webinar

HEALTH PROFESSIONALS

Thursdays Webinars

Advances in Diagnosis and Management of Diamond-Blackfan Anemia Syndrome: A Hematology Focus

Thierry LEBLANC
Pediatric Hematology Departement, Hôpital Robert-Debré, Assistance-Publique Hôpitaux de Paris, Université Paris Cité, National Reference Center for aplastic anemias

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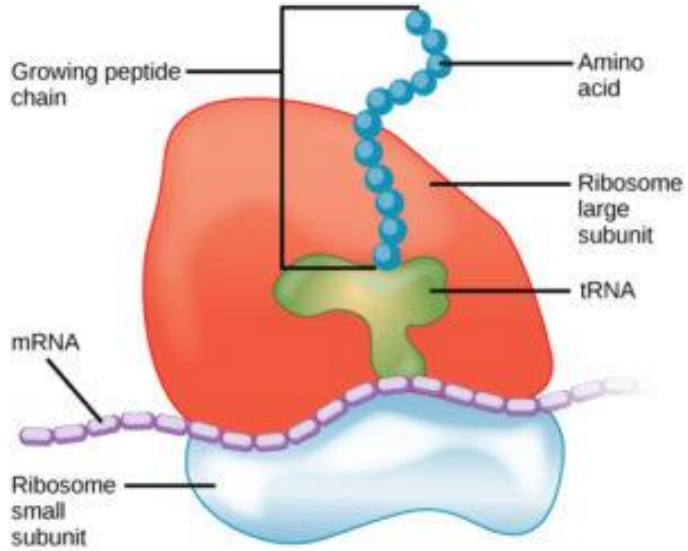
ERN | EuroBloodNet

Disclosure

I have nothing to disclose

DBAS in brief



Rare disease (5 to 7/1,000,000 live births in EU)

Main cause of constitutional erythroblastopenia

Ribosomopathy

Genetic transmission: mostly AD but not so simple:

- *De novo cases frequent*
- *Problem of «silent career»*
- *AR & X-linked transmission also reported*

☞ very heterogeneous disease both for genetic & for clinical aspects

Plan

Focus on:

- **New criteria for diagnosis**
- **Current therapeutic approaches**
- **New options for therapy**
- **DBAS patients surveillance with special focus on cancer**

Diagnosis, treatment, and surveillance of Diamond-Blackfan anaemia syndrome: international consensus statement

Marcin W Wlodarski*, Adrianna Vlachos*, Jason E Farrar*, Lydie M Da Costa, Antonis Kattamis, Irma Dianzani, Cristina Belendez, Sule Unal, Hannah Tamary, Ramune Pasauliene, Dagmar Pospisilova, Josu de la Fuente, Deena Iskander, Lawrence Wolfe, Johnson M Liu, Akiko Shimamura, Katarzyna Albrecht, Birgitte Lausen, Anne Grete Bechensteen, Ulf Tedgard, Alexander Puzik, Paola Quarello, Ugo Ramenghi, Marije Bartels, Heinz Hengartner, Roula A Farah, Mahasen Al Saleh, Amir Ali Hamidieh, Wan Yang, Etsuro Ito, Hoon Kook, Galina Ovsyannikova, Leo Kager, Pierre-Emmanuel Gleizes, Jean-Hugues Dalle, Brigitte Strahm, Charlotte M Niemeyer, Jeffrey M Lipton*, Thierry M Leblanc*, on behalf of the international Diamond-Blackfan anaemia syndrome guideline panel†

THE LANCET Haematology

- **New name: DBA syndrome**
- **New criteria for diagnosis** *(versus previous guidelines: Vlachos & al, 2008)*
- **New recommendations transfusion support, chelation, corticosteroids therapy & indications for HSCT**
- **New recommendations for surveillance with special focus on cancer**

Wlodarski & al, Lancet Haematology 2024

When to think to DBAS? In many circumstances !

Abnormal blood counts:
- **With or w/o anemia which maybe:** severe & non regenerative anemia in an infant (classic presentation), or ± mild (children & adults) with macrocytosis & low reticulocytes, or absent ± isolated macrocytosis
- **Associated leuconeutropenia** is frequent +++

DBAS

Congenital anomalies including severe malformative syndrome with or w/o anemia

Hypo-γ–globulinemia & CVD-like features

Complicated pregnancies
Hydrops foetalis
NB: genetic counseling difficult +++

Unusual solid tumors: early age, non-classic genetic aspects & unexpected toxicity of chemotherapy

Asymptomatic pts (at analysis)
- parent of affected-child
- donor screening for BMT

MDS/AML: high-risk pts, early cases (< 55 yrs)
Sometime in non-diagnosed pts: discovery of myeloid genes panel analysis

Diagnostic criteria

Diagnostic criteria

- Pathogenic or likely pathogenic mutation in a Diamond-Blackfan anaemia (DBA) syndrome gene (appendix p 4); or
- Haematological features consistent with DBA syndrome:[1] macrocytic anaemia* with reticulocytopenia and bone marrow erythroblastopenia; absence of dysplasia, dyserythropoiesis†, and sideroblasts; and exclusion of known differential diagnoses (see below)

More weight to genetic +++

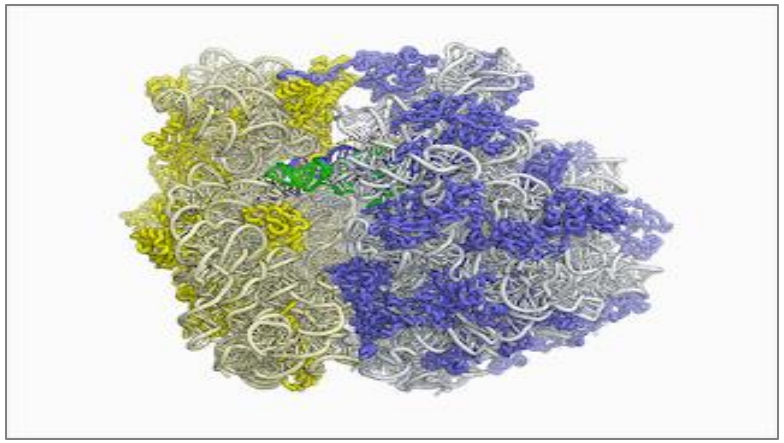
1: include patient with no current phenotype

Typical findings (not mandatory for diagnosis)‡

- Patients are younger than 1 year at onset of disease
- Elevated eADA activity (before first transfusion, in patients who have not received a transfusion, or in parents of patients)
- Elevated HbF (reliably assessed in patients older than 6 months)
- Positive family history or unexplained history of anaemia during infancy or childhood
- Congenital abnormalities (appendix p 5)
- Abnormal rRNA processing in patient cells§

DBAS: a model for ribosomopathies

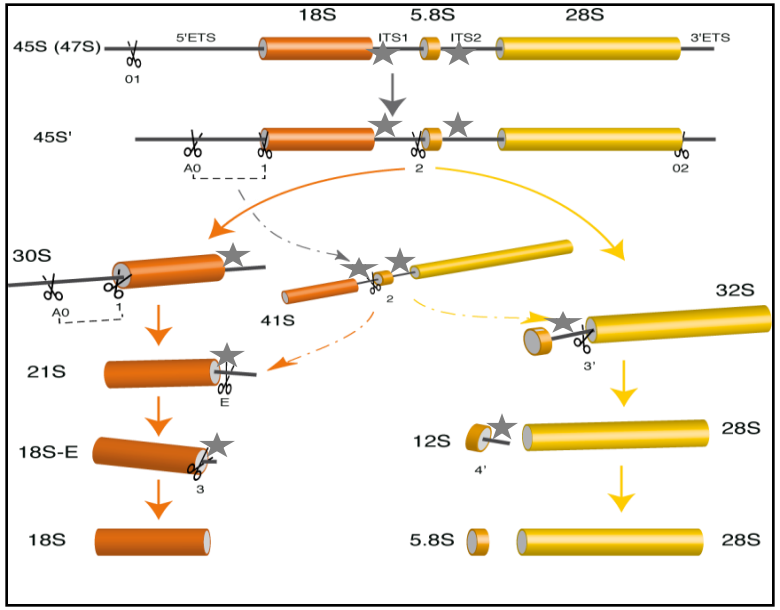
Ribosomes
(5 to 10 millions/cell)



Yellow: small sub-unit:
- 1 RNAr: 18S & 33 proteins
Blue: large sub-unit:
- 3 RNAr: 28S, 5.8S & 5S & 49 proteins

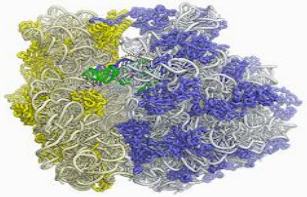
RNA pol I
⇩
precursor ⇨

rRNA maturation



Mature rRNA
+ rRNA 5S (RNA pol III)

DBAS genes: N = 26



Gene symbol	Inheritance	Chromosome location	New protein symbol	Approximate frequency	References
DBA SYNDROME: RIBOSOMOPATHY[1]					
Small ribosomal subunit (11 genes)					
RPS7	AD	2p	eS7	< 1%	107
RPS10	AD	6p	eS10	3%	54
RPS15A	AD	16p	uS8	<1%	108
RPS17	AD	15q	eS17	1%	109
RPS19	AD	19q	eS19	25%	110
RPS20	AD	8q	uS10	< 1%	57,111
RPS24	AD	10q	eS24	2.4%	112
RPS26	AD	12q	eS26	6.6%	54
RPS27	AD	1q	eS27	< 1%	113
RPS28	AD	19p	eS28	< 1%	114
RPS29	AD	14q	uS14	< 1%	115
Large ribosomal subunit (13 genes)					
RPL4	AD	15q	uL4	< 1%	116
RPL5	AD	1p	uL18	7%	55
RPL8	AD	8q	uL2	< 1%	117
RPL9	AD	4p	uL6	< 1%	13,54
RPL11	AD	1p	uL5	5%	55
RPL15	AD	3p	eL15	< 1%	32,118
RPL17	AD	18q	uL22	< 1%	15
RPL18	AD	19q	eL18	< 1%	119
RPL26	AD	17P	uL24	< 1%	120
RPL27	AD	17q	eL27	< 1%	113
RPL31	AD	12q	el31	< 1%	42
RPL35	AD	3q	uL29	< 1%	119
RPL35A	AD	9q	eL33	3%	121
Ribosomal protein chaperones (2 genes)					
TSR2	X	X		< 1%	114
HEATR3	AR	16q		< 1%	59

Gene symbol	Inheritance	Chromosome location	New protein symbol	Approximate frequency	References
DBA SYNDROME OTHER[2]					
GATA1	X	X		< 1%	23,122-124
TP53 (GOF)	AD	AD		< 1%	24,25
CANDIDATE GENES[3]					
RPS11	AD	19q	uS17	< 1%	47
RPL3	AD	22q	uL3	< 1%	
RPL10	AD	X	uL16	< 1%	
RPL10A	AD	6p	uL11	< 1 %	
RPL19	AD	17q	eL19	< 1%	
RPL34	AD	4q	eL34	< 1%	
RPL0	AD	12q	uL10	< 1%	
GENETIC PHENOCOPIES[4]					
ADA2	AR	22q11.1			27,29,43
EPO	AR	7q22.1			26

Most frequent genes:

RPS19 **: 25%**
RPL5 **: 7%**
RPS26 **: 6%**
RPL11 **: 5%**

Genotype rates:

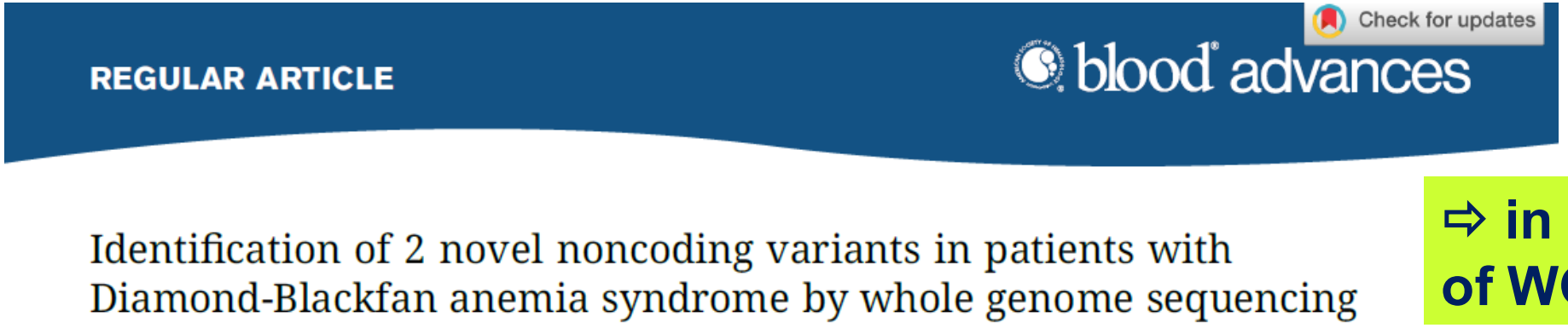
Registries : 70%
New cases : 85-90%

DBAS genes: more to find?

- Among RP genes? A few of them need to be functionally validated

- Among genes coding for proteins involved in ribosome biosynthesis like TSR2 and HEATR3?

- Non-classic ways of gene inactivation



⇨ in depth re-analysis of WGS data

RPS7 : splicing variant (inherited) at the end of non-coding exon 1

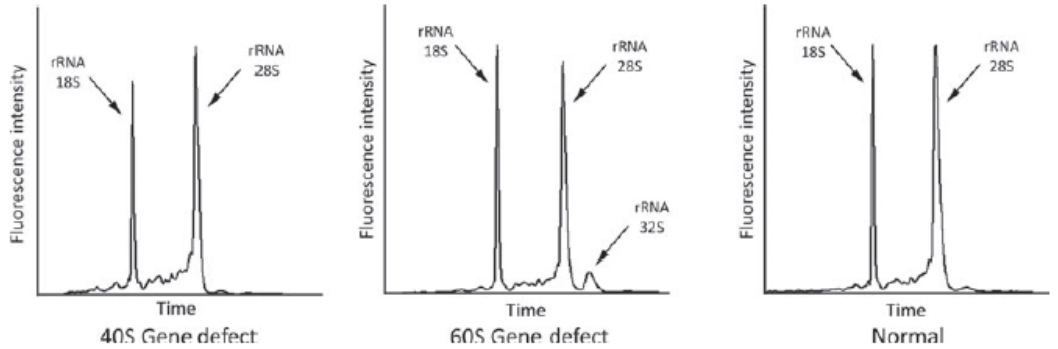
RPS19 : deep intronic variant (de novo)

Wen & al, 2025

How to diagnose DBAS w/o genetics?

Other biological tools:

- **Typical BM cytology *(in severely anemic patients)* with erythroblastopenia, no dysplasia, and overall rich marrow**
- **ADAe ⇗ (> 3 months post transfusion)**
- **fetal Hb ⇗ (> 6 months of age)**
- **± rRNA processing studies**



Quarello & al, Br J Haematol 2016

+ systematic exclusion of parvovirus B19 infection & DADA2 syndrome
± (according to presentation) exclusion of other IBMFs (FA, SDS, telomeropathies,…)

DBAS: diagnostic situations

Classic: Infant with severe anemia	**Hematologic: work-up for:** - Erythroblastopenia (PRCA?) - Macrocytic anemia - Cytopenias (severe neutropenia, anemia + neutropenia) - MDS in a young patient	**Immunologic:** - Syndromic hypogamma-globulinemia
Genetic: - systematic analysis in a child with congenital anomalies - Screening in young pts with MDS - Familial screening	**Oncologic:** - Intolerance to chemotherapy (mostly unexpected anemia) - MDS post cancer	**Obstetrical** - Complicated pregnancies in anemic patients

More and more atypical cases thanks to genetic analysis !

Therapeutic options in DBAS

<u>To date</u>:

Corticosteroids

Transfusions

HSCT

± *leucine*

NB: at a given time about 20% of pts are free of any treatment

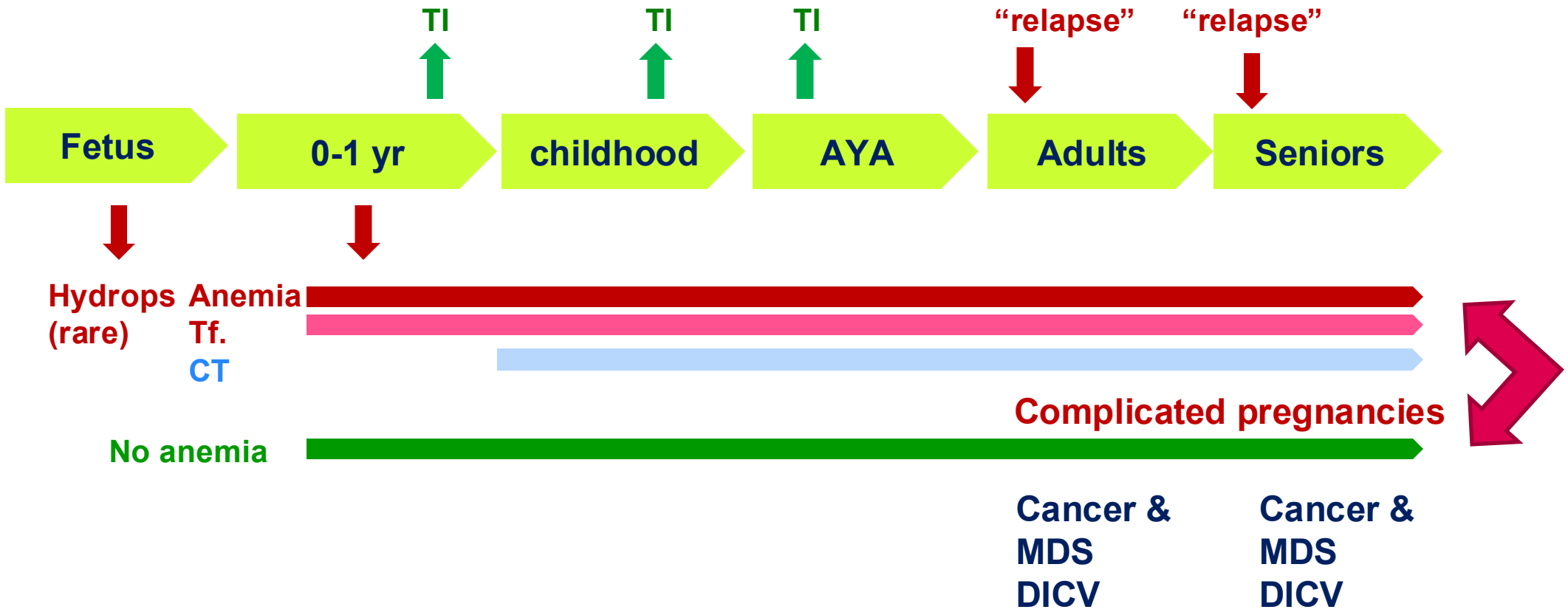
Not active: Epo, sotatercept, immunosuppressive agents,…

Not useful: vitamins B9 & B12

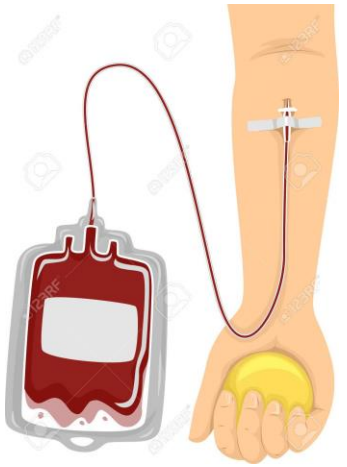
<u>Future:</u>

- **Small molecules**
- **Luspatercept?**
- **Gene therapy (*RPS19*)**

DBAS phenotype & treatment according to age



DBAS: transfusion support: curent guidelines



Panel 3: Recommendations for transfusion support

Indications and timing

- Any patient with severe anaemia
- Patient younger than 12 months
- Patient not responding to steroids or experiencing substantial side-effects
- Patient responding to steroids and showing acute haemoglobin drop (eg, due to viral illness)
- Patient on steroid holiday (to improve growth during adolescence)
- Pregnant patient with anaemia

General principles

- Hepatitis B vaccination
- Red blood cell antigen typing, and repeat red blood cell antibody screening
- Haemoglobin goal before transfusion (nadir haemoglobin): ≥9–10 g/dL or a higher concentration at which the patient is asymptomatic, independent of age
- Transfusion process: volume* is 10–15 mL/kg in children and approximately 2–3 red blood cell units in adults, and the interval† is every 3 (2–4) weeks

Only option in infants

Hb to be maintained > 90 g/L (or more in adult pts)

Support > vs other red-cell diseases

DBAS: curent guidelines for chelation

Monitoring of iron overload

- The diagnostic gold standard is MRI for liver and cardiac iron assessment
  - Start by age 5 years at the latest (earlier if possible, especially when evidence of high iron load and when planning allogeneic hematopoietic stem-cell transplantation)
  - Follow up with annual MRI liver iron (more frequently if required according to iron status) and annual MRI heart iron (more frequently if cardiac iron load present)
- Serial monitoring of ferritin concentration and transferrin saturation*

Goals and adjustment plan

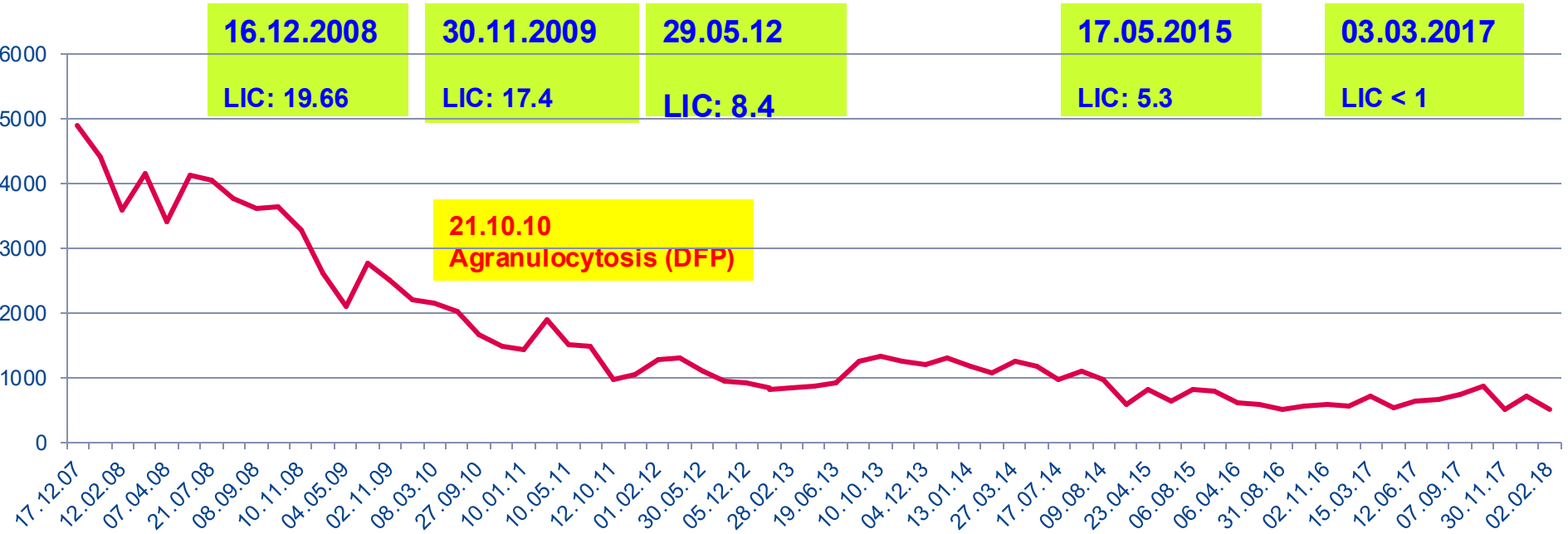
- Adjust therapy frequently on the basis of efficacy and toxicity (typically every 3–6 months)
- The optimal target values for iron overload† are:
  - MRI liver iron content <3 mg/g‡ dry weight
  - MRI heart T2* >20 ms§
  - Serial ferritin: <500 ng/mL
- If MRI is not available (not standard) reduction or stopping rules based on ferritin are
  - If ferritin 500–1000 ng/mL, consider dose reduction
  - If ferritin 300–500 ng/mL, reduce dose or temporarily pause therapy
  - If ferritin <300 ng/mL, temporarily pause therapy
- For patients with low ferritin (<500 ng/mL), but high liver iron by MRI (>5 mg/g dry weight), consider chelation at lower dose and with intensified monitoring for toxicity

Key points:

- **Iron overload is more severe in DBAS than in other RCD**
- **Chelation should be started early, often in infants**
- **Combination of chelators is frequently required**
- **Use DFP with caution (10% risk of agranulocytosis)***
- **Dedicated outpatient visits +++**

** Lecornec & al, Br J Haematol 2022*

Woman, born in 79. DBA. Past history: hepatitis C. On transfusions: 2 units every 3 weeks then 3 units/ month. 1st visit (25.10.05): ferritin: 5014µg/L (chélation stopped for years); clinical hemochromatosis: hypothyroïdy, diabetes & hypogonadism



Chelation changes according to efficacy, chelator toxicity & patient adhesion):

25.05.07	D1 DFX 1500mg/d	27.03.13	DFX 1000 mg/d
29.08.07	DFX 2000mg	08.01.14	DFX 500mg x 2/d x 4 days a week
08.12.08	DFX 2125 mg	14.05.14	DFX same dose for 5 days
02.07.10	DFO + DFP	13.05.15	DFX a 625 mg x 2 for 5 days
06.10.07	DFP dose correction	16.09.15	DFO 3 d a week + DFX for 5d 750 mg x 2
21.10.10	Agranulocytosis	14.02.18	DF0+DFX new formulation: 360mg x2/d
08.06.11	DFO + DFX 1500 mg/d x 2d/w		

DBAS: corticosteroid therapy

Indications and timing

- First trial
  - In patient with chronic transfusions
  - Start steroid treatment when patient is 12 months or older, possible start at 15–18 months in children with failure to thrive, and earlier start (age approximately 9 months) if unable to provide safe venous access or safe transfusions
- Second trial
  - In patients who previously did not respond to steroids (1–2 years after first unsuccessful trial), recommended before planned allogeneic haematopoietic stem-cell transplantation
- Additional trials are not recommended

Therapeutic considerations

- Before steroid treatment
  - Live viral vaccines (first dose measles, mumps, rubella, and varicella vaccines) given optimally at least 3 weeks before first steroid trial
- Dosing
  - Drug: oral prednisone or prednisolone (equal potency)
  - Starting dose: 2 mg/kg per day in children (max 80 mg) and 80 mg per day in adults
  - When to start: 1 day or approximately 10–14 days after last transfusion
  - Initial response assessment: reticulocytes and haemoglobin at day 10–14
- Tapering principles and stopping rule
  - Initial response: start taper after 2 weeks but not later than 4 weeks, and reduce by 0·5 mg/kg approximately every 2 weeks.
  - From 0·5 mg/kg slow taper to arrive at maximum maintenance dose (0·3 mg/kg per day or 0·6 mg/kg on alternate days)
  - Further passive or active taper to reach minimally effective dose
  - No response at 4 weeks after starting therapy: stop initial dose without unnecessarily extending therapy

Corticosteroid therapy in practice

DBAS is unique considering efficacy of very low-dose of steroids & for treatment duration

Goal: to define the lowest active dose: at best < 0.15 mg/kg/d

NB: max dose: 0.3 mg/kg/j or 10 mg/d in adults

Loss of response is not rare with aging: "too much steroids" (e.g. 15 or 20 mg/d) OR transfusion support?

Profiles of response:

1. Very corticoresponsive pts

2. Responsive pts but at "high-doses" e.g. 0.2 to 0.3 mg/kg/d and limited response (Hb range 8-9 g/dL) : to be maintained?

3. Dose required > 0,3 mg/kg/d ☞ STOP treatment

4. Non responders (20-30%)

Leucine

Received: 22 June 2020 | Revised: 17 September 2020 | Accepted: 18 September 2020
DOI: 10.1002/pbc.28748
HEMATOLOGY: RESEARCH ARTICLE
Pediatric Blood & Cancer
aspho The American Society of Pediatric Hematology/Oncology
WILEY
Check for updates

L-leucine improves anemia and growth in patients with transfusion-dependent Diamond-Blackfan anemia: Results from a multicenter pilot phase I/II study from the Diamond-Blackfan Anemia Registry

N = 43

Leucine/ 700 mg/m² x 3/d for 9 months

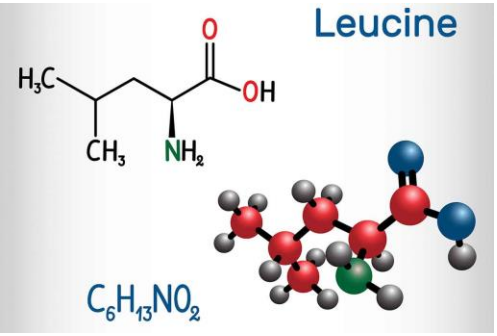
Growth acceleration: 11/26 pts (42%%)

Very few & limited hematologic responses:

- **2 pts reach independence from transfusion (1 with low Hb: 8.7-9.5 range)**
- **5 pts with rise in reticulocytes counts but no significant impact on Hb**

Vlachos & al, 2020

Leucine in practice



Cheap, non-toxic, given at rather low-dose…

<u>In children</u>:

Potential benefit for growth (responses in 40%!):

☞ OK for a try & to be started early

<u>In adults</u>:

May improve general status, appetite,… : why not?

Open question: is leucine may improve response to steroids?

Indications for HSCT & donor choice

Age

- In general, before age 10 years in patients who receive chronic transfusions
- If possible, preferably at the pre-school age (age 2–5 years) to minimise risk of toxicities
- In individual patients, HSCT for transfusion dependence can be considered after age 10 years (low transfusion burden, optimal iron balance, and adequate organ function)
- In adults, HSCT is generally not advised solely for the avoidance of transfusion dependence*

Indications, in order of increasing urgency and clinical necessity

- Chronic transfusions in patients not responding to steroids
- Chronic transfusions in patients with non-manageable iron overload (chelator failure or severe toxicity)
- Chronic transfusions in patient with alloimmunisation to red blood cells
- Severe immunodeficiency or multilineage cytopenia, or both
- Myelodysplastic syndrome or acute myelogenous leukaemia

Donor choice, in order from most to least optimal

- Human leukocyte antigen (HLA)-matched sibling donor, after exclusion of Diamond-Blackfan anaemia syndrome in potential donor (genetic testing, complete blood counts, and erythrocyte adenosine deaminase)
- Matched unrelated donor: 10/10 HLA match based on molecular testing
- HLA-mismatched unrelated donor and HLA-mismatched family donor†: only in the absence of alternative therapies (patients with myelodysplastic syndrome or acute myelogenous leukaemia) or in context of clinical trials

☞ **new guidelines: OK for MUD 10/10**

French & German experience

N = 70 transplants (1985-2017)

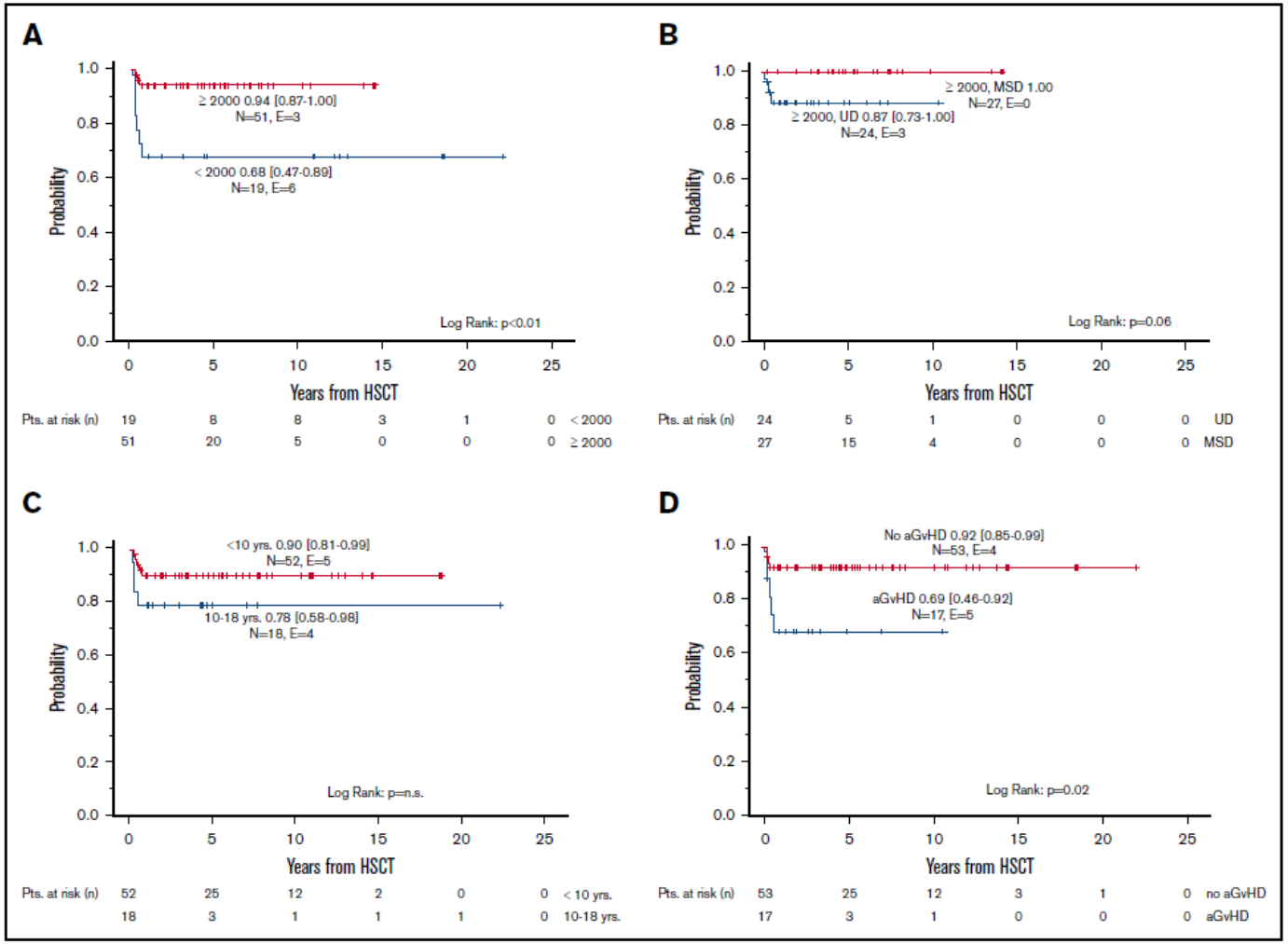
Median age: 5.5 ans [0.9-17.3]

Donor: MSD: 64%

☞ cGFS: 87%

NB: tranplants > 2000:

- **cGFS: 94%**
- **No severe aGVH**
- **No death**



Strahm & al, Blood Adv 2020

HSCT in DBAS patients: in practice

<u>During childhood:</u>

- Children non responsive to steroids: HSCT at best before 3-5 yr

- Limit: 10 yr

<u>Adult age</u>: very few indications:

- Only for MDS/AML?

DBAS & gene therapy

PRO

BM is reach: HSC collection should not be a problem

Attractive option in adult pts not fit for HSCT

Any partial result will be clinically valuable: reduction of transfusion support and iron overload

CON

26 genes…

We have to correct an haplo-insufficiency: good enough but not too much!

BM is reach: we will need a myelobaltive conditinning regimen

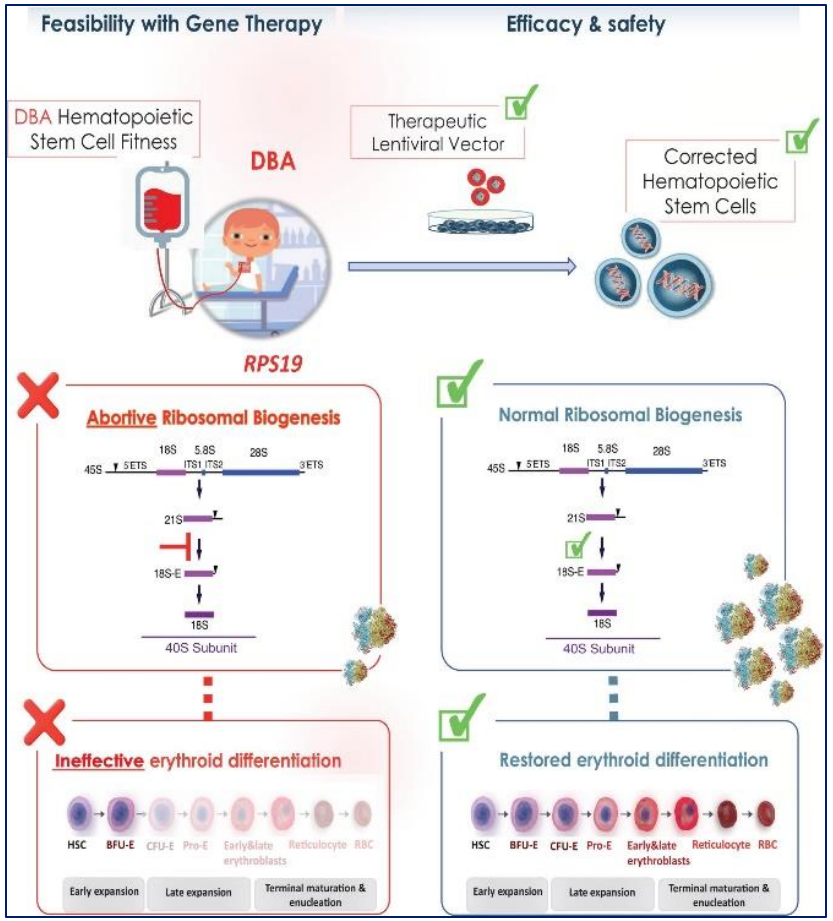
European consortium: DBA Gene cure lead by J. Bueren team
Goal: to achieve all pre-clinical studies required to gene therapy in DBAS patients

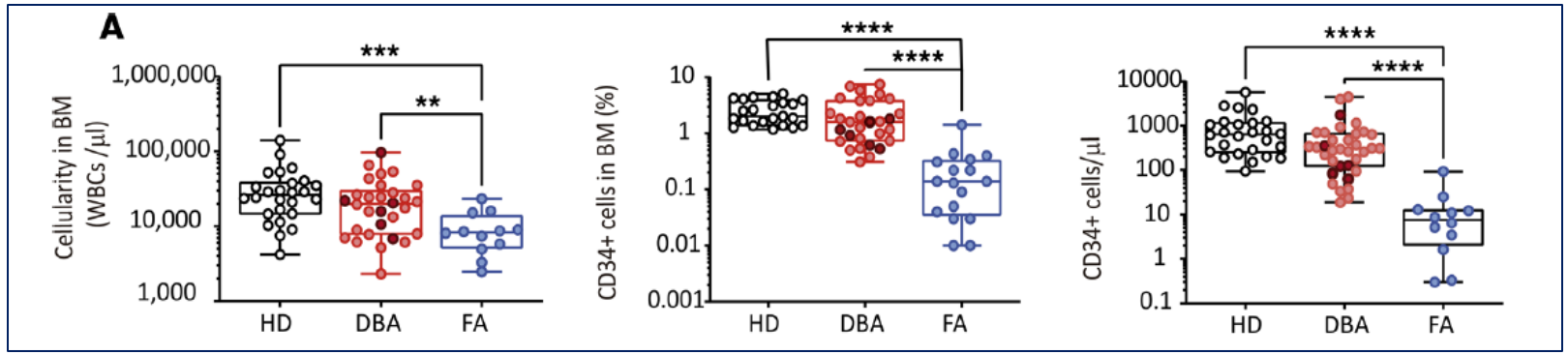
Lentivirus-mediated gene therapy corrects ribosomal biogenesis and shows promise for Diamond Blackfan anemia

Yari Giménez,[1,2,3] Manuel Palacios,[1,2,3] Rebeca Sánchez-Domínguez,[1,2,3] Christiane Zorbas,[4] Jorge Peral,[1,2,3] Alexander Puzik,[5] Laura Ugalde,[1,2,3] Omaira Alberquilla,[1,2,3] Mariela Villanueva,[1,2,3] Paula Río,[1,2,3] Eva Gálvez,[6] Lydie Da Costa,[7,8] Marion Strullu,[9] Albert Catala,[10] Anna Ruiz-Llobet,[10] Jose Carlos Segovia,[1,2,3] Julián Sevilla,[6] Brigitte Strahm,[5] Charlotte M. Niemeyer,[5] Cristina Beléndez,[2,11,12] Thierry Leblanc,[9] Denis L.J. Lafontaine,[4] Juan Bueren,[1,2,3] and Susana Navarro[1,2,3]

J Clinical invest, 2024

GT in DBAS: preclinical results





The data show that, unlike pts with FA), the HSC reservoir of DBAS pts is not significantly reduced

Two clinically applicable lentiviral vectors were developed

Preclinical experiments showed that transduction of DBA pt CD34+ cells with the *PGK.CoRPS19 LV* restored erythroid differentiation, & demonstrated the long-term repopulating properties of corrected DBA CD34+ cells

Gimenez & al, J Clinical invest, 2024

GT in DBAS: where do we stand?

2025: no activated clinical trial
2026: at least 3 clinical studies should start (EU: 1, USA: 2) all for *RPS19*

☞ on the market in 2030?

Other genes?
- Juan Bueren group (Madrid): preclinical studies done for *RPL5*
- US : *GATA1*?

GATA1 expression as a universal gene therapy for Diamond Blackfan Regulated Anemia. Voit RA & al. Cell Stem Cell. 2025

So: what to tell your *RPS19*-mutated patients?
- **Child with good indication for HSCT and a good donor: do not wait for GT…**
- **Adult: get an optimal control of IO in order to be fit for…**

Do we have new drugs to treat our patients?

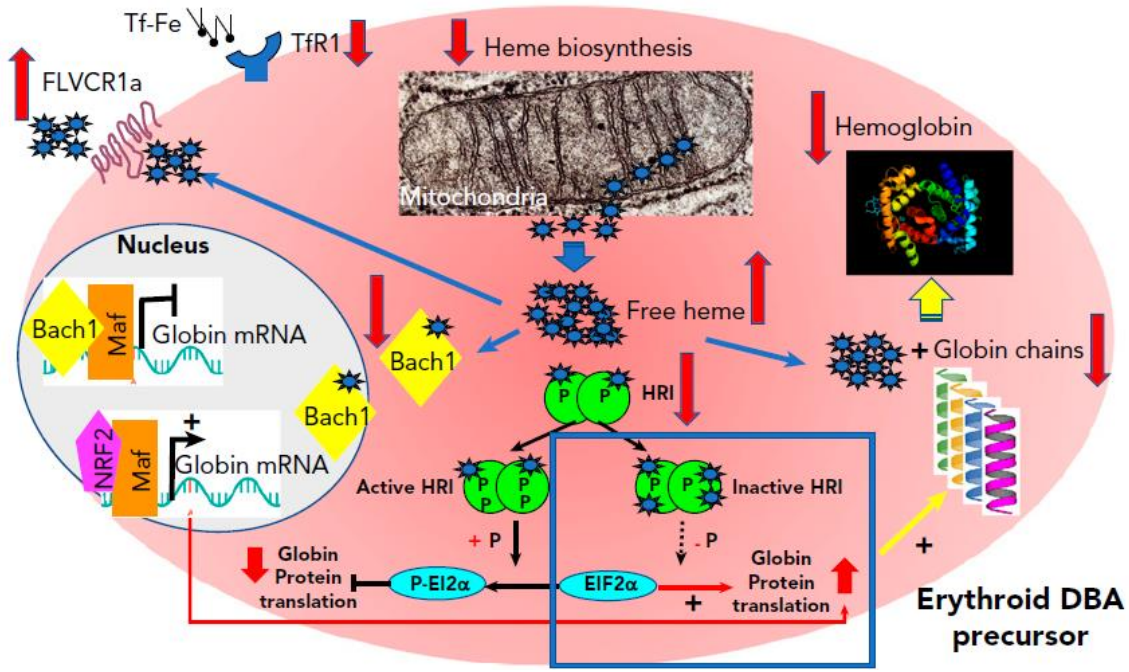
Good point: many cellular & animal models are currently available:
☞ drug-screening possible: different compounds are on study (pre-clinical)

Luspatercept: an EuroBloodNet-sponrored clinical trial (LUSPARA trial) will open soon for pts with CDA, CSA & a very specific subset of DBAS pts (*RPS19*-, *RP5*-, *RPL11*-mutated, non-transfused, low Hb on steroids or w/o treatment). The study is planned to open in September (France & Italia)

Bitopertin: only ongoing clinical study

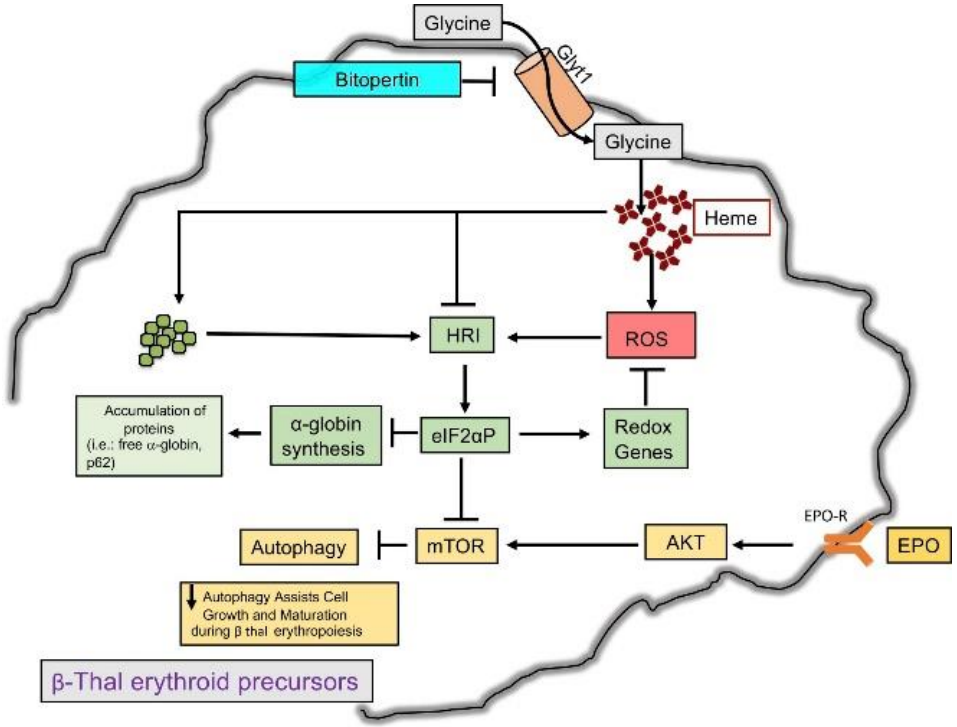
Bitopertin

Known free heme toxicity in DBAS



Da Costa & al, Blood 2020

Biopertin: inhibitor of Gly-T1: Gly mitochondrial transporter



Bitopertin clinical trial

In vitro (BM cells from *RPS19*, *RPS26*, *RPL5*, *RPL11 mutated DBA pts*)
NB: clically active in a thal mouse model (Matte & al, JCI Insight 2019)

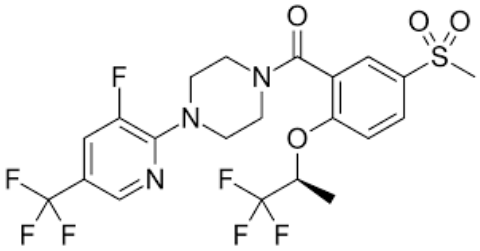
See ASH 2023:
Abstract 1086
Clinical study design
Abstract 1355
Pre-clinical studies

Clinical trial OPEN in the US: NCT05828108: phase 1/2

DBA adult pts non responsive to (or intolerant to) steroids and either on transfusion or in TI with Hb < 9 g/dL

Dose escalation study: 5 to 60 mg/d

Response at S32 (drug may be given up to 32 months)



NIH U.S. National Library of Medicine
ClinicalTrials.gov

Surveillance of DBAS patients: in brief

Children

Growth +++

Systematic visit with endocrinologist

Possible interventions:

- **STOP steroids (for 24-36 months)**
- **GH therapy**

Howell JC & al. Pediatr Blood Cancer 2015

Adults

Hypo-γ-globulinemia screening

Cancer screening

Pregnancies management

Incidence of neoplasia in Diamond-Blacfan anemia: a report from the Diamond Blackfan anemia registry

N = 608

(9458 person-years)

Median at 1st cancer: 41 yr

<u>Types:</u>

- ST: 15 (+++ OS & Colon)

- LAM & SMD: 2

Table 3. Observed cancers, O/E ratios, and 95% CIs

Cancer type	No. of observed cancers*	O/E Ratio	95% CI
Events with significant O/E ratios			
All cancers	18*	5.4	3.2-8.6
Colon (adenocarcinoma)	3	36.2	7.5-105.8
Bones (osteogenic)	2	32.6	4.0-117.7
Female genital†	3	12.0	2.5-35.1
AML‡	2	27.9	3.4-100.9
MDS‡	4	287.0	77.2-734.7
Events with nonsignificant O/E ratios			
Oral cavity	1	15.9	0.4-88.3
Soft tissue sarcoma	1	9.8	0.3-54.8
Lung	1	8.3	0.2-46.4
Testis	1	8.3	0.2-46.1
Non-Hodgkin lymphoma	1	5.7	0.1-31.7
Melanoma	1	4.5	0.1-25.3
Breast	2	4.1	0.5-14.9

All data shown are significant at $P < .05$.

*Eighteen cancers in 17 individuals. One person had breast cancer, colon cancer, and MDS at ages 43, 49, and 51 years.

†Female genital included cervix, uterus, and vagina. Respective O/E ratios were 11.27 (0.29-62.78), 14.2 (0.36-79.14), and 270.81 (6.86-1508.83).

‡MDS is not included in the cancers. One patient had MDS followed by AML and is counted in both groups. A second patient is referred to above, with breast, colon, and MDS.

Vlachos & al, Blood 2012

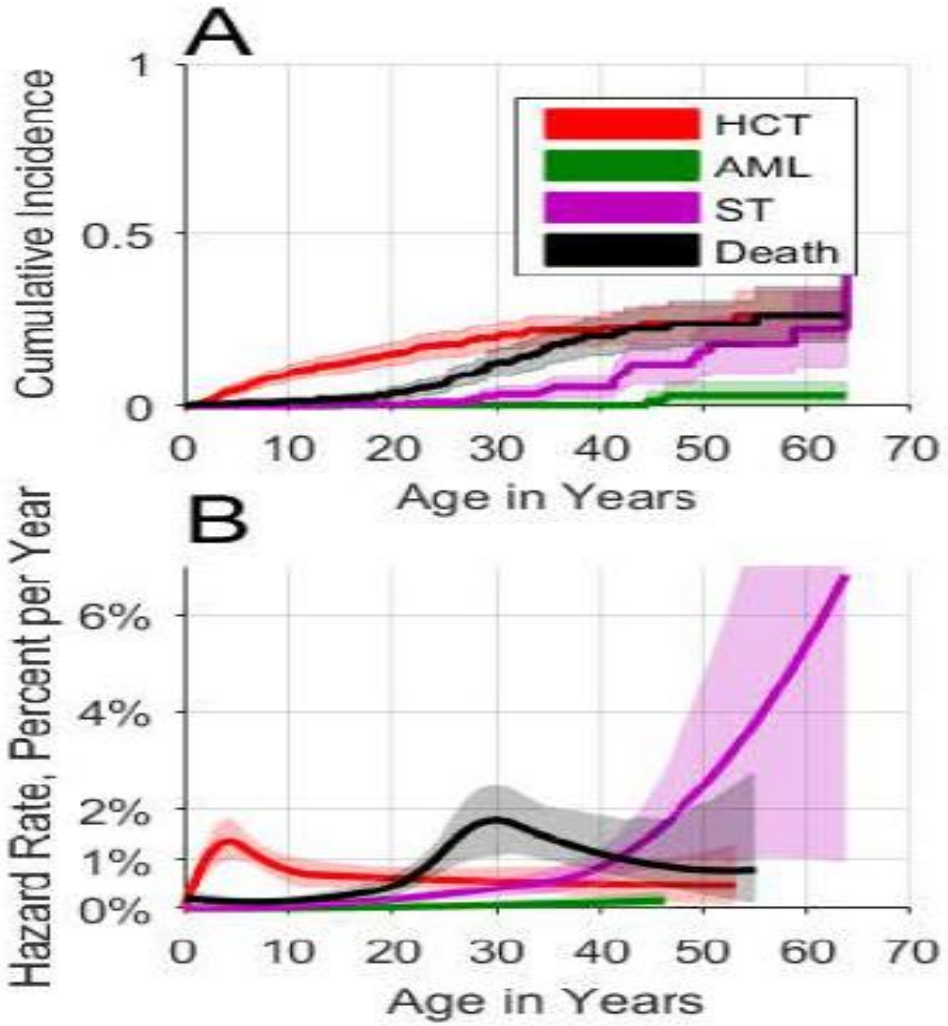
Increased risk of colon cancer and osteogenic sarcoma in DBA running head: neoplasia in DBA

DBAR: N = 702

☞34 cancers (pts w/o HSCT):

- Median age at 1st cancer: 35yr [11-70]

- CI at 45 yr: 13.7%



Vlachos & al, Blood 2018
Lipton & al, Pediatr Blood Cancer 2021

Surveillance of DBAS pts MDS/AML & ST Risk

- Patient education, healthy lifestyle (avoid smoking, alcohol, toxins, unprotected sun exposure)
- HPV vaccination
- Patient adherence to screening procedures as in the general population
- Colonoscopy beginning age 20 years, every 5 years or more often if clinically indicated
- Bone marrow analysis: consider as baseline in adolescents/ young adults before transitioning to adult care, otherwise in any patient with significant unexplained cytopenia or rise in reticulocytes
- Unexplained joint/bone pain: risk of osteogenic sarcoma (low threshold for x-ray / imaging)

For MDS/AML:

- **BCC every 3 months whatever the status**
  (including pts with "silent phenotype")
- **BMA (or biopsy) if worsening of cytopenias (thrombocytopenia +++) or blasts**
- **Is there a benefit associated with sequential NGS analysis on blood samples?**

Pt 1: W, 49 yr: (1) cancer history

Rectorragia ⇨ rectal adenocarcinoma
T4 N1 M0 ; no mutation in MMR[1] genes

09 to 12/2020
FOLFIRINOX[2]
6 cycles

01 to 02/2021
CAP50[3]

05/2021
Surgery

06 to 07.2021
FOLFOX[4]

Age at diagnosis:
49 yr ; no treatment

Age

Gene: *RPS17*

Overall good tolerance ; neutropenia G°1 anemia G°2

Red-cell transfusions (2/month)

Only 2/6 cycles:
Pb: persistent thrombocytopenia

Part of the hematological landscape: poor tolerance to chemotherapy ± cumulative effect

☞ STOP chemotherapy (2022.07)

1: Mismatch repair
2: FOLFIRINOX: 5-fluorouracil, irinotecan, oxaliplatin
3: CAP50: RT 50 Gy + capecitabin
4: FOLFOX: 5-fluorouracil, oxaliplatine

Pt 1: W, yr: (2) MDS history

Hb OK (10-11 g/dL) but persistent thrombocytopenia (70-100 G/L)

HSCT: 2022.10
MUD 9/10

Palliative care

Death

2022.08: BMA
Blast 1% + MLD

Pre-HSCT BMA
Stable

2023.04:
BMA: (-)
BMB: MDS relapse

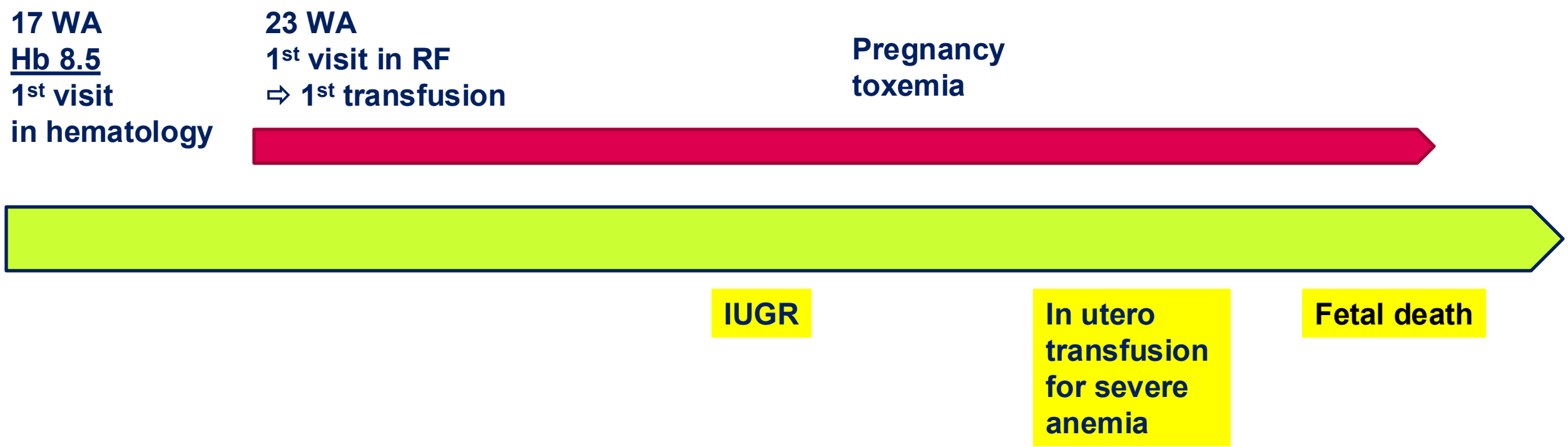
Progression to overt AML (blasts 85%) + clonal evolution

Karyotype:
- 45, XX, del(5q)(q1?; q3?3), -7 [5]
- 45, idem, add(2)(q1?2), add(3)(p2?1), t(10;18)(q2?4; p11), 11, 2 x dic(11;22)(p1?3;q11), der(19)t(2;19)(q?14; p1?2), del(20)(q11) [9]
- 46, XX [12]

+ TP53 mutated

DLI?
AZACYTIDINE: no response
AZACYTINE-VENETOCLAX: no response

Woman, DBAS, *RPS19*-mutated, on steroid during childhood then TI (usual Hb: 10.5-11 g/dL), lost to follow-up



☞ Guidelines: Hb to be maintained > 10.5 g/dL + potential indication for aspirin

Faivre & al, Haematologica 2006

Conclusion

DBAS is highly polymorphic and may present in many ways

New recommendations (2024) available ; please use Suppl. Tables…

Need to improve diagnosis, follow-up and management of adult patients

Reasonable hope of new therapeutic approaches in the medium term

Thank you for your attention

thierry.leblanc@aphp.fr

MaRIH network: Reference centers for rare Immunological and hematological diseases

APLASIE MEDULLAIRE centre de référence

MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

AFMBD

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- *Hematology labs: Lydie DA COSTA*
- *Clinical research assistants: Isabelle MARIE, Isabelle BRINDEL*

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