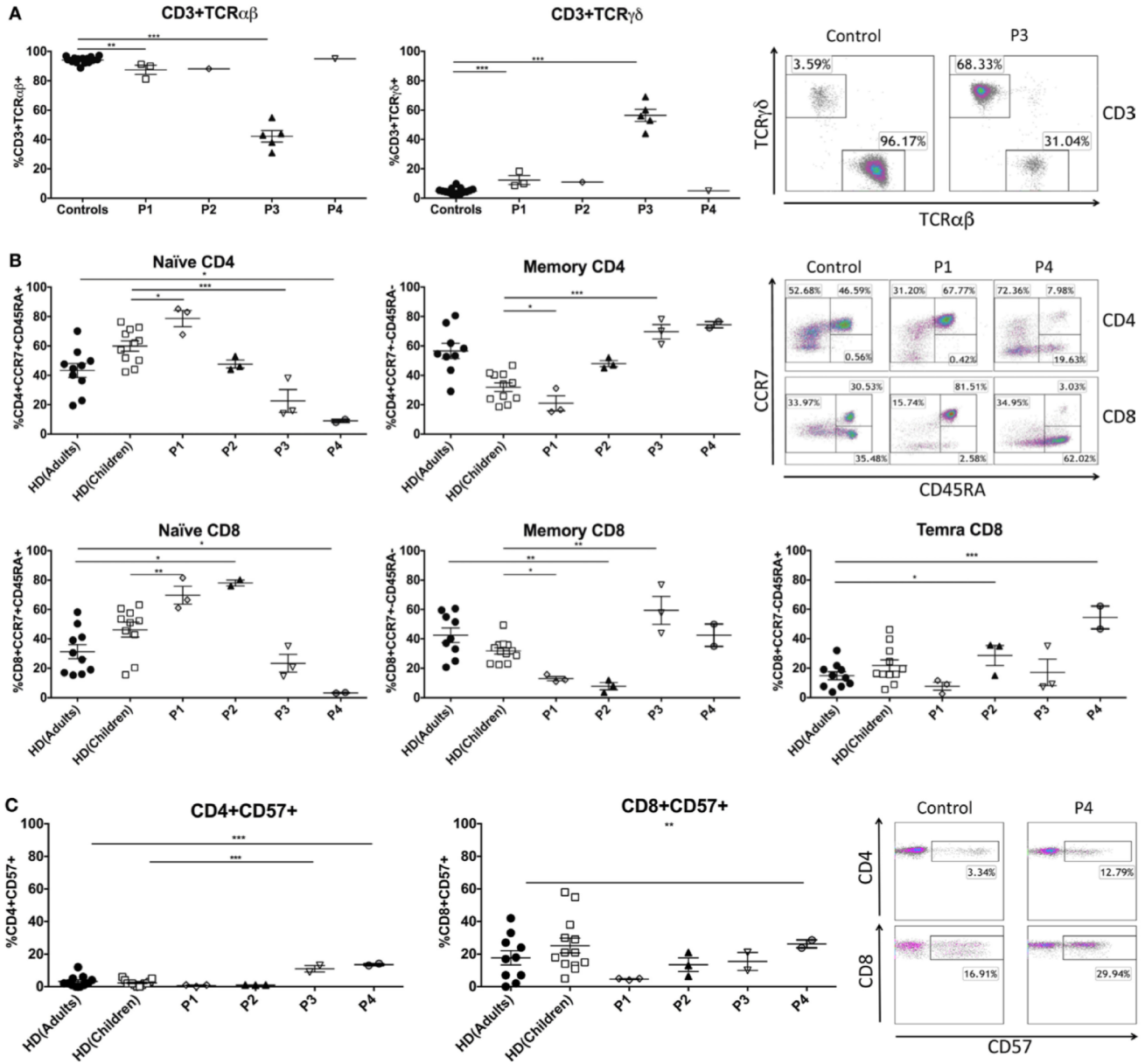
frontiers in Immunology

ORIGINAL RESEARCH
published: 12 July 2017
doi: 10.3389/fimmu.2017.00802

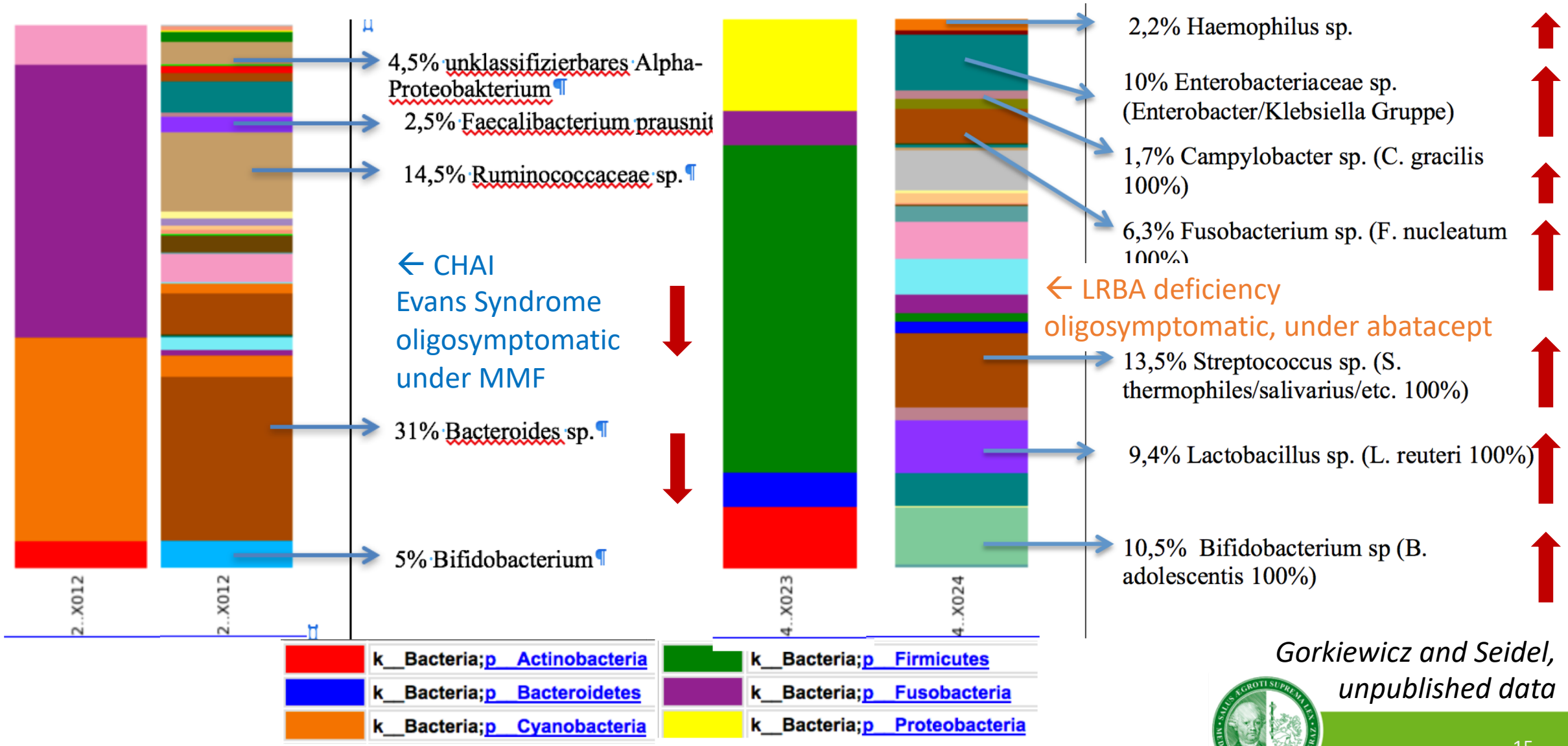
Acquired Senescent T-Cell Phenotype Correlates with Clinical Severity in GATA Binding Protein 2-Deficient Patients

Raquel Ruiz-García[1,2], Carmen Rodríguez-Vigil[3], Francisco Manuel Marco[4], Fernando Gallego-Bustos[1], María José Castro-Panete[1,2], Laura Diez-Alonso[1], Carlos Muñoz-Ruiz[4], Jesús Ruiz-Contreras[2,5], Estela Paz-Artal[1,2,6,7], Luis Ignacio González-Granado[2,5†] and Luis Miguel Allende[1,2†]*

FIGURE 1 | Peripheral blood T-cell compartment in GATA2-deficient patients. **(A)** Percentage of $CD3^+TCR\alpha\beta^+$ and $CD3^+TCR\gamma\delta^+$ T cells of GATA2 patients and healthy donors. Example representing $CD3^+TCR\alpha\beta^+$ and $CD3^+TCR\gamma\delta^+$ T cells from P3 and a healthy control. **(B)** $CD4^+$ and $CD8^+$ T cells subsets and examples of P1, P4, and a control (adult). Naïve $CD4^+$ ($CCR7^+CD45RA^+$), memory $CD4^+$ ($CCR7^+CD45RA^-$), naïve $CD8^+$ ($CCR7^+CD45RA^+$), memory $CD8^+$ ($CCR7^+CD45RA^-$), and TEMRA $CD8^+$ ($CCR7^-CD45RA^+$). P1 and P3 were compared with children controls whereas P2 and P4 were compared with adult controls. Lines represent mean and bars represent the standard error of the mean. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.



Epigenetic regulators: Microbiome & cytopenias? prospective studies warranted



Gorkiewicz and Seidel, unpublished data

Severe Immune Cytopenia Registry: www.SIC-reg.org

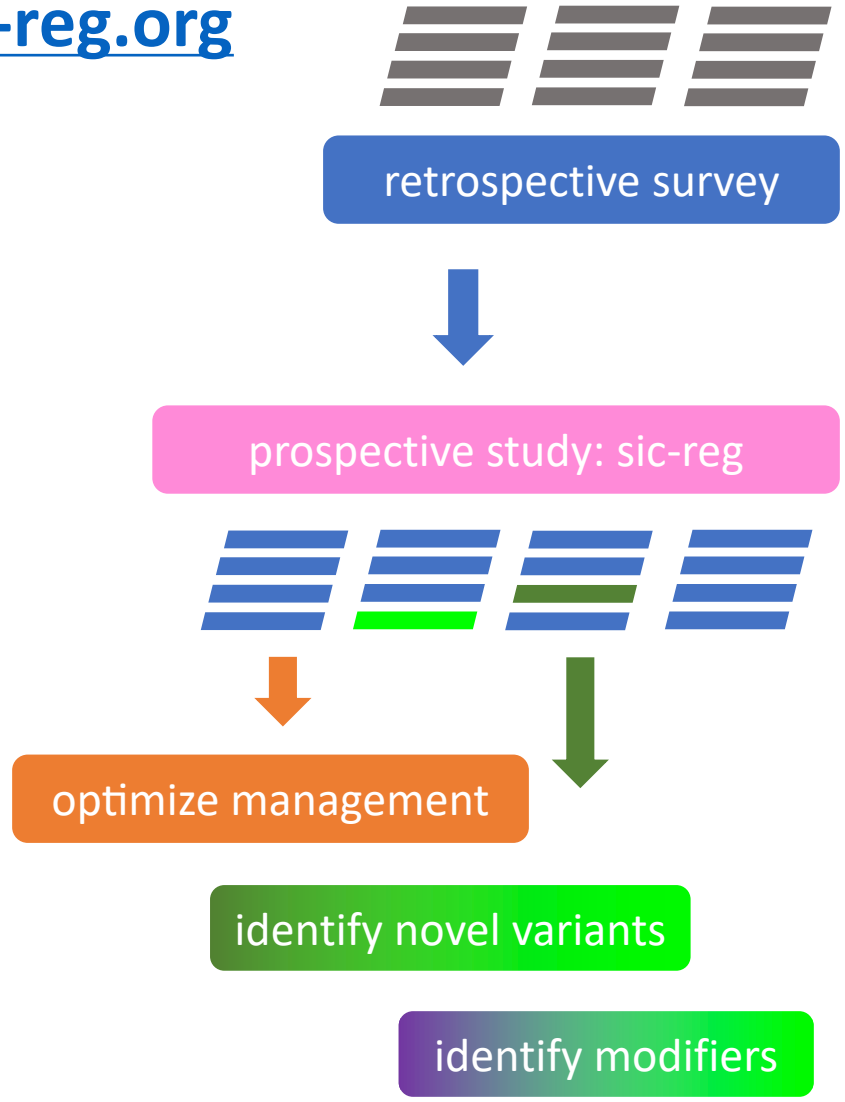
Developed with help of Oliver Kindler, diploma student, now M.D.

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



Synopsis

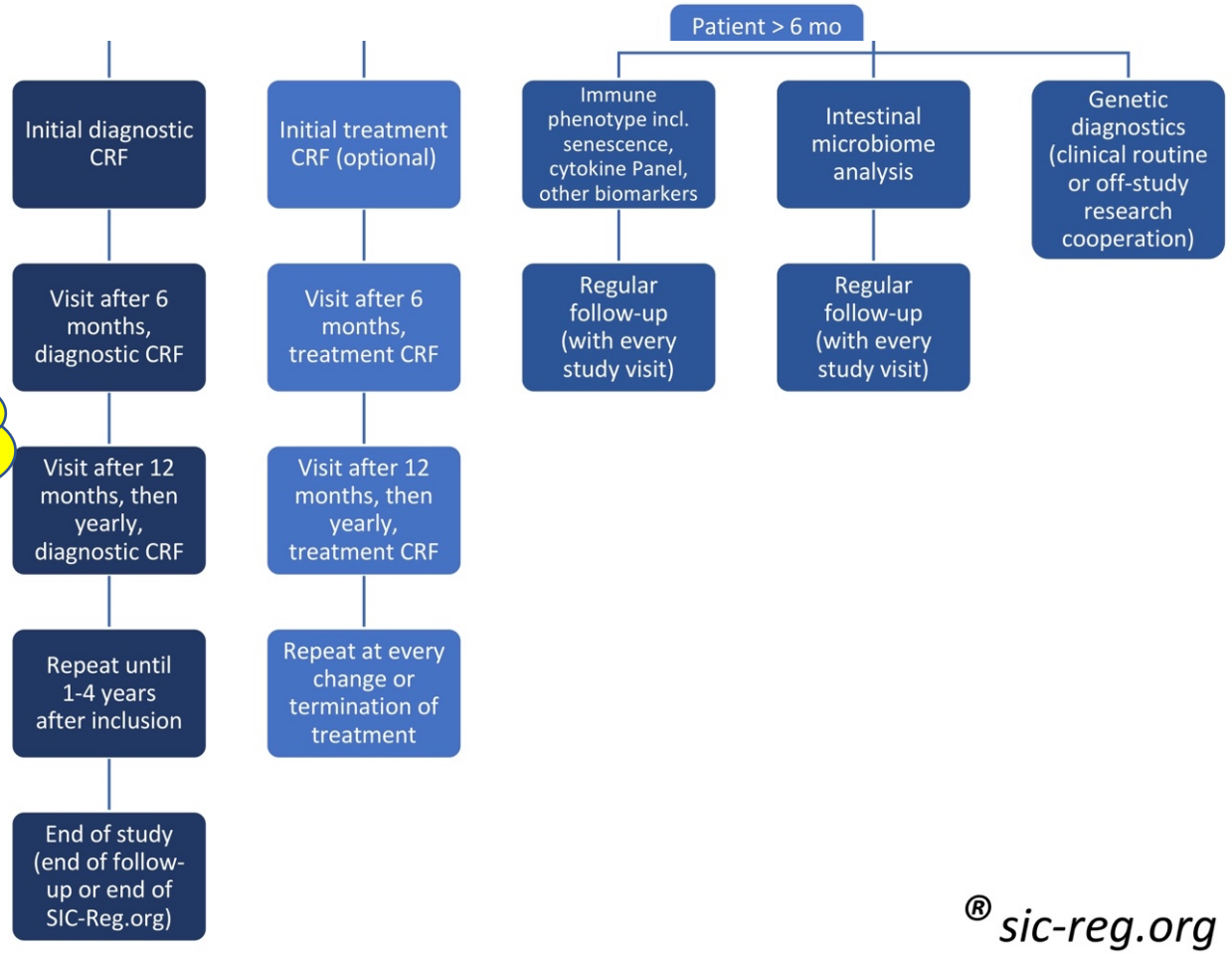
Inclusion criteria:

1. Patient >6m <25yrs
2. persistent & chronic ITP (>6 months after first manifestation)
3. AIHA (immediately)
4. Evans Syndrome (immediately)

Exclusion criteria:

1. No malignancy or HSCT

cause of secondary ID → secondary ITP



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- Time points (months): 0, 6, 12, 24, 36, 48
- CRF, blood, stool
- Everything may be done locally
- Biomarker analyses may be sent to Graz
- *Non-exclusive:* patients will be registered within appropriate disease-specific other registries as well (e.g. PARC-ITP; EWOG-MDS; Fanconi Anemia Registry…)

hematological causes

Congenital TP	giant platelets? MPV, IPF morphology	family history (kidneys, cataract...)	GPS, MYH9, WAS, BSS, GT, ... (IFM, FACS)	vWS II, HUS, coagulation, vWF:Ag, vWF:Rco, ADAMTS13	3 extremely rare genetic diseases discovered
Hemolytic anemia	morphology, hemolysis ? MCV, RDW, Reti fragmentocytes	Coombs blood group Plt/Neutroph-Abs	Hb el'phor, B12, folate, RBC-enzymes, methylmalonacid-uria, homocystein	CAD cold/warm agglutinins, C3d; TMA sC5-9, C3	hematology gene panel (WES)#
BMF, malignancy	MDS-RCC, [SAA], OP, DBA, RD BM-morphology cytog	Fanconi A. MC)	SDS stool/elastase Gaucher's D. enzyme/gene	DKC (Telomeres), PNH (FACS), GATA2 (DC-ratio)	hematology gene panel (WES)#

Secure early diagnosis to start correct treatment

Searching for a common pattern

immunological causes

Primary immuno-deficiency	ALPS DNT, biomarkers	CVID Bmem,IgG,A,M vaccin. Ab, IgE	CID naive T, TRECs, gdT, proliferation	senescence* cytokines* CTLA4*, LRBA*	PID gene panel
Auto-immune disease	SLE ANA, dsDNA, ESR, APLA, CH50/AH50	AITD, DM autoantibodies	enteropathy celiac d., VitA calprotectin, other: neurological, joints, skin, etc.	IGF, BP3, HGH PTH, VitD3 P-STAT3/5*	gene panel (WES)#
Infection	CMV parvo-B19 HHV6, ...	HCV, HIV EBV, AdV	Helicobacter, Campylobacter	stool: microbiome*	

2 extremely rare genetic diseases discovered

Searching for a common pattern

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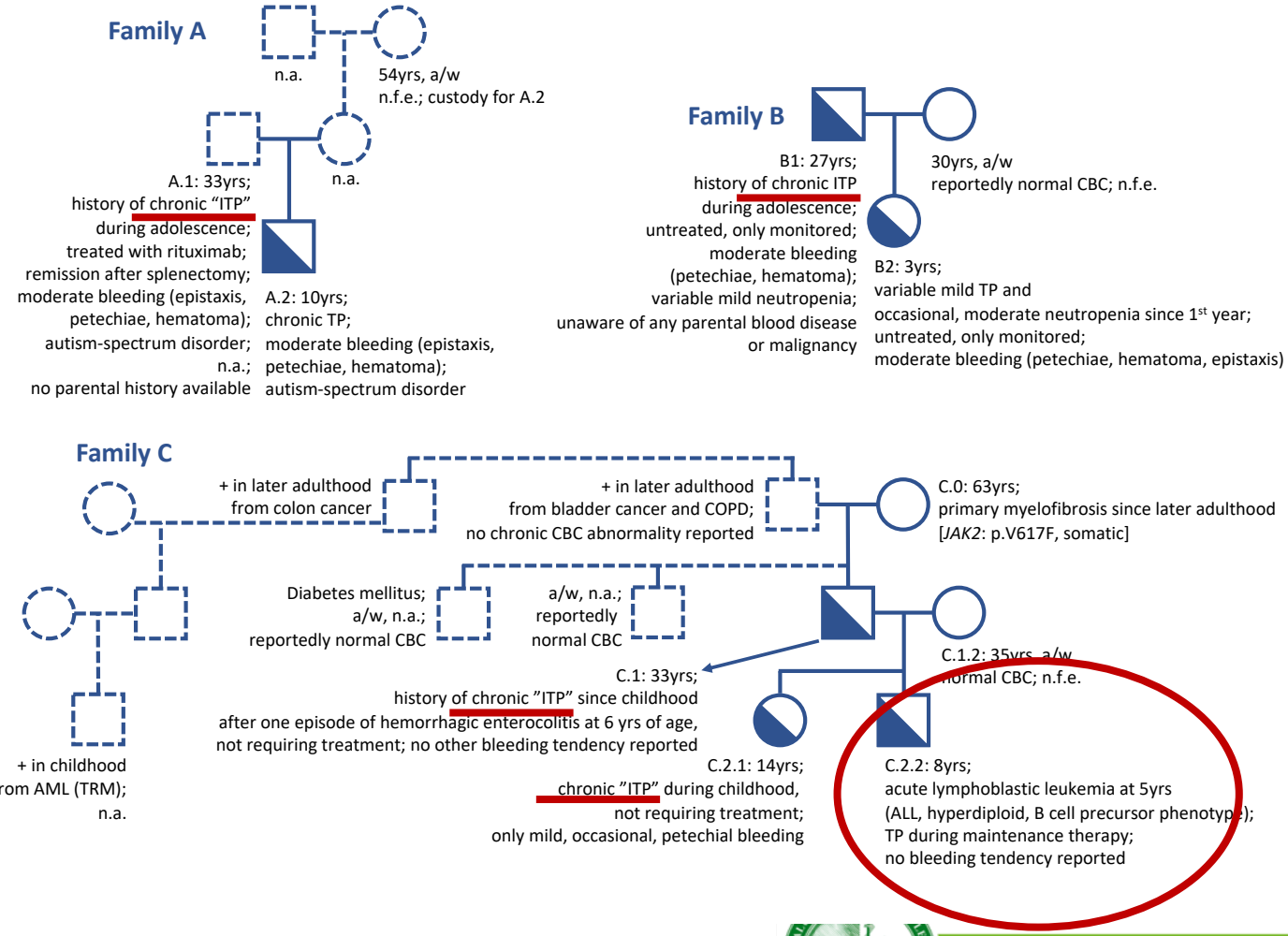
DD congenital thrombocytopenia, examples

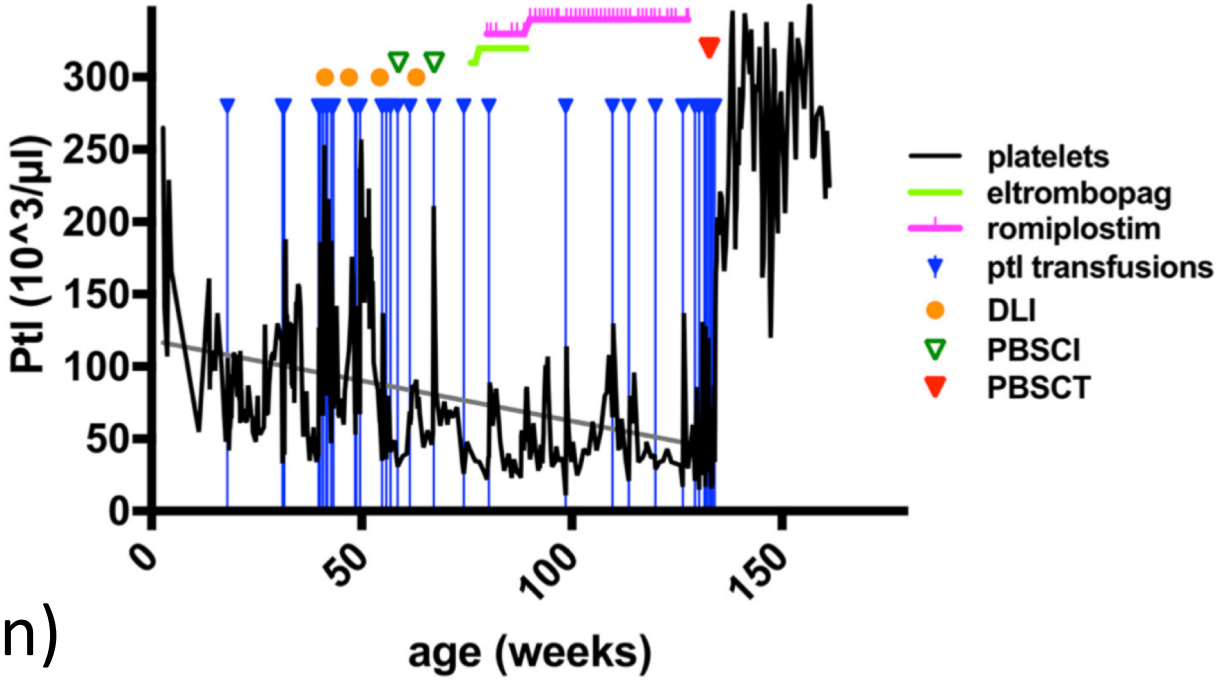
- 16 of 65 chronic TP (admission Dg = ITP) in Graz cohort → not ITP!
- 4 (+ 3 adult relatives) with *ETV6*-linked leukemia/familial thrombocytopenia syndrome (ELFTS) – the most frequent
- GFI1b, GATA2, MYH9, osteopetrosis, M. Gaucher…
- DKC (TINF2)
- PNH, FA, RCC

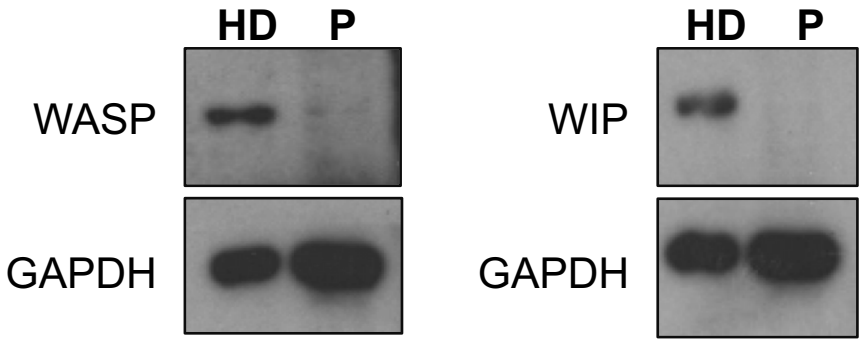
Suppl. Figure 1.

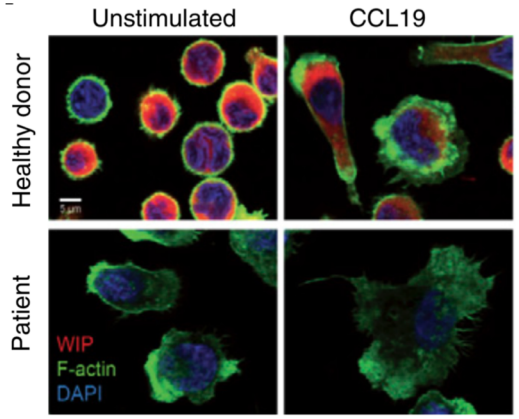


DD primary immunodeficiency, example

- Infant with CMV bronchiolitis and thrombocytopenia
- >90days mechanical ventilation
- Klebsiella sepsis
- Low naïve T cells
- Diagnosed with **WIP deficiency** (Wiskott Aldrich interacting protein)







Front. Immunol. 2018; 9:2554.

BLOOD 2017; 130:1949-1953

Treatment is only documented

Extract of international recommendations, *sic-reg.org* assumes no liability whatsoever

AIHA, ES: goal = remission

first line options:

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

second line options#:

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

Rituximab 375mg/m2 qw, 4 times, or 2x1g/m2 q2 wks (consider prior vaccination pneumoc., HiB, meningoc.)

[Methylprednisolone 10-30mg/kg/d>4days]

[Dexamethasone 5-10mg/m2>4days]

third line options#:

danazol, AZT, VCR, splenectomy, bortezomib$, carfilzomib$, eculizumab* (CAD, PNH), CY, CSA, ibrutinib$, daratumumab$,…, HSCT

No liability!

cITP: goal = no risk of hemorrhage, QoL

first line options -if treatment is needed at all:

IVIG 0.5-0.8 g/kg according to local standards
- 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 options#:

MMF 1200mg/m2/day ± prednisolone
- if DNT ↑: sirolimus instead of MMF
- if signs of CID, consider targeted therapy*, HSCT

TPOR-Agonists: eltrombopag 25-50mg/day (0.8-1.2mg/kg <6yrs); or romiplostim 100-250µg/m2/week (1-10µg/kg)
- wean off MMF after 6-12 months over 3-6 months#

third line options#:

rituximab, danazol, AZT, VCR, Dapson, (Retinoids$)

adults: splenectomy (vaccinate!, OPSI-prophyl.)…

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No liability!

*#order depending on immune or phenotypical abnormality; * if underlying disease is identified (e.g. p110 inhib. in APDS-study, abatacept in LRBA-deficiency & CTLA4 haploinsufficiency, eculizumab in PNH, TMA, or TTP….), ideally within clinical studies; $largely anecdotal evidence, ideally done within clinical studies; grey font used for approaches with scarce evidence.*

Kühne T. Hamostaseologie. 2016 Oct;37(1):36–44. ; Teachey DT, Lambert MP. Pediatr Clin North Am. 2013 Dec;60(6):1489–511. ; Grace RF, Neunert C. Hematology. 2016;2016(1):698–706. ; Miano M. Br J Haematol. 2016 Feb;172(4):524–34. ; Go RS, Winters JL, Kay NE. Blood. 2017;129(22):2971–9. ; Miano M, Scalzone M, Perri K, Palmisani E, Caviglia I, Micalizzi C, et al. Br J Haematol. 2015 Oct;171(2):247–53. ; Panigrahi A, Clark A, Myers J, Raj A. Pediatr Blood Cancer. 2017 Feb;64(2):287–93. ; Ladogana S, Maruzzi M, Samperi P, Perrotta S, Del Vecchio GC, Notarangelo LD, et al. Blood Transfus. 2017 May;15(3):259–67. ; Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Crowther MA, et al. Blood. 2011 Apr;117(16):4190–207. ; Cuker A, Neunert CE. Blood. 2016 Sep;128(12):1547–54.

Recruitment & Participating centers

- Opened April 2018
- https://clinicaltrials.gov/ct2/show/NCT03576742

- Officially as “pilot phase”
  (additional analyses and grant proposal are planned)

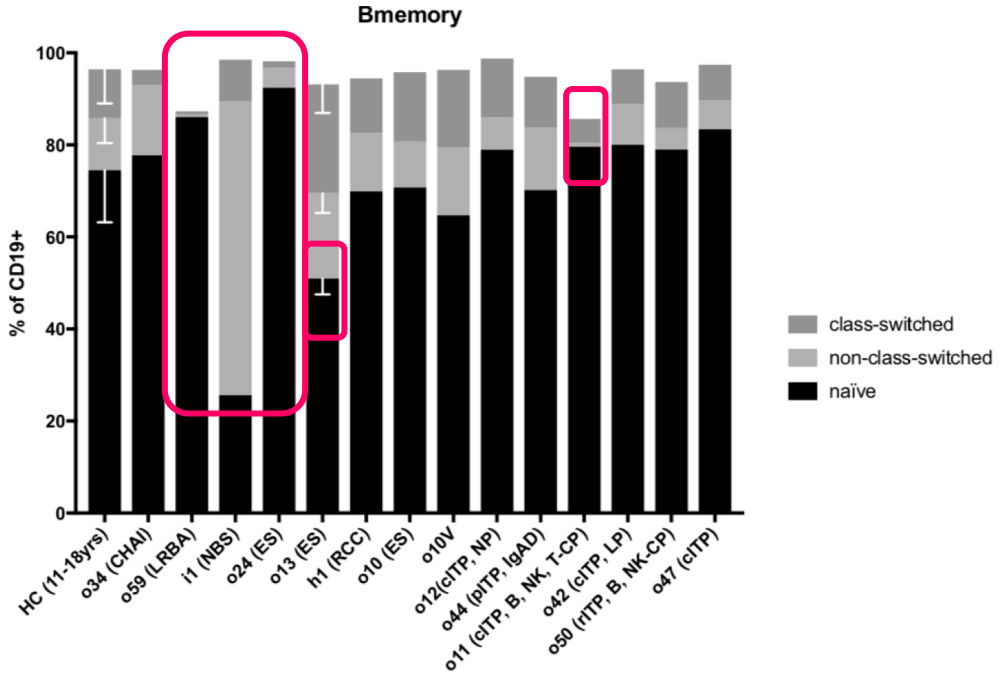
- Patient characteristics as of Aug.2019:
  - 14 patients | 8:6 f:m | 3-22yrs (median 8)
  - cITP:6, ES: 5, AIHA:3,
  - “real prospective” (at initial episode): 10
    “at relapse or follow-up”: 4

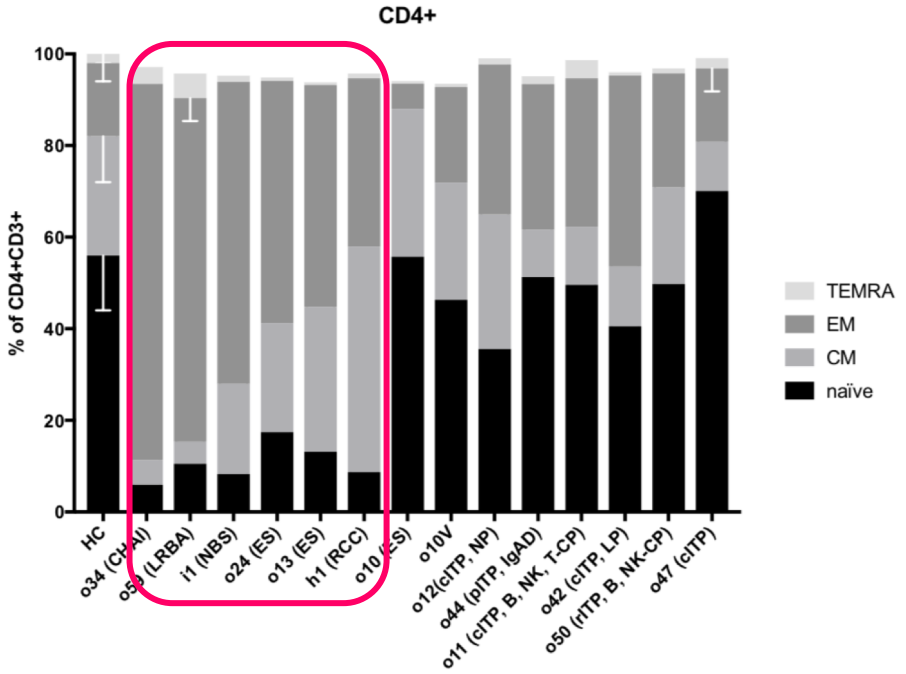
- Centers : patients
  - Austria:
    - Graz / ped. hem.-onc.: 12
    - Graz / adult hematology: 1
    - Klagenfurt peds.: 1
    - Innsbruck: 0
  - Italy:
    - Padua started enrolling (ethics approval pending)
    - Florence (in preparation)
    - Brescia (planned)
    - Monza (planned)
    - Rome (in preparation)
  - Solvenia and Bulgaria
    - Planned
  - Spain
    - Madrid (in preparation)

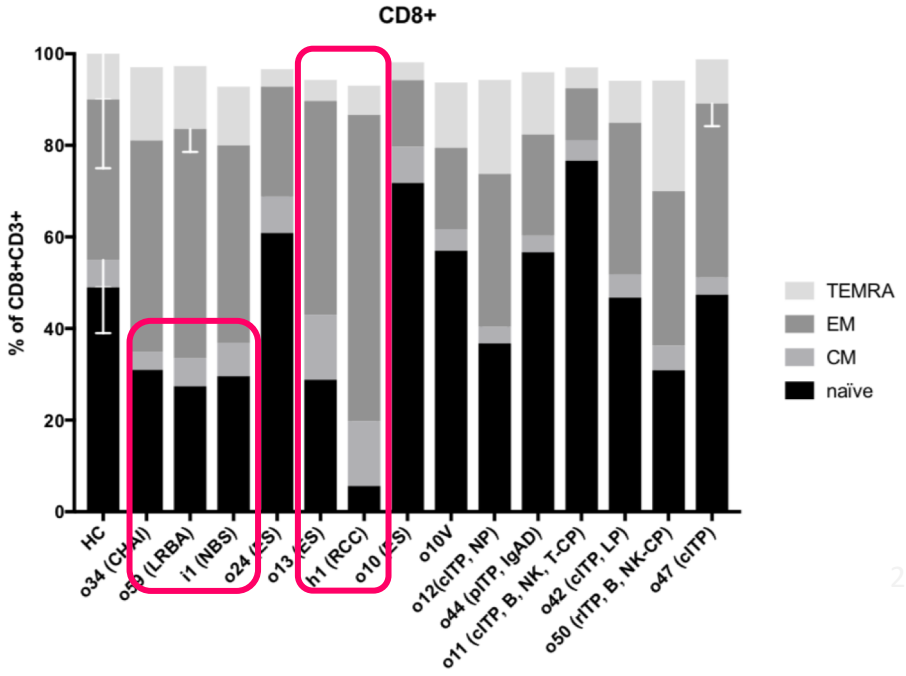
Memory markers | B and T cell differentiation

Preliminary data:

- Cluster formation, especially in CD4+ T cells
- Differences between Evans Syndrome and cITP
- Known clear PIDs „stick out“



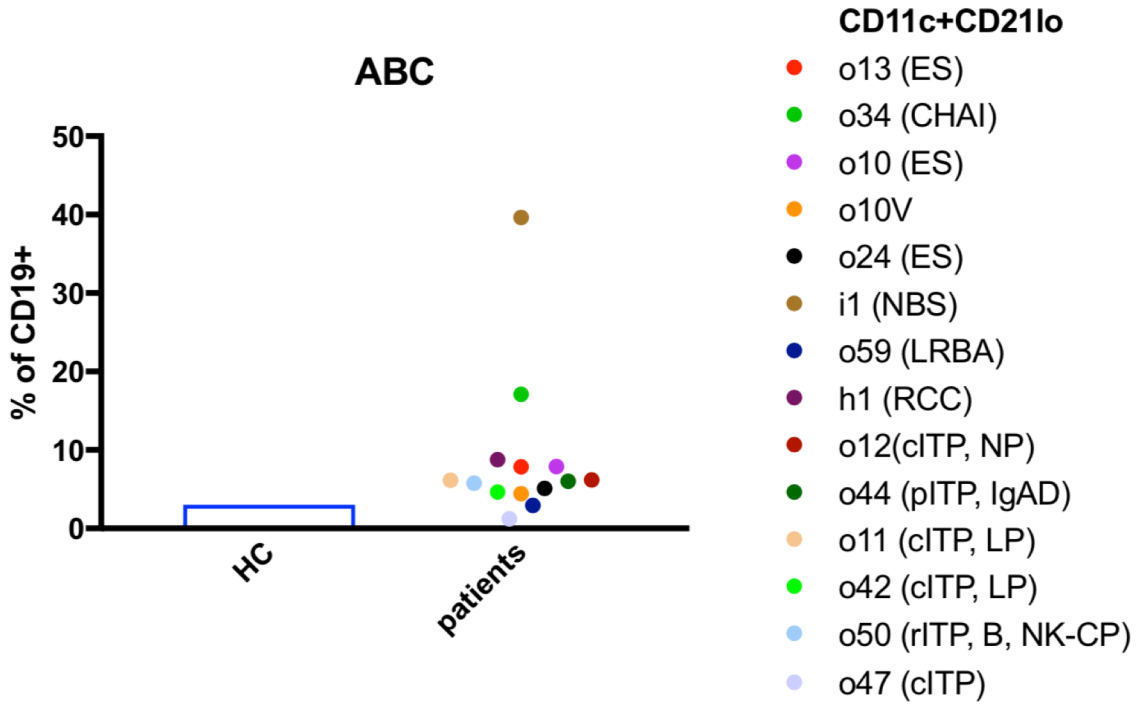


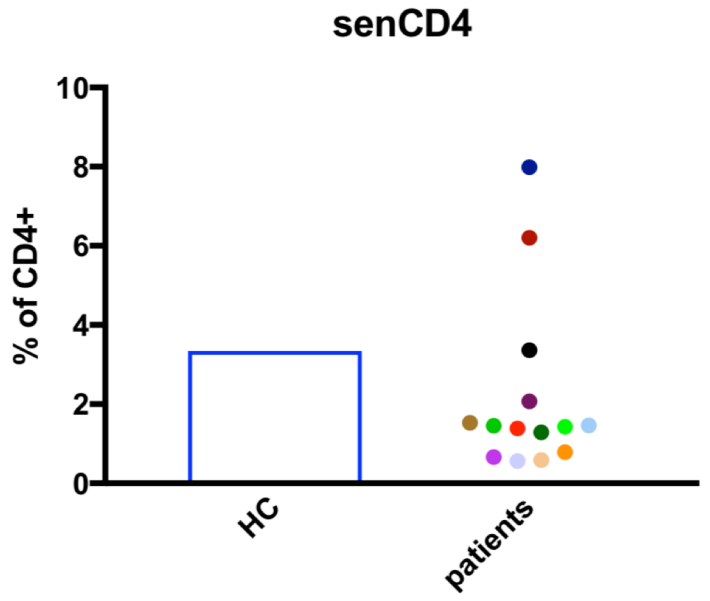


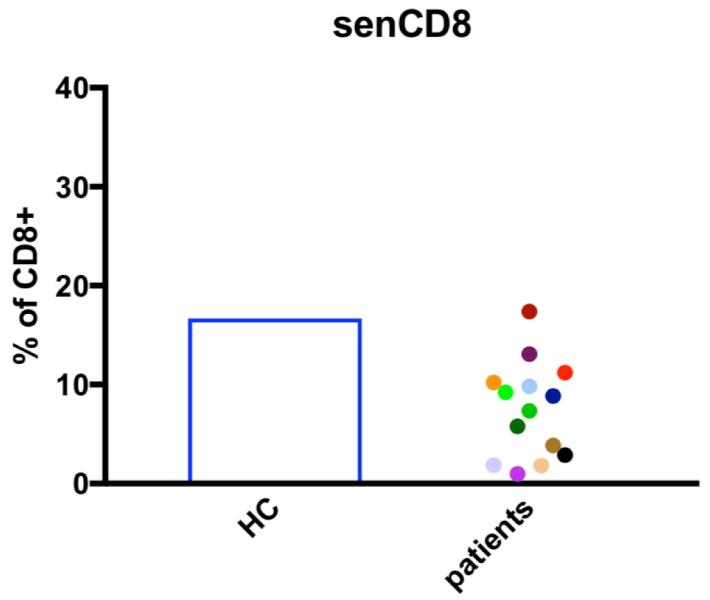
Senescence markers | B and T „ageing“

Preliminary data:

- Only some PIDs stick out

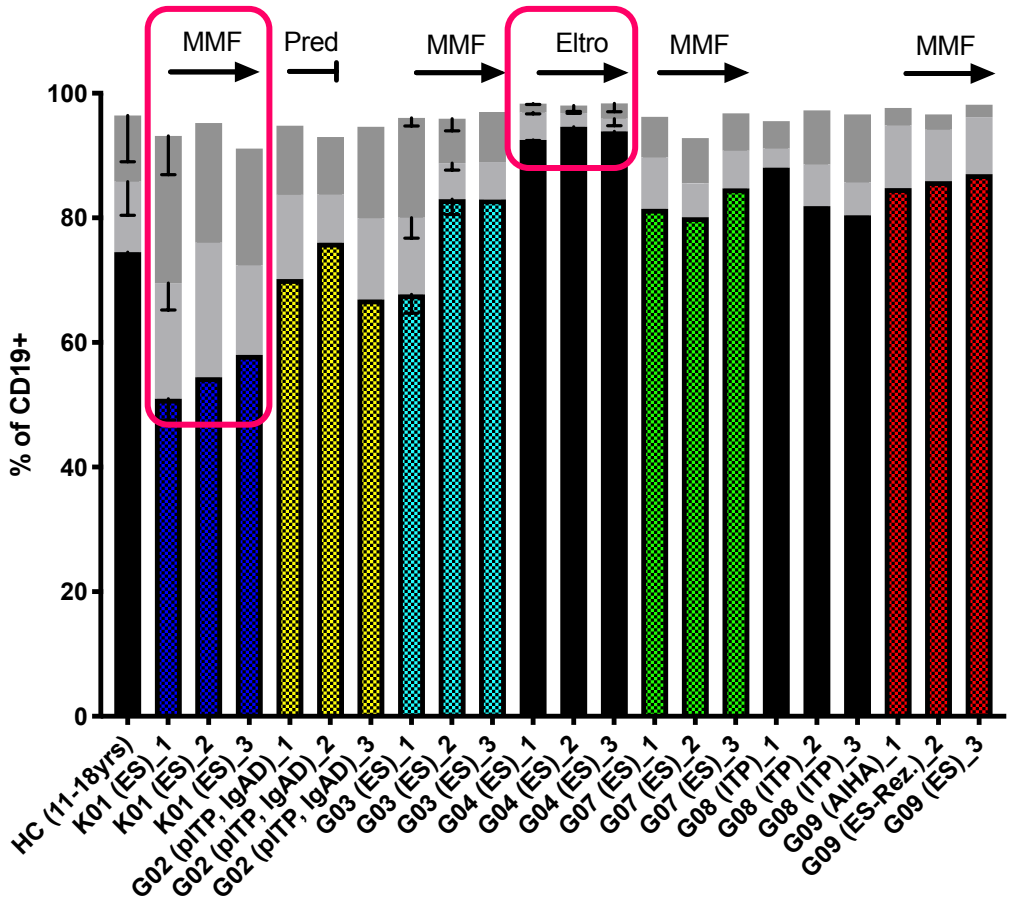


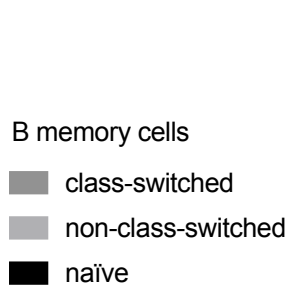


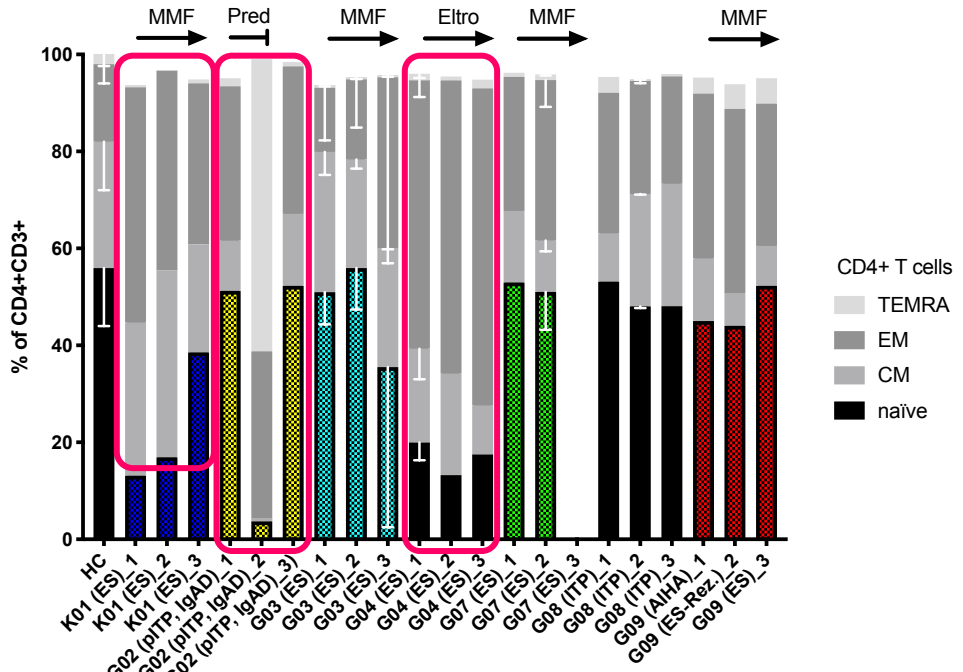


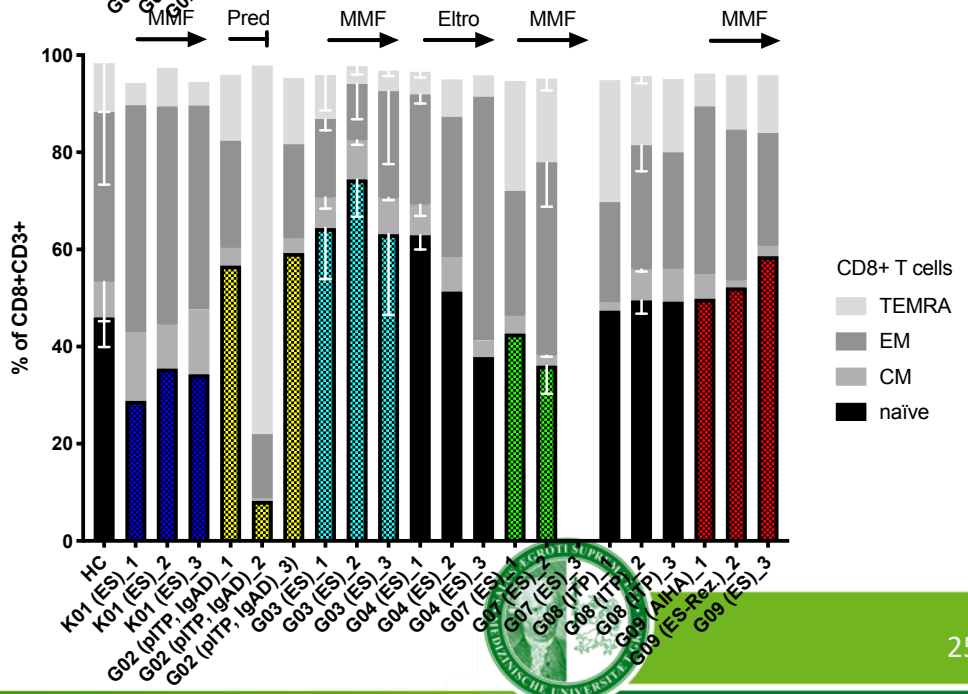
Longitudinal analyses

- Per patient/treatment phase









Data documentation

- History
- Clinical
- Lab
- Treatment

- → documented at each time point and evaluated later
  - longitudinally (per patient) and
  - cross-sectionally (per disease / cohort)

- PARC-ITP items (CRF) will be forwarded directly
  - additional ICF for patients with ITP
  - currently 3 of 14 pts (in progress)

- If other DD is found, then patient is registered in respective registry
  - Used as “observational patient” in sic-reg to compare lab phenotype
  - 1x follow-up in 6-12m

Conclusions and perspectives

- There are abundant causes of “secondary” ITP or SIC in children and adolescents
- A prospective clinical registry study is needed
- A standardized diagnostic algorithm, mainly to raise awareness of other DD and exclude them, is available at www.sic-reg.org
- Patient boards and “counseling” are part of the study
- Biomarker study will be extended
- Additional participating centers are welcome (including Swiss pediatric hem/oncology, German GPOH, ASPHO…)!
  Email: markus.seidel@medunigraz.at or office@sic-reg.org

background ker DD SIC-REG study results conclusions

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Thank you for your attention!