



EHA-GBMTA-AHA Hematology  
Tutorial:

# New aspects in diagnostic choices and treatment options of hematological malignancies

Session: Immunotherapy in Myeloid  
diseases

**Dr Shahram Kordasti MD, PhD**



# DISCLOSURES OF COMMERCIAL SUPPORT

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
Celgene	x						
Novartis	x				x	x	
Boston Biomed			x				
API			x				
Alexion			x				
Beckman Coulter					x		
MorphoSys	x						
Pfizer			x		x		

**KING'S**  
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**LONDON**



Systems Cancer  
Immunology Lab  
(SCI)  
NOT CSI

Alessandra Ferrelli  
Andreea Baloc  
Cristina Tentori  
Elena Riva  
Elena Torre  
Karen Larios  
Katy Strange  
Nicolas Sompairac  
Rita Reis  
Rosa Andres Ejarque  
Ziying Zhang

# Aims

To know more about the role of immune system in BMF

- Potential mechanisms.
- Differential Dx and clinical scenarios.
- Novel treatment approaches.
- Case review

# Bone marrow failure syndromes

**RBDS** – Ribosomal Dysgenesis Syndromes

**DC** – Dyskeratosis Congenita

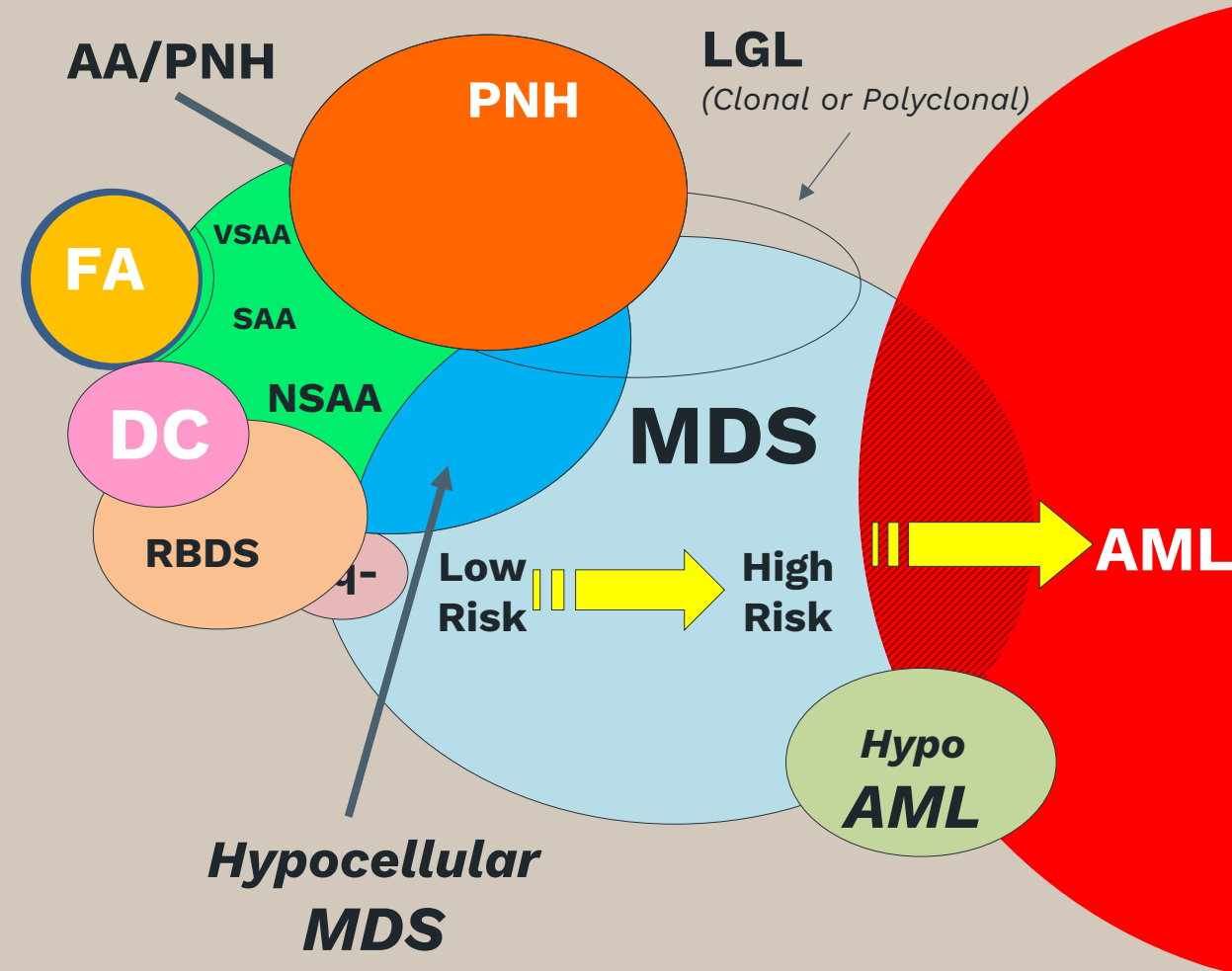
**FA** – Fanconi Anaemia

**AA** – Aplastic Anaemia, **SAA** – Severe AA, **NSAA** – Non severe AA, **VSAA** – Very Severe AA

**PNH** – Paroxysmal Nocturnal Haemoglobinuria

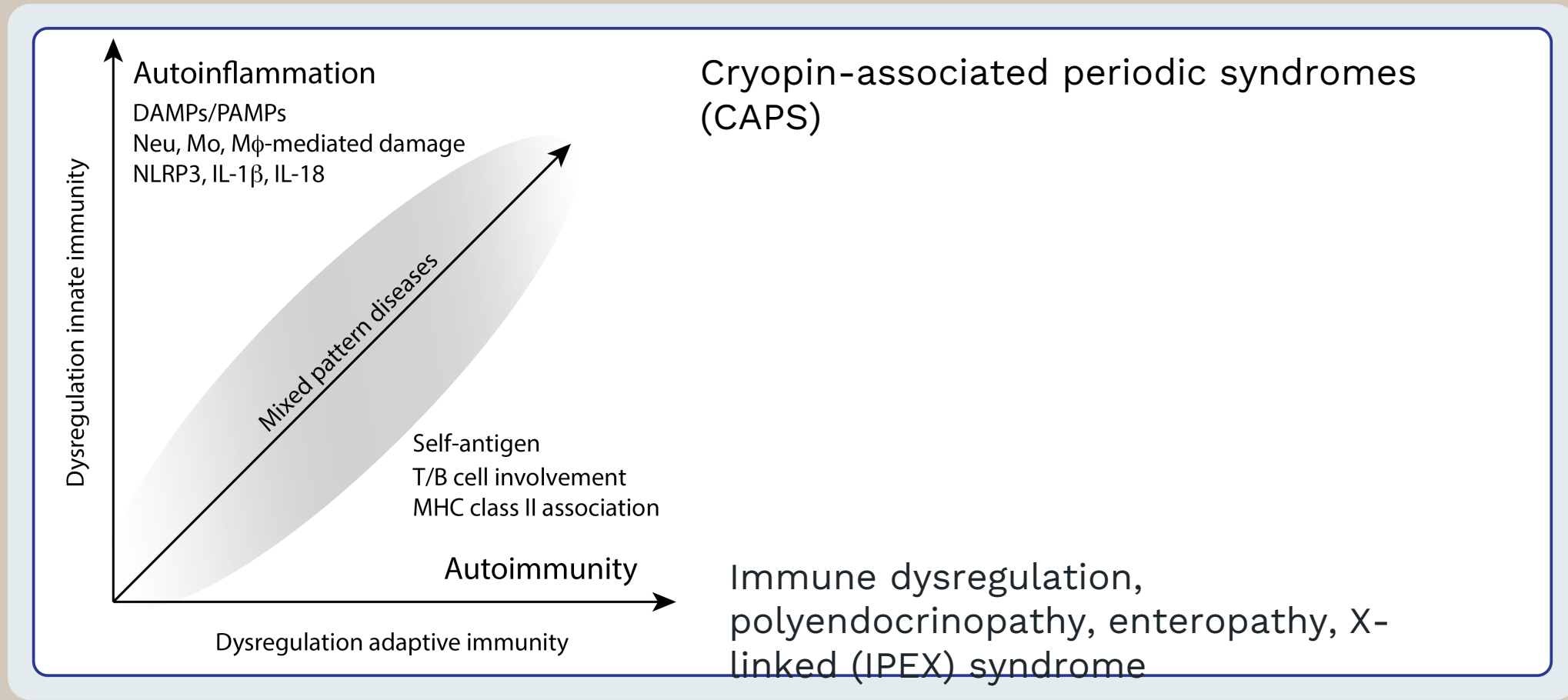
**LGL** – Large Granular Lymphocytosis

**AML** – Acute Myeloid Leukaemia

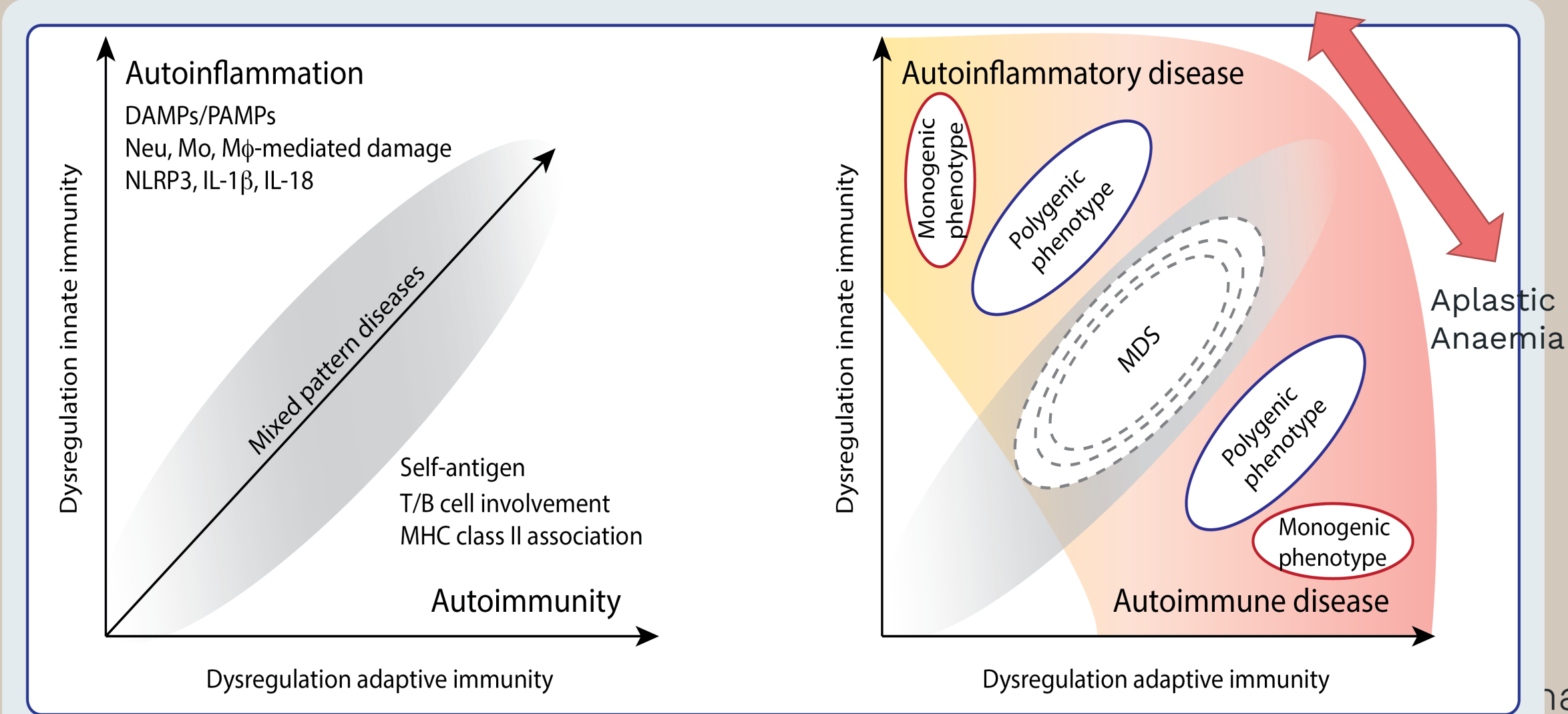


**Immune dysregulation**

# Autoinflammation vs Autoimmunity



# Autoinflammation vs Autoimmunity



Winter et al, JCO 2020

# Evidence of loss of immunological tolerance to self components

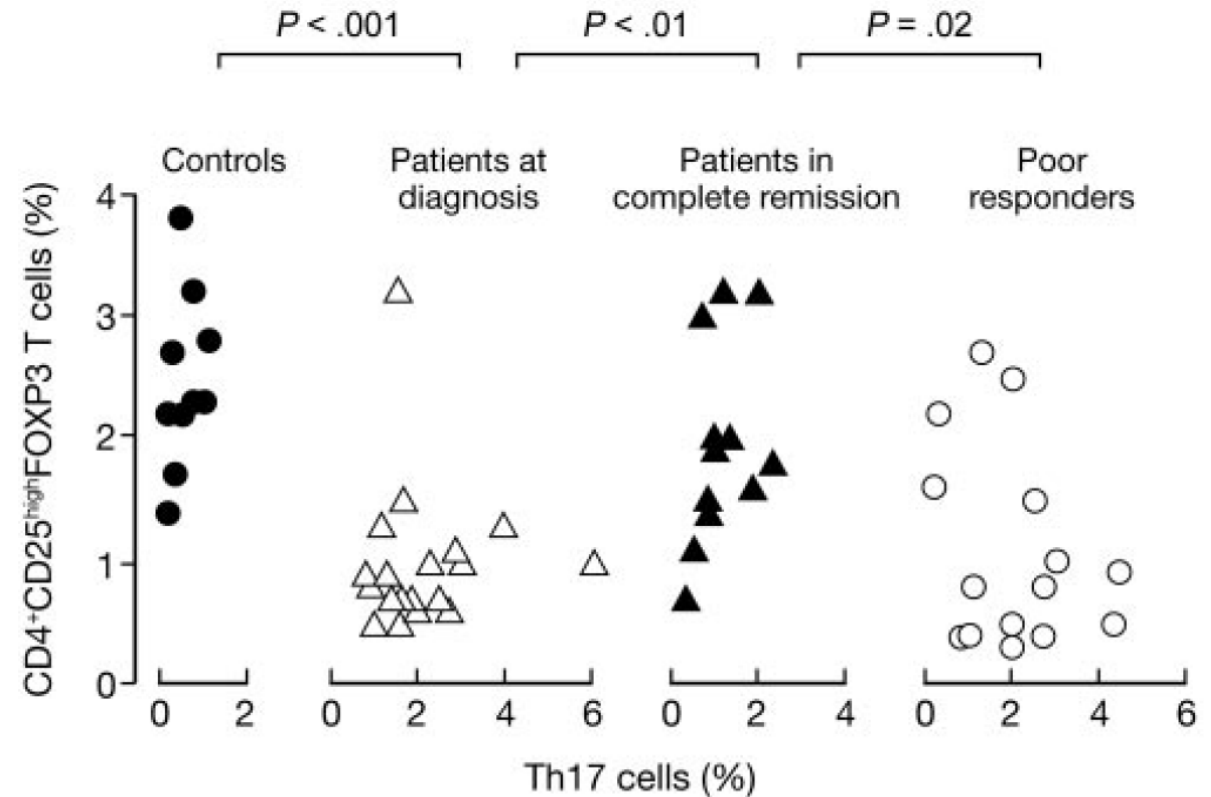
## In-vivo dominant immune responses in aplastic anaemia: molecular tracking of putatively pathogenetic T-cell clones by TCR $\beta$ -CDR3 sequencing

Antonio M Risitano, Jaroslaw P Maciejewski, Spencer Green, Magdalena Plasilova, Weihua Zeng, Neal S Young

## Changes in T-cell receptor VB repertoire immunosuppressive regimens

Hoon Kook, Antonio M. Risitano, Weihua Zeng, Marcin Wlodarski, Cr John Barrett, Neal S. Young, and Jaroslaw P. Maciejewski

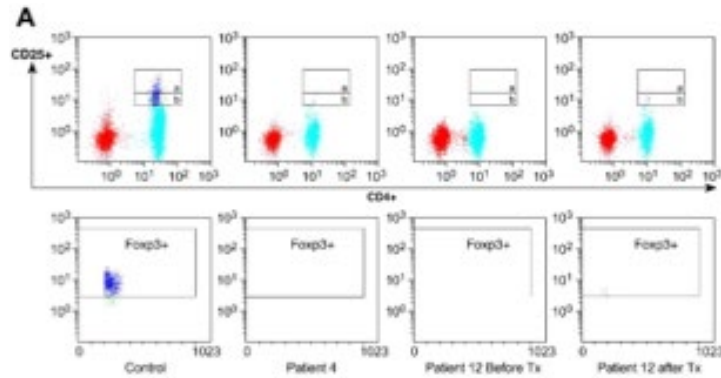
BLOOD, 15 MAY 2002 • VOLUME 99, NUMBER 10



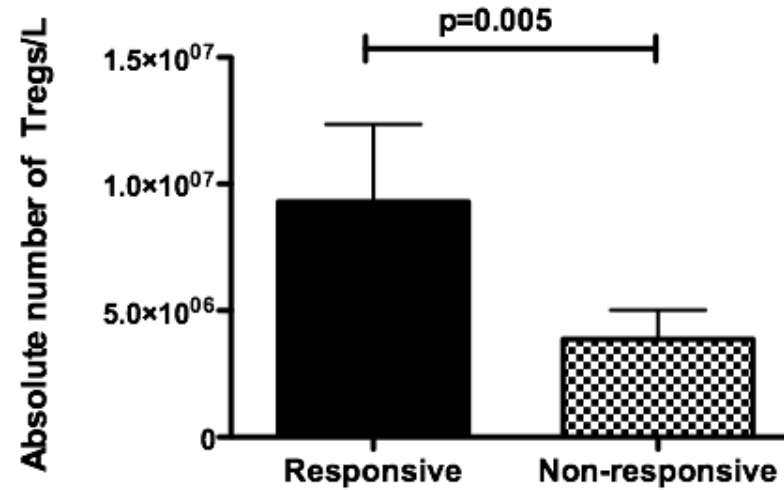
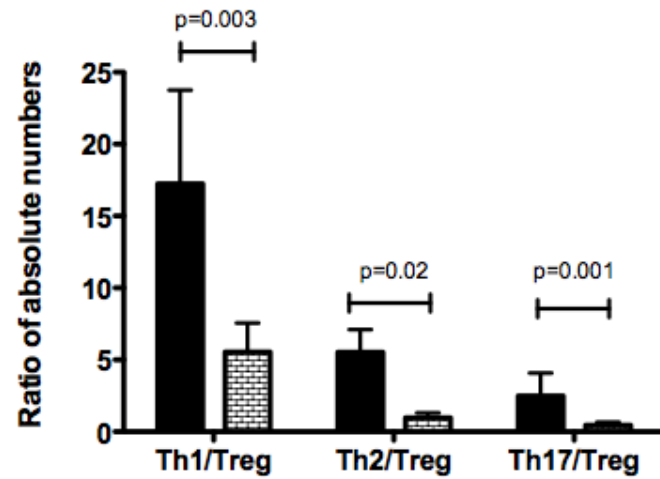
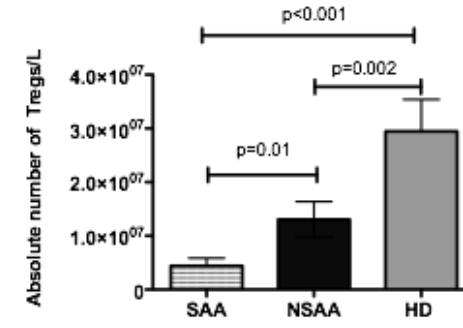
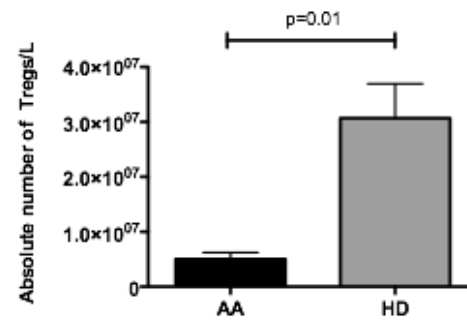
de Latour R P et al. Blood 2010;116:4175-4184



# Tregs in AA



Solomou E E et al. Blood 2007;110:1603-1606



Kordasti S et al. Blood 2012;119:2033-2043

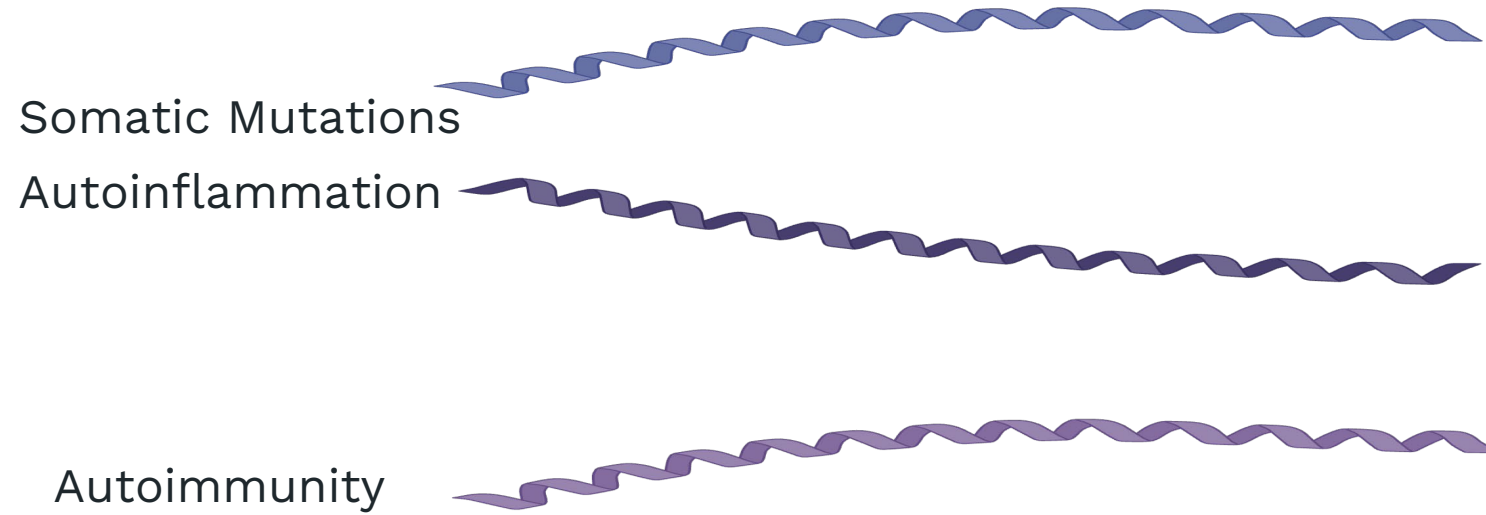
# Autoimmunity as a Predisposing Factor for MDS



A previous **history of any autoimmune disease** was associated with a 1.7-fold (95% CI, 1.5 to 1.9) increased risk for AML and **2.1-fold (95% CI, 1.7 to 2.6) increased risk for MDS.**

A population-based study included 9,219 patients with AML, 1,662 patients with

# Autoimmune "side" of MDS



# Inflammation and adaptive immune response

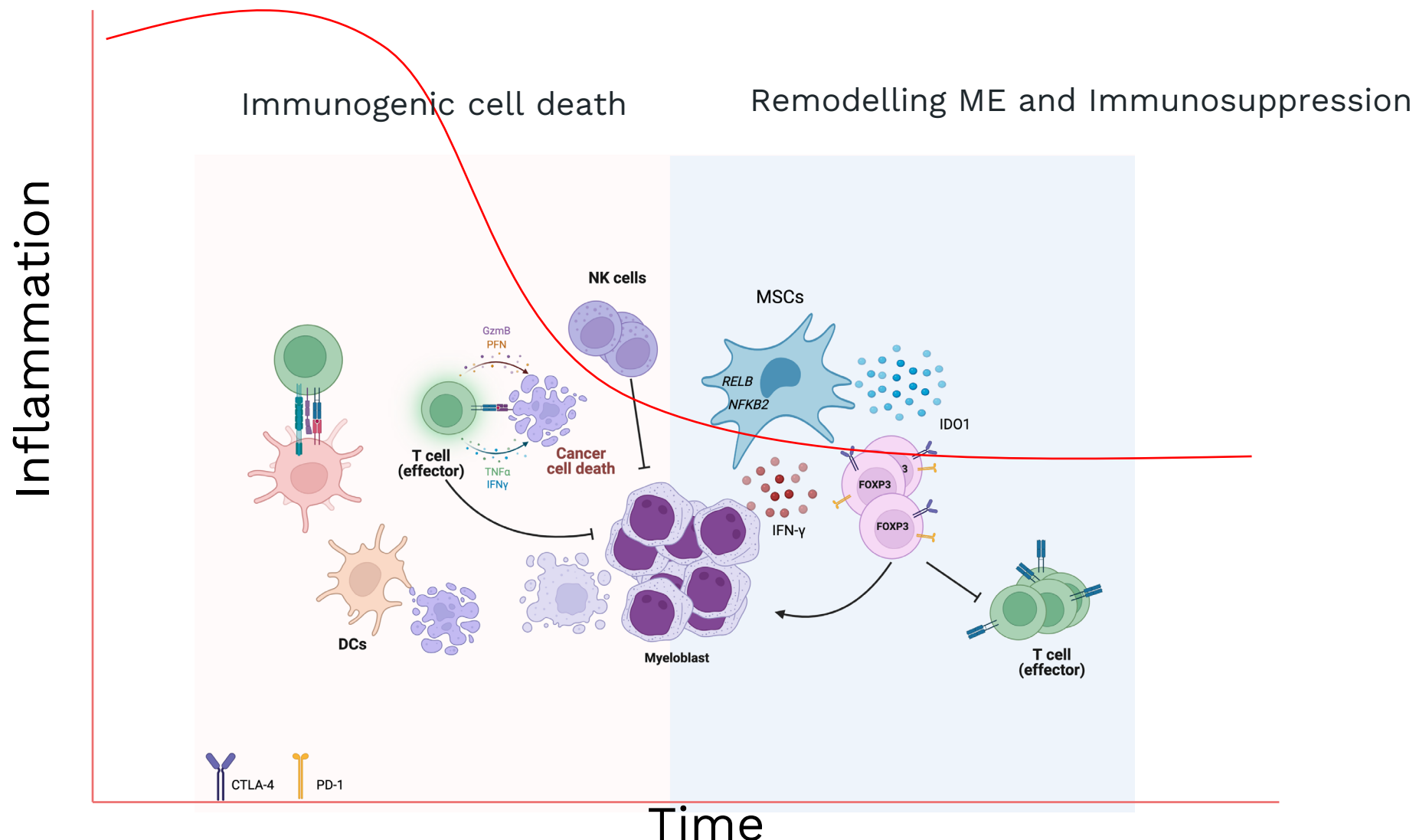
It's not binary

Time and Intensity

Dynamic and multifactorial

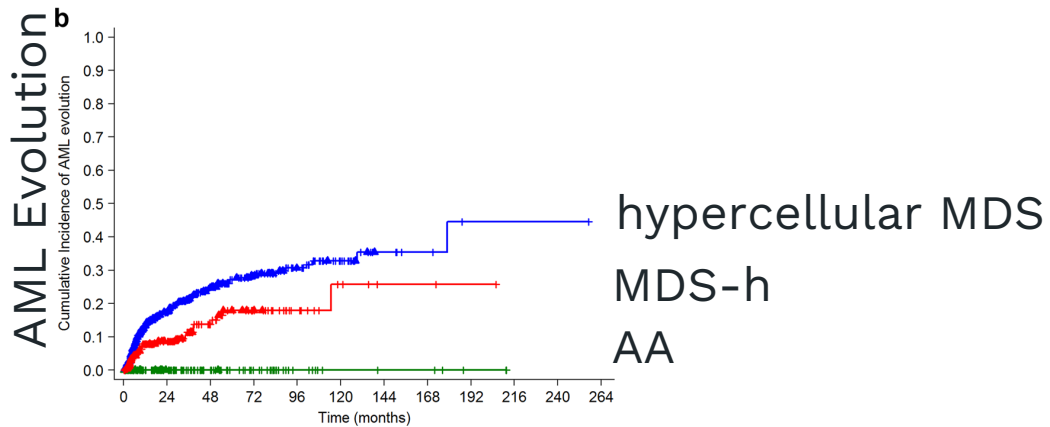
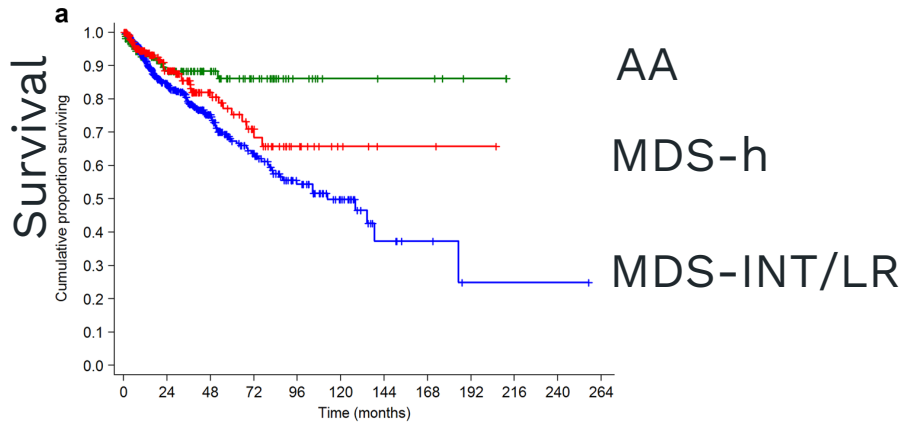


# Longer term effect of inflammation

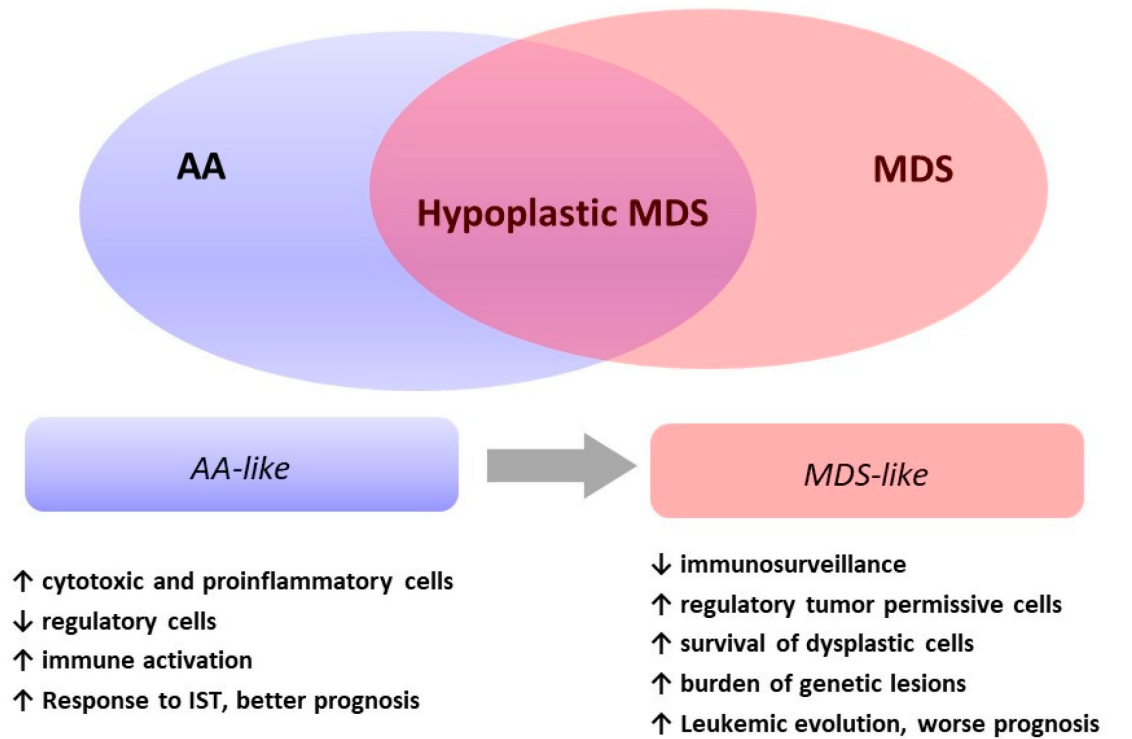


P. B. Ferrell and S. Kordasti, Clin Cancer Res, 2022  
Corradi, et al, Clin Cancer Res, 2022

# Clinical Importance

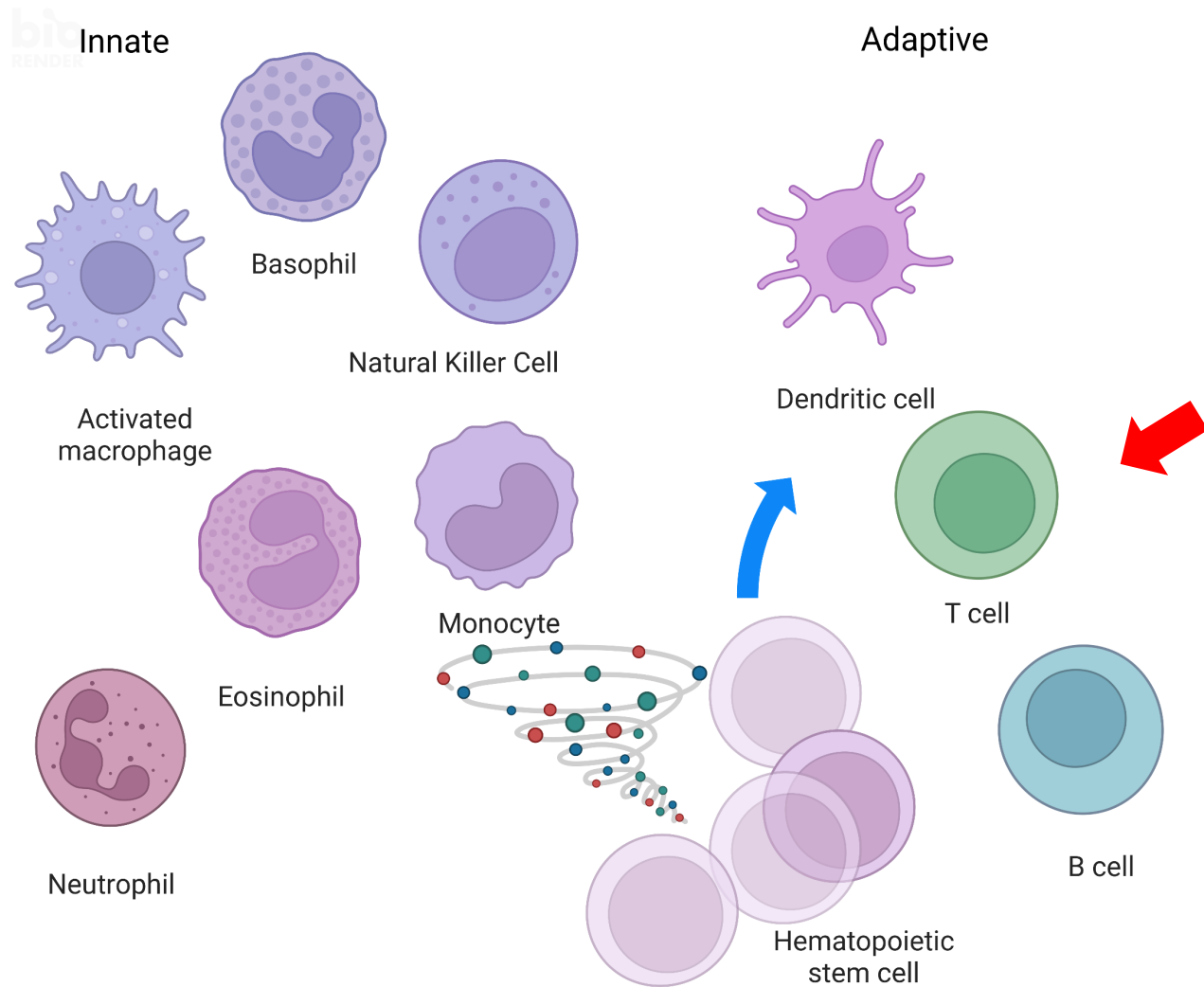


Bono et al, Leukemia 2019



Fattizzo et al, Cancers 2021

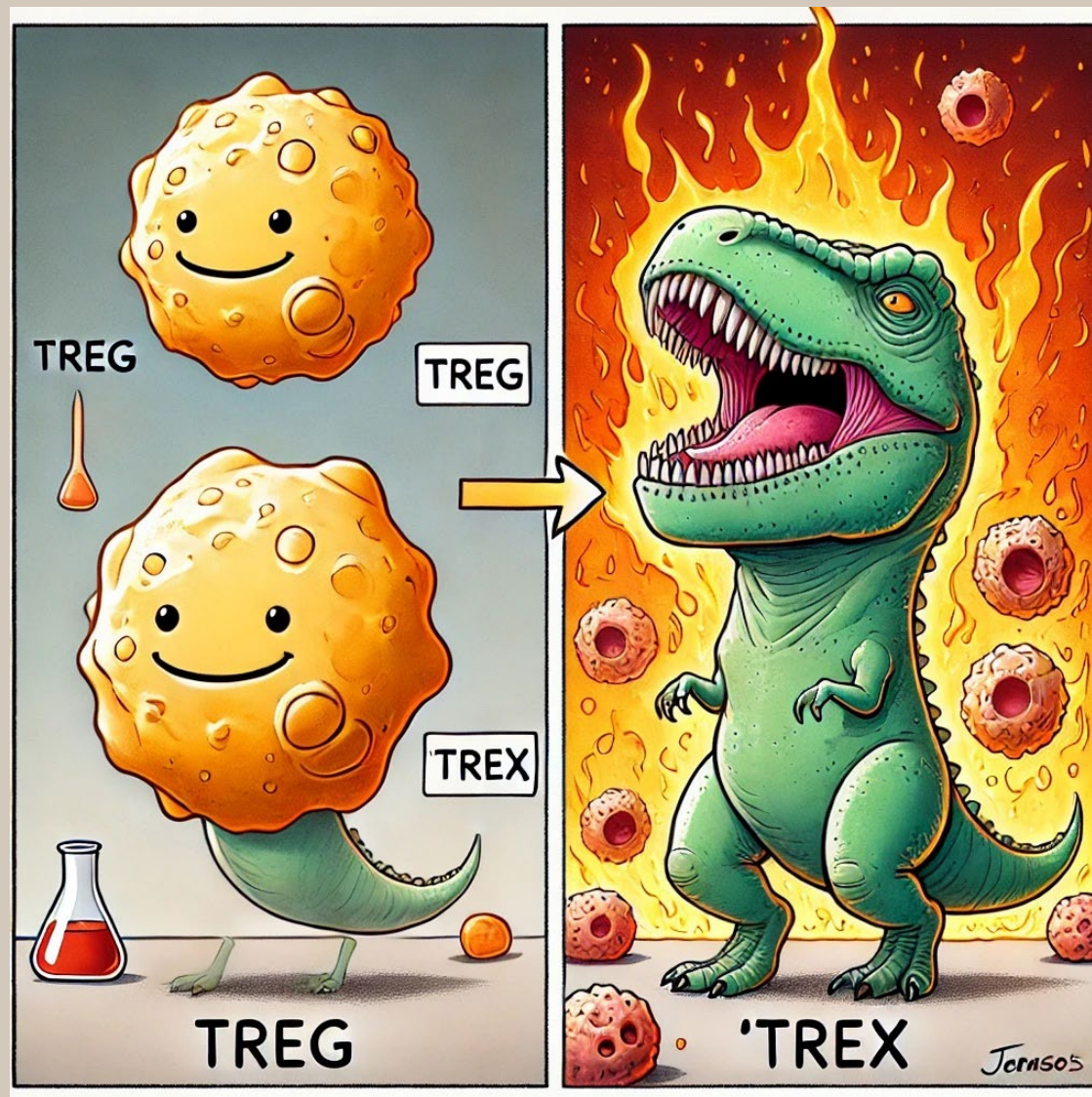
# Immunological Mess!



## Regulatory T cells (Tregs)

- Regulate immune response
- Affected by the immune response and reflect “the overall immune set-point”
- Plasticity as a potential target for treatment

# From Tregs to Trex!





# Immune Aplastic Anaemia (iAA) Clinical Aspects

# Diagnosis

Diagnosis of acquired AA requires the presence of **two of these cytopenias**:

- Hemoglobin  $<10\text{g/dL}$
- Platelet count  $<50 \times 10^9/\text{L}$
- Neutrophil count  $<1.5 \times 10^9/\text{L}$

# Diagnosis

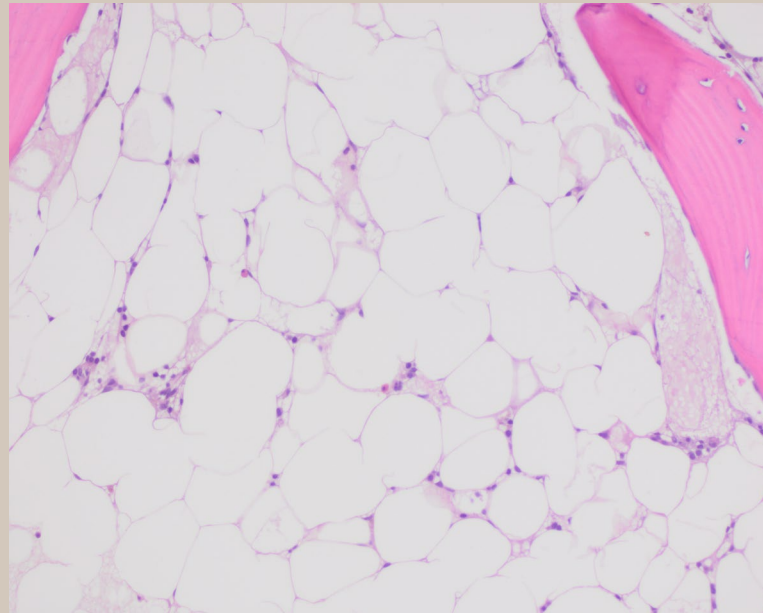
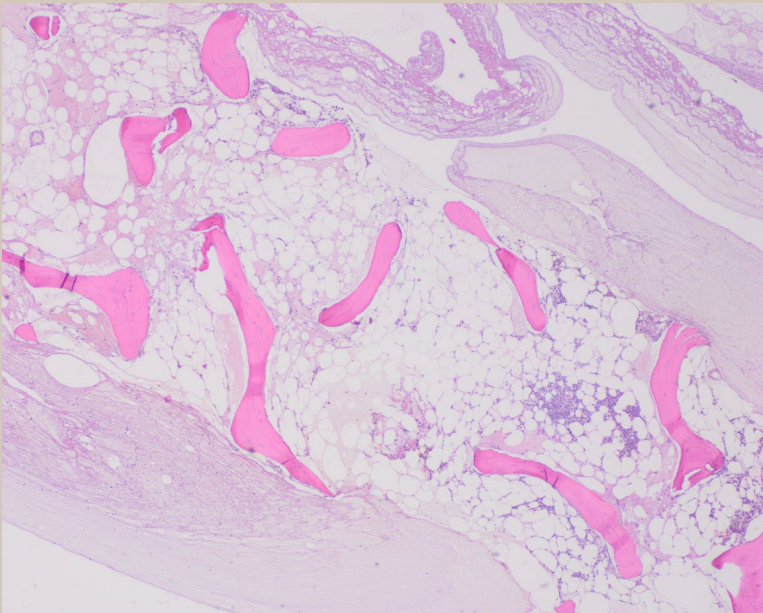
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Hemoglobin  $<10\text{g/dL}$

Platelet count  $<50 \times 10^9/\text{L}$

Neutrophil count  $<1.5 \times 10^9/\text{L}$

Diagnosis of AA is **confirmed** by bone marrow biopsy which shows hypocellular marrow with no abnormal infiltrate or increase in reticulin content.



# Severity

The severity of AA is defined based on degree of cytopenias and is considered severe if **two of these criteria** are present:

- Neutrophil count  $<0.5 \times 10^9/L$
- Platelet count  $<20 \times 10^9/L$
- Reticulocyte count  $<60 \times 10^9/L$  (automated counter) or  $<20 \times 10^9/L$  (manual counting).
- AA is deemed very severe when the neutrophil count is less than  $0.2 \times 10^9/L$ .

# Differential Diagnosis

- Aplastic Anaemia
- MDS and AML patients have hypercellular marrow but in up to 15% of cases a hypocellular marrow is seen.
- Malignant bone marrow infiltration i.e. hairy cell leukemia, Hodgkin and non-Hodgkin lymphomas, myelofibrosis, solid tumors as well as non-malignant diseases such as storage diseases (Gaucher's disease), histolytic disorders, osteopetrosis, atypical mycobacterial infection could lead to bone marrow failure and cytopenias.
- Anorexia nervosa and prolonged starvation.

# Additional tests

- Flow cytometry is mainly needed to detect and quantify **Paroxysmal Nocturnal Hemoglobinuria (PNH) clone**.
- Liver function tests as well as viral screening for hepatitis and HIV infection need to be done before establishing AA diagnosis.
- Auto immune screening which includes antinuclear antibody (ANA) and double stranded DNA (dsDNA) to rule out Systemic Lupus Erythromatosus.
- Radiological screening including chest X ray and abdominal ultrasound are necessary to exclude infections or malignancies.
- Serum levels of vitamin B12 and folate need to be measured as pancytopenia can be seen in severe cases of megaloblastic anaemia.
- **Chromosomal breakage analysis for spontaneous or induced chromosomal fragility to rule out Fanconi Anemia.**
- **Next generation sequencing for constitutional gene mutations such as for inherited telomeropathies ( DKC1, TERT, TERC among others), SBDS for Schwachman Diamond anaemia, GATA2 insufficiency.**
- Next generation sequencing for somatic mutations. Presence of acquired somatic mutations which are typical for myeloid malignancies such as MDS and AML could help to distinguish hypoplastic MDS from AA.

*However, presence of DNMT3a or ASXL1 mutated clones are reported in AA and by itself does not change the diagnosis.*

# Treatment

- The choice of treatment in AA largely **depends on patient's age and disease severity**.
- If suitable donor is available, allogeneic bone marrow transplantation is the treatment of choice in young (<40-50 years) patients with severe and very severe immune/ idiopathic AA which leads to 70-90% long term survival.
- Anti-thymocyte globulin (ATG) or Alemtuzumab is usually added to the conditioning regimen and radiation therapy should be avoided.

# Treatment

- Non-severe AA may not require therapy if the symptoms are mild. All patients with severe AA need supportive care including red cell and platelet transfusion as well as antibiotics for prophylaxis and treatment of infections.
- Immunosuppression with ATG and cyclosporine have shown convincing response in AA patients, although up to 35 % of patients may relapse.
- Horse ATG is more efficient than rabbit ATG but rabbit ATG can be used as second line following relapse or lack of response to the first line IST.
- Up to 50% of non-responsive patients may also respond to Eltrombopag, a thrombopoietin receptor agonist.

hATG 40 mg/kg/day for 4 days followed by Cyclosporin for 6 months

hATG 25mg/kg/day (low dose) can also be used.

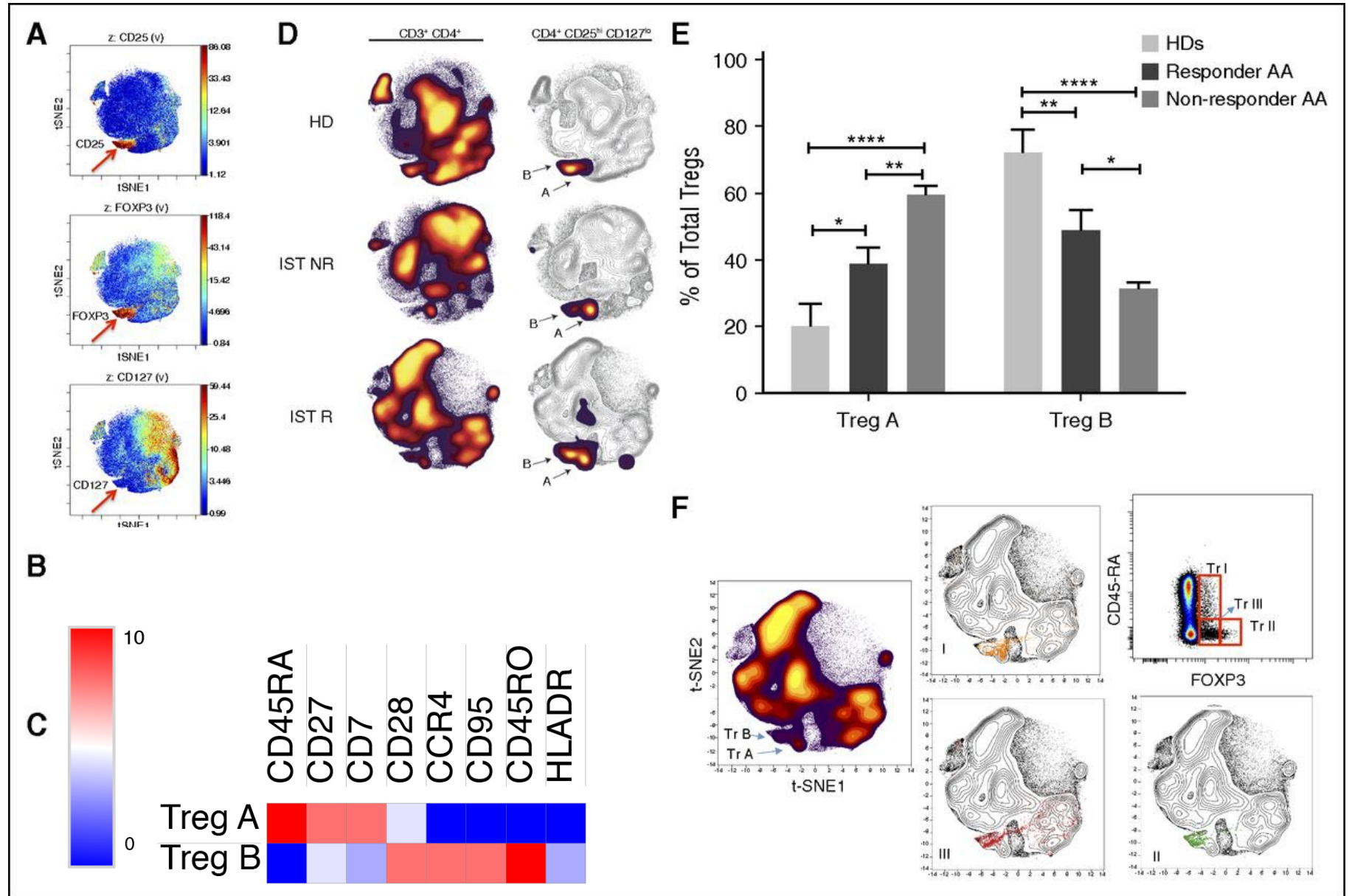


# Treatment

- Using **Eltrombopag** in combination with IST is another strategy which improves response, and improves the response rate to around 80% but relapse may still occur and there is a risk of evolution to myeloid malignancies similar to standard IST.
- **Androgens** are less efficient than IST but Danazol (a synthetic androgen) improves blood counts in up to 80% of patients with telomere disease.
- In patients with a large **PNH clone** (ie >50%) the risk of vascular thrombosis increases and treatment with complement blocker such as eculizumab should be considered to prevent thrombosis and correct intravascular **haemolysis**.

# Novel Approaches

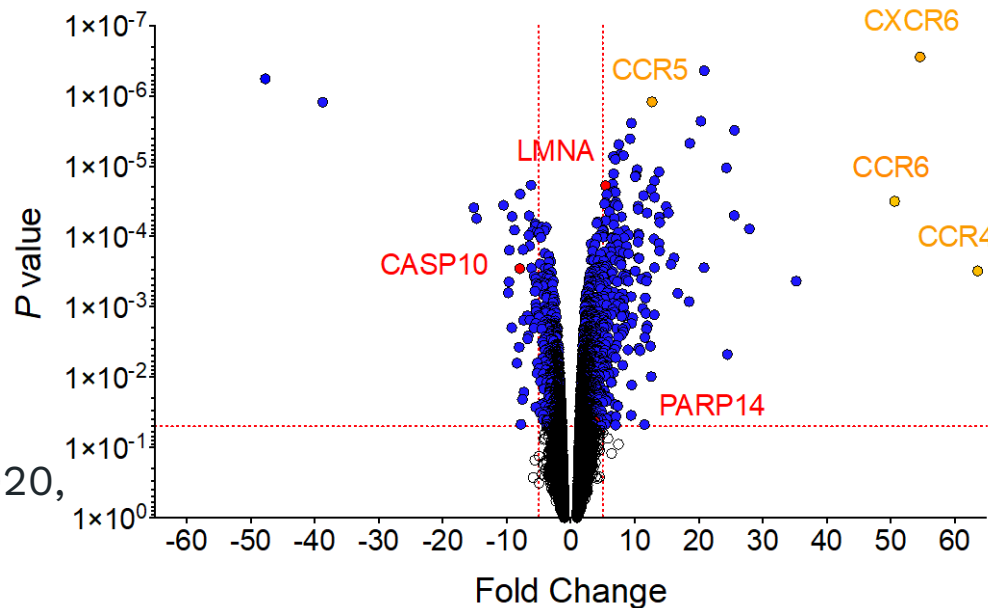
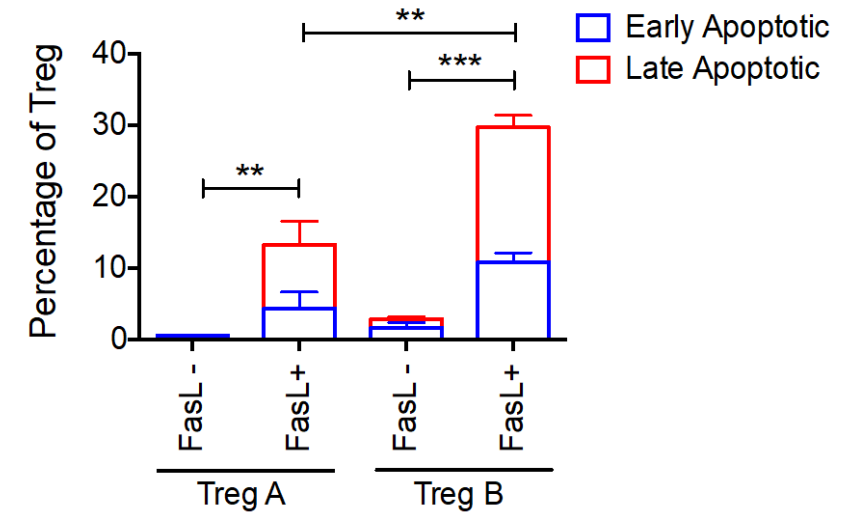
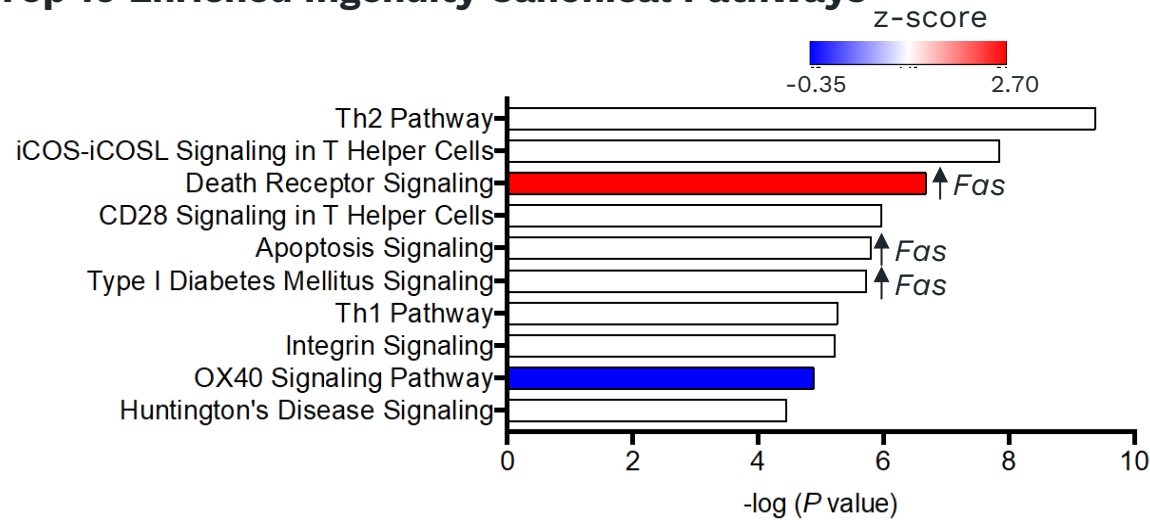
# Tregs in AA



Kordasti et al. Blood 2016

# Why Tregs are low in AA?

## Top 10 Enriched Ingenuity Canonical Pathways

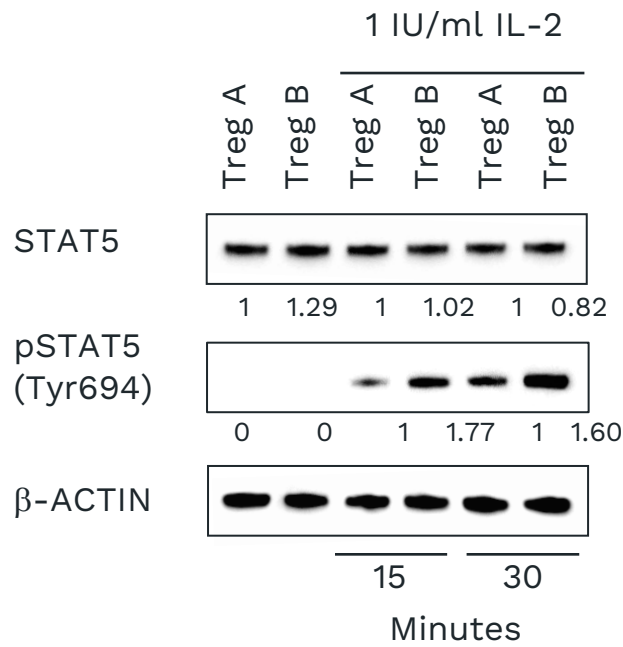


Lim et al, Blood 2020,

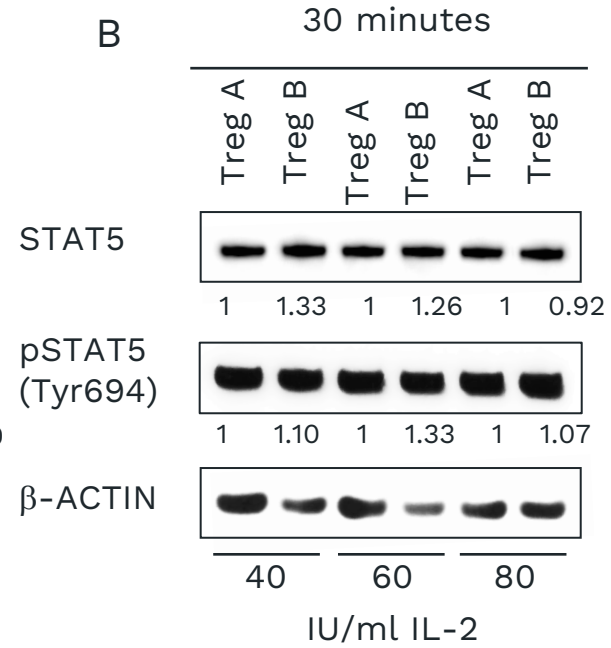
After adding FAS-L (5 mg/ml) for 5 h, Treg B (and CD4<sup>+</sup>) have a higher rate of apoptotic and dead cells than Treg A.

# AA Tregs can be expanded

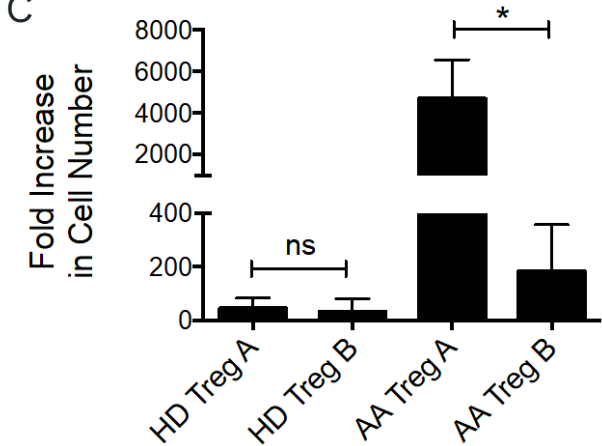
A



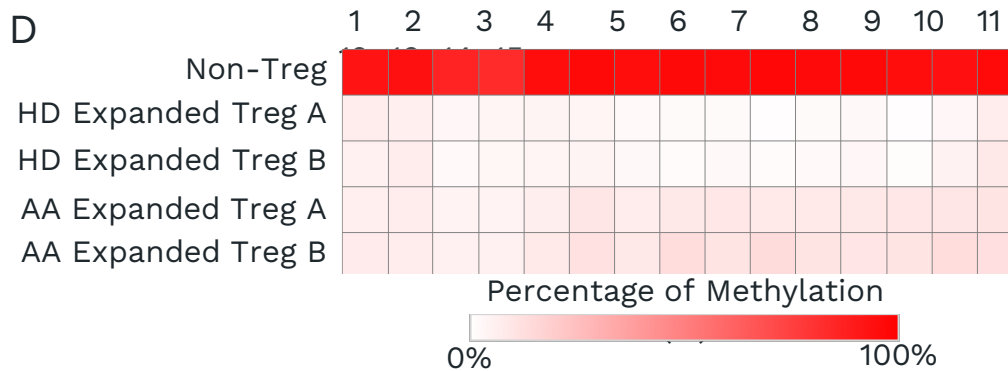
B



C

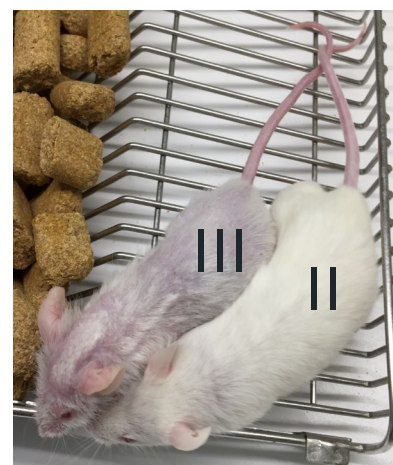
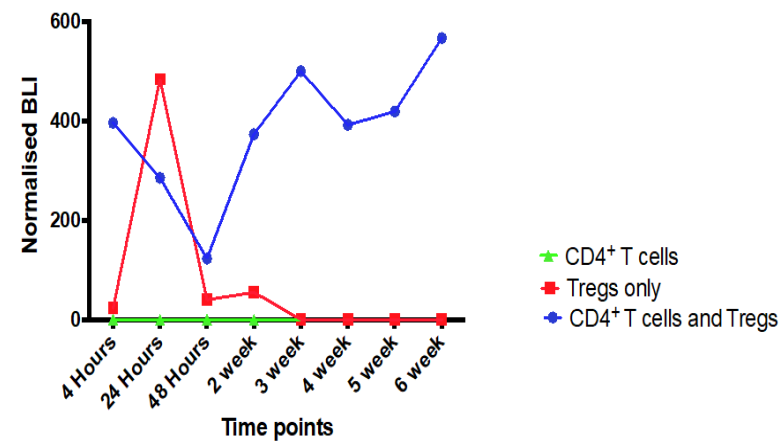
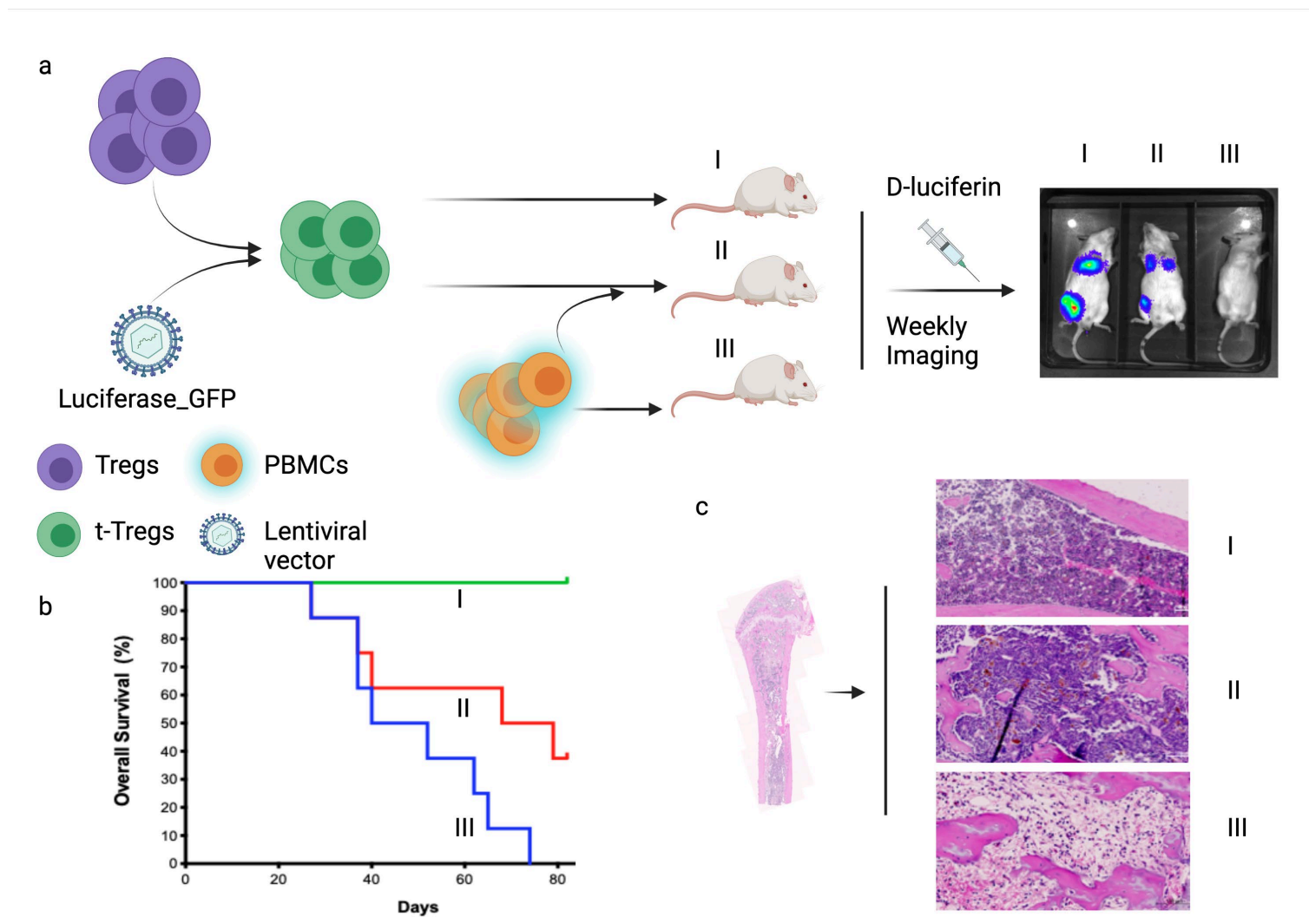


D



Lim et al, Blood 2020

# Tregs *in-vivo* Function



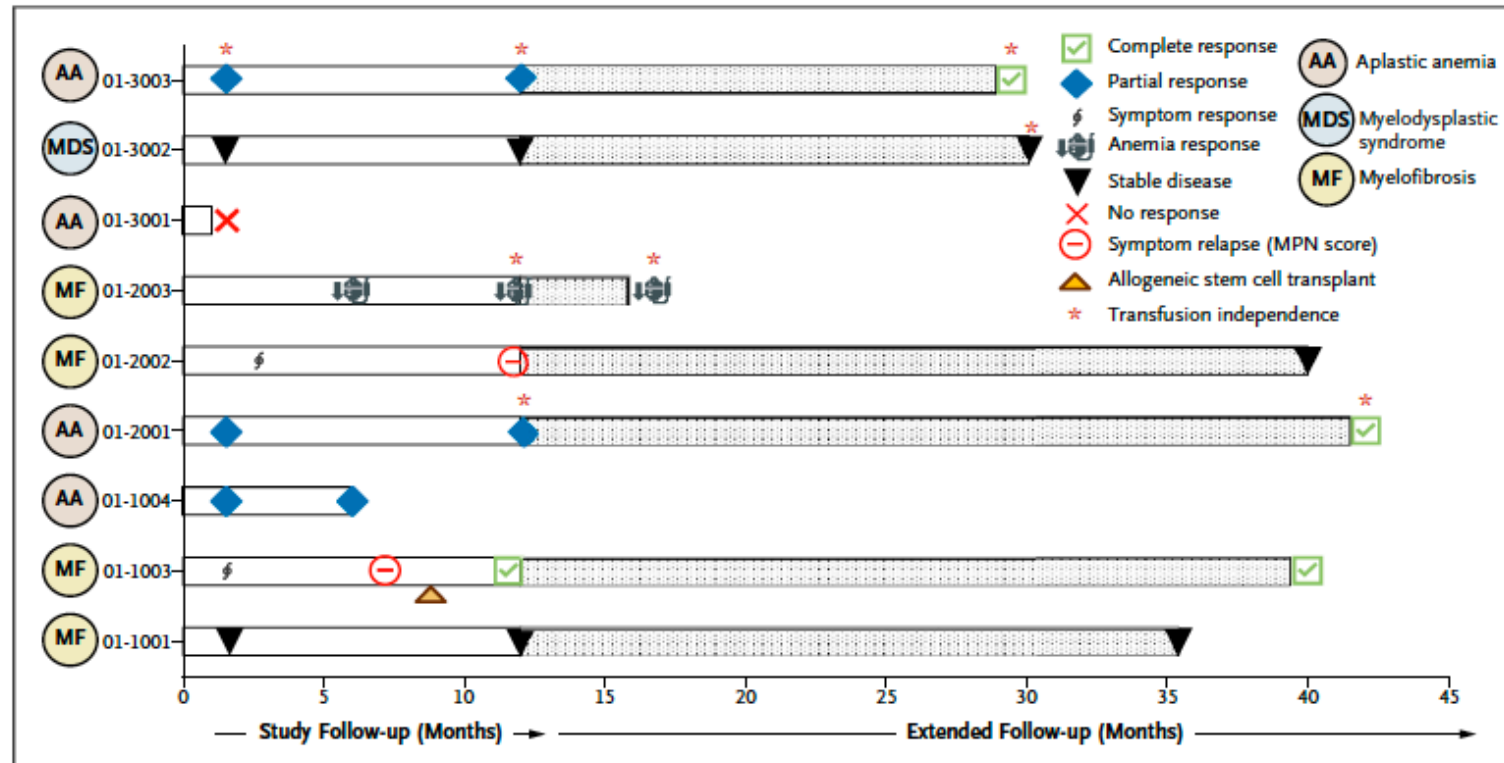
# Clinical Trial

**Autologous Tregs for Aplastic Anaemia (TIARA)**, ClinicalTrials.gov ID

NCT05386264

Sponsor King's College Hospital NHS Trust (Open).

# Phase 1 Study of CK0801 in Treatment of Bone Marrow Failure Syndromes.





# Summary

- Autoimmunity/Autoinflammation are important features of BMF syndromes.
- AA diagnosis is largely based on excluding all other diagnoses.
- Immune mediated AA is a rare disease BUT we shouldn't forget about it!
- MDS could also have overlapping autoimmune features with AA.
- Treatment options are HSCT and IST and depends on age and severity of the diseases.
- The non-malignant iAA can transform to myeloid malignancy, even after response to IST.
- Novel cell therapy with Tregs could become a treatment option in these patients.

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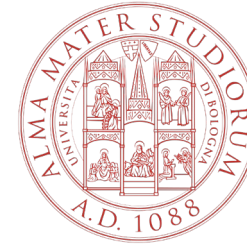
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US DOD BMF  
Programme



THANK YOU

