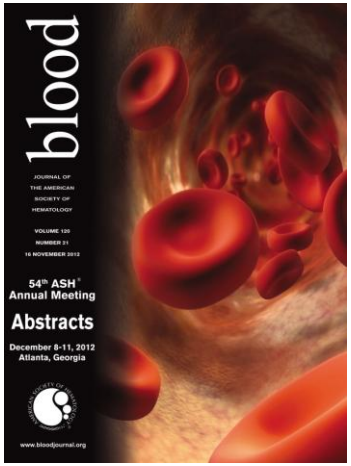


Red Blood cell disorders

Highlights of the 54th ASH annual meeting

Dr A.Gilles
CHU Saint Pierre
ULB


whiskas
Winston
felix

Emerging « A » therapies for hemoglobinopathies

agonists antagonists antisicklings anti oxydants and arginine

- SCD and Thal have distinct mutations and phenotypes
- In SCD polymers formation leads to membrane damage,VOC,hemolysis and hypoxia reperfusion injury
- In Thal globin chain unbalance leads to membrane injury; hemolysis ineffective erythropoiesis;iron dysregulation

- They share common vasculopathy with endothelial damage
- Phosphatidyl serine membrane exposure, hemolysis
- Free hemoglobin and NO deficiency
- Increased endothelial adherence; inflammation, procoagulant activation;oxydative injury; decrease of antioxydants

- *Eliott Vichinsky Educationnal Session*

Recently novel agents targeting multiple pathways in the pathology of hemoglobinopathies are emerging

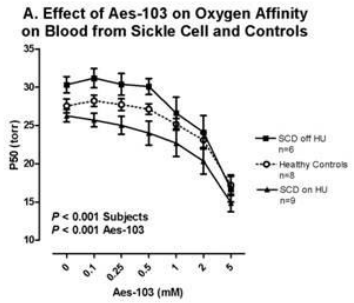
Table 1. Novel therapeutic agents in hemoglobinopathies

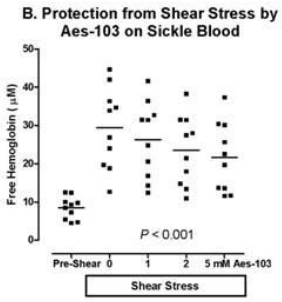
Category	Therapeutic agent	Mechanism of action
Adhesion	GMI-1070	A pan-selectin inhibitor that decreases neutrophil adhesion
	Heparin, pentosan polysulfate	Decreases P-selectin and VCAM-induced sickle cell adhesion
	Eptifibatide	α_{IIb}/β_3 antagonist; decreases platelet activation and increases vasodilation
	Prasugrel	ADP receptor antagonist that inhibits platelet activation
	Propranolol	Beta adrenergic receptor agonist that decreases adhesion to endothelial cells
Inflammation	Regadenoson	$A_{2A}R$ agonist that blocks iNKT cell activation
	Statins	Decreases inflammation and improves endothelial function
	Zileuton	5-lipoxygenase inhibitor that decreases inflammation; used in asthma
	MP4CO	A hemoglobin conjugated with polyethylene glycol and saturated with carbon monoxide that decreases inflammation and hypoxia reperfusion injury
NO	L-arginine	Substrate of NO that increases NO synthesis
	Tetrahydrobiopterin (R-BH4)	Essential cofactor for NO production
	Nitrite, niacin	NO donor
Oxidative injury	Glutamine	Substrate of glutamate that increases NADPH and NO generation and decreases adhesion
	Alpha-lipoic acid	Increases NF-κB and glutathione synthesis
	Acetyl-L-carnitine	Decreases lipid peroxidation
	N-acetylcysteine	Decreases phosphatidylserine exposure and increases glutathione
	Omega-3 fatty acids	Antithrombosis and inflammation
	Curcuminoids	Decreases non-transferrin-bound iron and lipid peroxidation
Erythropoiesis	Transferrin	Improves erythropoiesis and hepcidin regulation
	Jak-2 inhibitors	Decreases ineffective erythropoiesis
Iron metabolism	Hepcidin agonist	Decreases iron absorption and improves erythropoiesis
	Hepcidin antagonist	Increases iron absorption and improves inflammation-induced anemia

Single magic bullet -> multimodality therapies

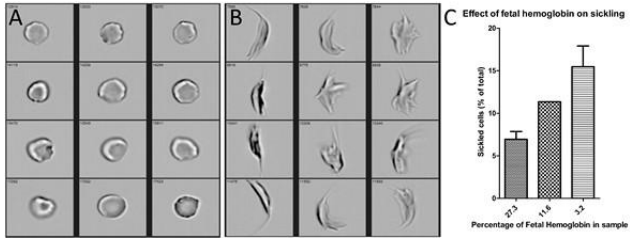
Aes 103(5-HMF) a novel antisickling agent

- Increases oxygen affinity of sickle and healthy control blood
- Decreases RBC fragility in vitro *#85 Mendelsohn*





- Decreases sickling induced by 2% oxygen in vitro measured in a novel imaging flow cytometry assay *# 2105 Van Beers*

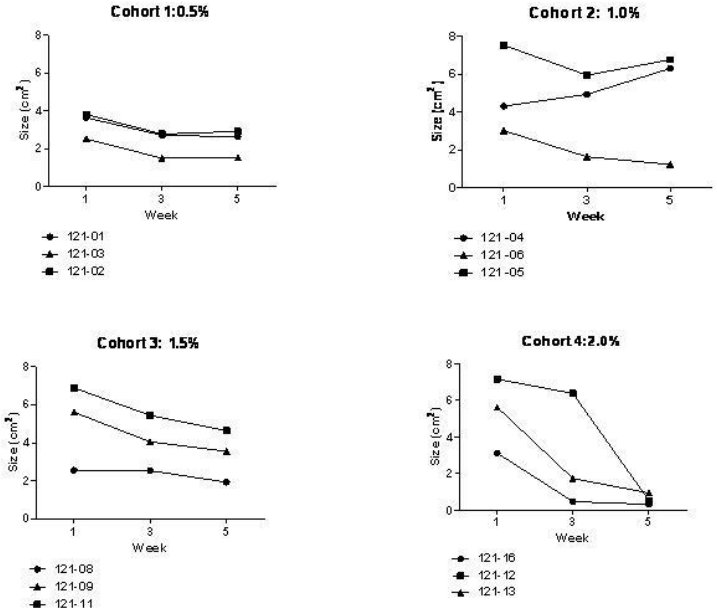


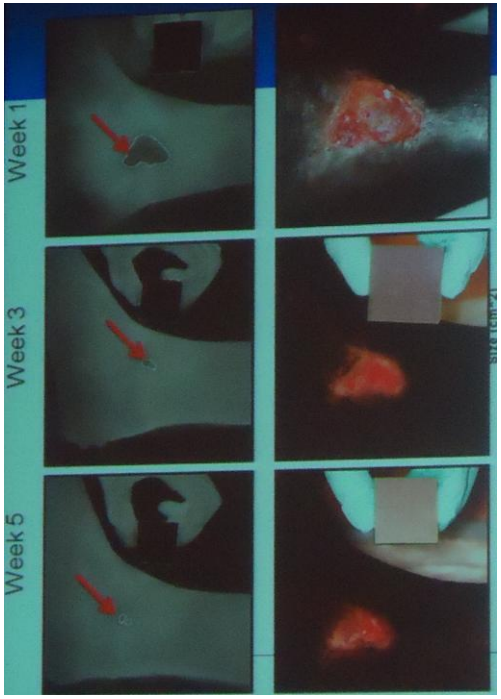
- Well tolerated in phase 1 healthy volunteer study; preliminary resistance to desaturation during hypoxia challenge *#3210 Stern*
- Phase 1/2a study in SCD on way at NIH clinical center

A phase 1 dose escalation study of topical sodium nitrite in patients with SCA and leg ulcers

#86 Minniti

- Topical application of 2% sodium nitrite cream reduced leg ulcer size in 12 pt enrolled
- No SAE
- No biological/clinical change during and after treatment





Effects of HU on lymphocytes subsets and the immune response to pneumococcal measles mumps and rubella vaccination in the pediatric HU Phase III clinical trial BABY HUG

#243 Lederman NCT00006400

- 91HU vs 81 PL Children 9-18 mo of age

- HU significantly decreases ALC
  absolute CD4 and CD4/CD45RO memory cell
- HU does not Impair Ig response
  to 23 V PS pneumococcal vaccine
- HU delays the ab response to MMR vaccine
  but the difference does not persist longer than 30 days
- HU did not cause any significant increase
  of infection of any kind

Figure 1: IgG Ab levels to Pnu PS type 26 (6B)

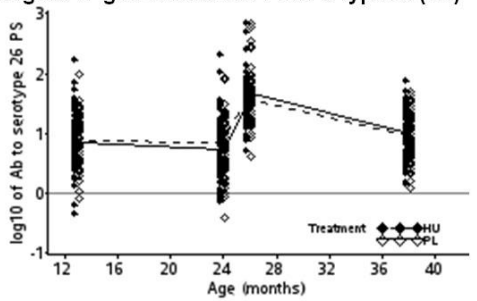
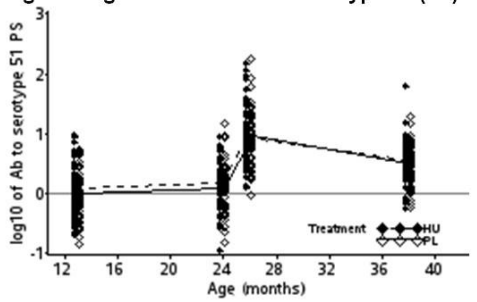


Figure 2: IgG Ab levels to Pnu PS type 51 (7F)



#3212 De Montalembert :

SCD children previously vaccined with PPSV23 respond well to PCV13

Flash Info on HU

- *#242 Bachir:* HYDREP study :a significant impairment of all sperm parameters was observed after a 6 months use of HU.
- Sperm Cryopreservation is advised before beginning HU treatment

- *# 1004 Willen:* starting HU at a younger age, when HbF is >20%, leads to persistence of HbF production and overall improvement in hematological efficacy.
- This was not simply the result of achieving MTD at a younger age before physiologic decline of HbF.

- *# 3211 Laurin:* HU is associated with lower albuminuria prevalence in adult SCD patients

Two studies from the Walk PHASST cohort

- *#90 Ayyappan : Chronic kidney disease*

- Chronic kidney disease is common in SCD but more severe in SS than in SC patients
- Depressed eGFR is associated with age,high TRV and markers of renal dysfunction
- Albuminuria is common and associated with hemolysis;high TRV and possibly mortality
- acid-base and electrolyte derangement are associated with conventional markers of renal disease and with hemolysis

- *#3240 Gladwin: mortality*

- a cut-off value of TRV ≥ 3.0 m/sec as defining Pulmonary Hypertension is associated with the highest unadjusted and adjusted risk for death of any measured variable.

Prevalence of extracranial internal carotid arteriopathy in stroke free SCA children: a new risk factor for silent strokes *# 88 Verlhac*

- Assessment in 435 consecutive pt median age 8,5 y (1,3 -18,7)
- eICA doppler Submandibular window, 2Mhz probe

- Cut off velocity >160cm/sec is highly predictive of stenosis on MRA
- Prevalence 10,3%(45/435)
- eICA stenosis and iICA stenosis are independent risk factors for silent infarcts
- This may explain why silent infarcts still occurred in patients early assessed by TCDI exploring only intracranial arteries.

- Extracranial Doppler assessment should be routinely done with TCD to evaluate the full extent of cerebral vasculopathy in SCA.

More about stroke…

- *# 224 Hyacinth :*

- High frequency of RBC transfusion in the STOP study was associated with reduction of serum biomarkers of neurodegeneration; vascular remodeling and inflammation
- These markers may be useful for monitoring children with SCA receiving stroke prevention therapies
- and for designing treatment targets.

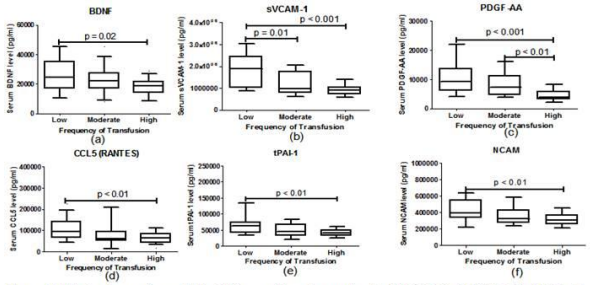


Figure 1. Indicates the median and 10 – 90th percentiles of serum levels of BDNF (a), SVCAM-1 (b), PDGF-AA (c), CCL5 (d), tPAI-1 (e) and NCAM (f) of subjects who received low (< 20), moderate (20 – 39) or high (≥ 40) frequency RBC transfusion. The figure shows that serum levels of these biomarkers were significantly higher among the low compared with the high frequency transfusion groups. Furthermore, the serum levels of sVCAM-1 was higher in the low compared with moderate frequency transfusion group, while that for PDGF-AA was higher in the moderate compared with high frequency transfusion group.

- *#1003 Vieira:*
- Cross sectionnal study of TCD in 1135 SCD patients ;
- Compared to patients with HbSS and Hb/βthalassemia, in Hb SC mean Tamm was significantly lower. (98.7 cm/sec ; SD 18.3 cm/s.)

- Suggesting that for HbSC pts there is different TCD velocities values for an increased risk for stroke values above 135.3 cm/s could be considered high values.
- Needs to be studied prospectively

HRQL in patients with hemoglobinopathies

J.Panepinto Educationnal session

- HRQL is a unique and robust way to represent patient's voice
- There is enough evidence demonstrating the significant impairments in QOL in SCD
- Future work should focus on incorporating QOL measurements into all clinical trials of therapeutics and into the clinical management of patients with the ultimate goal of improving HRQL

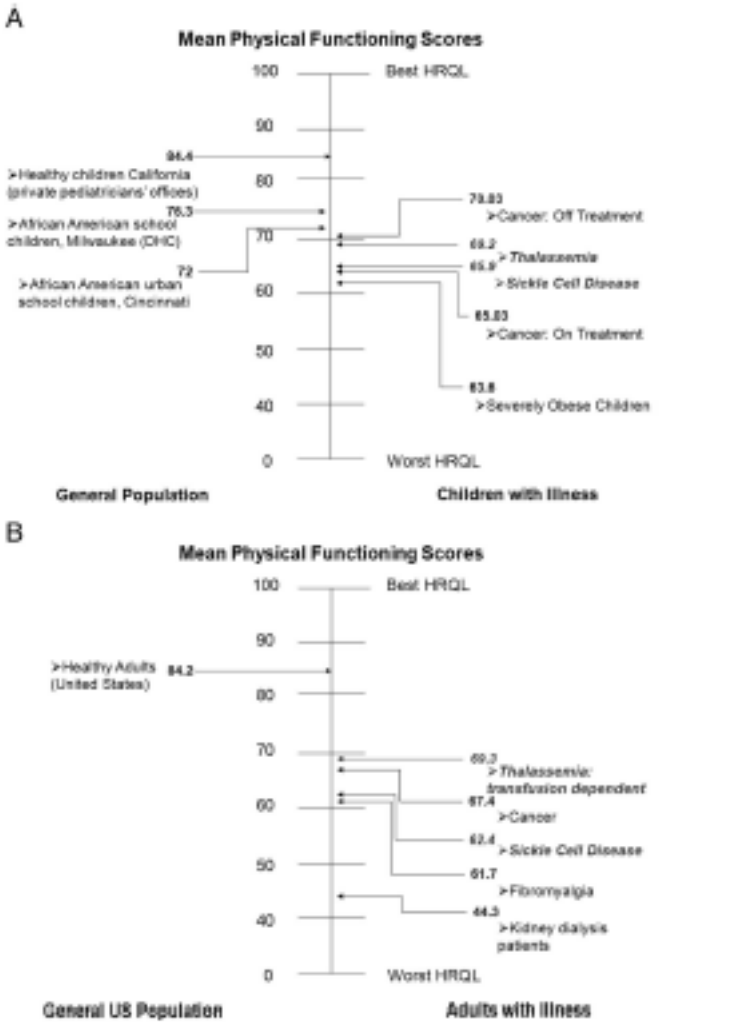


Figure 1. HQRL in children (A) and adults (B) with hemoglobinopathies compared with healthy populations and those with other chronic diseases.

Advances in stem cell transplantation and gene therapy in the beta hemoglobinopathies

E.Payen and P.Leblouch Educationnal session

- Only curative treatment is allo HSCT although < 25% patients have an HLA matched related donor
- Those who do still face the risk of engraftment failure and GVHD

- Children
- Transplantation of MSD cells when feasible provides excellent outcomes and high survival rates in SCD and Thal pediatric patient.
- Transplantation of unrelated matched CB cells has been reported for both SCD and Thal patients
- Results using MUD in SCD patients are not yet available

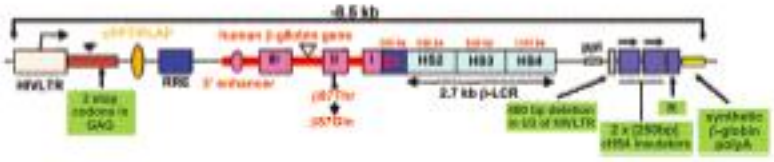
- Adults
- Only few adult patients have received transplantation because of TR toxicity and cumulative disease burden

- New conditionning strategies are being tested

- Ex vivo gene therapy by insertion of normal beta globin gene in patient's own HSC would alleviate both donor shortage and GVHD

- Use of lentiviral vectors capable of transferring the elaborated structure of the beta globin gene with fidelity; high titers providing high and erythroid specific expression
- Long term clinical benefit have been achieved in the first treated patient with severe beta thal
- Another patient is being analyzed

- Promising results; larger series needed : benefit risk ratios?
- Insertional mutagenesis?



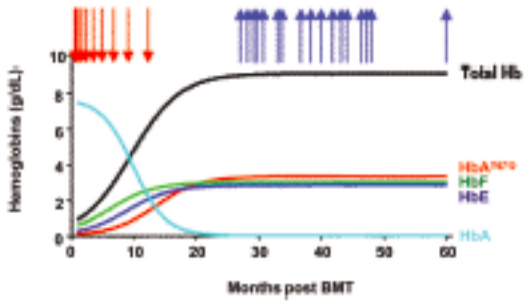


Figure 3. Concentration of hemoglobins in blood. Arrows indicate RBC transfusion (red) and phlebotomies (blue).

Iron chelation data

- *# 2124 Pennell:* CORDELIA study:
- The first randomized controlled trial comparing deferasirox with DFO for cardiac iron removal.
- Demonstrated non-inferiority of deferasirox vs DFO, with a trend for superiority. Same frequency of SAE.

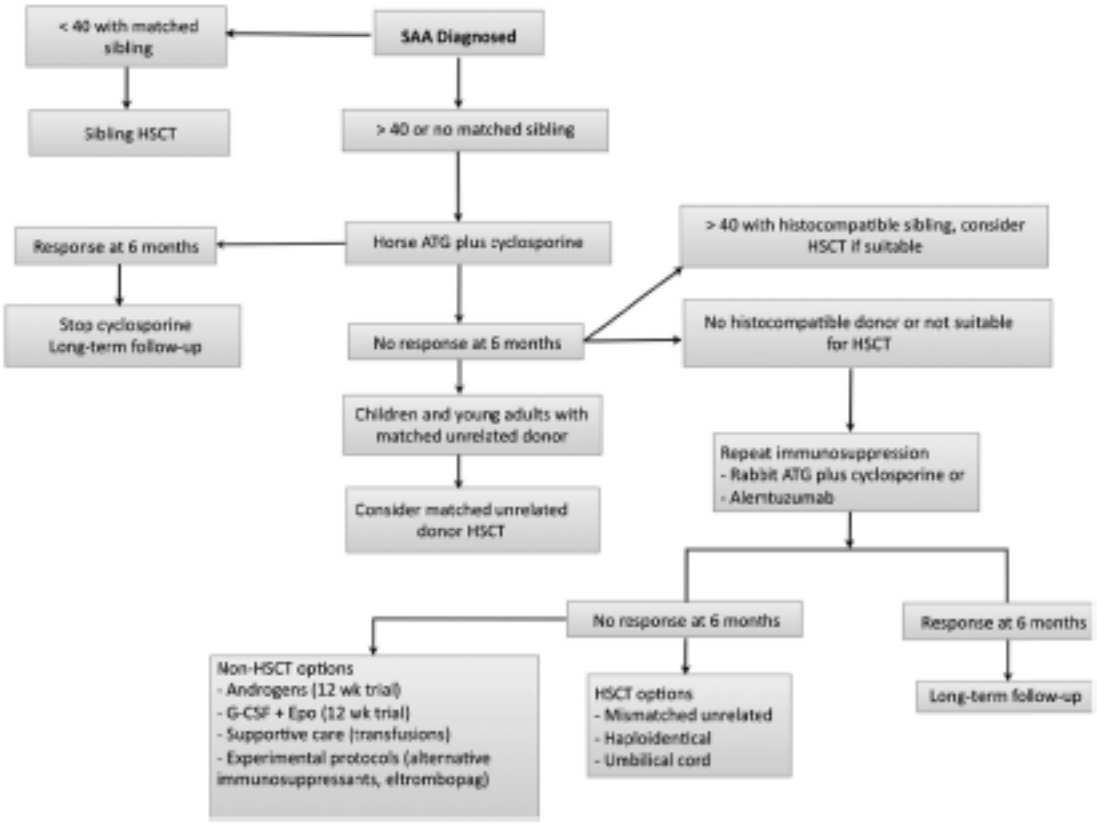
- *#2125 Vichinsky :* safety profile of deferasirox in very young pediatric patients (2-<6y) was consistent with the available evidence in adult patients, including the rate of creatinine and liver enzyme changes which did not appear to be progressive

- *# 3258 Taher:* Extension of the THALASSA study:
- Data confirm deferasirox efficacy in reducing iron overload in NTDT, with a safety profile over 2 years consistent with that in the core study.

- *#1026 Pongtanakul :*Twice daily dosing of Deferasirox significantly improves clinical Efficacy in Transfusion dependent thalassemias who were Inadequate Responders to standard once daily dose

Aplastic anemia therapeutic updates on immunosuppression and transplantation

P.Scheinberg Educationnal session



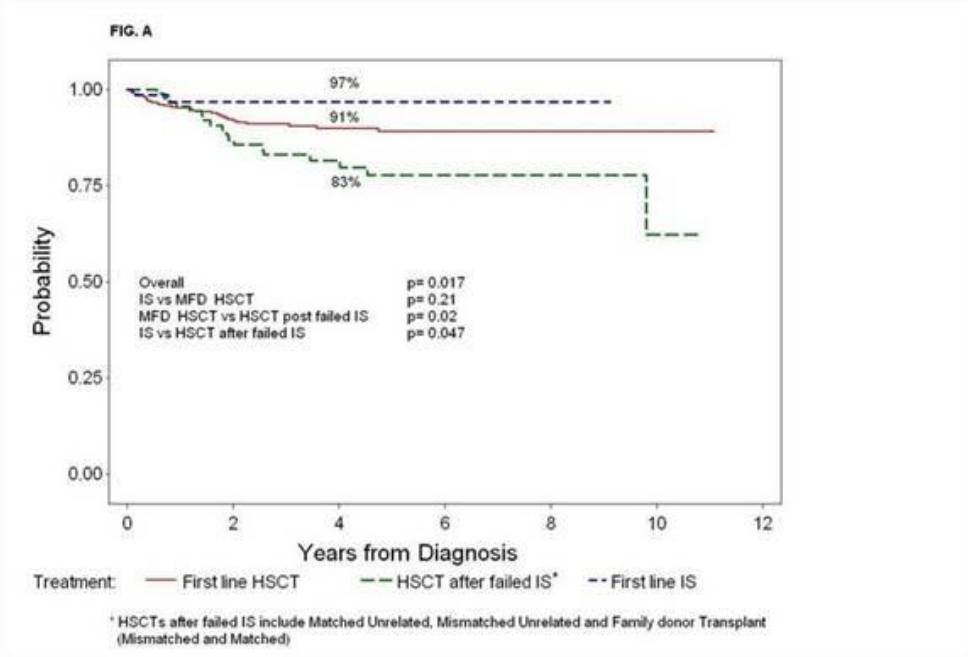
Outcome of Aplastic Anemia in Children.
A Survey On Behalf of the SAA and PDWP of the EBMT

#643 Dufour

- IS = excellent therapy for children with AAA
- in case of failure HCST is a very good salvage option

- HSCT is able to restore haematopoiesis more completely and more durably than IS
- if a matched family donor is available the preference of front line HSCT over front line IS can be justified.

- BM > PB as source



Even "Moderate" Dose Cyclophosphamide for Severe Aplastic Anemia Is associated with significant toxicities and does not prevent relapse and clonal evolution

#1259 Scheinberg

- Although Cy has activity in SAA, its toxicity is not justified when far less toxic alternatives, such as horse-ATG, are available.

Thank you for your attention