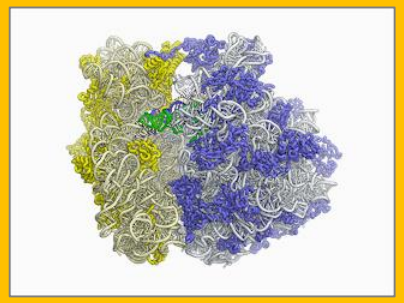
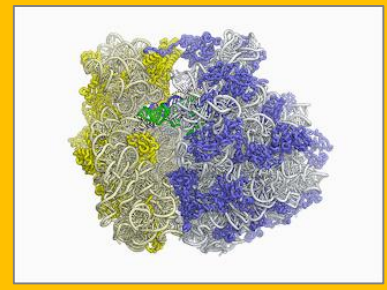
Anémie de Blackfan-Diamond: Actualités





Thierry Leblanc

XXIV^{ème} Journée de l'AFMBD

26-28 Octobre 2024 - Poitiers

Université Paris Cité

APLASIE MEDULLAIRE centre de référence

maladies rares

MaRIH Filière de santé Maladies Rares Immuno-Hématologiques

EuroBloodNet

Hôpital Robert Debré

maladies rares

euro DBA consortium

EuroBloodNet

MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

APLASIE MEDULLAIRE
centre de référence

Filière: MaRIH → **CRMR: CERAMIC** → **RIME & OFABD**

PNDS 2023 ⟷ **Guidelines 2024**

AFMBD

Help Find a Cure for Diamond Blackfan Anemia
www.dbafoundation.org

Etude en cours (1)
Phénotype hématologique chez les pts adultes

Aucune publication spécifique en dehors de l'étude sur les grossesses des femmes ABD

Auto-questionnaire (F & H) + données médicales

A l'idéal couplé à une inclusion dans OFABD/RIME

Objectif: 100 pts avec dossier « complet »

Hematological landscape of adult patients with DBA: the French DBA cohort results

Etude en cours (2)
Chélation chez les moins de 3 ans

Aucune publication disponible

Enfants SABD très mal chélatés (en particulier aux USA)

☞ Étude à partir des registres Italiens & Français

Objectif: 50 pts

Publications ABD en 2024

ABD: publications en 2024 (OCT 2023- OCT 2024)

☞ 24 articles (+1 pre-print) référencés sur PubMed

Physiopathologie : 7

(NEMO, Single-cell, iPSC, modèles animaux, métabolisme énergétique mitochondrial)

Aspects cliniques

- Phénotype : 1
- Corrélations GENO/PHENO : 6
- Cas cliniques : 3

Génétique : 1

Guidelines : 1

Allogreffe : 1

Revues & éditoriaux : 4

PubMed.gov PubMed.gov PubMed.gov PubMed.gov PubMed.gov

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

- **Nouveau nom**

- **Nouveaux critères diagnostiques**

- **Nouvelles recommandations pour le support transfusionnel (> 9g/dL), la chélation, la corticothérapie & les indications de greffe**

- **SABD & cancer**

Wlodarski & al, Lancet Haematology 2024

SABD: critères diagnostiques

Poids +++ à la génétique:

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: macrocytic anaemia* with reticulocytopenia and bone marrow erythroblastopenia; absence of dysplasia, dyserythropoiesis†, and sideroblasts; and exclusion of known differential diagnoses (see below)

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§

NB: on ne parle plus de “porteur sain”

SABD Corticothérapie

Panel 4: Recommendations for steroid treatment

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

Posologie maximale: baissée à 0,3 mg/kg/j
Posologie discutable: 0,15 à 0,3 mg/kg

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

SABD & chélation

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

NB: particularités SABD: 1) début précoce, < 1 ans, 2) traitement combiné

Greffe chez les enfants SABD

Panel 6: Recommendations for allogeneic HSCT

General

- Assessment of iron overload (liver and heart MRI) before planning haematopoietic stem-cell transplantation (HSCT)
- Iron overload: chelation before HSCT and consider phlebotomies after HSCT

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

Plus de 10 ans?

Discussion au cas par cas

Non recommandée chez pts adultes

Sources alternatives de CSH?

Discussion au cas par cas…

Au mieux dans le cadre d'une étude clinique

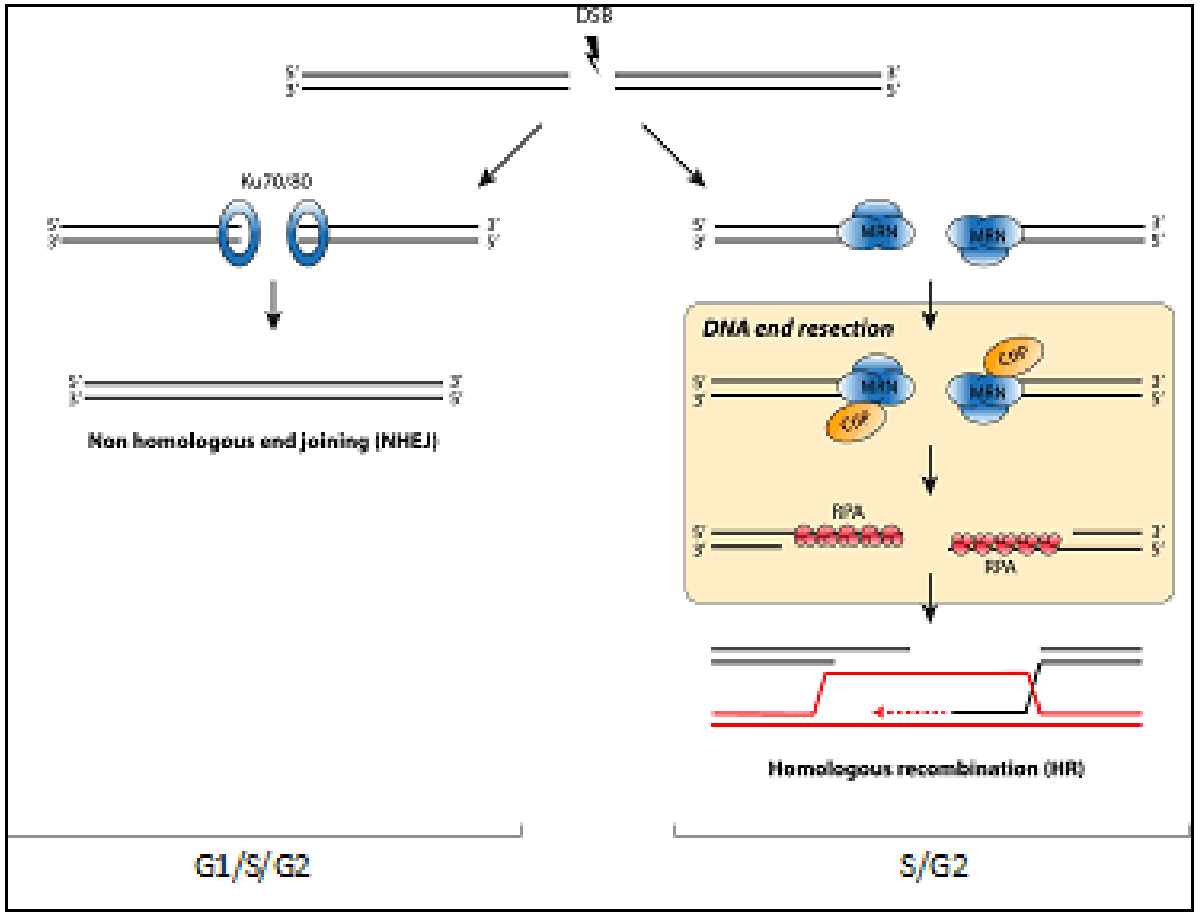
RPS19 and RPL5, the most commonly mutated genes in DBA , impact DNA double-strand break repair

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

DBA pt-derived lymphoblastoid cells had persistent γ-H2AX foci following IR suggesting DNA DSB repair defects

RPS19-KD decreased the efficiency of pathways requiring extensive end-resection

RPL5-KD increased end-joining pathways



BioRxiv via PubMed, 2024

Probable digenic inheritance of DBA

Fille, ABD

Phénotype très sévère

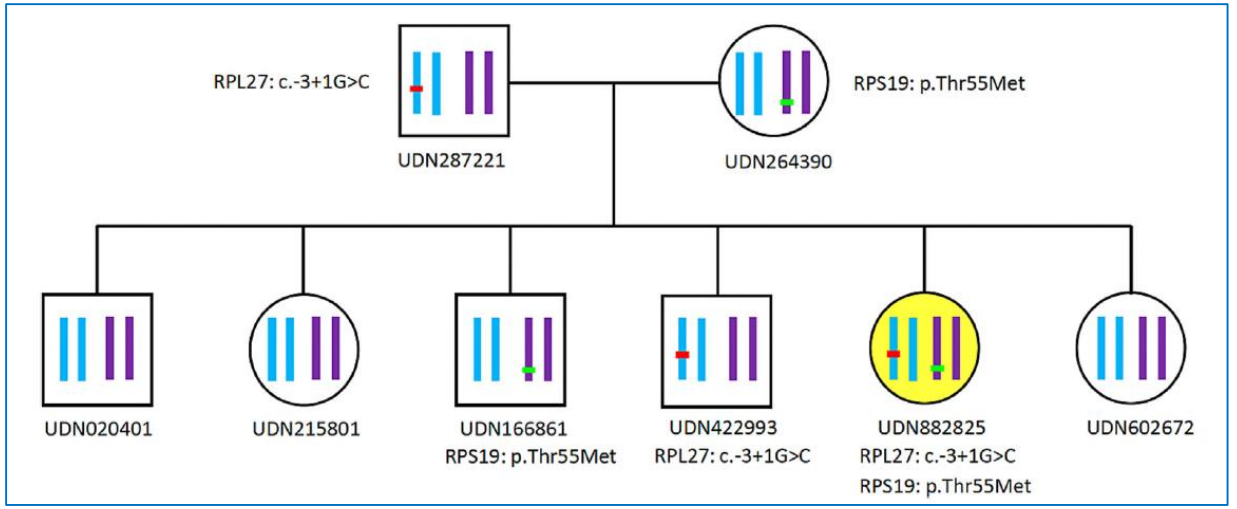
Anémie & érythroblastopénie

(HbF & ADAe ⇗)

RSP & déficit en GH, microcéphalie, glaucome, cardiopathie, reins dysplasiques, scoliose, *genu valgus*

☞ **Enquête génétique (-) sauf variant RPS19 classé VSU**

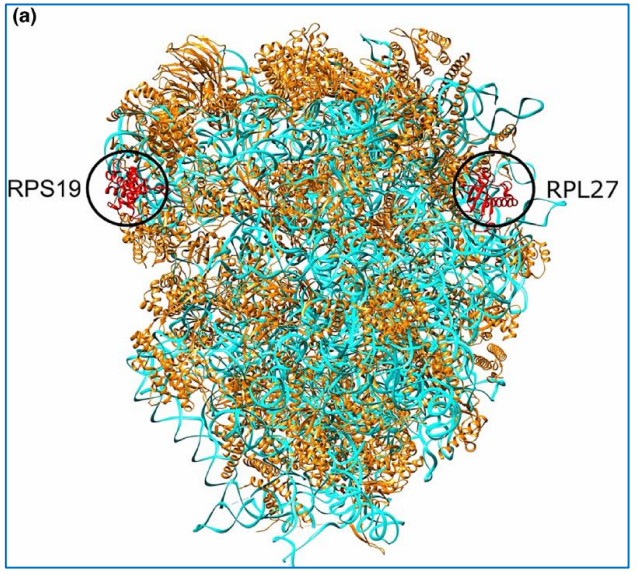
☞ **2ème variant finalement identifié: *RPL27* classé 4**



Machine learning structural model

⇩

Interaction between the 2 products



Furuta & al, Am J Med Genet 2024

Conditionnement de greffe

Un conditionnement de greffe permet:

- **d'éliminer la moelle du receveur**
- **D'éliminer le système immunitaire du receveur**

Balance entre l'efficacité & la toxicité

MAC : *Myelo-Ablative Conditioning regimen*

RIC : *Reduded-Intensity Conditioning regimen*

Exemple de RIC: Fludarabine : 30 mg/m²/j x 5
Thiotepa : 10 mg/kg/j x 1
Melphalan : 70 mg/m²/j x 2 ± SAL si MUD

→ **Etude**

Reduced toxicity conditioning for hematopoietic stem cell transplantation in children with DBA

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age at diagnosis in months/age at HSCT in years	3/14 ⬆	3/8 ⬆	4/5	8/8 ⬆
DBA mutation	*RPS17* (whole gene deletion)	*RPS26* (p.R87*)	*RPS19* (p.Ala100Trpfs*12)	*RPS19* (exon 2-3deletion)
BM cellularity pre-HSCT, %	90	60-70	40-50	30
LIC: highest/pre-HSCT, mg/gm liver tissue	12.8/2.98	8.76/4.18	14.06/5.75	7.04/2.23
Ferritin pre-HSCT, ng/mL	895	4,301	1,054	227
Donor type/graft source	MSD/BM	MUD/BM	MUD/BM	MUD/BM

NB: MVO

☞ ***4/4 vivants sans GVH à 11-21 mois de la greffe***

Amr Qudeimat & al, Haematologica 2024

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Nouvelles approches thérapeutiques en cours?

Etudes & essais cliniques

57 études enregistrées sur le site: la plupart: études sur les registres (dont RIME), modalités de greffe, ou chélation (pas d'étude spécifique pour les pts ABD)

Eudes de greffe: donneurs alternatifs: MUD, UCB, partially-matched, T-cell depleted, α/β T-cell & CD19- depleted,…

Etudes cliniques évaluant un traitement hors greffe:

- **Anciennes études toujours sur le site mais arrêtées et non concluantes** *(sotatercept, eltrombopag, trifluoperazine, lenalidomide, rituximab)…*
- **1 étude de phase 1/2: bitopertin**
- **Pas d'étude actuellement ouverte de thérapie génique**

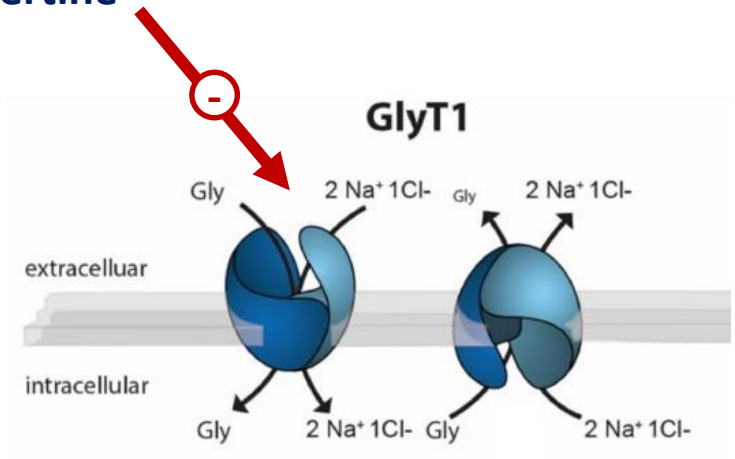
NIH U.S. National Library of Medicine ClinicalTrials.gov

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

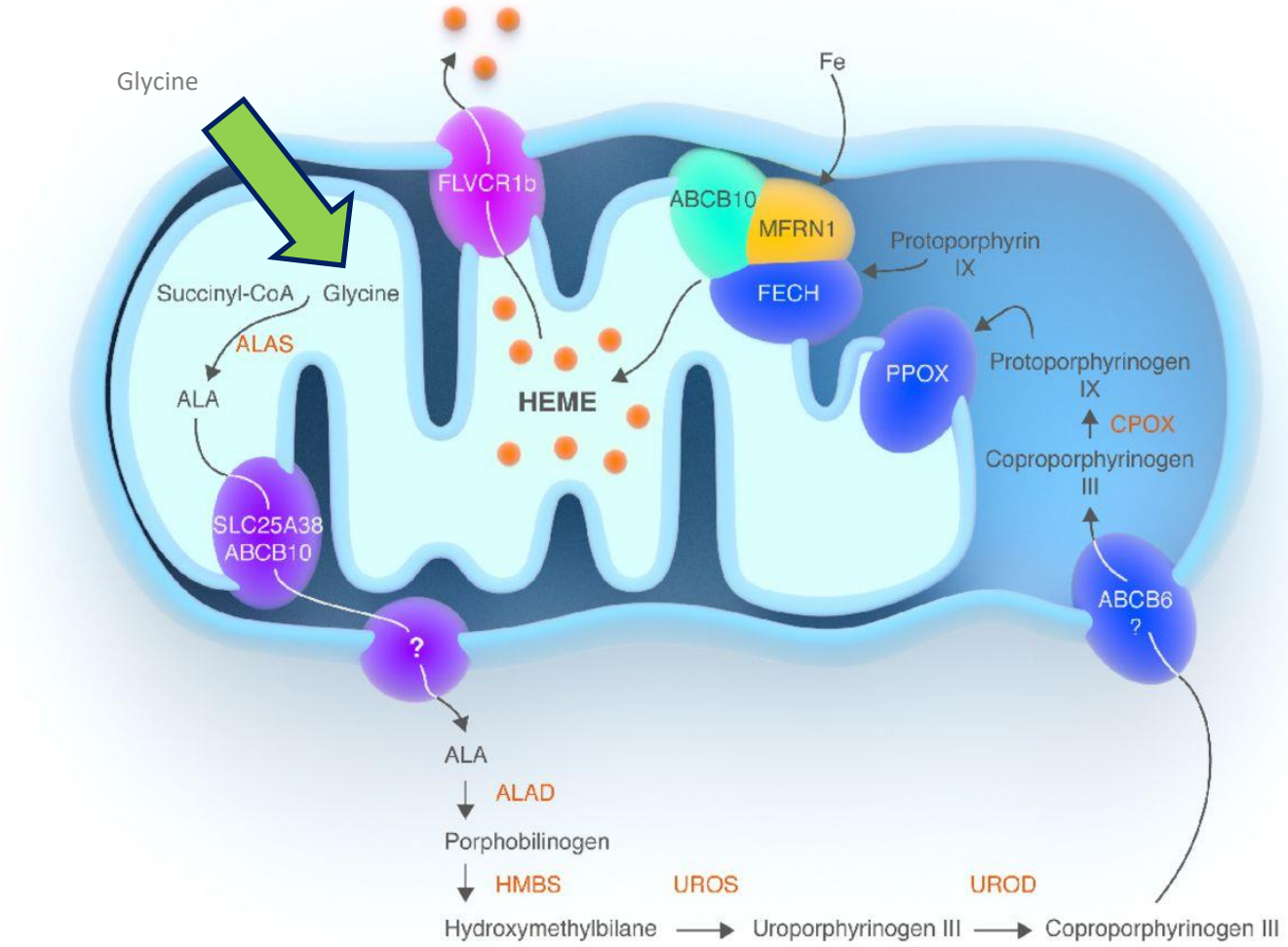
NIH U.S. National Library of Medicine ClinicalTrials.gov

Synthèse de l'hème

bitopertine



Transporteur de la Glycine qui est nécessaire à la 1ère étape de la synthèse de l'hème



Chiabrando & al, Haematologica 2014

A Phase I/II, Intra-Patient Dose-Escalation Study of the Selective GlyT1 Inhibitor, Bitopertin for Steroid-Refractory Diamond-Blackfan Anemia

Actuellement ouverte aux inclusions (N = 30 pts prévus)

Etude monocentrique (NIH)

ASH 2023:

1086: Description étude

1355: Études pré-cliniques

Pts ABD adultes:

Non-répondeurs aux corticoïdes:

- patients transfusés
- patients non transfusés mais avec Hb < 9 g/dL

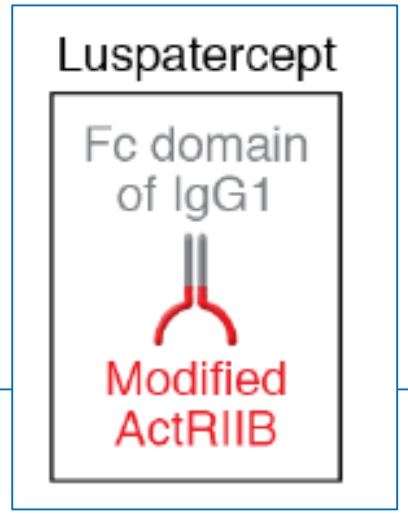
Patients intolérants aux corticöides

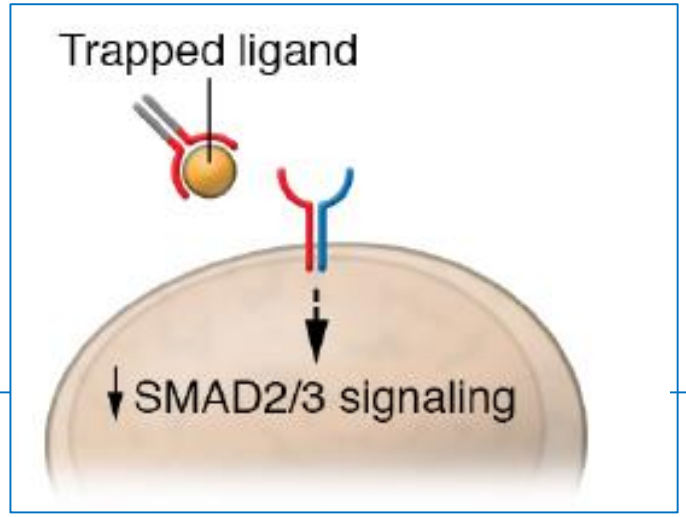
Luspatercept

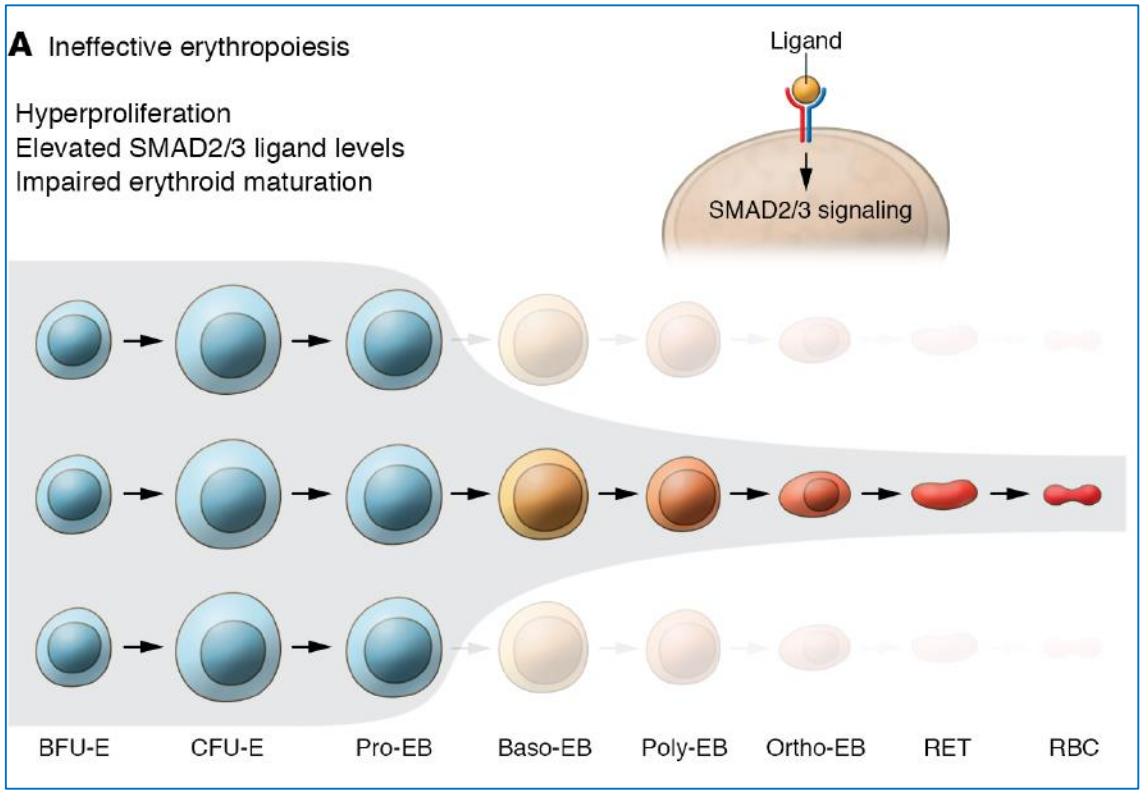
Les ligands de la voie SMAD2/3 (activine & GDF) ont un effet régulateur (-) sur l'érythropoïèse

<u>LUSPA & Co</u>: ligand-traps

☞ **Restauration de l'érythropoïèse**







Verma & al, J Clin Invest 2020

Luspatercept & anémies constitutionnelles

Syndrome thalassémiques:

- β thalassémies majeures et thalassémies NDT

- Hémoglobinose H (α thalassémie)

***Anémies rares*:**

- Anémies sidéroblastiques constitutionnelles
- Dysérythropoïèses constitutionnelles
- Syndrome de l'Anémie de Blackfan Diamond?

} **à évaluer**

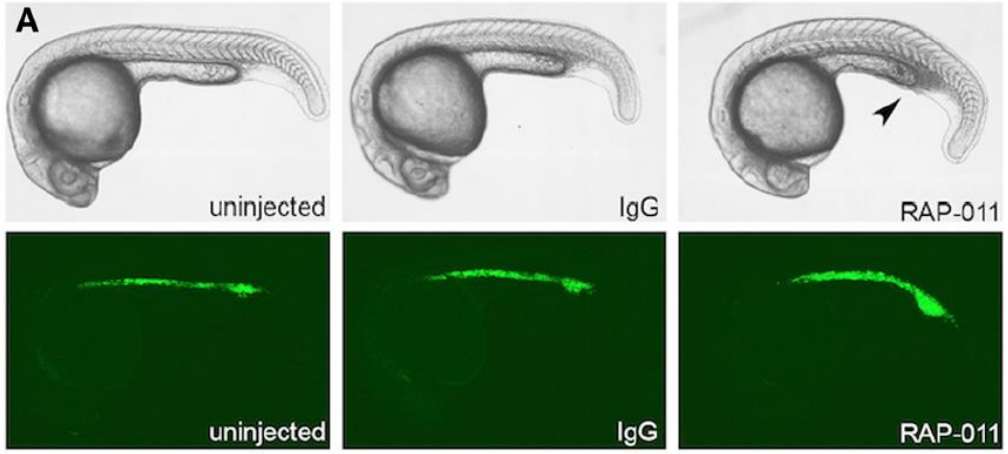
RAP-011 improves erythropoiesis in zebrafish model of DBA through antagonizing lefty1

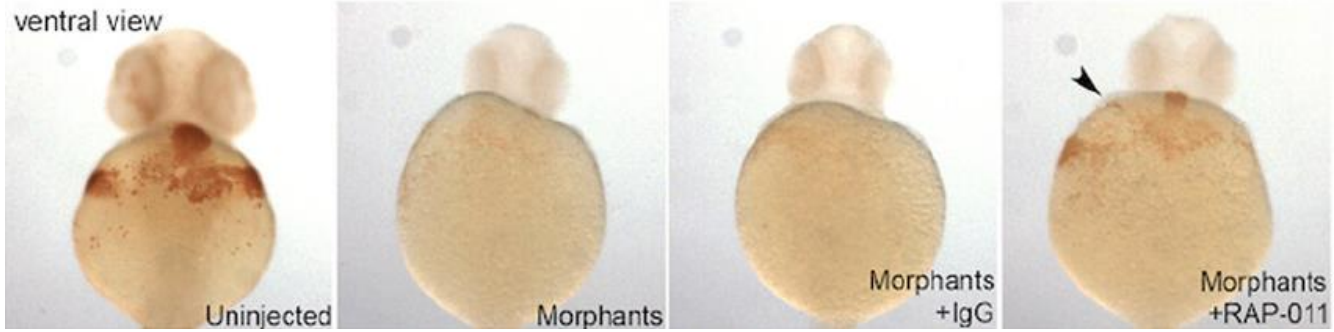
Modèle animal: zebrafish / *RPL11*

RAP-011 ⇗ la prolifération érythroïde

Effet aditif de la déxaméthasone

RAP-011 antagonise l'effet de l'hyper-expression de Lft1 (famille TGF-β)





Ear & al, Blood 2015

Essai avec le sotatercept

Etude USA

Uniquement pts adultes TRANSFUSES

7 pts inclus dont 2 arrêts précoces:

- **Bien toléré**
- **Pas de réponse….**

LUSPARA trial

Population de l'étude: pts adultes, ayant une anémie rare génétiquement caractérisée, transfusés ou non

Dont SABD: mais ici patients TRES sélectionnes:

- **uniquement pts non transfusés:**
  - **Sous corticoïdes ou en indépendance thérapeutique**
  - **MAIS anémiques: Hb < 10 g/dL**
- **Gène identifié: 2 sous-groupes: *RPS19* vs *RPL5* & *RPL11***

LUSPARA trial

Protocole: injection SC toutes les 3 semaines

3rd dose reduction	2nd dose reduction	1st dose reduction	Starting dose	1st dose increase
0.45 mg/kg	0.6 mg/kg	0.8 mg/kg	1.0 mg/kg	1.25 mg/kg

Conclusion

Guidelines disponibles: devraient améliorer le diagnostic du SABD et la prise en charge des patients

Greffe de moelle: nouvelles approches?

Nouveaux espoirs thérapeutiques avec 3 approches en cours d'évaluation:

- **Bitopertine**
- **Thérapie génique**
- **Luspatercept**

Merci pour votre attention

thierry.leblanc@aphp.fr

MaRIH network: Reference centres for rare Immunological and hematological diseases

Patients associations

Anémie de Blackfan-Diamond en France

- ***Site pédiatrique: Mony FAHD, Jean-Hugues DALLE & Thierry LEBLANC***
- ***Site adulte: Flore SICRE de FONTBRUNE & Régis PEFFAULT DE LATOURL***
- ***Laboratoire (génétique & recherche): Lydie DA COSTA***
- ***OFABD: Isabelle MARIE***

Reconnue par le Ministère de la Santé

MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques