Anémie de Blackfan-Diamond
Actualités

AFMBD

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thierry.leblanc@rdb.aphp.fr

Revue de la littérature

Oct. 2009 ►Oct. 2010: 39 articles publiés

Articles cliniques:

- Etude clinique : 2 + 1*(PGD)* + *1(IBMF)*
- Etude biologie clinique/génétique : 1/5
- Corrélations phénotype/génotype : 1
- Case reports : 9
- Revues: DBA/IBMF : 4 / 4

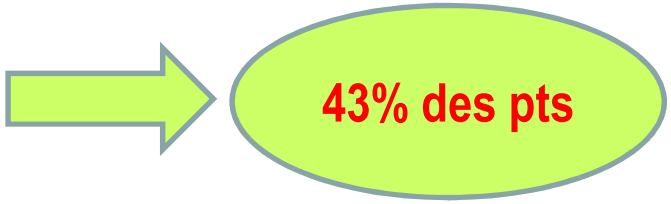
Articles « basic science »

- Ribosomes & ribogénèse : 4
- Modèles animaux/autres : 1 / 2
- Revues : 4

Ribosomal protein genes RPS10 & RPS26 are commonly mutated in DBA. Doherty & al, 2010

RPS19, RPS24, RPS17, RPS7

RPL35A, RPL5, RPL11



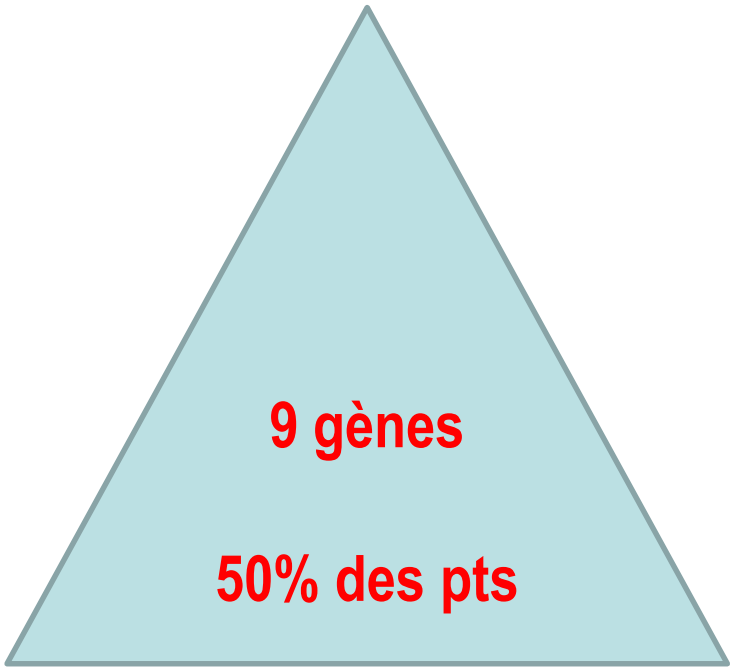
Cohorte de 117 pts: séquence de 35 gènes codant pour des RP:

➔ *RPS10*: 5 pts mutés

➔ *RPS26*: 12 pts mutés

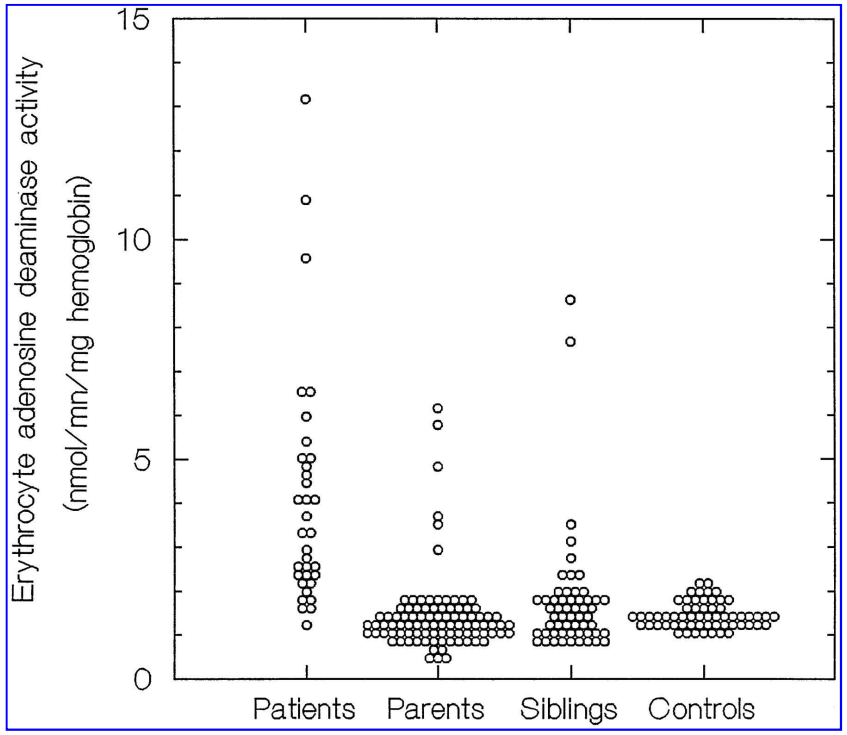
Corrélations P/G:

- Excès de CR pour *RPS26*?



Determination of adenosine deaminase activity in dried blood spots

Mesure du taux d'ADAe



ADAe chez des pts DBA

Méthode sur buvard

(reversed-phase high-performance liquid chromatography)

Intérêt +++ : facilité du prélèvement

(stable 1 an à 4° …)

Severe iron overload in BDA: a case control study. Roggero & al, Am J Hematol, 2009

N = 31 pts régulièrement transfusés & ayant au moins 1 évaluation par SQUID

Comparaison avec des pts β-thal bien chélatés

- Aucun patient avec SQUID normal
- Surcharge sévère (LIC > 15 mg Fe/g Liver d.w.) : 54%
- Ferritine moyenne: 1760 ng/ml (chélation inadéquate: 51%)
- Corrélation Ferritine/SQUID
- 3 pts évalués en T2*: 1 avec T2* à 7,7 ms

(fille, 9 ans, moderate LIC, non-optimal chelation, fonction VG nle)

LIC > chez DBA vs β-thal

➔ **Surcharge plus importante chez les pts DBA?**

Choix d'un chélateur

DEFEROXAMINE	DEFERIPRONE	DEFERASIROX
Voie SC, IM, IV	Voie Orale (3/24h)	Voie Orale (1/24h)
Référence	Observance	Observance
OK chez < 2 ans	Surcharge cardiaque	
	Peut être associé	
(toxicité > si surcharge faible)	(toxicité > si surcharge majeure)	(toxicité > si surcharge faible)
Toxicité OPH & ORL	Agranulocytose	Toxicité rénale
Infections	*(> chez ABD?)*	Foie, GI
Dysplasies osseuses	Arthropathies	Toxicité OPH & ORL
Arthralgies, myalgies	Foie, GI	Nouveau médicament
Réactions locales	Carence en Zinc	Cœur ?

Seule indication d'association validée: DFO + DFP

Indication: surcharge cardiaque (T2* court)

Nouvelles associations de chélateurs?

Modèle animal

Methods—Thirty-two female Mongolian gerbils 8–10 weeks old were divided into 4 groups (sham chelated, DFO, DFX, DFO/DFX). Each received 10 weekly injections of 200 mg/kg iron dextran prior to initiation of 12 weeks of chelation. Experimental endpoints were heart and liver weights, iron concentration and histology.

Results—In the heart, there was no significant difference among the treatment groups for wet-to-dry ratio, iron concentration and iron content. DFX-treated animals exhibited lower organ weights relative to sham-chelated animals (less iron-mediated hypertrophy). DFO-treated organs did not differ from sham-chelated organs in any aspects. DFX significantly cleared hepatic iron. No additive effects were observed in the organs of DFO/DFX-treated animals.

Conclusions—Combined DFO/DFX therapy produced no detectable additive effect above DFX monotherapy in either the liver or heart, suggesting competition with spontaneous iron elimination mechanisms for chelatable iron. Combined therapy was well tolerated, but its efficacy could not be proven due to limitations in the animal model.

(Acta Haematol. 2008 ; 120(2): 123–128)

Données cliniques ?

Retrospective study on the combination of desferrioxamine and deferasirox for treatment of iron-overloaded thalassemic patients: first evidence of more than 2 years.

J Pediatr Hematol Oncol. 2010 Jul;32(5):400-3. *Jetsrisuparb A & al (Thailand)*

Abstract

Some iron-overloaded patients have problems being treated with iron chelators. We therefore retrospectively studied 7 iron-overloaded thalassemic patients. Within the same week, patients received 20 to 30 mg/kg/d of oral deferasirox for 4 consecutive days, then a subcutaneous infusion of 20 to 40 mg/kg/d of desferrioxamine for 8 to 12 hours on the next 3 consecutive days. The median treatment duration was 25 months (range, 8 to 32). All of the patients showed a decrease in serum ferritin without any side effects. The protocol, combining deferasirox and desferrioxamine in sequence, was effective and safe: more cases should be studied.

Safety of Deferasirox and Deferoxamine Combined Chelation Therapy in Thalassemia Major patients
Protocol Deferasirox/Deferoxamine 'Combo Trial' CICL670AUS24T

Study Design

Non-randomized safety clinical trial of combined DSX/DFO therapy

GROUP A (n = 5)

- Age >18 yr
- LIC <15 mg/gm dry wt
- PLUS Iron-related end organ dysfunction

→

- DSX 20-30mg/kg/day
- DFO 50mg/kg IV/SC 12-24 hrs per day 3 days per week

GROUP B (n = 5)

- Age >18 yr
- LIC >15 mg/gm dry wt
- PLUS/MINUS Iron-related end organ dysfunction

→

- DSX 20-30mg/kg/day
- DFO 50mg/kg IV/SC 12-24 hrs per day 5-7 days per week

GROUP C (n = 5)

- Age 8-18 yr
- LIC >5 mg/gm dry wt
- Plus Iron-related end organ dysfunction

→

- DSX 20-30mg/kg/day
- DFO 35-50mg/kg IV/SC 12-24 hrs per day 3-5 days per wk

Conclusions

- Simultaneous administration of DSX and DFO at these doses is well tolerated and has low potential for toxicity
- In subjects who previously had limited success with single chelator, the combination therapy was effective in
  - Lowering body iron
  - Removing myocardial iron
- A larger clinical trial is needed to assess the benefits of long-term combined chelation therapy in thalassemia major

Applicabilité aux patients DBA?

(ASH, 2009)

Nouvelles
règles de prescription?

CAT devant une Ferritinémie < 500 µg/l?

Recommandation actuelle: idem: si 2 ferritinémies successives sont < 500, il faut arrêter transitoirement et reprendre dès que > 500

Tendance (hors AMM et non validée): poursuivre à des doses plus faibles (5 à 10mgkg/j) sous surveillance rénale +++

NB: étude Novartis en discussion dans les thalassémies:

"Multicenter, single arm, open label, phase II, prospective study to determine maintenance dose of deferasirox in transfusion-dependent ß-thalassemia pts with SF above normal but less than 500 µg/L"

Etude chez les patients ayant une hémochromatose génétique

Phase 1/2 avec escalade de doses (5, 10 ou 15 mg/kg/j)

N= 49 ➡ inclusions séquentielles: 5 puis 10 puis 15

Ferritinémie à l'entrée: 300 à 2000 µg/l

Conclusion:

- **Efficace**
- **Toxicité (faible) est dose-dépendante**
- **Dose recommandée: 10 mg/kg/j**

(Phatak & al, Hepatology, 2010)

Intérêt du dosage du DFX

Deferasirox pharmacokinetics in patients with adequate versus inadequate response

Deborah Chirnomas,[1-3] Amber Lynn Smith,[1] Jennifer Braunstein,[1] Yaron Finkelstein,[2,4,5] Luis Pereira,[4] Anke K. Bergmann,[1,2] Frederick D. Grant,[2,6] Carole Paley,[7] Michael Shannon,[2,4] and Ellis J. Neufeld[1-3]

[1]Hematology/Oncology, Children's Hospital Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Dana-Farber Cancer Institute, Boston, MA; [4]Clinical Pharmacology Unit, Children's Hospital Boston, MA; [5]Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, University of Toronto, Toronto, ON; [6]Division of Nuclear Medicine, Children's Hospital Boston, MA; and [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ

Tens of thousands of transfusion-dependent (eg, thalassemia) patients worldwide suffer from chronic iron overload and its potentially fatal complications. The oral iron chelator deferasirox has become commercially available in many countries since 2006. Although this alternative to parenteral deferoxamine has been a major advance for patients with transfusional hemosiderosis, a proportion of patients have suboptimal response to the maximum approved doses (30 mg/kg per day), and do not achieve negative iron balance. We performed a prospective study of oral deferasirox pharmacokinetics (PK), comparing 10 transfused patients with inadequate deferasirox response (rising ferritin trend or rising liver iron on deferasirox doses > 30 mg/kg per day) with control transfusion-dependent patients (n = 5) with adequate response. Subjects were admitted for 4 assessments: deferoxamine infusion and urinary iron measurement to assess readily chelatable iron; quantitative hepatobiliary scintigraphy to assess hepatic uptake and excretion of chelate; a 24-hour deferasirox PK study following a single 35-mg/kg dose of oral deferasirox; and pharmacogenomic analysis. Patients with inadequate response to deferasirox had significantly lower systemic drug exposure compared with control patients ($P < .00001$). Cmax, volume of distribution/bioavailability (Vd/F), and elimination half-life ($t_{1/2}$) were not different between the groups, suggesting bioavailability as the likely discriminant. Effective dosing regimens for inadequately responding patients to deferasirox must be determined. This trial has been registered at http://www.clinicaltrials.gov under identifier NCT00749515. (Blood. 2009;114:4009-4013)

Actualités thérapeutiques

Succesful treatment of a DBA patient with amino acid leucine

Patient sélectionné sur les données in vitro

Fille de 7 ans ; diagnostic de DBA à 6 mois

RSP; RVU; RPS19 non mutée; corticorésistante

Leucine : 500 mg x 2/j

Amélioration de l'état général en 3 semaines

Amélioration hémato. lente sur 6 mois

Réponse actuelle: indépendant des T avec un taux d'Hb entre 9 et 10.5 g

(Pospisilova & al, Haematologica, 2007)

➡ **Un essai clinique est en cours aux USA**

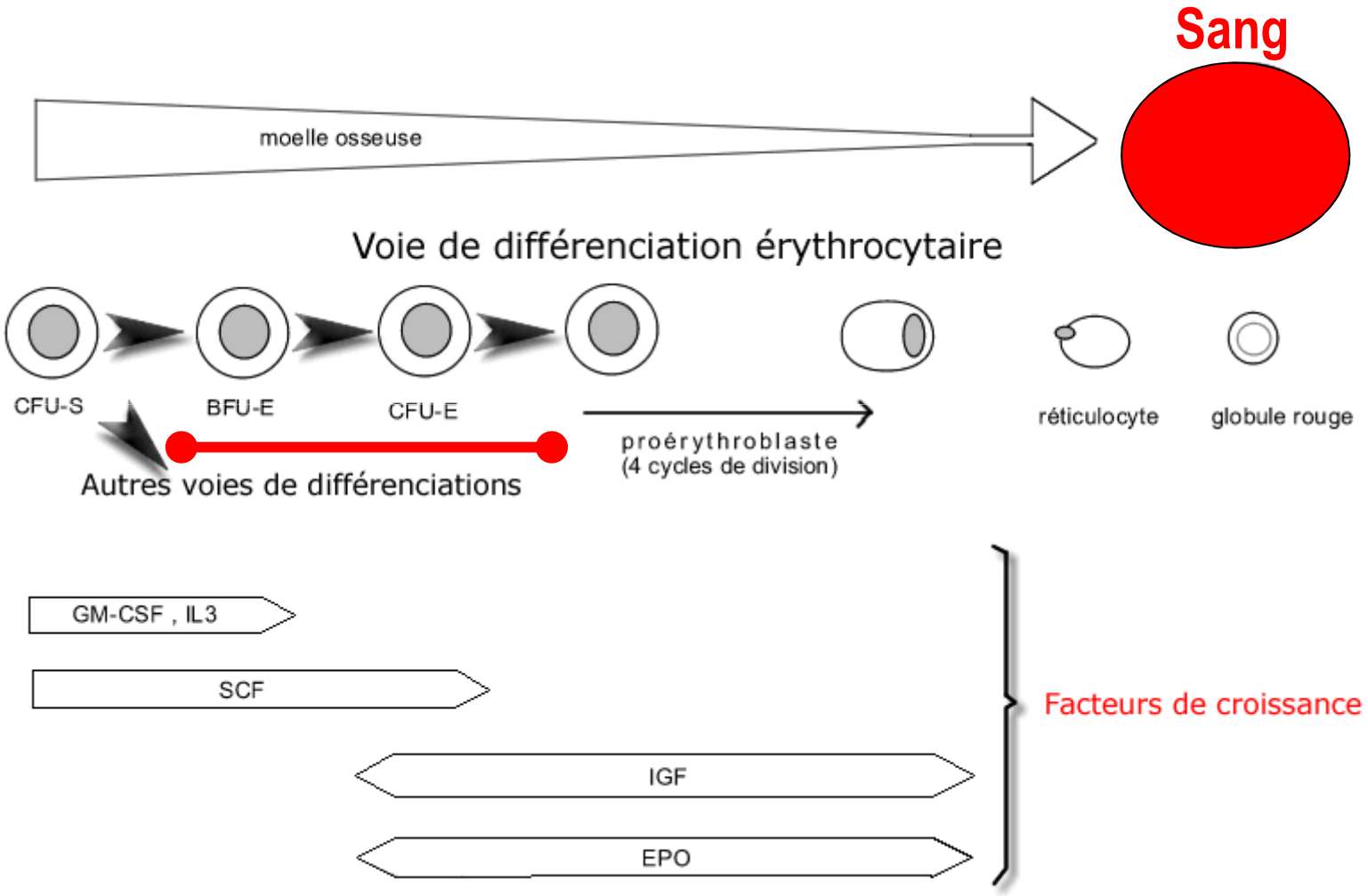
Essai clinique à venir en France?

Nouvel agent stimulant l'érythropoïèse

- Actuellement en cours de discussion
- Phases I & II en cours dans d'autres indications
- Essai chez des pts DBA?
  - Population cible: pts adultes dépendants des transfusions

➡ RV à la réunion des adultes…

Erythropoïèse

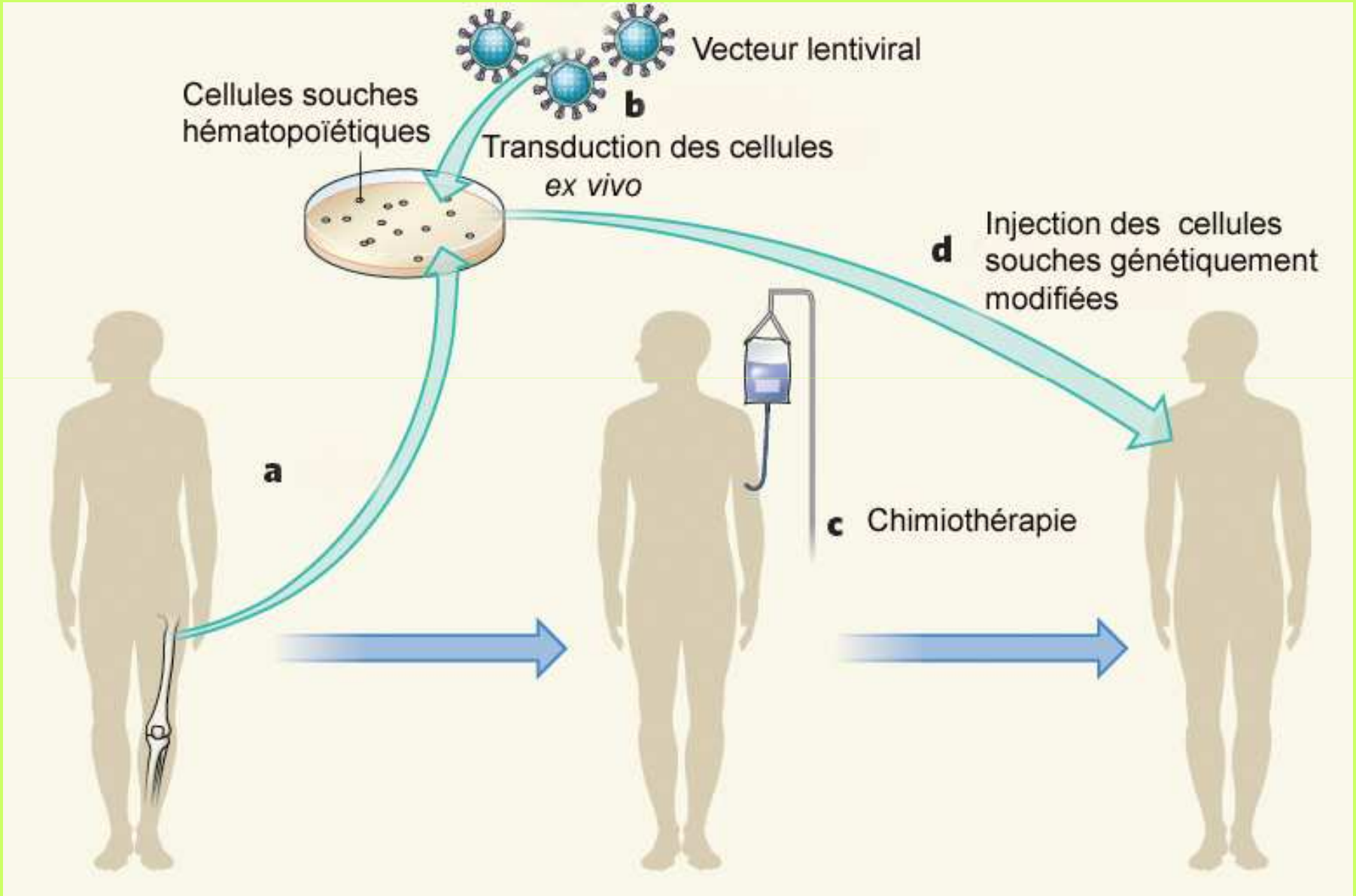


Actualité : Bêta-thalassémie : une première de thérapie génique à confirmer

Un patient de 18 ans ➡ indépendance transfusionnelle (taux d'Hb entre 9 et 10 g/dL)

M. Cavazzana-Calvo et al., Transfusion independence and HMGA2 activation after gene therapy of human β-thalassaemia, Nature, vol. 467, pp. 318-322, 2010

Principes de la thérapie génique



Préalables à la mise en place d'une thérapie génique chez l'homme

Cas général:

1. Connaître le gène, ses fonctions, sa régulation
2. Disposer d'un vecteur *(rétrovirus ➔ lentivirus)*
3. Disposer d'un modèle animal
4. Disposer d'assez de cellules à transduire

Cas d'un patient DBA:

1. Nombreux gènes… & physiopathogénie ?
2. Stade actuel: *in vitro* uniquement
3. Non disponible à ce jour
4. Difficulté +++ ici: pauvreté en CSH

Thérapie génique:
autres difficultés & risques

Toxicité du conditionnement, à ct & à lt…

Echec de la thérapie génique

- Taux insuffisant de cellules transduites +++
- Diminution au cours du temps de ce taux…

Mutagenese insertionnelle: *mutation causée par l'insertion de matériel génétique dans un gène déjà présent.* **Pb. théorique? ➡ Réalité…**

Thérapie génique dans l'ABD?

Gène *RPS19*…

Recherches en cours mais on est loin d'un essai clinique

Risques spécifiques à l'ABD?

Conclusion

Nouveaux gènes

Chélation toujours à optimiser! Individuellement & collectivement…

Pas de nouveauté thérapeutique mais essais en cours ou à venir