Erythropoïèse

Mécanismes physiopathologiques des anémies

(au moins de quelques-unes....)

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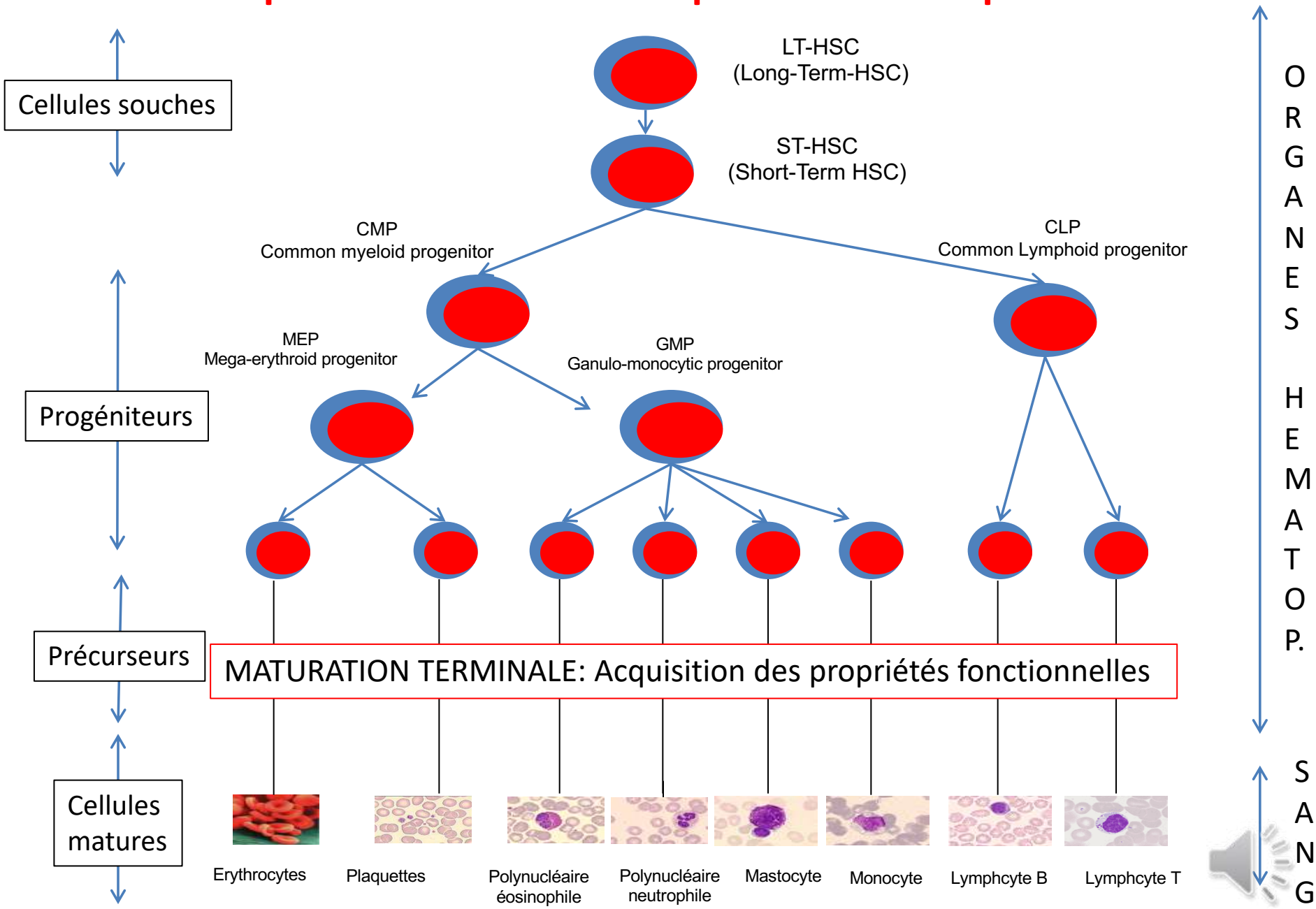
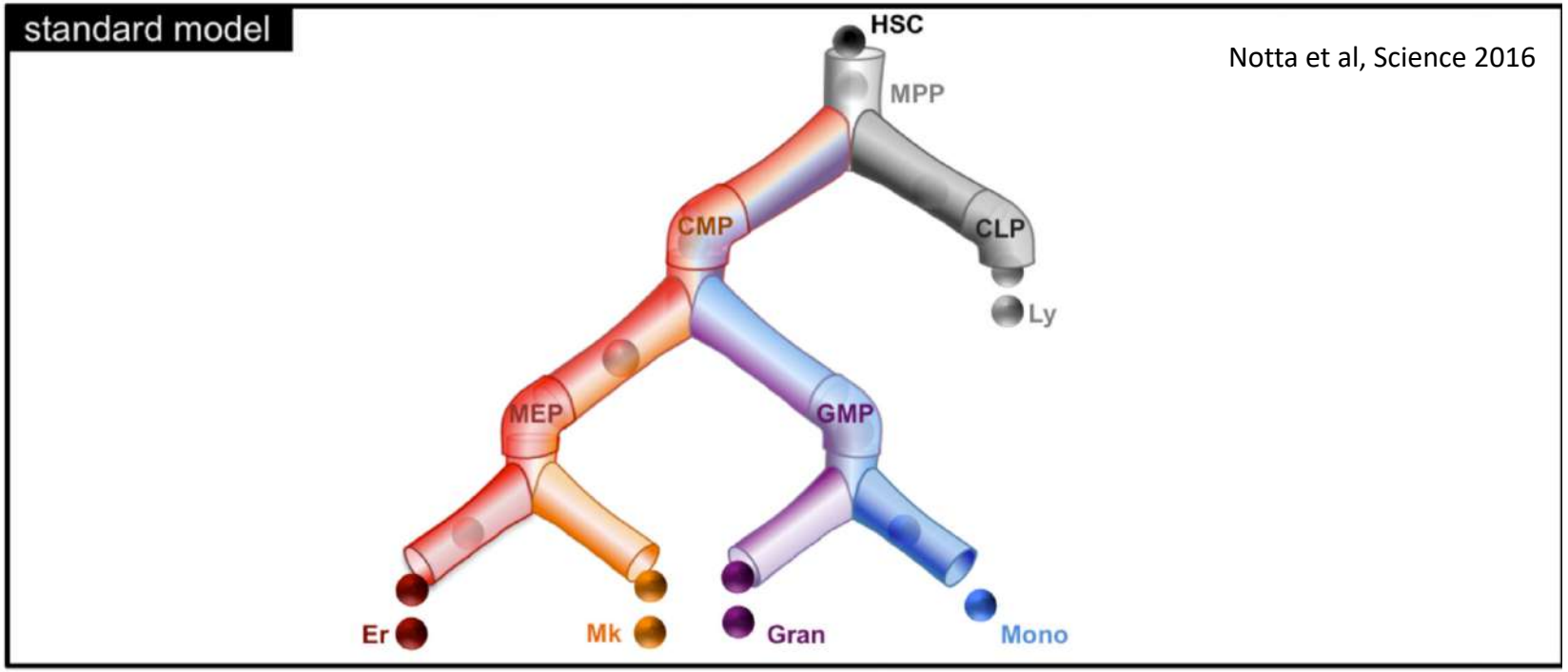
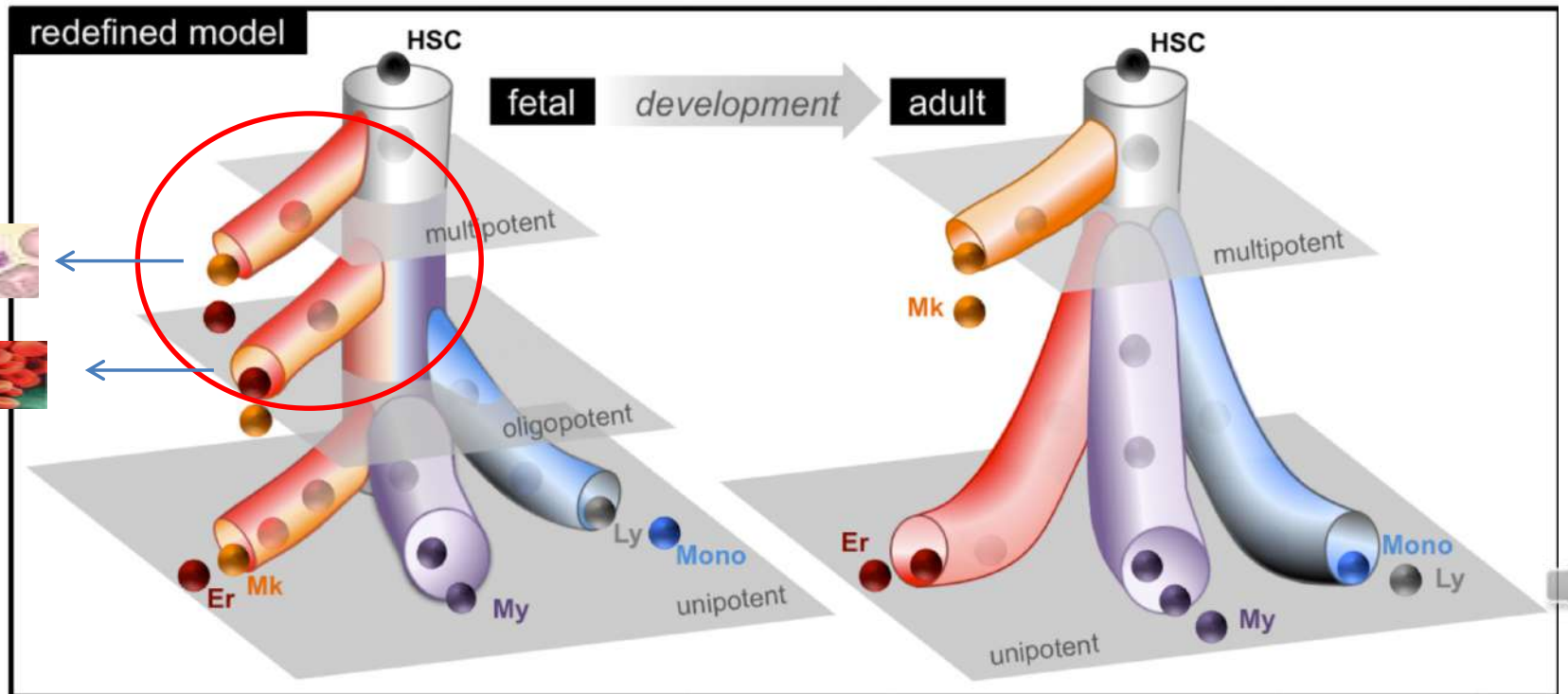
Représentation schématique de l'hématopoïèse





Notta et al, Science 2016



Mécanisme 1

Atteinte de la cellule souche hématopoïétique

- **VGM normal ou souvent augmenté**
- **CCHM normale**
- **réticulocytes diminués**
- **leucocytes et plaquettes diminués**

Exemple: SAA- critères de camitta

Table 4. Definition of disease severity based on peripheral values and BM findings

SAA[19]

At least two of the following three criteria have to be fulfilled:
Reticulocytes $< 60 \times 10^9$/L (using an automated analyzer) or
$< 20 \times 10^9$/l (manual count)[a]
Platelets $< 20 \times 10^9$/L
Neutrophil count $< 0.5 \times 10^9$/L

vSAA[20]

Same criteria of SAA have to be fulfilled; but the neutrophil count has to be $< 0.2 \times 10^9$/L

Non-severe AA

Patients not fulfilling the criteria for SAA and vSAA

Abbreviations: AA = aplastic anemia; SAA = severe AA; vSAA = very severe AA. [a]The different values are because automated count may over-estimate the counting at low level of reticulocyte counts, that is, it reads 50×10^9/L but in reality they are less.

Seminars in Hematology, Vol 52, No 1, January 2015, pp 31–37 Bone Marrow Transplantation (2013) **48,** 162–167

Les progéniteurs hématopoïétiques

Cellules restant rares dans la moelle osseuse
Non identifiables cytologiquement
Haut potentiel de prolifération

PROLIFERATION

Myéloïde

Lymphoïde

CFU- GEMM Ou CMP
Common myeloid progenitor

Potentialité large

CLP
Common Lymphoid progenitor

NK

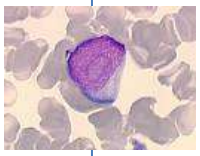
LT

LB

CFU- GM Ou GMP
Granulo Monocytic progenitor

MEP
Mega-Erythro Progenotor

Bipotente



CFU- M

CFU- G

BFU-E

CFU-MK

Monopotente

CFU-E

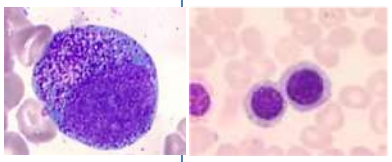
Monocytes

Polynucléaires

Erythropoïèse

Mégacaryopoïèse

Précurseurs:
Maturation terminale



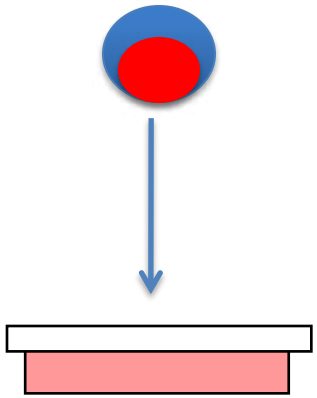
Cellules identifiables cytologiquement

MATURATION
DIFFERENCIATION

Erythropoïèse précoce: Progéniteurs BFU-E et CFU-E

-BFU-E: 0,001 % des cellules médullaires
-CFU-E:0,01%

- Identification par des tests de progéniteurs en milieu semi-solide

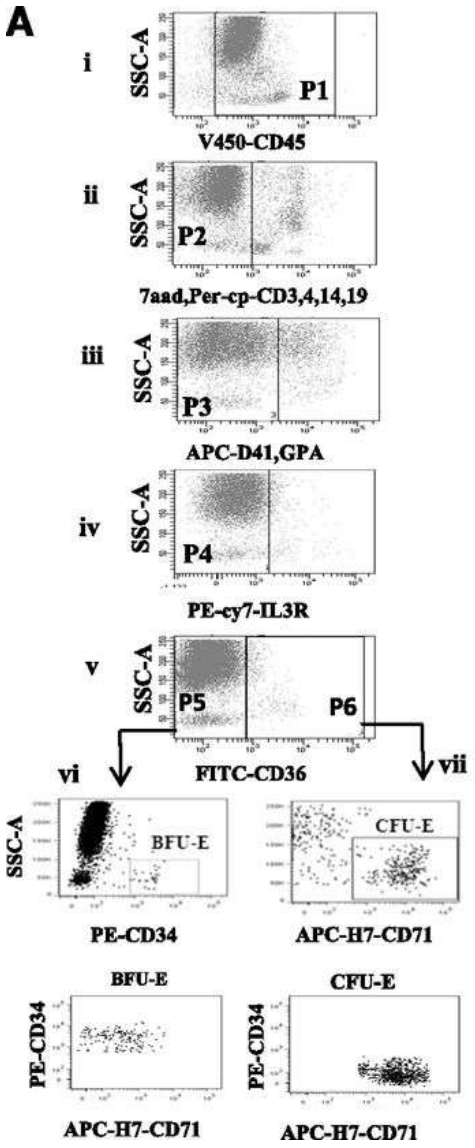


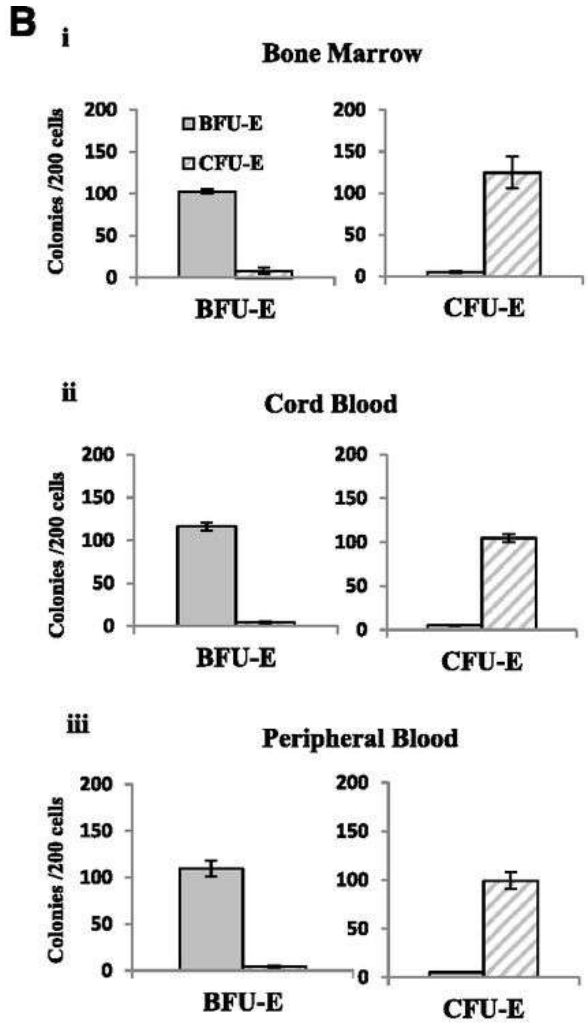
IL3-SCF-EPO

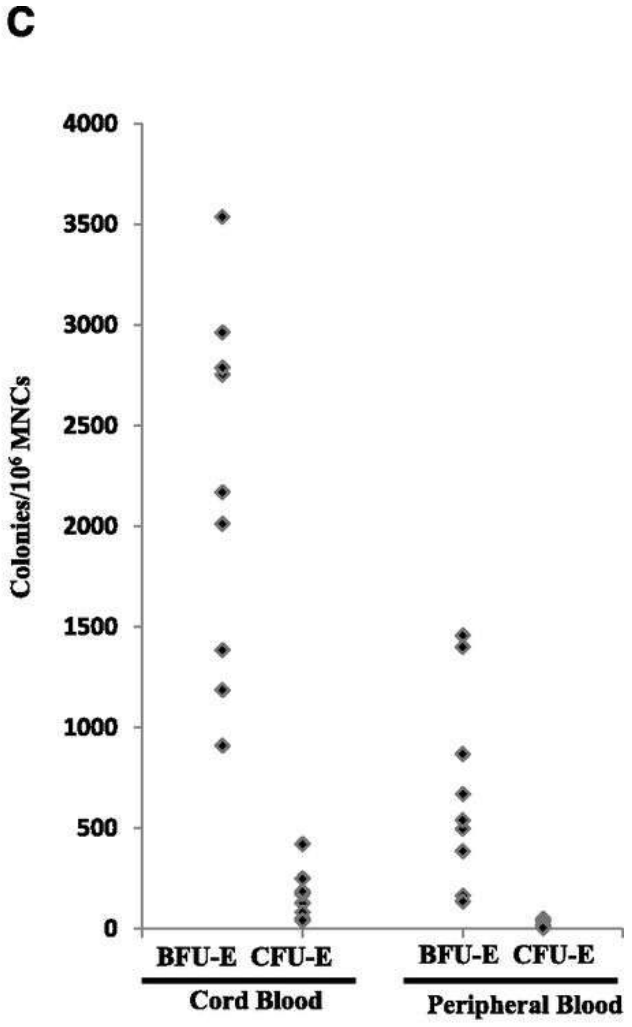
Jour 14

(SCF)-EPO

Isolation of and quantification of BFU-E and CFU-E cells from primary samples.







Jie Li et al. Blood 2014;124:3636-3645

Mécanisme 2

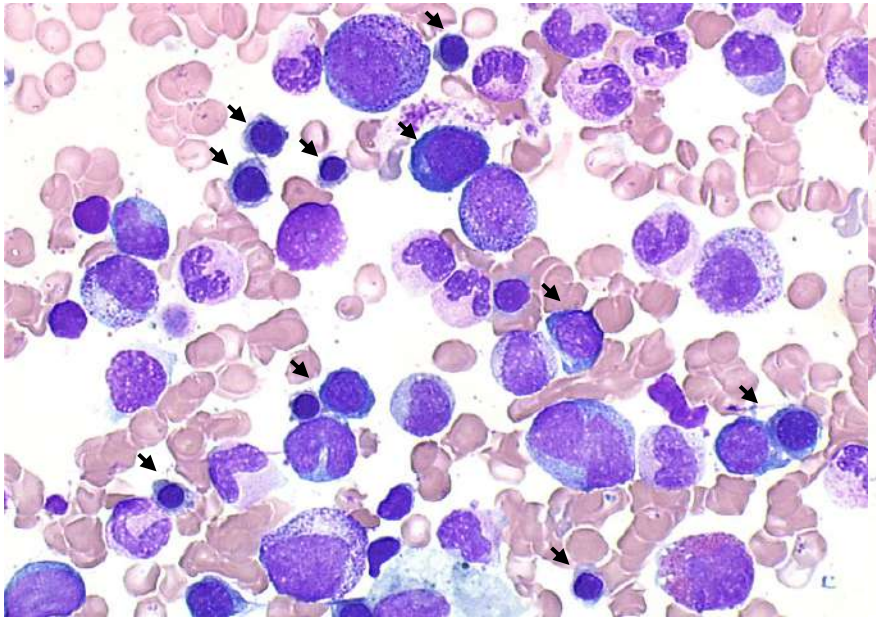
Atteinte du progéniteur monopotent

ERYTHROBLASTOPENIES

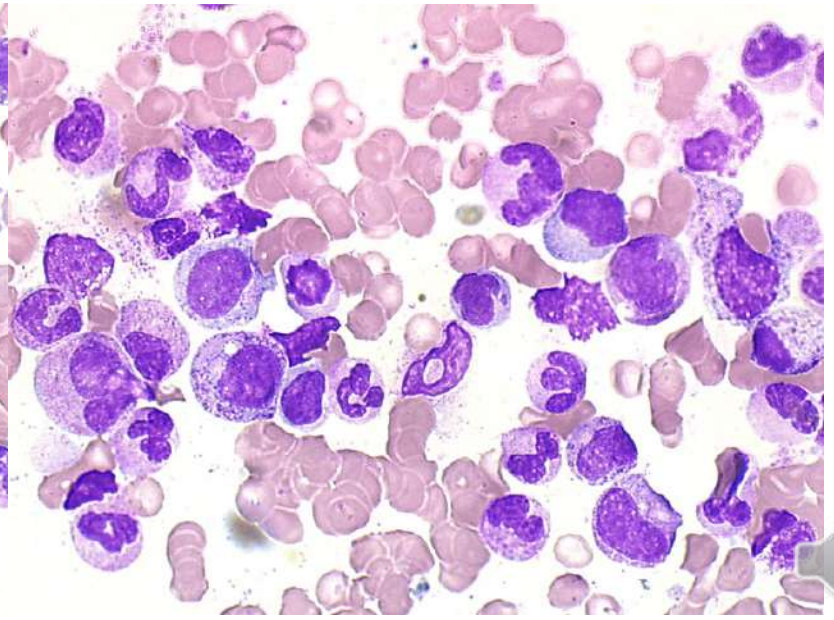
Erythroblastopénies

- Absence ou diminution du taux d'érythroblastes dans la moelle
- Anémie normochrome normo ou légèrement macrocytaire, arégénérative: Réticulocytopénie
- Myélogramme: moins de 5% d'érythroblastes, autres lignées normales

Moelle normale



Erythroblastopénie



Erythroblastes

Etiologies

- **Aigues:**

  - **Toxiques/médicamenteuses: chloramphénicol, thiophénicol,**
  - **Virales (hémolyse chronique): Parvovirus B19**
  - **Idiopathiques, probablement auto-immunes ou virales**
  - **TEC chez l'enfant (4 mois-4 ans)**

Chroniques:

- Constitutionnelles (Blackfan-Diamond)

- Auto-immunes associées (parfois à un thymome)

- Hémopathies lymphoïdes (LLC, LNH, LGL)

- Virales: parvo chronique ou autre virus (HIV, EBV, CMV, hépatites..) chez immuno-déprimé

- Anticorps anti-EPO chez IRC traités par EPO

Table 1. Classification of pure red cell aplasia

Congenital PRCA
Diamond-Blackfan anemia

Acquired PRCA
Primary
Primary autoimmune PRCA (includes transient erythroblastopeni
of childhood)
Primary myelodysplastic PRCA

Secondary, associated with:
Autoimmune/collagen vascular disorders
Systemic lupus erythematosus
Rheumatoid arthritis
Inflammatory bowel disease
Other immunologic mechanisms
ABO-incompatible stem cell transplantation
Pyoderma gangrenosum
Lymphoproliferative disorders
Chronic lymphocytic leukemia
LGL leukemia
Hodgkin disease
Non-Hodgkin lymphomas
Angioimmunoblastic lymphadenopathy
Multiple myeloma
Waldenstrom macroglobulinemia
Castleman disease
Other hematologic malignancies
Chronic myelogenous leukemia
Chronic myelomonocytic leukemia
Myelofibrosis with myeloid metaplasia
Essential thrombocythemia
Acute lymphocytic leukemia
Solid tumors
Thymoma
Gastric cancer
Breast cancer
Biliary cancer
Lung cancer
Thyroid cancer
Renal cell carcinoma
Carcinoma of unknown primary site
Infections
B19 parvovirus
Human immunodeficiency virus
T-cell leukemia-lymphoma virus
Infectious mononucleosis
Viral hepatitis (hepatitis A, B, C, and E)
Cytomegalovirus
Bacterial infections
Group C *Streptococcus*
Tuberculosis
Bacterial sepsis
Drugs and toxins
rhEpo-induced Epo antibody-associated PRCA
Other drugs (Table 2)
Other disorders
Pregnancy
Riboflavin deficiency

Causes toxiques médicamenteuses

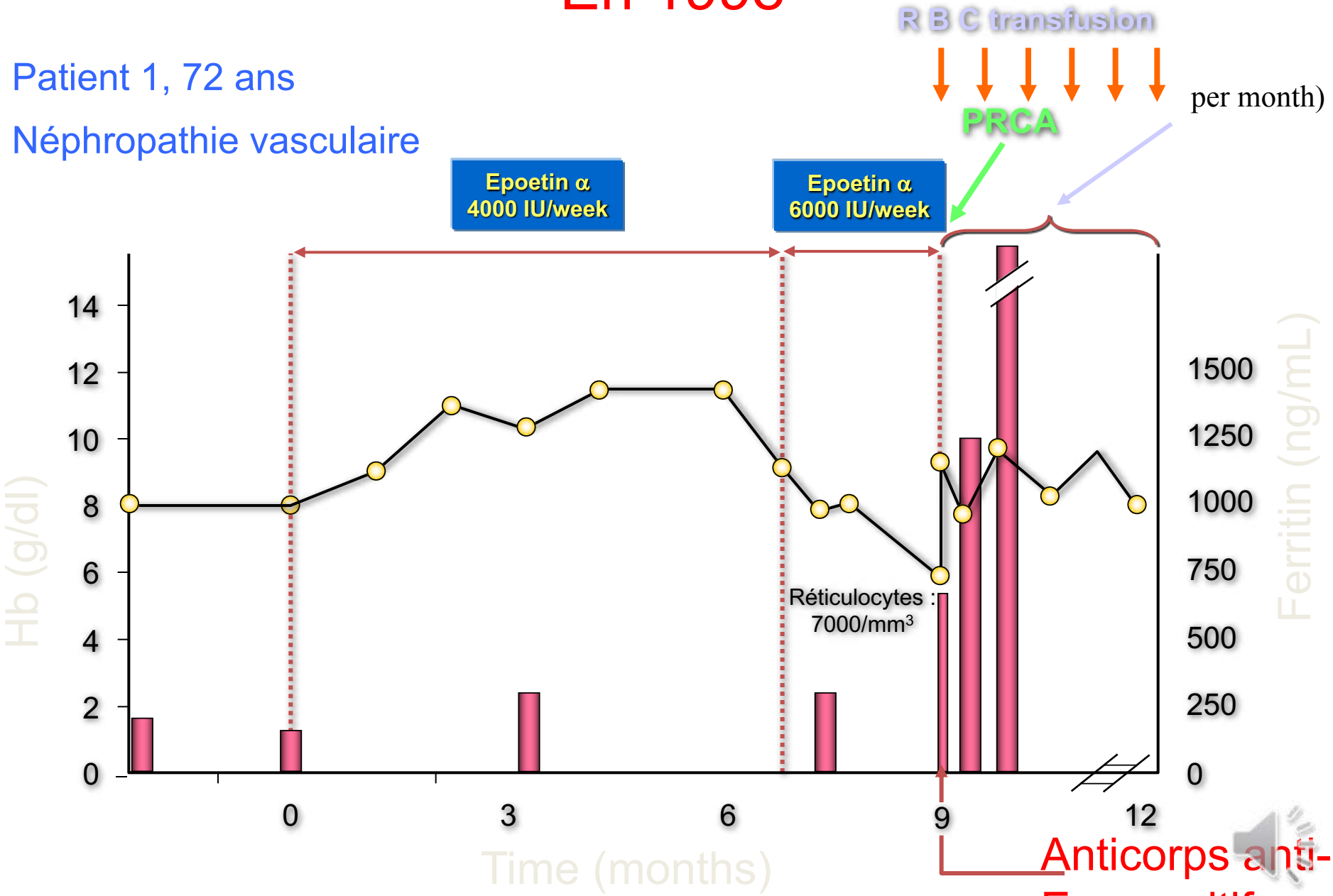
Agent
Alemtuzumab
Allopurinol
Ampicillin
Azathioprine
Carbamazepine
Cephalothin
Cladribine
Chlorpropamide
Chloroquine
Clopidogrel
Dapsone/pyrimethamine
Diphenylhydantoin
Recombinant Epo
Estrogens
Fenoprofen
Fludarabine
Interferon-α
Isoniazid
Lamivudine
Leuprolide
Linezolid
Micafungin
Mycophenolate mofetil
d-Penicillamine
Phenylbutazone
Procainamide
Ribavirin
Rifampicin
Sulfasalazine
Sulindac
Tacrolimus
Trimethoprim/sulfamethoxazole
Valproic acid
Zidovudine

Means et al, 2016

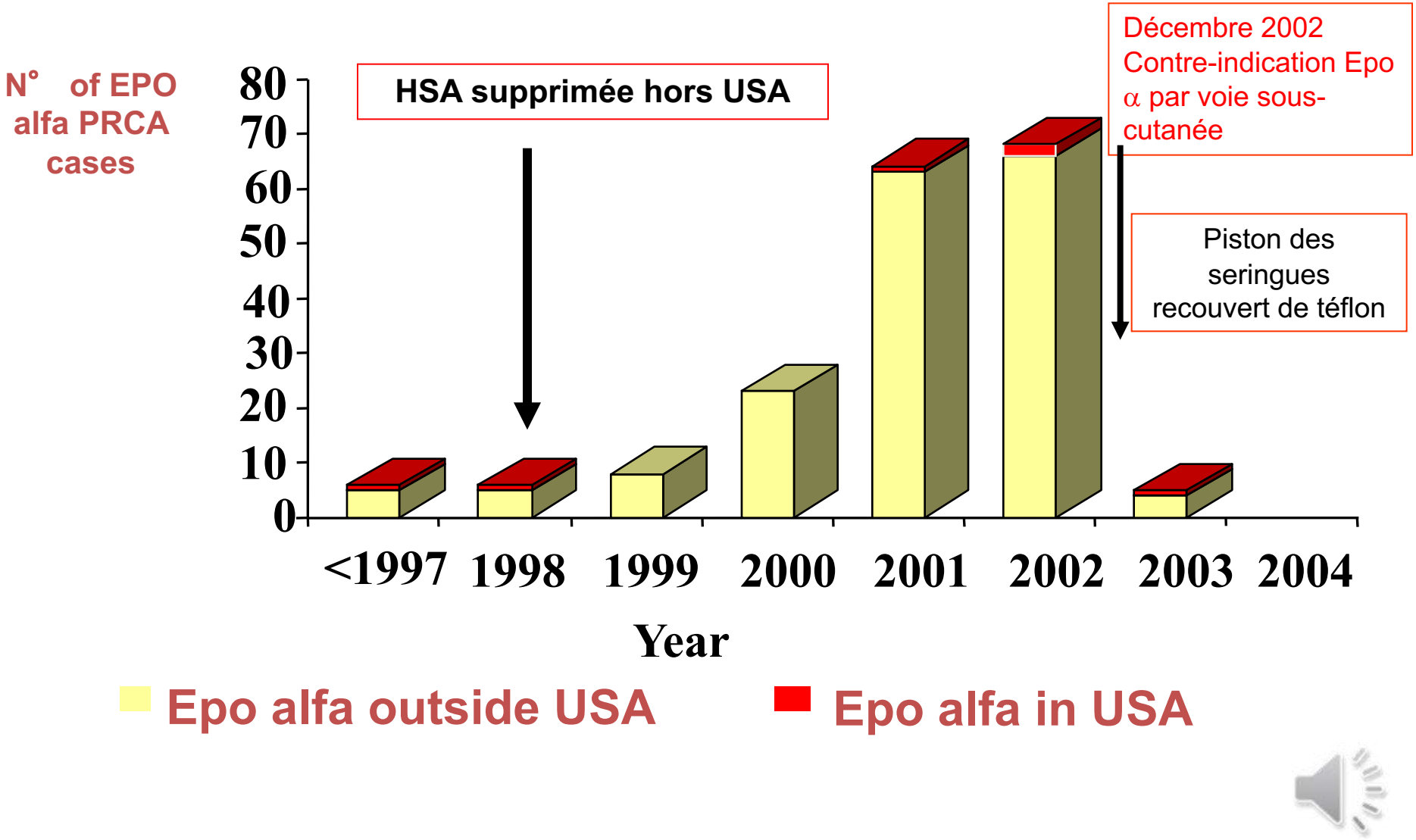
En 1998

Patient 1, 72 ans

Néphropathie vasculaire



Erythroblastopénies avec EPO alfa



Incidence des érythroblastopénies

	Incidence pour 10 000 patient–années
Seringues avec piston caoutchouc (→ 2002)	4.61
Seringues avec piston téflon (après 2002)	0.26

Boven *et al*. *Kidney Int* 2005; 67:2346–53

***P* < 0.0001**

Contre-indication levée en 2006

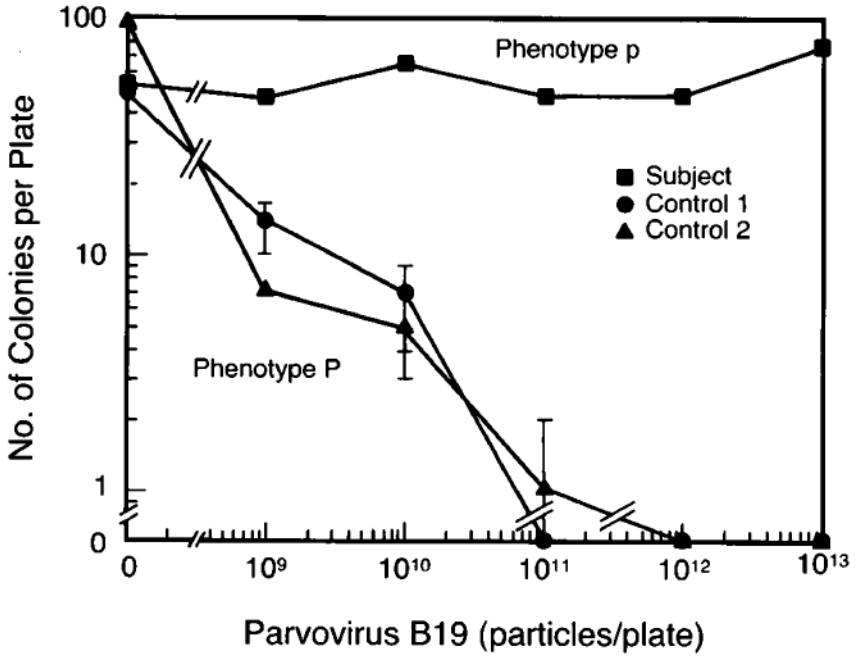
Les anticorps Anti-Epo en 2013

- **Dans l'insuffisance rénale**
  - Les érythroblastopénies avec Ac-anti érythropoïétine sont rares
    (1 à 3 /100 000 pts/année) observées avec tous les ASE
- En **dehors de l'insuffisance rénale**
  - 3 cas dans des myélodysplasies
  - pas de cas publié en oncologie
  - dans l'hépatite C, cas d'érythroblastopénies médiées par Ac anti-érythropoïétine chez des patients traités par :
    - Interferon
    - Ribavirine
    - Et ASE

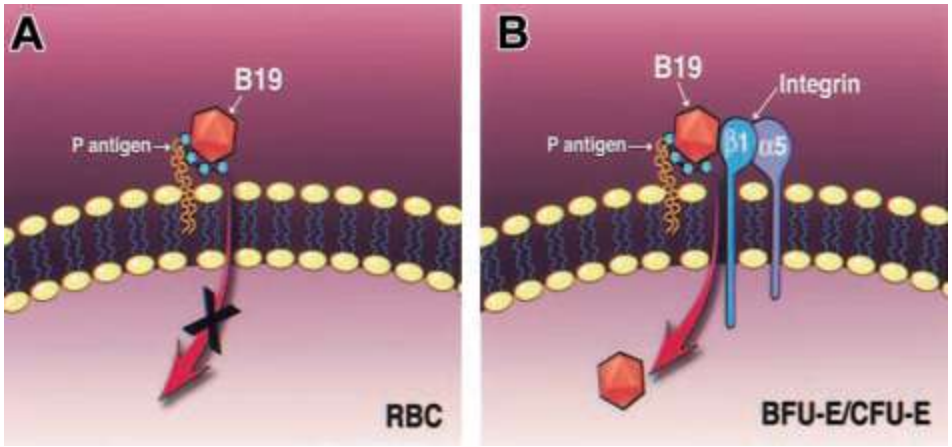
Érythroblastopénies et HPV B19

Nécessité de l'antigène P....

...et du complexe **intégrine** α5β1



Brown et al, NEJM, 1994



Weigel-Kelley et al, Blood, 2003

Érythroblastopénies et HPV B19

Sujet	Durée de vie des Globules rouges	Réponse Immune	Résultats
Normal	120 j	15 – 20 j	Anémie transitoire non décelée
Hémolyse chronique	< 20 j	15 – 20 j	Diminution transitoire de l'Hb = érythroblastopénie aiguë
Déficit Immunitaire *	120 j	0	Erythroblastopénie chronique

* HIV, LAL, Transplantation, Rituximab

Characteristic	Total	Our Series	Literature
No. of patients	133 (100)	10 (100)	123 (100)
Age, y, mean ± SD	37.1 ± 15.8	45.8 ± 15.6	36.3 ± 15.7
Male sex	78/117 (67)	3/10 (30)	75/107 (70)
Disease characteristics			
HIV	39/133 (30)	1/10 (10)	38/123 (31)
$CD4^+$, cells/mm^3, mean ± SD	94.3 ± 118.4	22 ± 0	96 ± 119.6
Solid-organ transplant	63/133 (47)	3/10 (30)	60/123 (49)
Kidney	45 (71)	3 (100)	42 (70)
Heart	3 (5)	0	3 (5)
Lung	4 (6)	0	4 (6)
Pancreas	1 (2)	0	1 (2)
Liver	8 (13)	0	8 (14)
Heart-lung or kidney-pancreas	2 (3)	0	2 (3)
Tacrolimus treatment	35 (56)	2 (67)	33 (55)
Other	30/133 (23)	5/10 (50)	25/123 (19)
Lymphoma	10 (7)	2 (20)	8 (6)
Systemic autoimmune and/or inflammatory disease	7 (5)	1 (10)	6 (5)
Hematopoietic stem cell transplant	10 (7)	2 (20)	8 (6)
Primary immune deficiency	2 (1)	0	2 (1)
Monoclonal antibody treatment	14 (10)	0	14 (11)
PRCA and HPV-B19 characteristics			
Delay between initiation of immunosuppression treatment and PRCA, mo, mean ± SD	18.3 ± 38.0	29.1 ± 44.9	17.1 ± 37.3
HPV-B19–related symptoms	34/133 (26)	6/10 (60)	28/123 (23)
HPV-B19–suggestive bone-marrow results	55/112 (49)	0/10 (0)	55/102 (54)
Positive anti–HPV-B19 IgM Abs at diagnosis	46/100 (46)	1/2 (50)	45/98 (46)
Positive anti–HPV-B19 IgG Abs at diagnosis	24/95 (25)	2/2 (100)	22/93 (24)
Positive blood or bone-marrow PCR results at diagnosis	95/133 (71)	10/10 (100)	85/123 (69)
Blood results	80/133 (60)	3/10 (30)	77/123 (63)
Bone-marrow results	37/133 (28)	7/10 (70)	30/123 (24)

Crabol et al, CID, 2013

Treatment	Total (N = 133)	Our Series (n = 10)	Literature (n = 123)
No. of IVIG courses, mean ± SD	2.8 ± 9.1	2.4 ± 1.8	2.9 ± 9 .4
IVIG course first dose, g/kg, mean ± SD	2.3 ± 1.3	1.4 ± 0.6	2.4 ± 1.36
IVIG course duration, d, mean ± SD	4.9 ± 3.3	2.6 ± 1.3	5.2 ± 3.4
Other treatments	27/133 (20)	4/10 (40)	23/123 (19)
Immunosuppression discontinuation	42/109 (38)	3/10 (30)	39/99 (39)
Switch tacrolimus to cyclosporin A	8/36 (22)	1/2 (50)	7/34 (21)
IVIG maintenance treatment	16/133 (12)	0/10 (0)	16/123 (13)
Outcome			
Death	14/133 (10)	0/10 (0)	14/123 (11)
Hemoglobin correction after first IVIG course	124/133 (93)	9/10 (90)	115/123 (93)
Time to reticulocytosis, d, mean ± SD	11.4 ± 10.1	26.8 ± 22.4	9.6 ± 3.6
Time to Hb correction, mo, mean ± SD	1.7 ± 1.6	2.6 ± 1.6	1.5 ± 1.6
Relapse after first course	42/124 (34)	0/9 (0)	42/115 (36)
Time to first relapse, mo, mean ± SD	4.3 ± 2.71	…	4.34 ± 2.71
No. of relapses, mean ± SD	1.4 ± 0.6	…	1.4 ± 0.6
Available follow-up data at 12 mo	96/133 (72)	10/10 (100)	86/123 (70)
Hb correction at 12 mo	45/96 (47)	9/10 (90)	36/86 (42)
Persistent anemia at 12 mo	51/96 (53)	1/10 (10)	50/86 (58)
Available follow-up data >6 mo after last IVIG course	79/133 (60)	10/10 (100)	69/123 (56)
Hb correction	63/79 (80)	9/10 (90)	54/69 (78)
IVIG dependence	6/79 (7)	0/10 (0)	6/69 (9)
No Hb correction	10/79 (13)	1/10 (10)	9 /69 (13)
HPV-B19 PCR negative results	29/95 (30)	5/7 (71)	24/88 (27)
Side effects	18/133 (13)	6/10 (60)	12/123 (10)

Data are No. (%) unless otherwise specified.

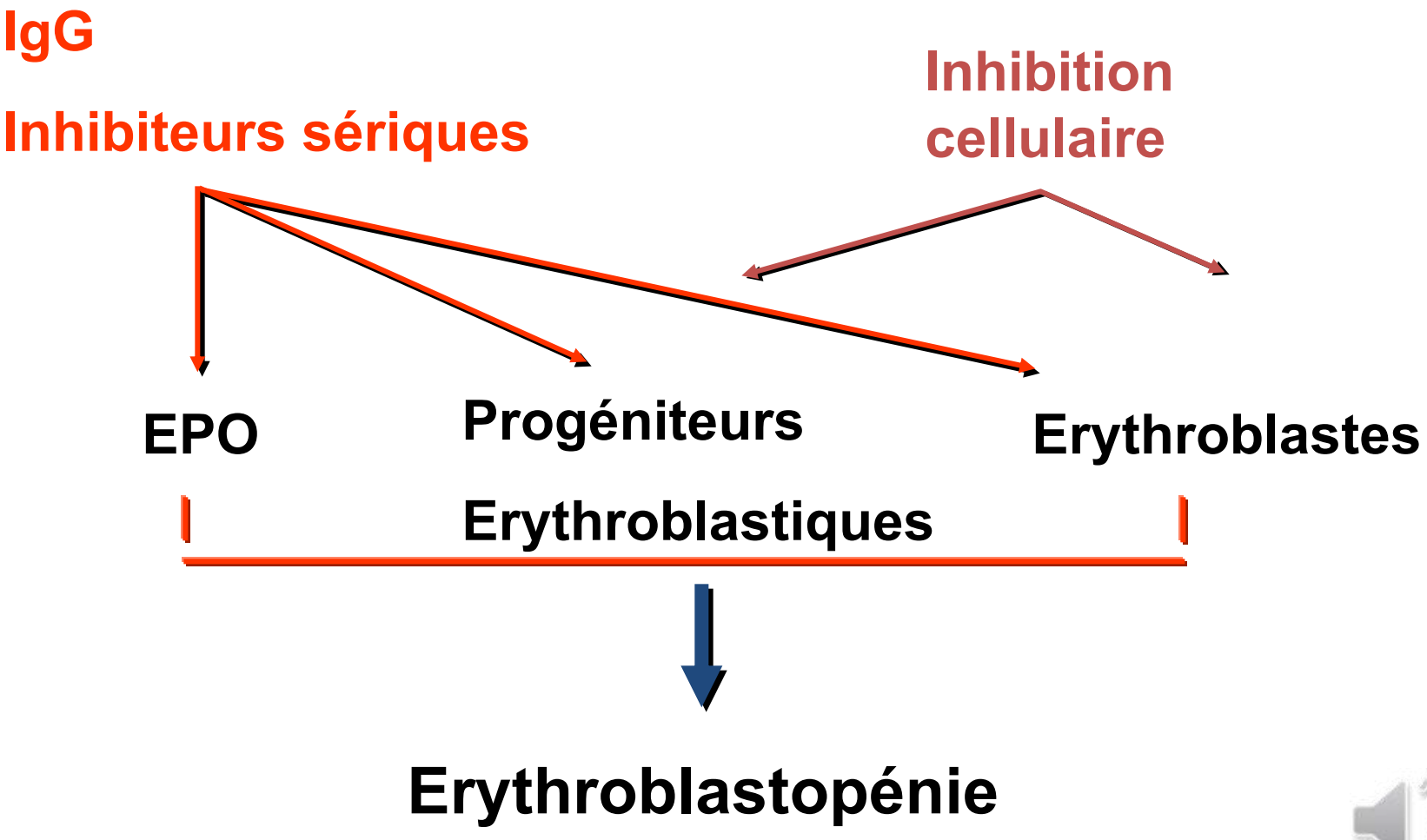
Abbreviations: Hb, hemoglobin; HPV-B19, human parvovirus B19; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction; SD, standard deviation.

Crabol et al, CID, 2013

Érythroblastopénie chronique acquise (adulte)

- Mécanisme:
  - Inhibition extrinsèque de l'érythropoïèse ? (autoimmune ?)
  - Anomalie cellulaire intrinsèque ?
    (pré-leucémique ? – myélodysplasie)

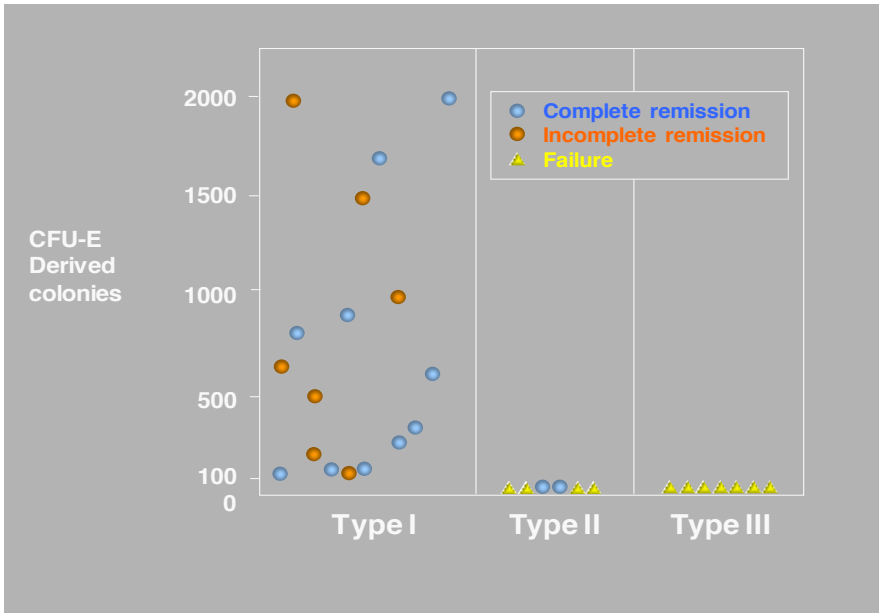
Mécanismes de l‘inhibition extrinsèque de l‘érythropoièse



Myélogramme et culture *in vitro* des progéniteurs érythroblastiques

- Différenciation erythroïde normale
  - Suggère une érythroblastopénie autoimmune "classique“

- Pas de différenciation érythroïde
  - Anomalie intrinsèque

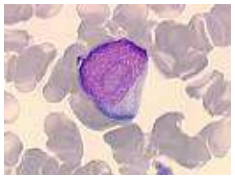


Corrélation entre la croissance in vitro des progéniteurs érythroblastiques et la réponse au traitement immunosuppresseur

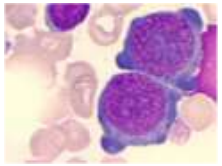
Krantz S. Blood 1972; 39:347-60.
Lacombe C et al. Blood 1984; 64:71-7.
Charles RJ et al. Blood 1996; 87:4831-8.

Mécanisme 3

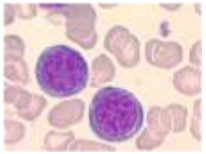
Atteinte de la maturation érythroblastique



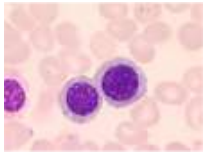
Progéniteur
<1%



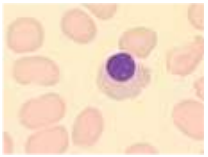
Proérythroblaste



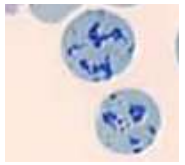
Erythroblaste basophile



Erythroblaste polychromatophile



Erythroblaste acidophile



Réticulocyte

24 à 48H

GR

Précurseurs
20-40%

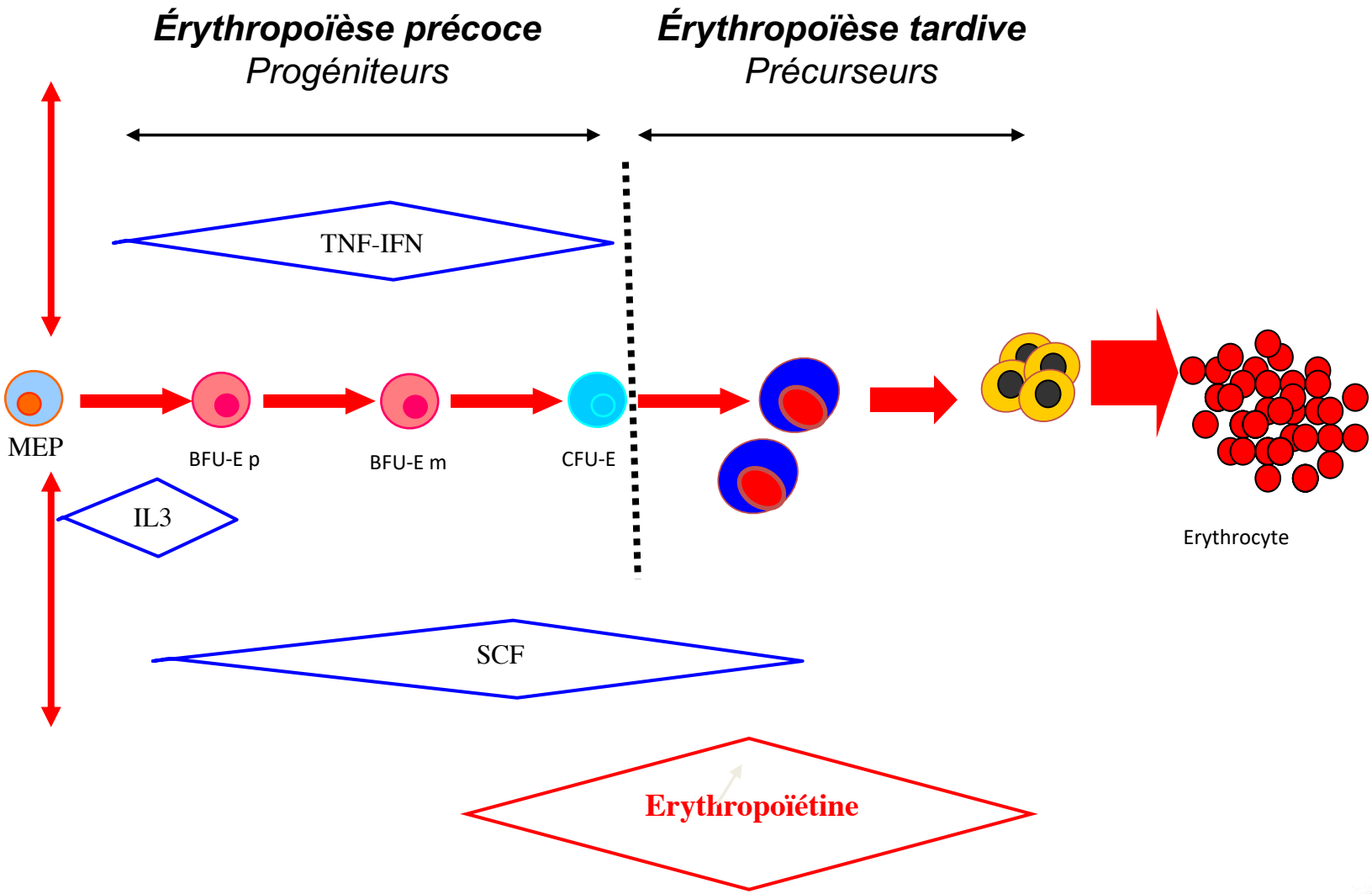
Moelle osseuse: 6 jours

Sang

Potentiel mitotique: 4 mitoses

CD71
Glycophorine A
R-EPO
Synthèse hémoglobine++

Facteurs de croissance hématopoïétique



Erythropoïétine

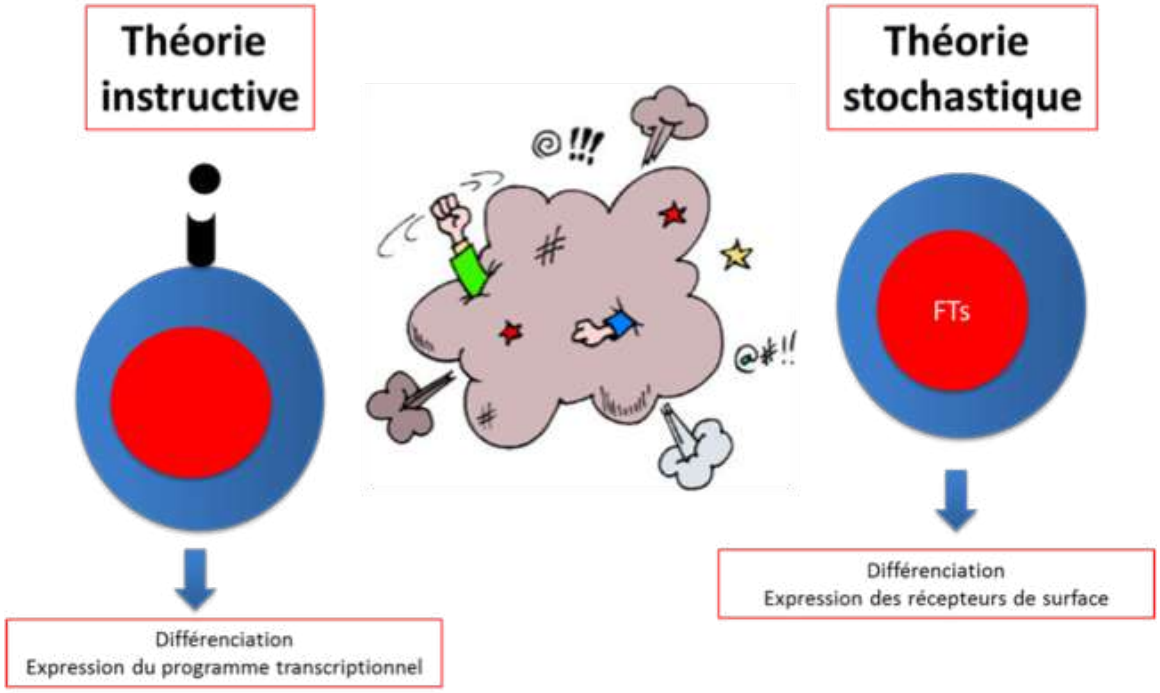
élément clé de l'érythropoïèse

1- Hormone glycopeptidique produite majoritairement par le rein

2- Production sous le contrôle de l'hypoxie locale

3- Agit en se fixant sur des récepteurs spécifiques à la surface de cellules cibles

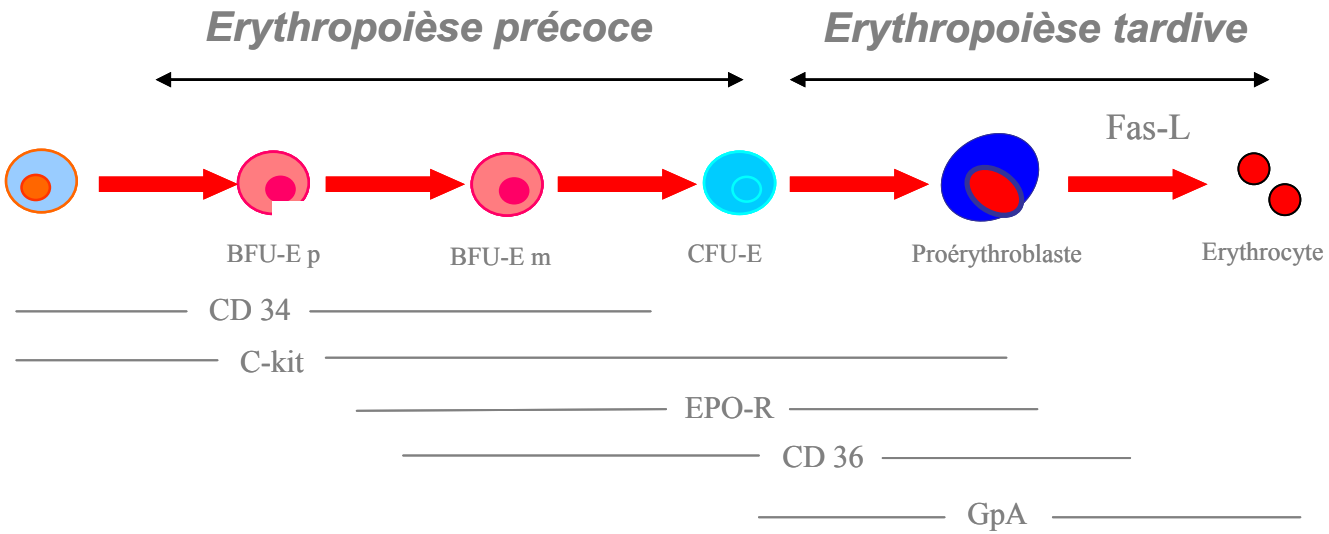
4-Facteur majeur de régulation de l'érythropoïèse



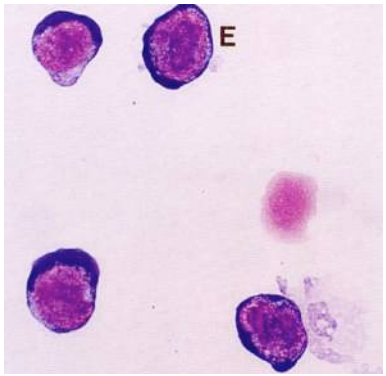
Epo-R instruit-il la différenciation érythroïde?

NON !

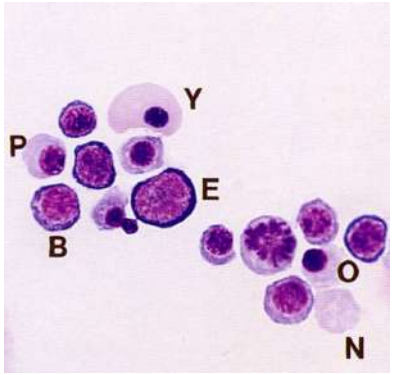
-*Expression tardive de EPO-R:*



-*Invalidation de EPO ou EPO-R chez la souris:*



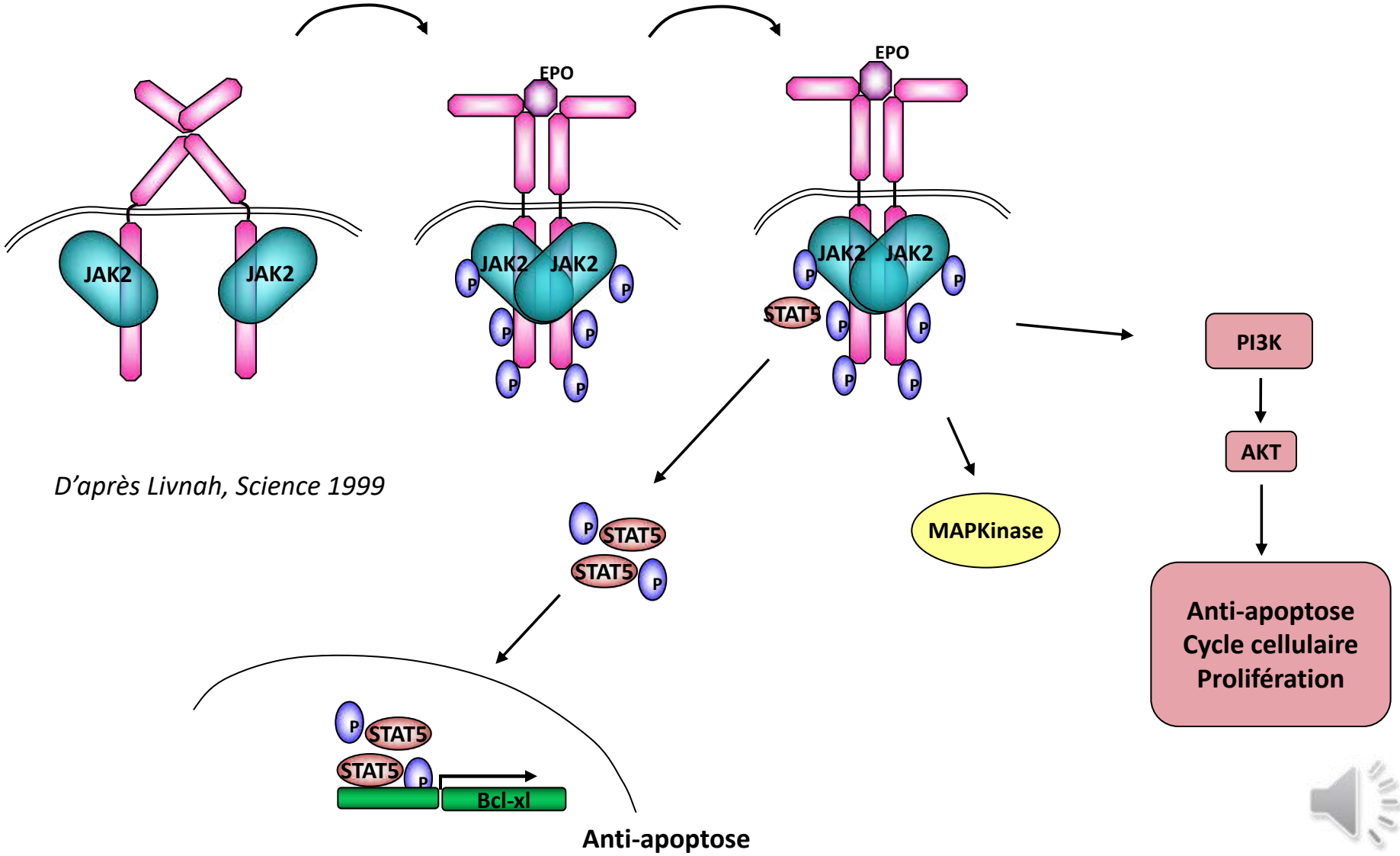
EPO-R $^{-/-}$



WT

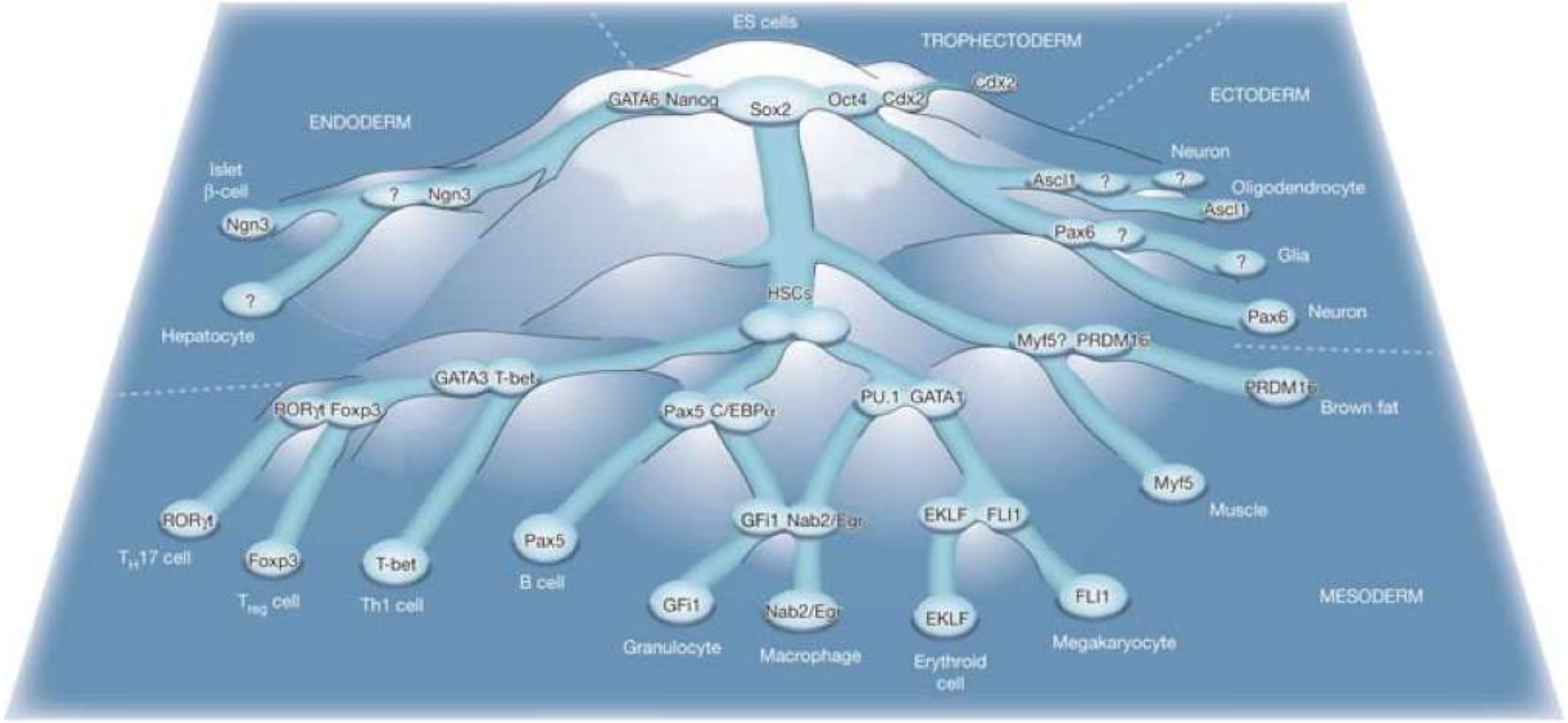
(Wu et al, 1995)

La voie du récepteur à l'Epo: rappel



D'après Livnah, Science 1999

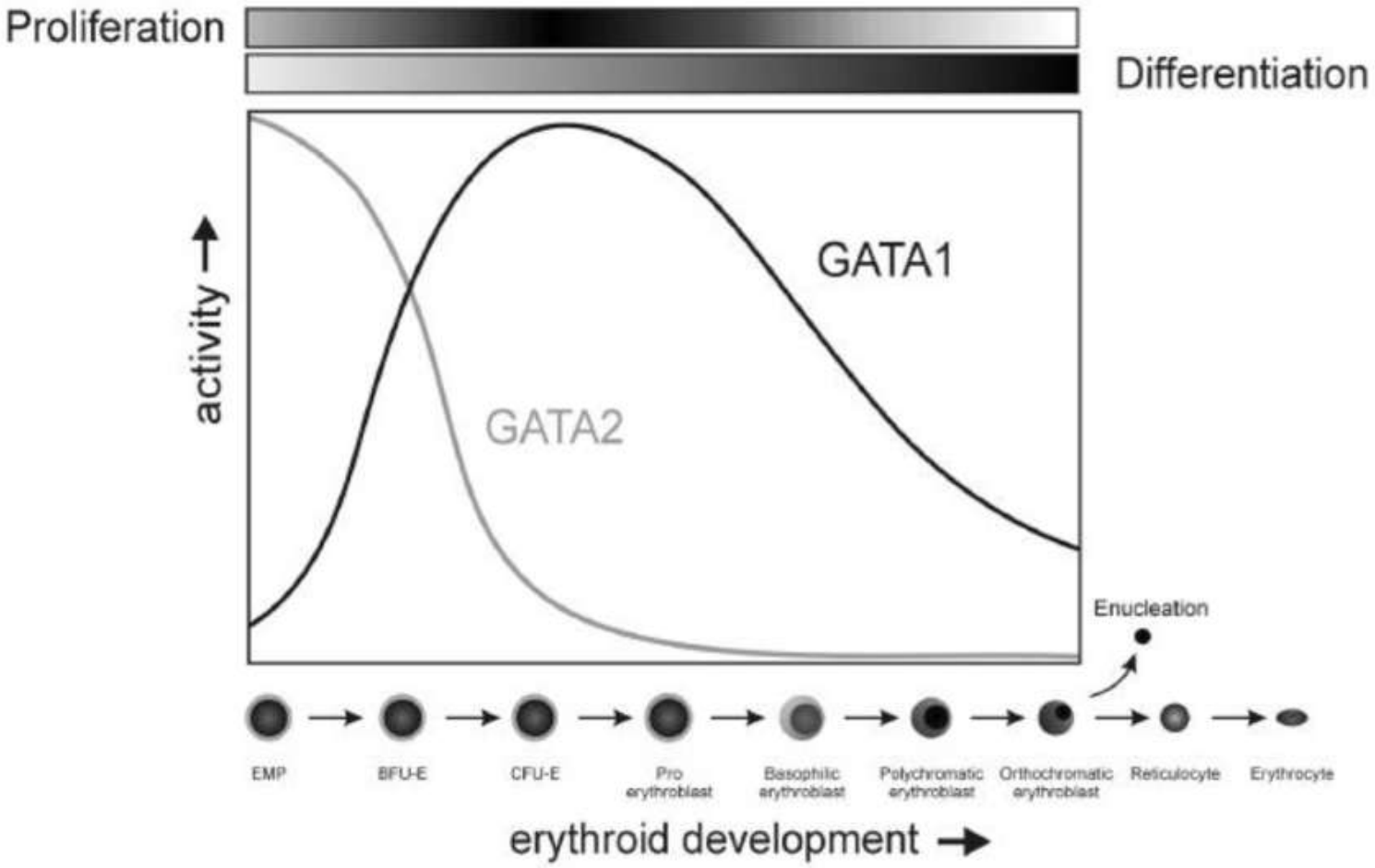
Rôle des facteurs de transcription dans le déterminisme de lignée



Thomas Graf & Tariq Enver *Nature 462, 587-594 (2009)*

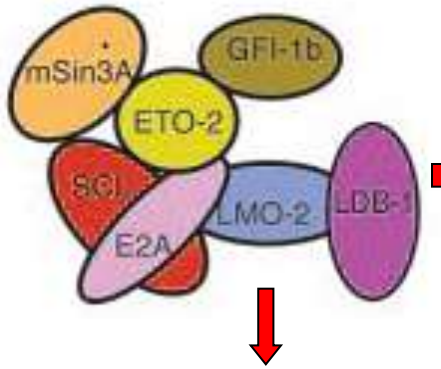
Expression séquentielle de FTs pour réguler la balance prolifération précoce/différenciation

Ex: le switch GATA1/GATA2

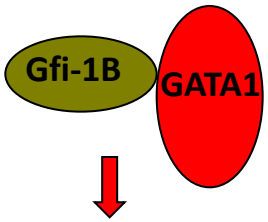


Ferreira et al, 2005

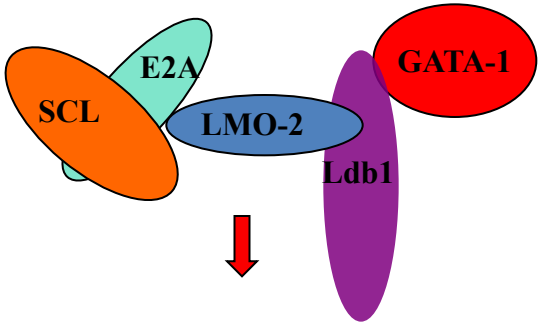
Complexes transcriptionnels régulant la différenciation



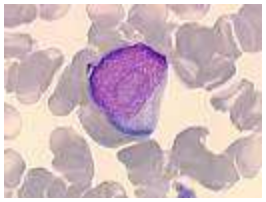
Répression de gènes dedifférenciation
Prolifération

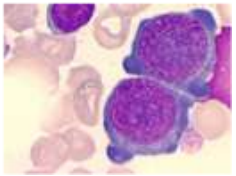


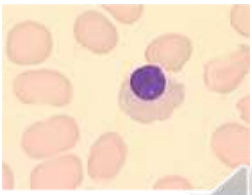
Répression de gènes de prolifération



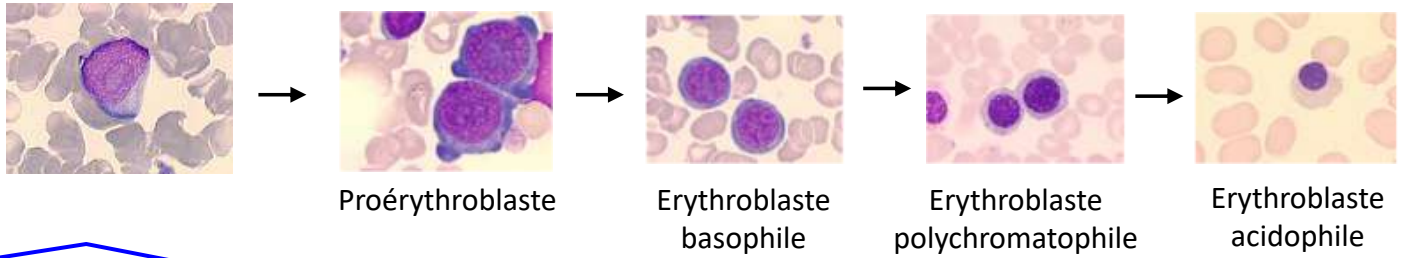
Induction de gènes de différenciation

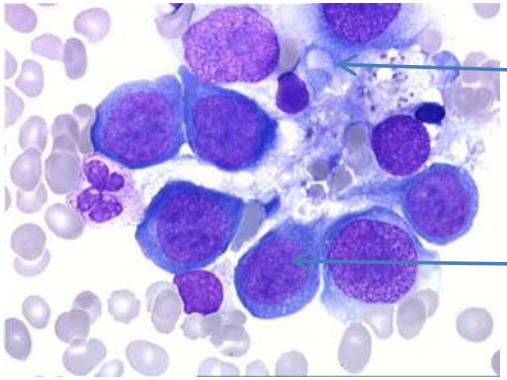






Erythropoïèse tardive:
Les précurseurs au sein de l ’ilot érythroblastique





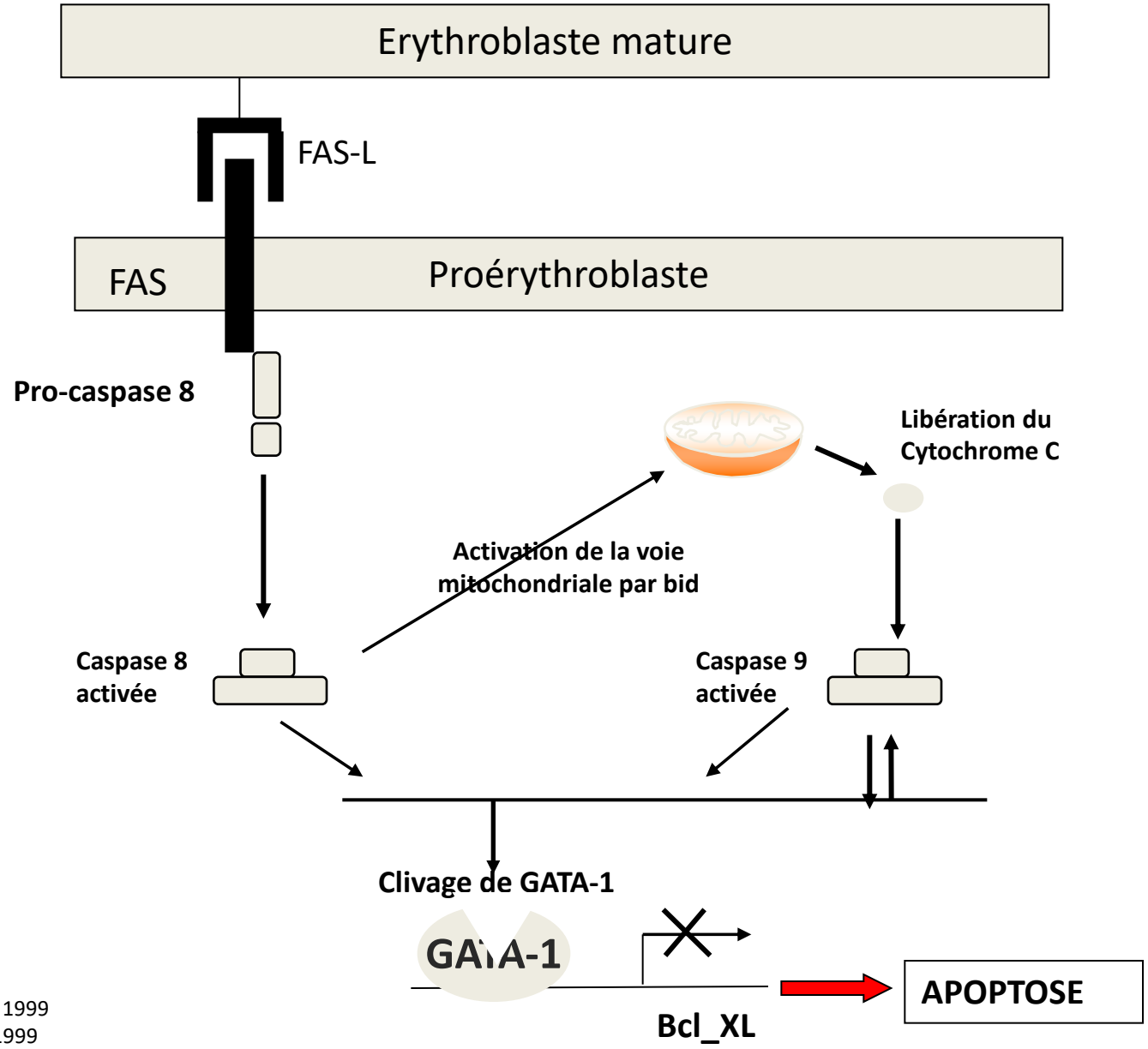
Nombreuses interactions macrophages/ Erythroblastes
Ex: Emp, VCAM1, ICAM4

➔Défaut d’érythropoïèse in vivo chez les modèles de souris déficientes pour ces protéines

Rôle essentiel dans la régulation de l’érythropoïèse:

- Le macrophage apporte des nutriments et du Fer
- Régulation de l’apoptose selon les besoins de l’organisme
-Phagocyte les noyaux après expulsion

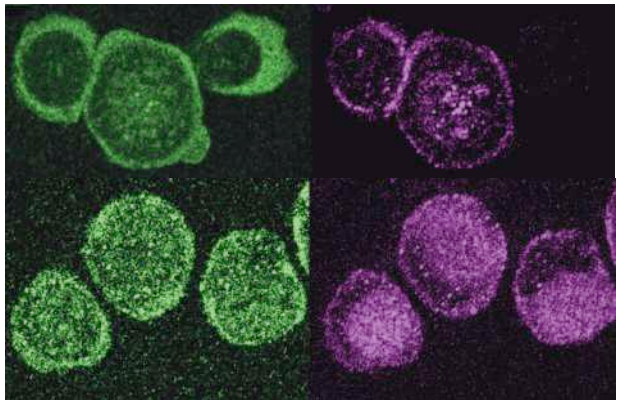
L’interaction entre précurseurs au sein de l ’ilot participe à la régulation de l’érythropoïèse



De Maria R et al, Nature 1999
De Maria R et al, Blood 1999

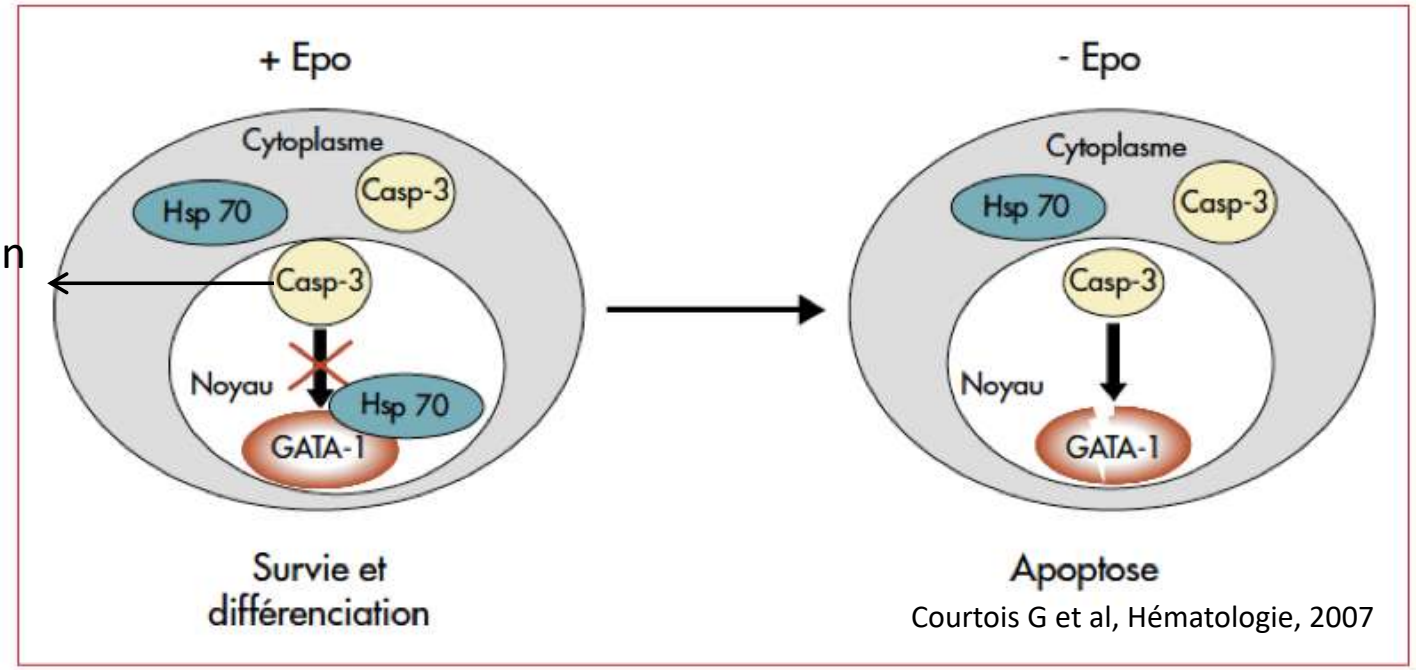
Rôle de la protéine chaperone HSP70 dans la protection de GATA1

HSP70 GATA1



Ribeil et al, Nature, 2007

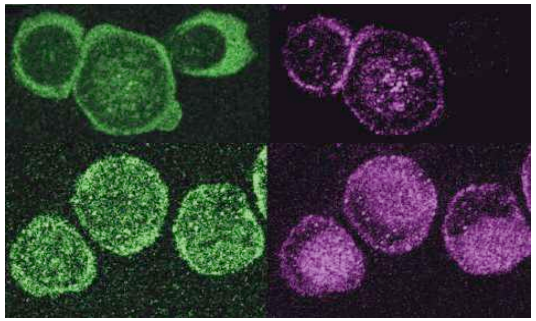
Condensation nucléaire



Courtois G et al, Hématologie, 2007

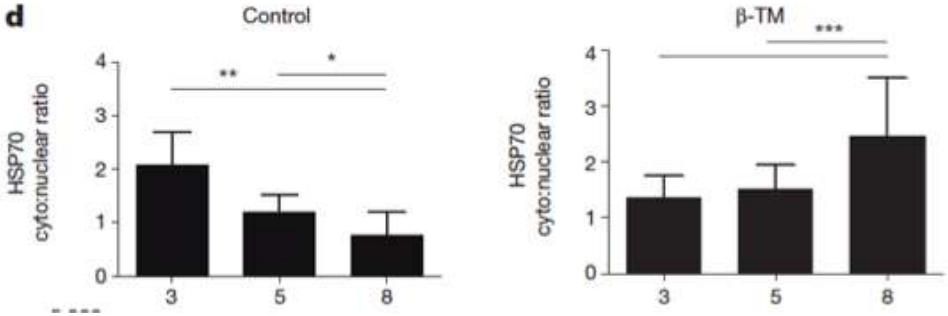
HSP70 sequestration by free α-globin promotes ineffective erythropoiesis in β-thalassaemia

Jean-Benoît Arlet[1,2,3,4]*, Jean-Antoine Ribeil[1,3,4,5]*, Flavia Guillem[1,3,4], Olivier Negre[6], Adonis Hazoume[7,8], Guillaume Marcion[7,8], Yves Beuzard[6], Michaël Dussiot[1,3,4,9], Ivan Cruz Moura[1,3,4,9,10], Samuel Demarest[11], Isaure Chauvot de Beauchêne[11,12], Zakia Belaid-Choucair[1,3,4], Margaux Sevin[7,8], Thiago Trovati Maciel[1,3,4,9,10], Christian Auclair[11,12], Philippe Leboulch[6,13], Stany Chretien[6], Luba Tchertanov[11,12], Véronique Baudin-Creuza[14], Renaud Seigneuric[8], Michaela Fontenay[4,15], Carmen Garrido[7,8,16]§, Olivier Hermine[1,3,4,17]§ & Geneviève Courtois[1,3,4]§

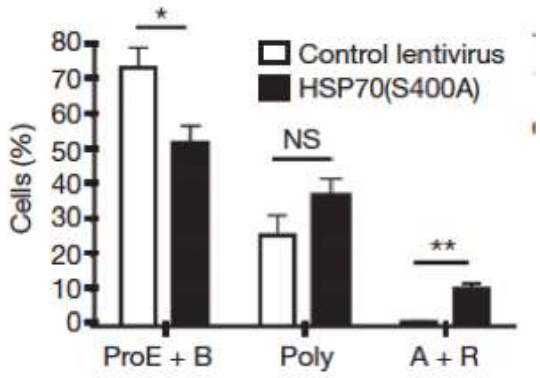


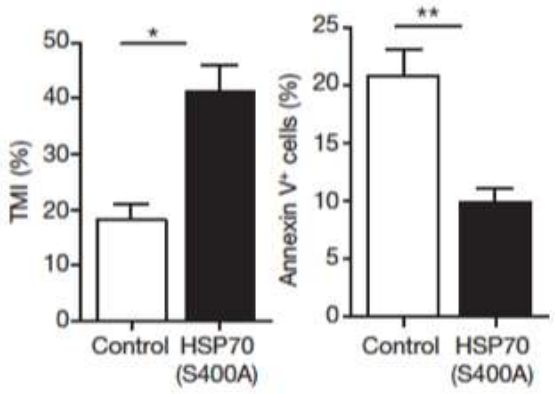
Béta-Thal majeure

Contrôle

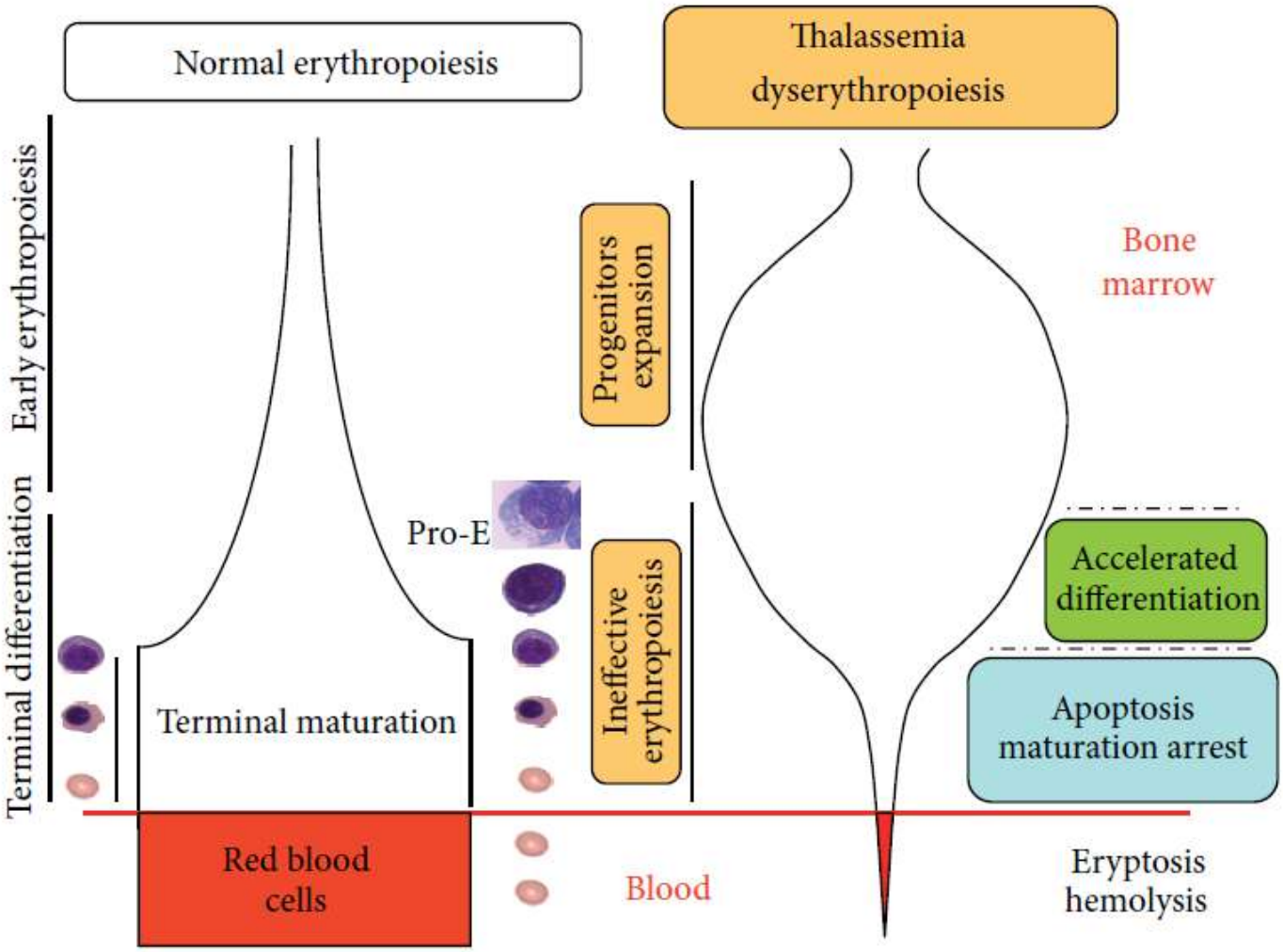


Surexpression HSP70 restaure l'érythropoïèse





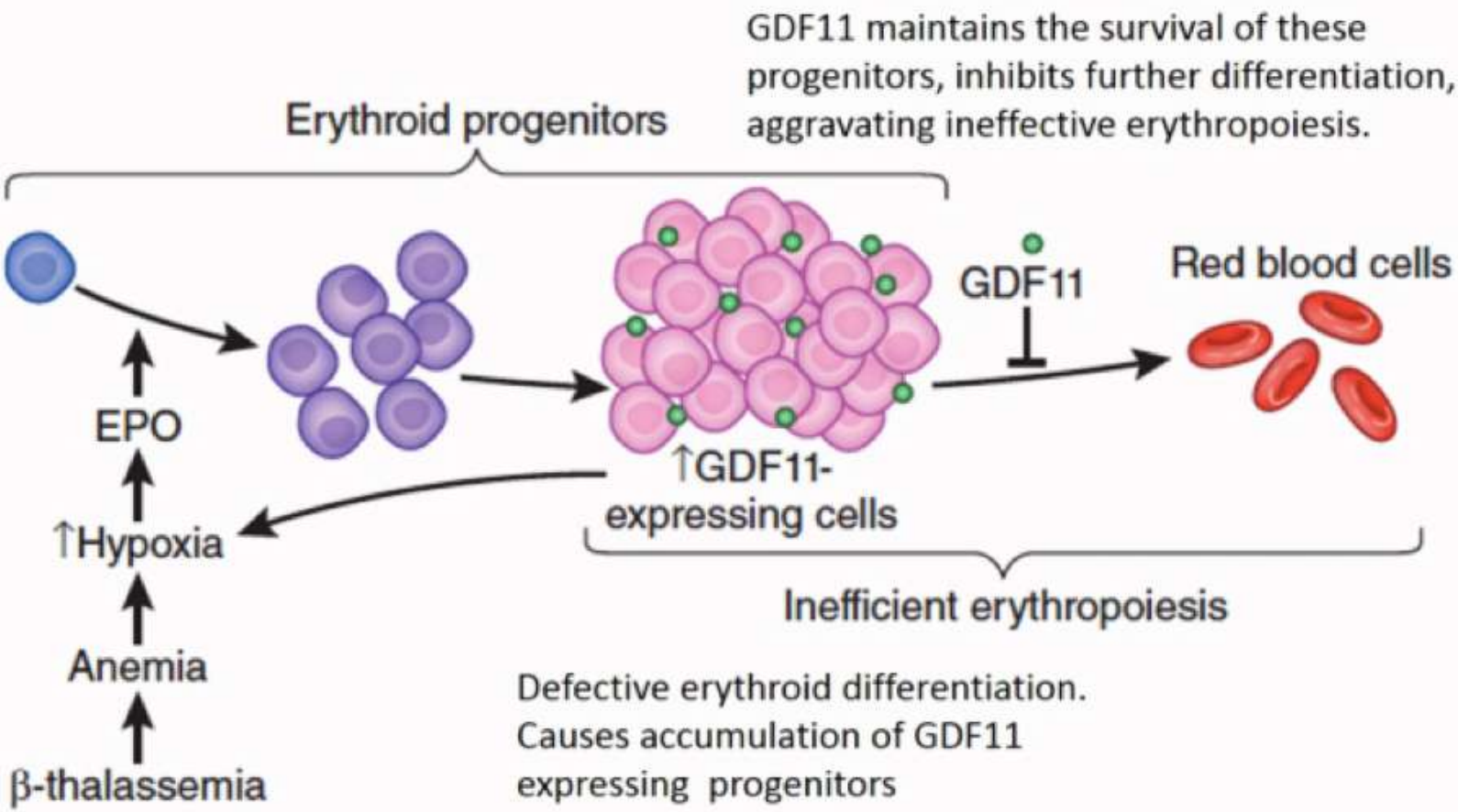
Les “nouveaux” régulateurs



J. B Arlet et al, 2013

An activin receptor IIA ligand trap corrects ineffective erythropoiesis in β-thalassemia

Michael Dussiot, Thiago T Maciel, Aurélie Fricot, Céline Chartier, Olivier Negre, Joel Veiga, Damien Grapton, Etienne Paubelle, Emmanuel Payen, Yves Beuzard, Philippe Leboulch, Jean-Antoine Ribeil, Jean-Benoit Arlet, Francine Coté, Geneviève Courtois, Yelena Z Ginzburg, Thomas O Daniel, Rajesh Chopra, Victoria Sung, Olivier Hermine & Ivan C Moura



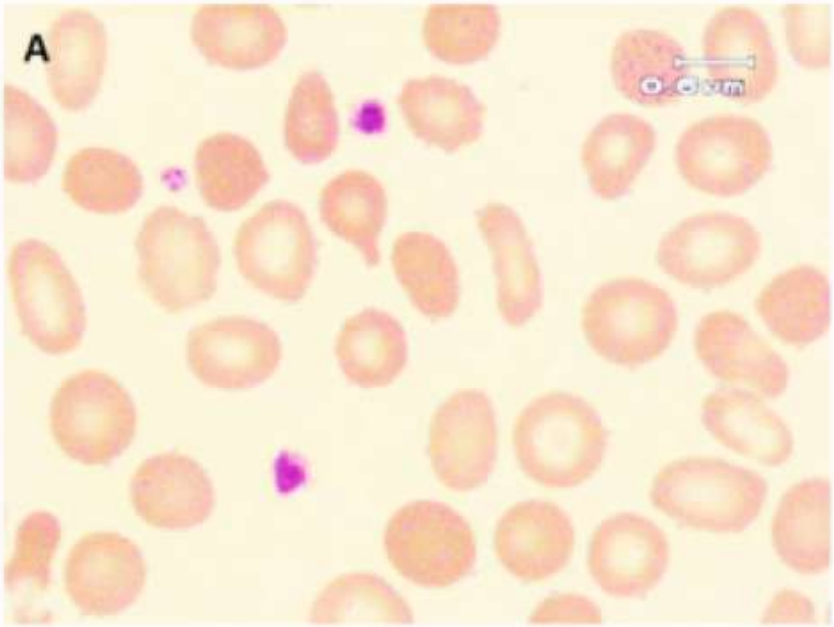
Paulson. Nature Medicine Editorial , 20 , 4 , 2014
After: Dussiot *et al.* Nat Med, 4, 398-407, 2014

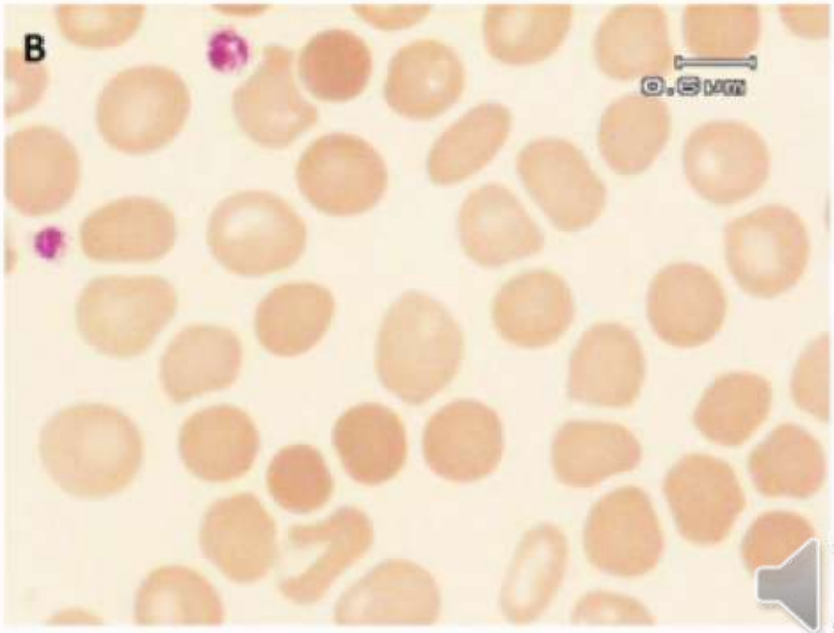
Dans les syndromes thalassémiques

RBC morphology before (A) and after (B) 4.5 months of treatment (6 doses) with sotatercept 0.75 mg/kg in a 65 year old Indian female

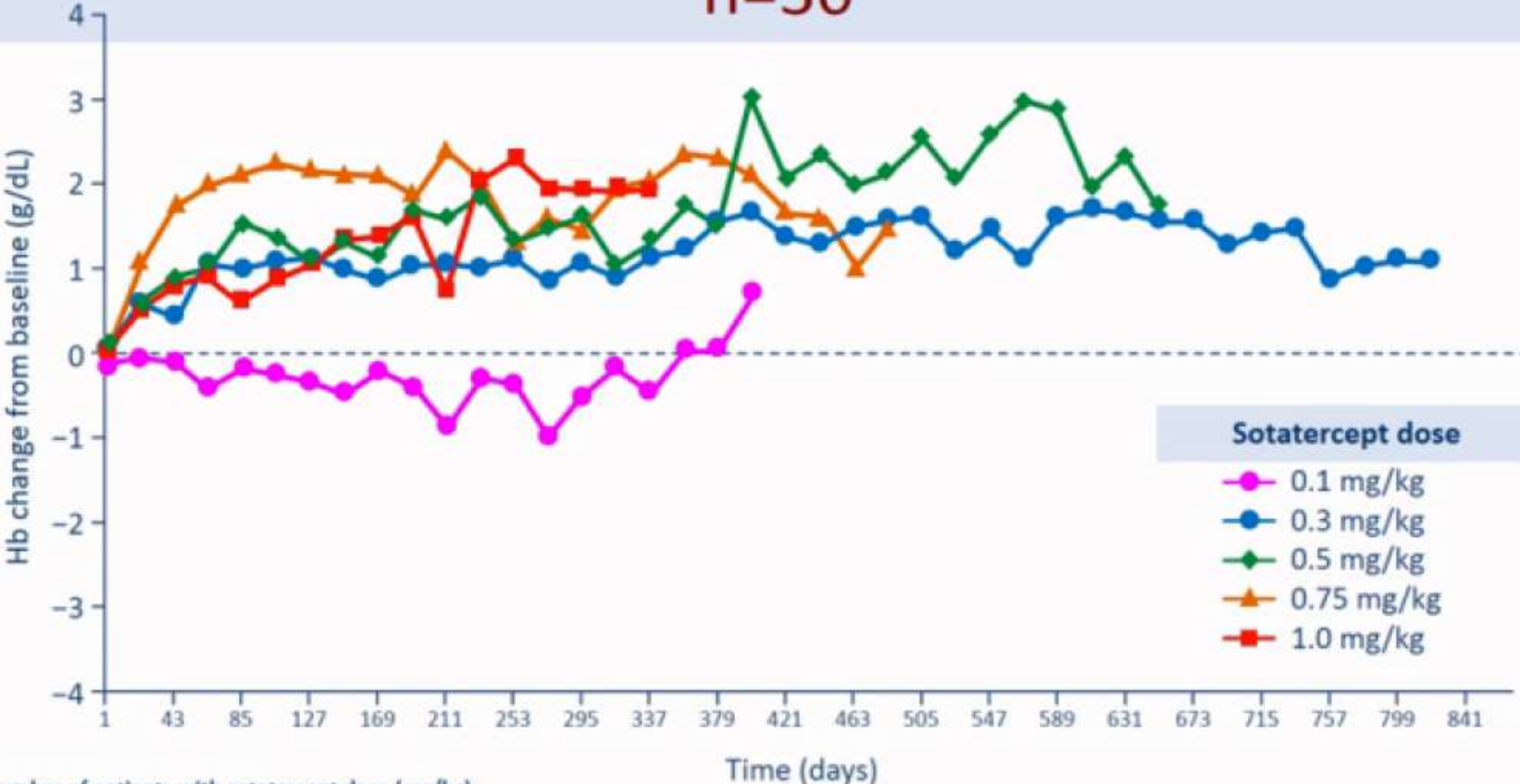
Baseline Hb was 8.7 g/dL

Hb at 4.5 months was 11.2 g/dL





ACE-11 Mean Change in Hb From Baseline in NTD Thalassemia Patients n=30



Number of patients with sotatercept dose (mg/kg)

0.1 mg/kg	6	6	6	5	5	3	3	3	3	3	3	3	3	3	3	2	2	2	2	1																			
0.3 mg/kg	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	5	5	4	4	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1
0.5 mg/kg	6	6	6	6	5	5	5	5	5	4	4	4	4	4	4	4	4	3	3	2	2	2	2	2	2	2	2	2	2	2	2	1							
0.75 mg/kg	7	7	7	7	6	6	6	6	6	6	5	5	3	3	3	3	3	3	3	2	2	2	2	2															
1.0 mg/kg	5	5	5	5	5	4	4	3	2	2	2	1	1	1	1	1	1																						

EHA Oral presentation 2015

Interim data as of May 6, 2015.

Dans les syndromes myélodysplasiques

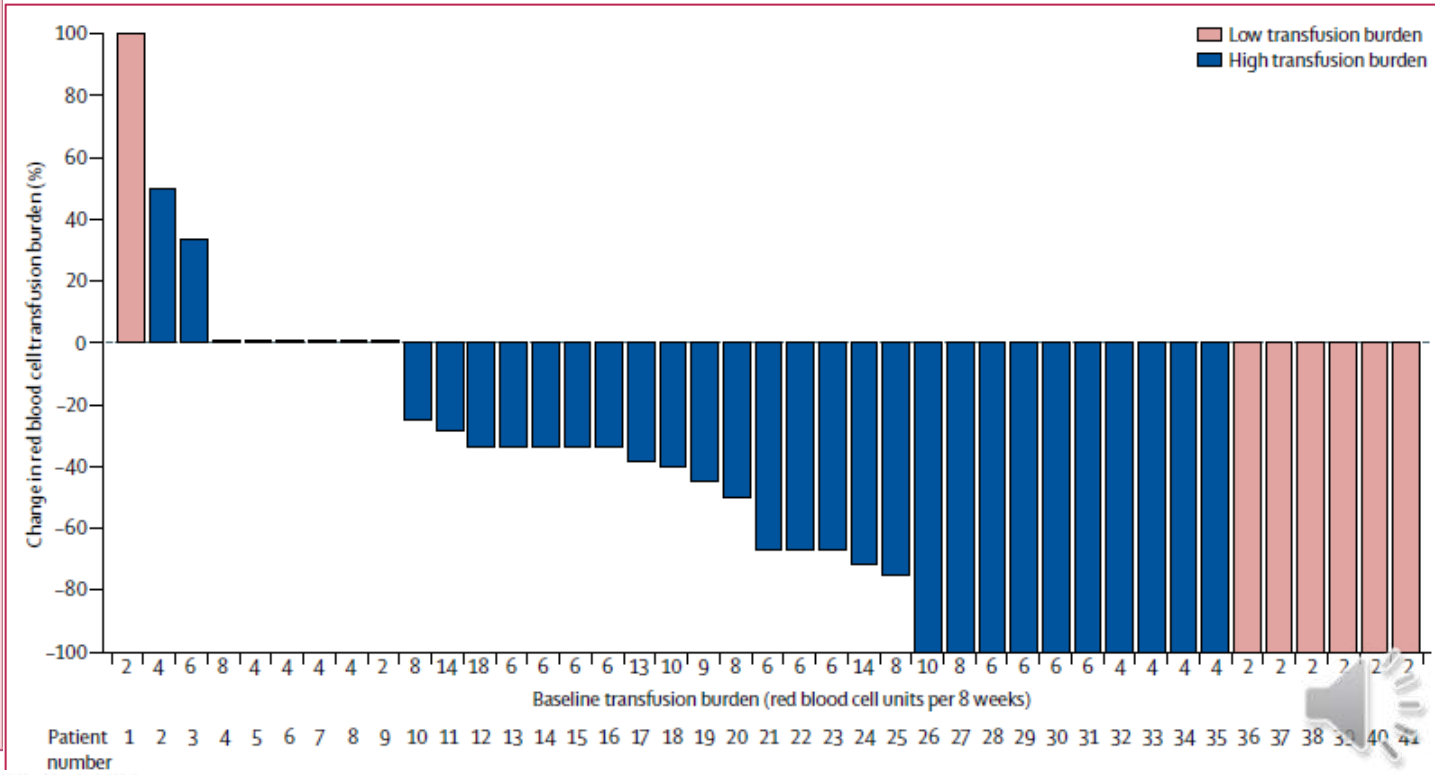
Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study

Uwe Platzbecker, Ulrich Germing*, Katharina S Götze*, Philipp Kiewe*, Karin Mayer*, Jörg Chromik*, Markus Radsak*, Thomas Wolff*, Xiaosha Zhang, Abderrahmane Laadem, Matthew L Sherman, Kenneth M Attie, Aristoteles Giagounidis**

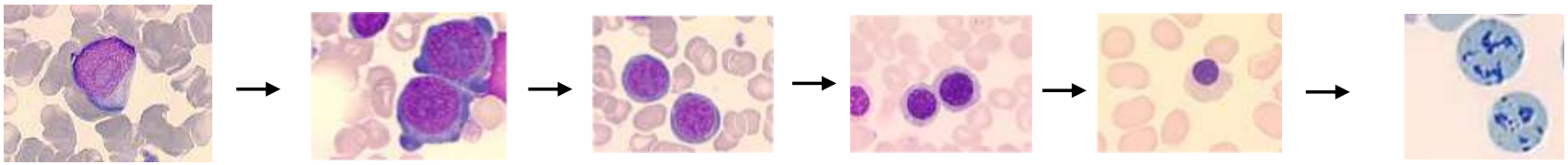
	IWG HI-E*	RBC-TI†
All patients	32/51 (63%)	16/42 (38%)
Transfusion burden		
Low transfusion burden (<4 red blood cell units per 8 weeks)	11/17 (65%)	6/8 (75%)
High transfusion burden (≥4 red blood cell units per 8 weeks)	21/34 (62%)	10/34 (29%)
Previous use of ESAs		
Yes	21/34 (62%)	11/29 (38%)
No	11/17 (65%)	5/13 (39%)
Previous use of lenalidomide		
Yes	5/8 (63%)	1/8 (13%)
No	27/43 (63%)	15/34 (44%)
Serum erythropoietin concentration		
<200 IU/L	19/25 (76%)	10/19 (53%)
≥200 IU/L to ≤500 IU/L	7/12 (58%)	4/9 (44%)
>500 IU/L	6/14 (43%)	2/14 (14%)
Ring sideroblast status		
Positive (≥15% ring sideroblasts)	29/42 (69%)	14/33 (42%)
Negative (<15% ring sideroblasts)	3/7 (43%)	2/7 (29%)
Unknown	0/2	0/2
SF3B1 mutation status		
Positive	24/31 (77%)	11/25 (44%)
Negative	6/15 (40%)	5/13 (39%)
Unknown	2/5 (40%)	0/4
Any splicing factor‡		
Positive	27/37 (73%)	15/30 (50%)
Negative	5/14 (36%)	1/12 (8%)
IPSS classification		
Low risk	18/23 (78%)	7/14 (50%)
Intermediate 1 risk	14/27 (52%)	9/27 (33%)
Intermediate 2 risk	0/1	0/1
IPSS-R classification		
Very low to low risk	20/31 (65%)	11/23 (48%)
Intermediate risk	10/17 (59%)	5/16 (31%)
High to very high risk	2/3 (67%)	0/3

Data are n/N (%). ESA=erythropoiesis-stimulating agent. HI-E=haematological improvement-erythroid. IPSS=International Prognostic Scoring System. IPSS-R=Revised International Prognostic Scoring System. IWG=International Working Group. RBC-TI=red blood cell-transfusion independence. *For low transfusion burden patients, IWG HI-E is defined as 1·5 g/dL or higher increase in haemoglobin concentration over 8 weeks; for high transfusion burden patients, IWG HI-E is defined as a reduction of 4 or more red blood cell units over 8 weeks. †Patients with a baseline transfusion burden of 2 or higher red blood cell units per 8 weeks were included in the RBC-TI evaluable population. ‡Splicing factors assessed were *SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*.

Table 2: Patients treated with luspatercept 0·75–1·75 mg/kg achieving IWG HI-E and RBC-TI over 8 weeks in the base and extension studies (n=51)



Régulateurs extrinsèques de l'érythropoïèse



1- Facteurs de transcription/miRNA/Epigénétique (GATA1, KLF1..)

2- Facteurs de croissance hématopoïétique

3- Facteurs impliqués dans la synthèse de l'ADN

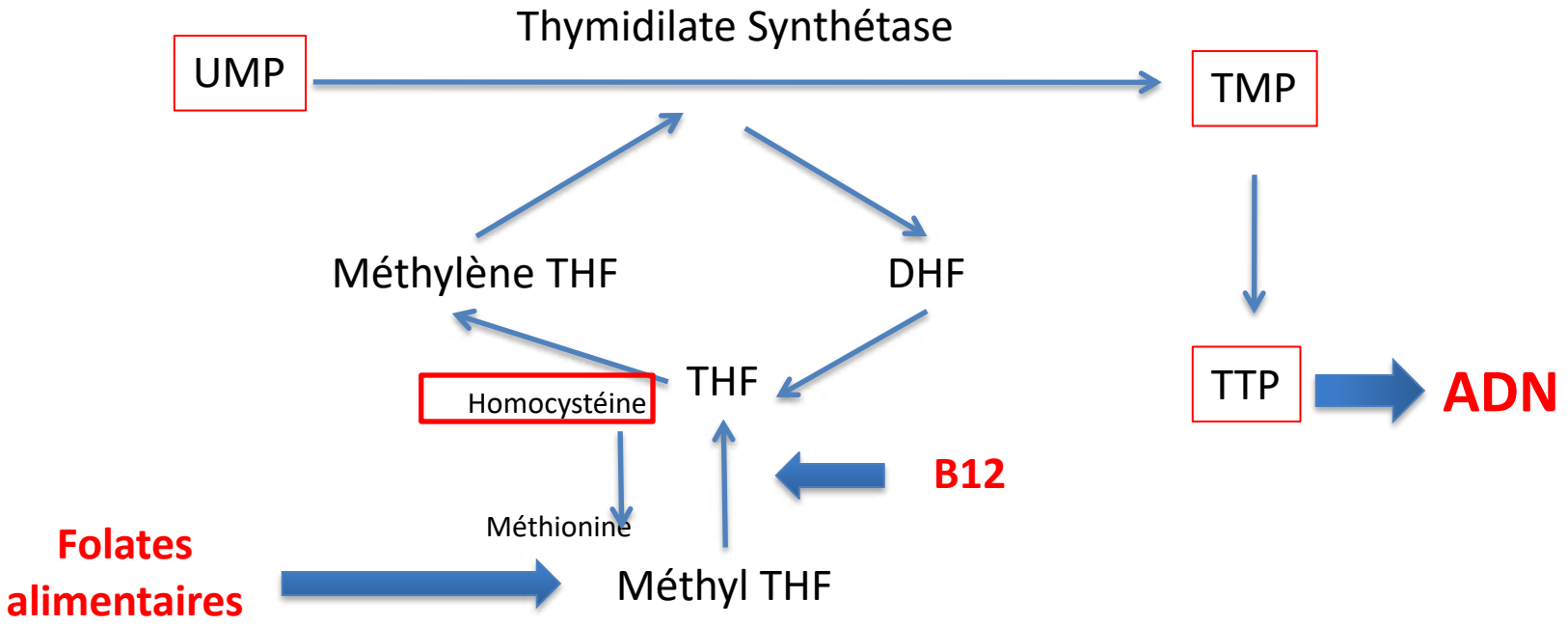
4- Facteurs impliqués dans la synthèse de l'hémoglobine

5-Facteurs hormonaux

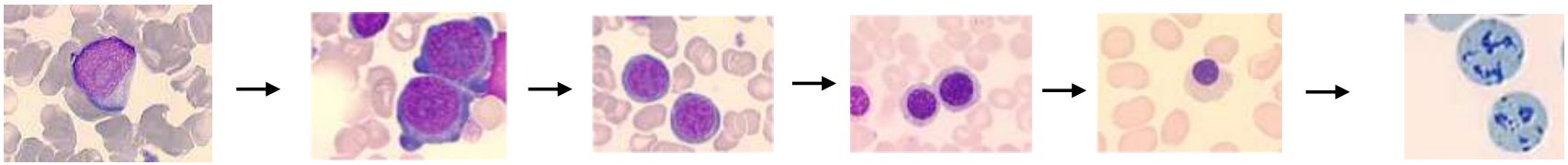
6- Autres: épissage, traduction, modifications post traductionnelles....(MDS…)

Facteurs impliqués dans la synthèse de l'ADN

Erythrocytes: production de 200.10^9 par jour à l'état basal



Régulateurs extrinsèques de l'érythropoïèse



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5-Facteurs hormonaux

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Facteurs impliqués dans la synthèse de l'hémoglobine

Anémie microcytaire hypochrome

Défaut de synthèse de l'hémoglobine

↓

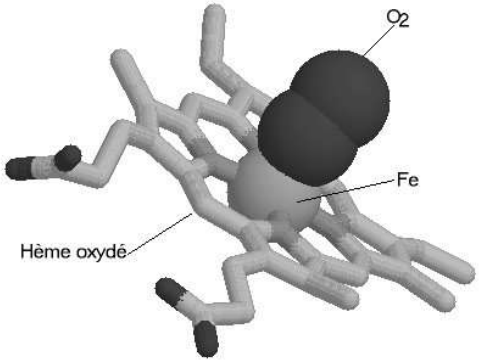
Concentration en hémoglobine trop faible dans les érythroblastes de la moelle

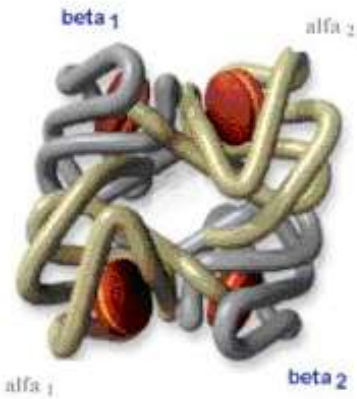
↓

Mitoses supplémentaires avec diminution du volume

Synthèse de l'hème

Déficit quantitatif de synthèse de globine

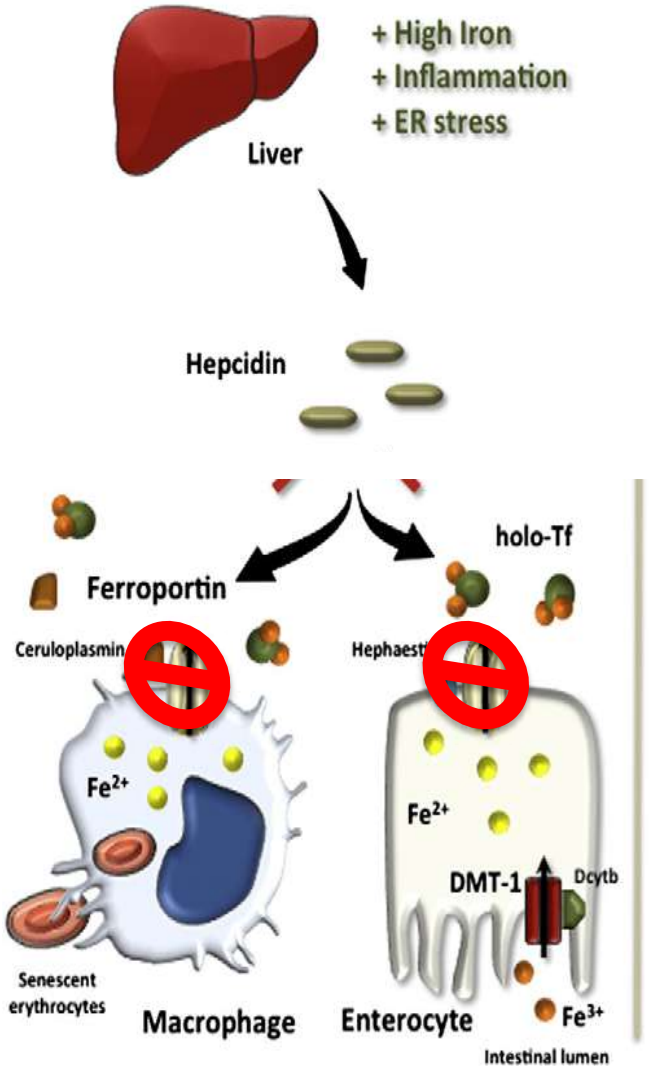


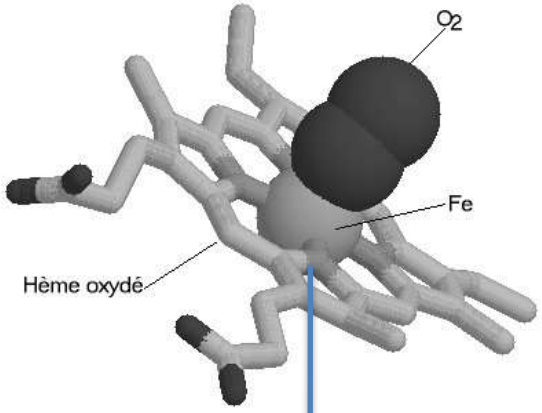


← Alpha-thalassémie

← Béta-thalassémie

http://www.librairiedemolecules.education.fr/molecule.php?idmol=54



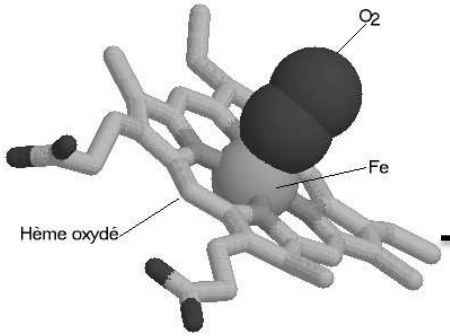


Carence
Hepcidine BASSE

IRIDA
Carence résistante au ttt per os
Hepcidine HAUTE

Carence fonctionnelle
Hepcidine ELEVEE

IRC, Insuff cardiaque, MICI:
Cs<20%
ET/OU
Ferrtine <100 ng/Ml
Cappellini et al, Am J Hematol,2017



SLC25A38 Autosomal Recessive CSA

Glycine ? ALA CP'gen III Heme Fe

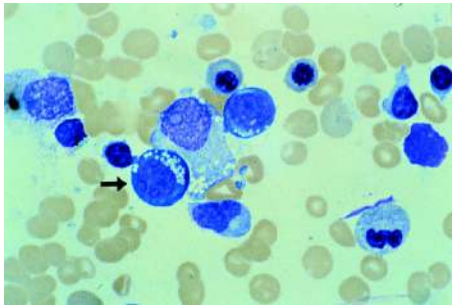
MFRN1

Glycine ALA B6 PPIX Heme Cu Fe

ALAS2 FECH Pb

Succinyl-CoA

X-linked Sideroblastic Anemia (XLSA)



Carence en vitamine B6
- OH
- Antituberculeux, phénicolés

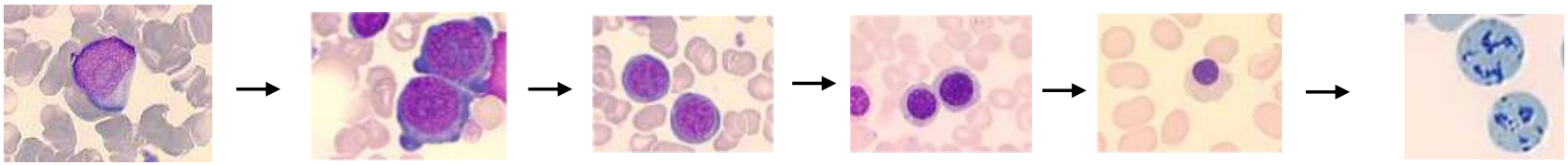
Porphyrie érythropoïétique

Carence en cuivre:
- NPT
- Intox Zn

Mark D. Fleming Hematology 2011;2011:525-531

Irving J et al CMAJ. 2003 Jul 22; 169(2): 129–131.

Régulateurs extrinsèques de l'érythropoïèse



1- Facteurs de transcription/miRNA/Epigénétique (GATA1, KLF1..)

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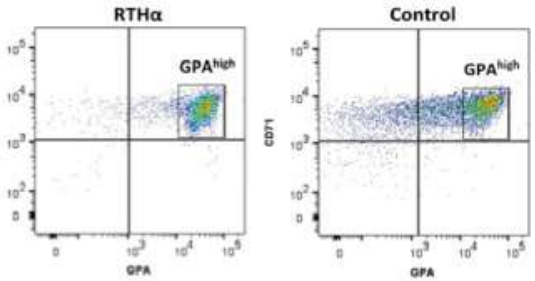
4- Facteurs impliqués dans la synthèse de l'hémoglobine

5-Facteurs hormonaux

Facteurs hormonaux

- Hormones thyroidiennes

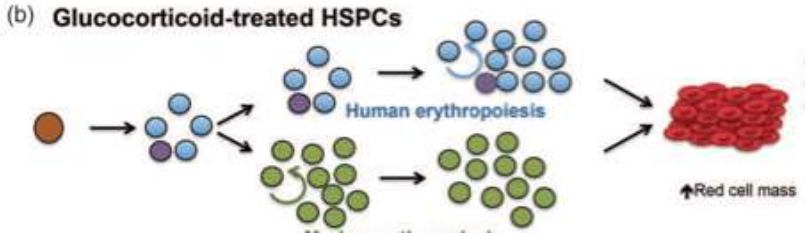


Van Gucht et al, J Clin Endocrinol Metab. 2017 Sep 1; 102(9): 3517–3525.

-Androgènes

- Effet sur progéniteurs et les précurseurs
- Effet sur production d' EPO
- Effet sur absorption du fer (hepcidine)

-Glucocorticoïdes



Dulmovits et al, Curr Op Hematol, 2017

DBA

80% CS → 40%CD ou CR

20%CR → 40% sous ST au long cours

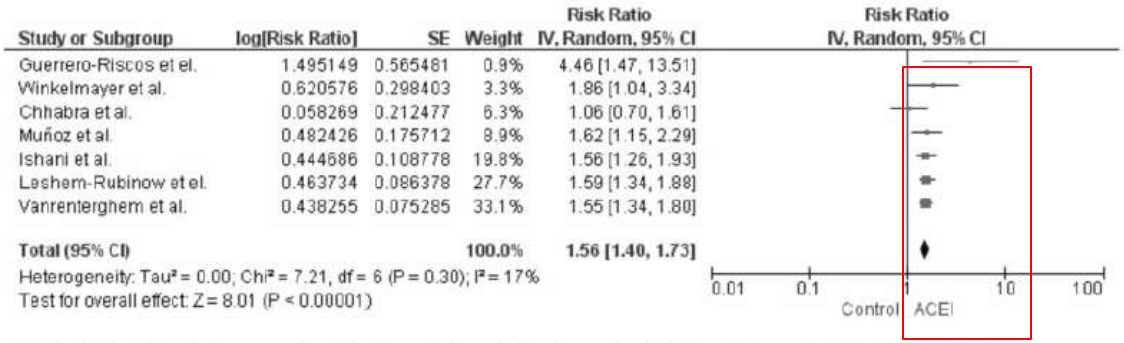
Facteurs hormonaux

- L'angiotensine II

Deux mécanismes:

1- Stimulation des récepteurs à l'AT II de type 1 à la surface des progéniteurs éythroïdes en synergie avec l'EPO

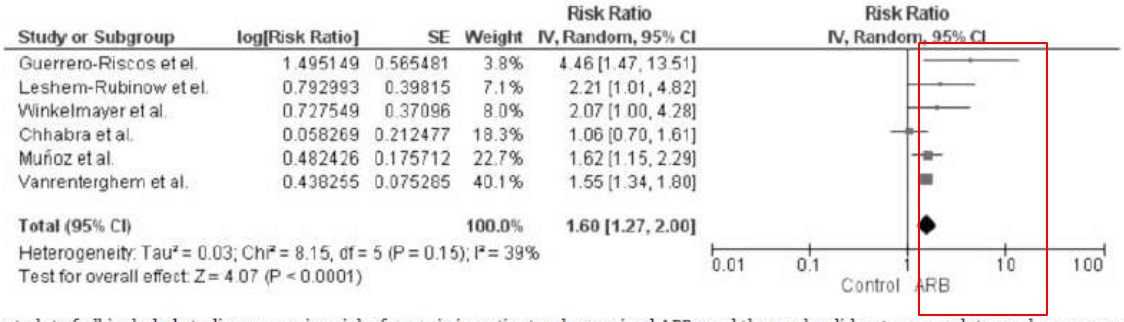
2- Stimulation de la production d'EPO au niveau rénal



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Guerrero-Riscos et el.	1.495149	0.565481	0.9%	4.46 [1.47, 13.51]
Winkelmayer et al.	0.620576	0.298403	3.3%	1.86 [1.04, 3.34]
Chhabra et al.	0.058269	0.212477	6.3%	1.06 [0.70, 1.61]
Muñoz et al.	0.482426	0.175712	8.9%	1.62 [1.15, 2.29]
Ishani et al.	0.444686	0.108778	19.8%	1.56 [1.26, 1.93]
Leshem-Rubinow et el.	0.463734	0.086378	27.7%	1.59 [1.34, 1.88]
Vanrenterghem et al.	0.438255	0.075285	33.1%	1.55 [1.34, 1.80]
Total (95% CI)			**100.0%**	**1.56 [1.40, 1.73]**

Heterogeneity: Tau² = 0.00; Chi² = 7.21, df = 6 (P = 0.30); I² = 17%
Test for overall effect: Z = 8.01 (P < 0.00001)

Figure 1. Forest plot of all included studies comparing risk of anemia in patients who received ACEIs and those who did not; square data markers represent RRs; horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. IV, inverse variance; SE, standard error.



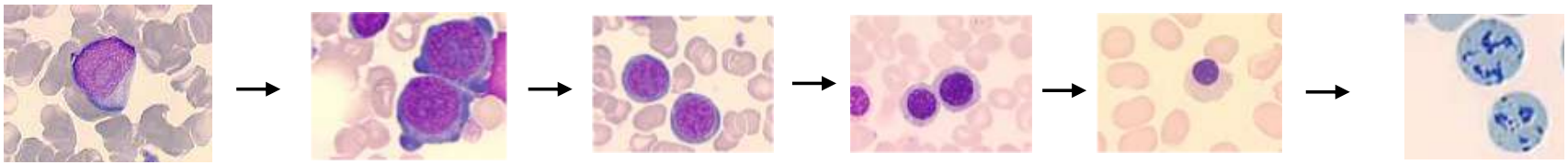
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Guerrero-Riscos et el.	1.495149	0.565481	3.8%	4.46 [1.47, 13.51]
Leshem-Rubinow et el.	0.792993	0.39815	7.1%	2.21 [1.01, 4.82]
Winkelmayer et al.	0.727549	0.37096	8.0%	2.07 [1.00, 4.28]
Chhabra et al.	0.058269	0.212477	18.3%	1.06 [0.70, 1.61]
Muñoz et al.	0.482426	0.175712	22.7%	1.62 [1.15, 2.29]
Vanrenterghem et al.	0.438255	0.075285	40.1%	1.55 [1.34, 1.80]
Total (95% CI)			**100.0%**	**1.60 [1.27, 2.00]**

Heterogeneity: Tau² = 0.03; Chi² = 8.15, df = 5 (P = 0.15); I² = 39%
Test for overall effect: Z = 4.07 (P < 0.0001)

Figure 2. Forest plot of all included studies comparing risk of anemia in patients who received ARBs and those who did not; square data markers represent RRs; horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. IV, inverse variance; SE, standard error.

Cheungpasitporn et al, QJM, 2015

Régulateurs extrinsèques de l'érythropoïèse



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4- Facteurs impliqués dans la synthèse de l'hémoglobine

5-Facteurs hormonaux

6- Autres:

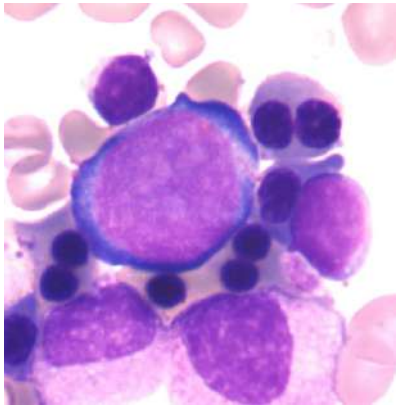
Epissage (SF3B1)
Traduction (RPS14 sur del(5q)
Apoptose (FAS-FAS L)
Hyperméthyaltion, anomalie de localisation de HSP70……

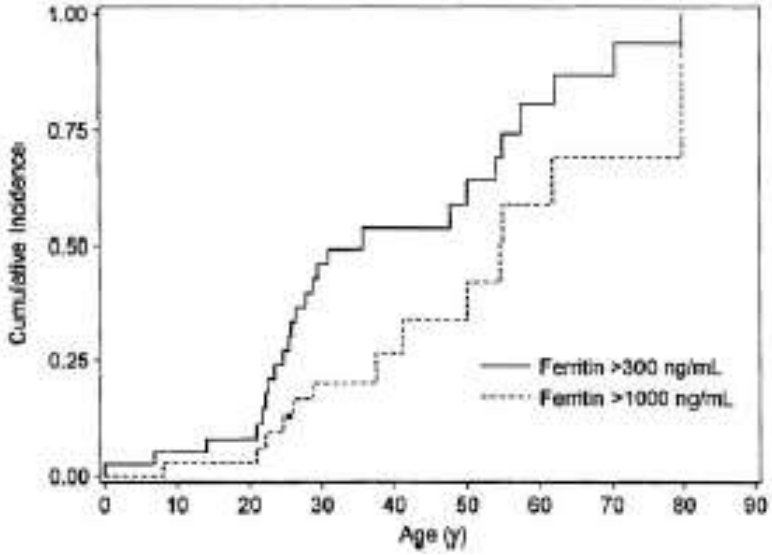
Et….Fer et érythropoïèse inefficace

Exemple des dysérythropoïèses congénitales

CDA II

Mutations *Sec23b*

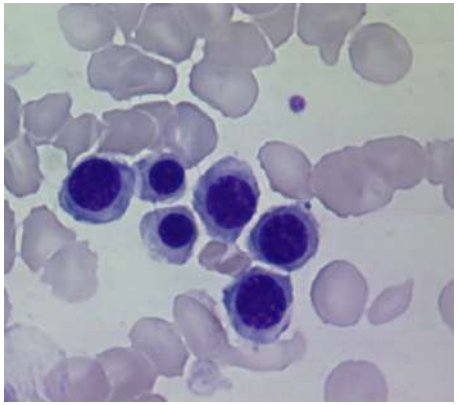


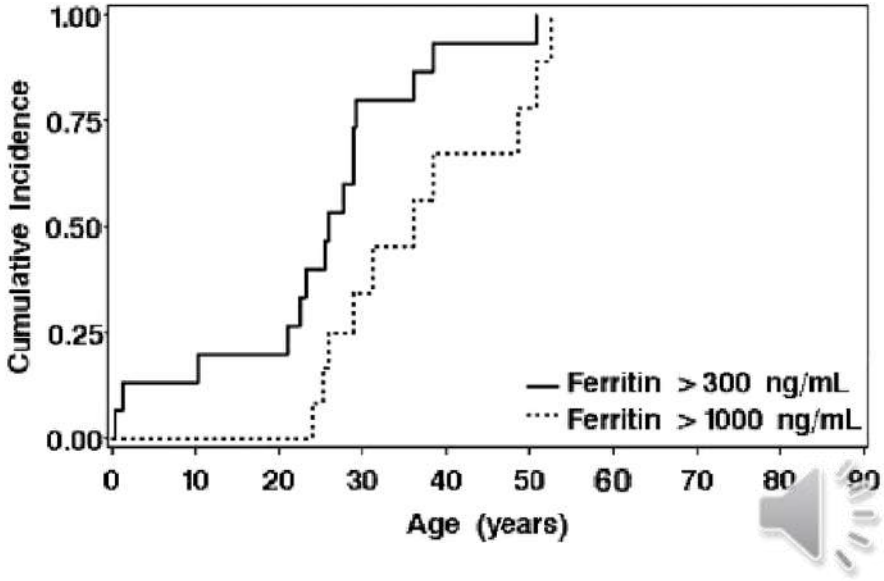


Iolascon et al, Blood, 2001
Heimpel et al, Blood, 2003

CDA I

Mutations *CDNAI*



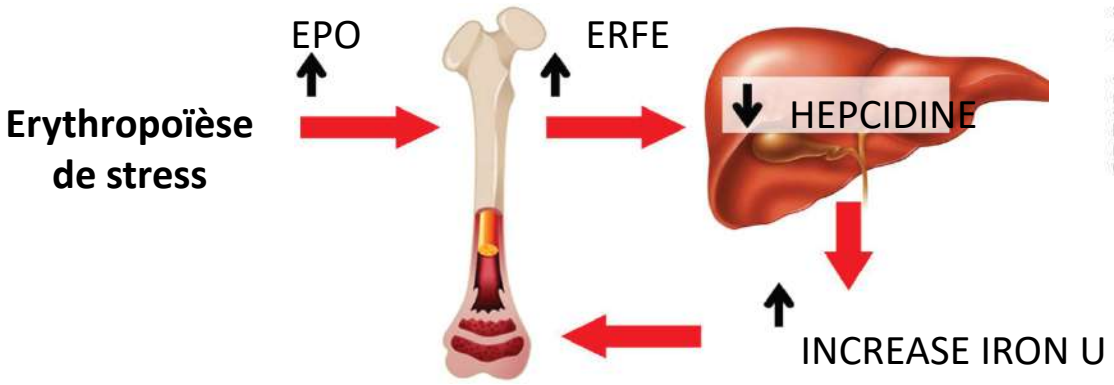


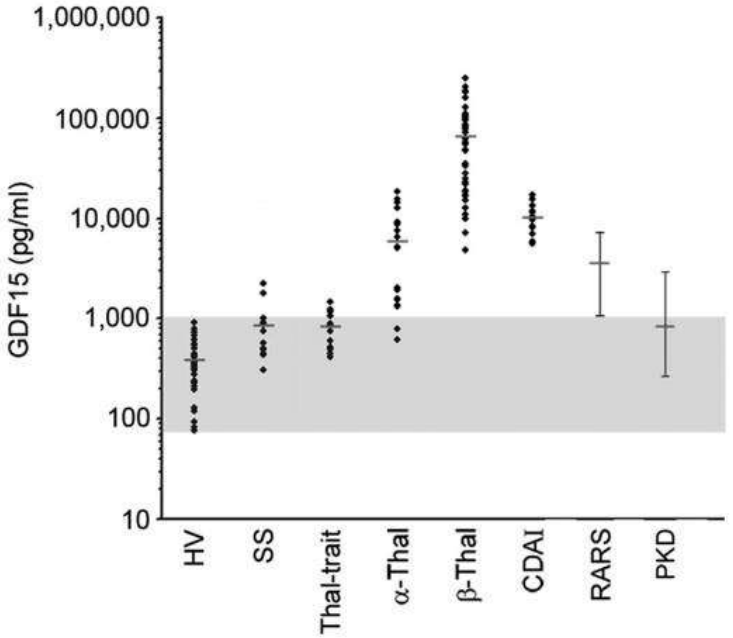
Heimpel et al, Blood, 2001

Erythropoïese et hepcidine

Erythroferrone/GDF 15

- **Expression par les progéniteurs érythroïdes en réponse rapide à l'érythropoïèse de stress**
- **Réprime la synthèse d'hepcidine par le foie**



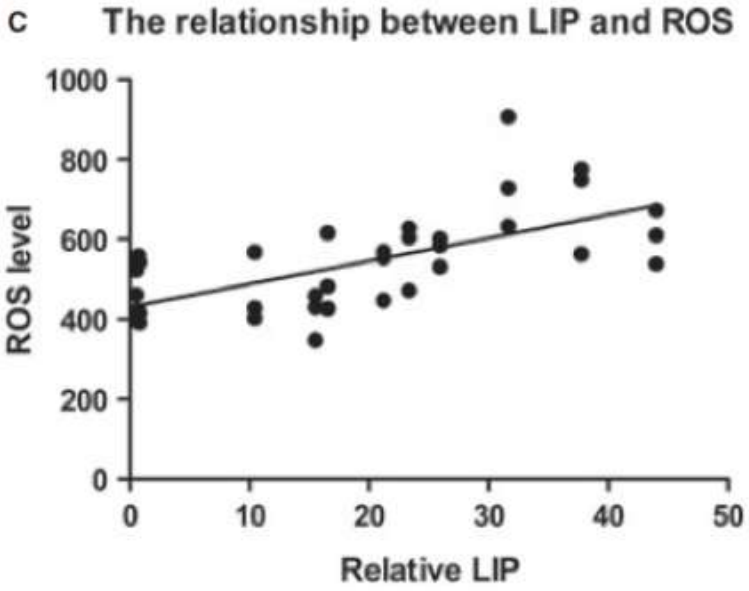


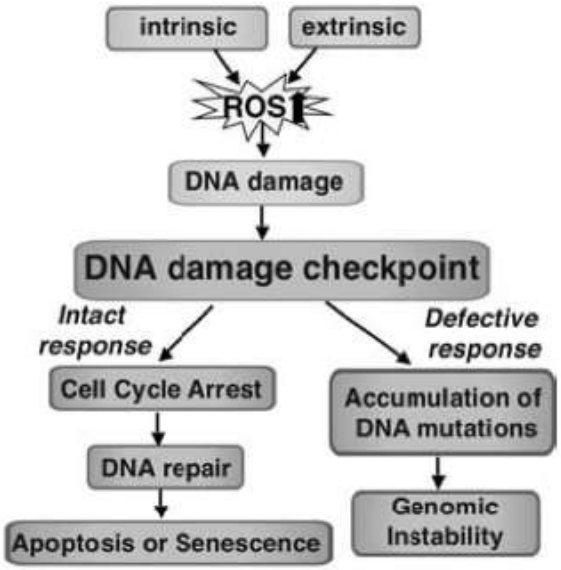
Tanno et al, Curr Op Hematol, 2014

Kautz L et al, Nat Gen, 2014

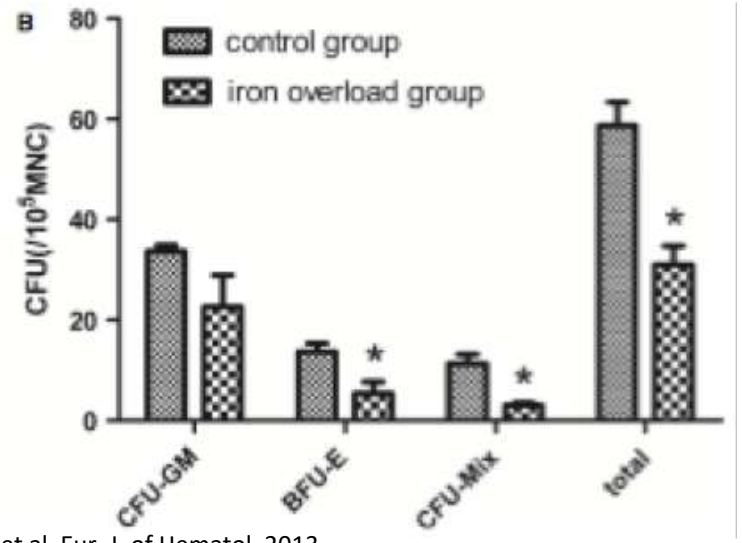
Kim A, Curr Op Hematol, 2015

Toxicité liée au LIC

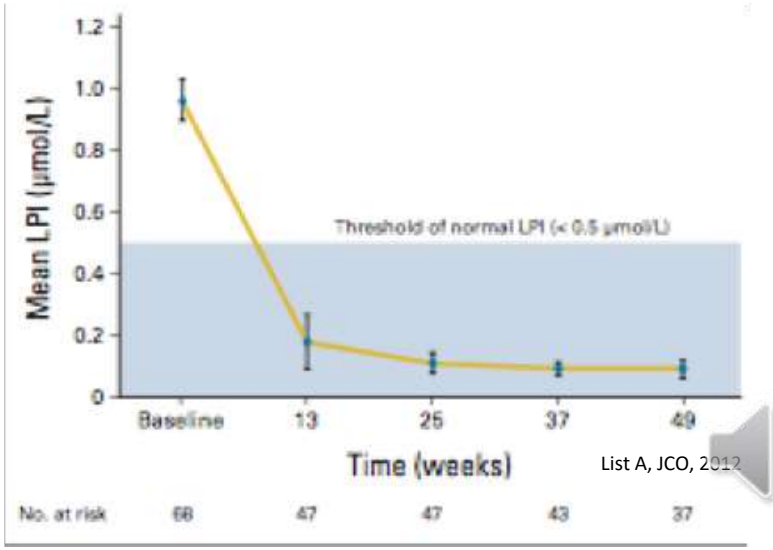




Naka K et al, 2008



Lu W. et al, Eur. J. of Hematol, 2013



List A, JCO, 2012

Amélioration de l'érythropoïèse par la chélation ?

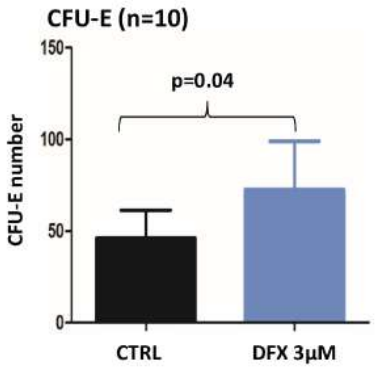
55 SMD de bas risque transfusion dépendant
Traitement pat Deferasirox
16 réponses / 55

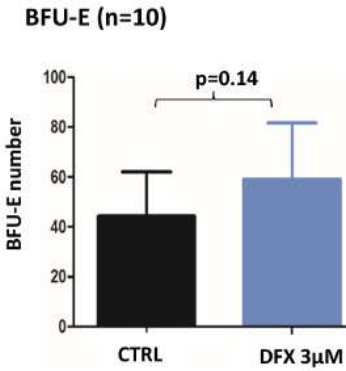
Improta S et a, 2013

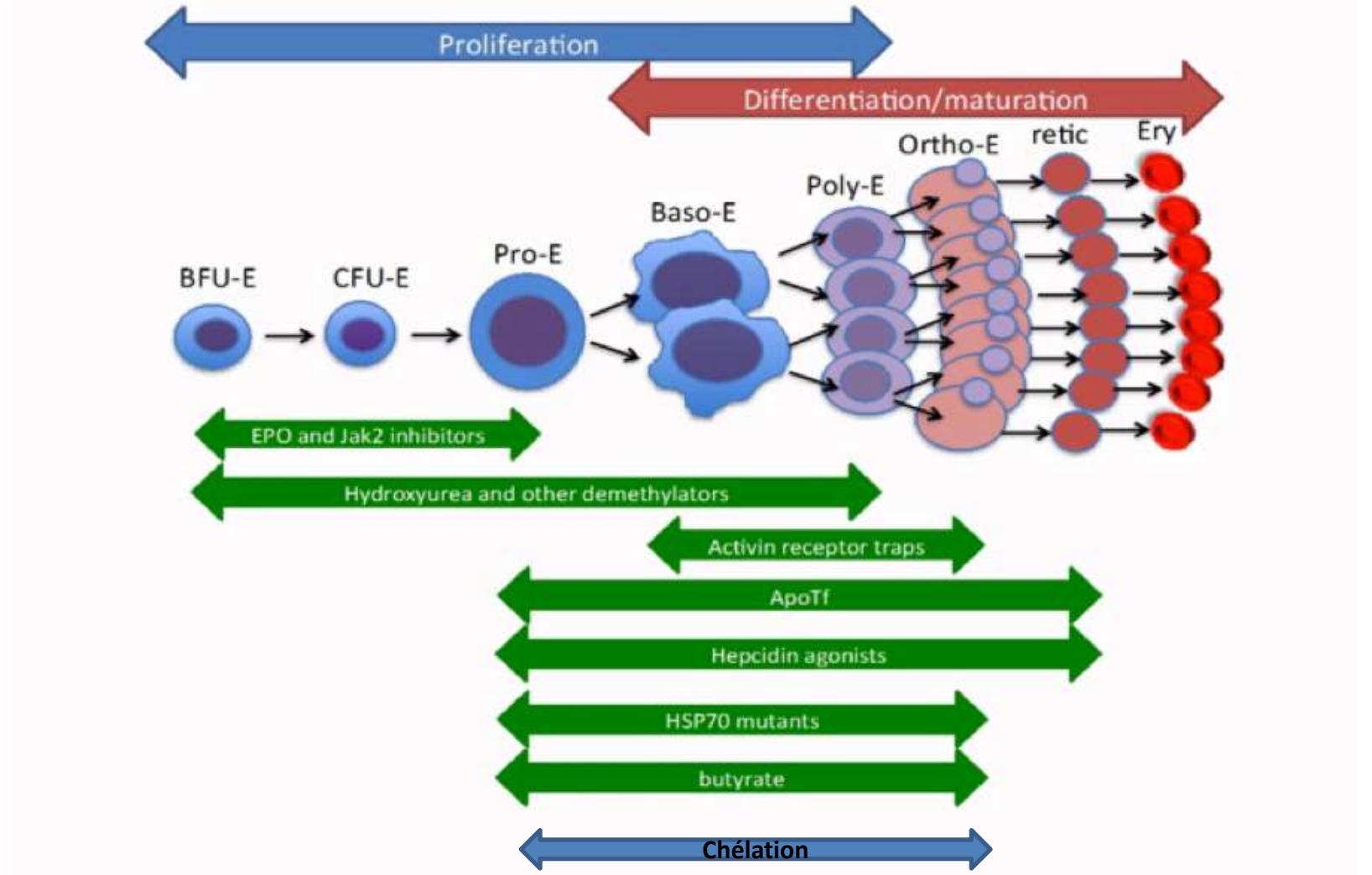
Gender	Age (years)	Histological classification	Prognosis (IPSS)	Transfusion support (units/month)			Serum ferritin (ng/ml)		Haemoglobin (g/dl)		
				Baseline	6 months	24 months	Baseline	24 months	Baseline	24 months	Change
M	72	RA	INT-1	3	2	1	2400	850	7.0	8.6	1.6
M	72	RARS	INT-1	3	2	1	2420	850	7.3	8.8	1.5
M	72	RA	INT-1	3	2	1	2440	850	7.3	8.8	1.5
M	60	RA	LOW	3	2	1	2350	750	7.3	8.9	1.6
M	73	RCMD	INT-1	3	2	1	2450	850	7.3	8.8	1.5
M	60	RA	LOW	3	2	1	2350	750	7.4	9.0	1.6
F	72	RA	LOW	3	2	1	2100	450	7.3	8.8	1.5
M	60	RA	LOW	3	2	1	2450	750	7.2	8.8	1.6
M	67	RARS	LOW	4	3	2	2540	700	7.0	8.6	1.6
M	67	RARS	LOW	4	3	2	2540	700	7.0	8.6	1.6
M	67	RARS	LOW	4	3	2	2540	700	7.0	8.6	1.6
M	74	RA	LOW	3	1	1	2350	800	7.2	8.7	1.5
F	74	RA	LOW	3	1	1	2350	800	7.4	9.1	1.7
M	74	RARS	INT-1	3	1	1	2350	800	7.0	8.6	1.6
F	67	RA	LOW	4	3	1	2340	700	7.0	8.5	1.5
M	74	RA	LOW	3	1	0	2350	800	7.0	8.8	1.8

IPSS, International Prognostic Scoring System; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; INT-1, intermediate-1.

Interet du Deferasirox
Low dose dans les MDS?
S. Park, Grenoble





Meunier M et al, Oncotarget, 2017

Comment améliorer l'érythropoïèse dans l'EI?