SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

# *Terapie innovative e chelazione*

***Ferrara 12/11/2017***

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**DH per la Cura della Talassemia e Emoglobinopatie**

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**Azienda Ospedaliero-Universitaria**

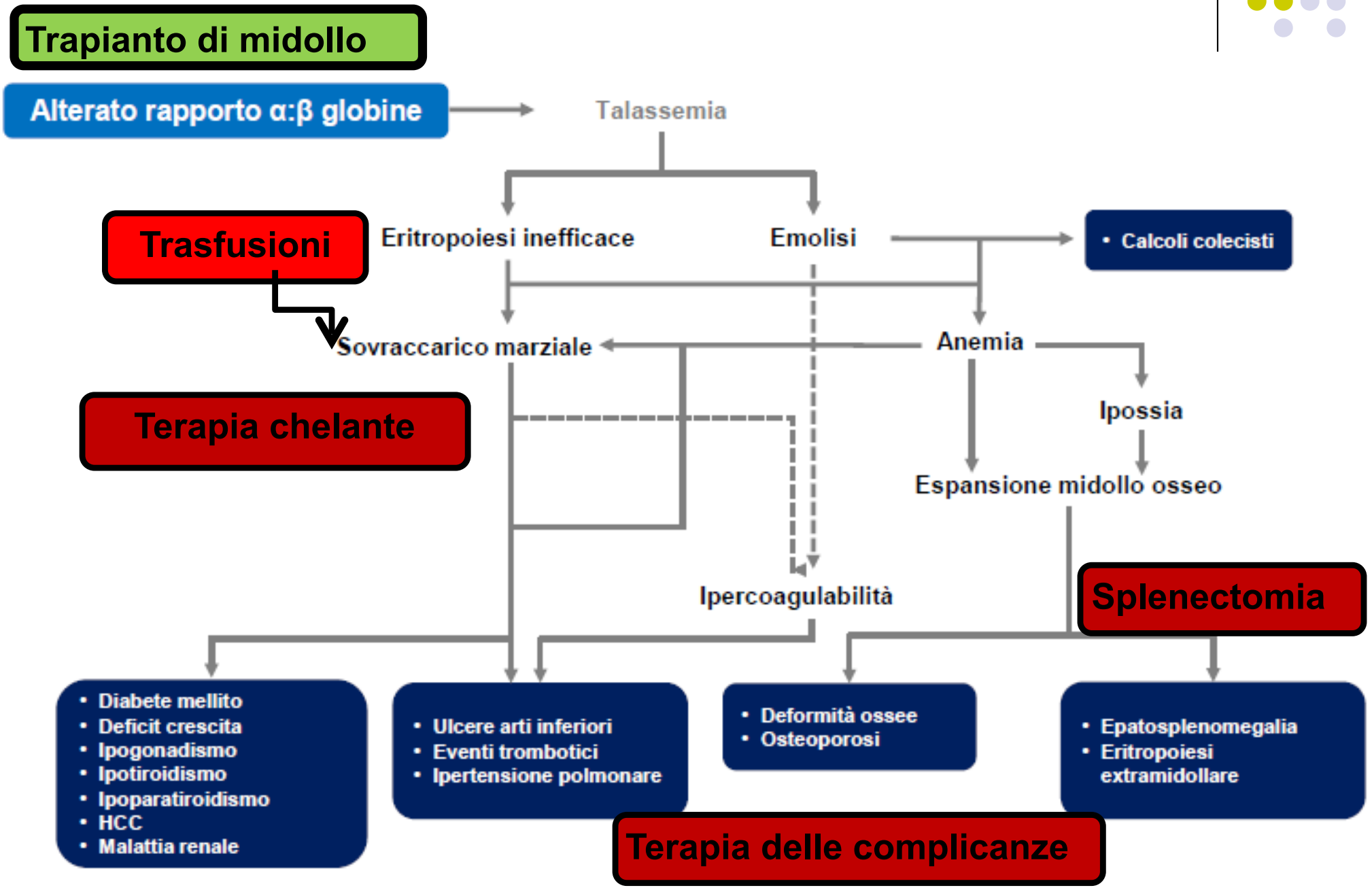
**FERARARA**

# Agenda

Terapie innovative: fase di sperimentazione clinica 1-2-3

- **Terapia chelante:**
  - **nuovi chelanti**
  - **modulatori del metabolismo del ferro:**
    - **amlopidina (calcio-antagonista)**
    - **miniepcidine**
    - **repressori della Matriptase-2**
- **Modulatori della eritropoiesi:**
  - **ACE-536**
  - **Jak-inibitori**
- Induttori Hb Fetale
- Terapia genica

# Terapia standard della talassemia



# Terapie innovative

**Induttori della HbFetale**

**Terapia genica**

**Alterato rapporto α:β globine** → Talassemia

**ACE, JAK2- inibitore**

Talassemia → Eritropoiesi inefficace

Talassemia → Emolisi → • Calcoli colecisti

**Nuovi chelanti**

Eritropoiesi inefficace → Sovraccarico marziale

Emolisi → Anemia → Ipossia → Espansione midollo osseo

**Modulatori del metabolismo ferro:**

- **Amlopidina (Ca+ antagonista)**
- **Miniepcidine**
- **Repressori Matriptase-2**

Emolisi → Ipercoagulabilità

Sovraccarico marziale →
- Diabete mellito
- Deficit crescita
- Ipogonadismo
- Ipotiroidismo
- Ipoparatiroidismo
- HCC
- Malattia renale

Ipercoagulabilità →
- Ulcere arti inferiori
- Eventi trombotici
- Ipertensione polmonare

Espansione midollo osseo →
- Deformità ossee
- Osteoporosi

Espansione midollo osseo →
- Epatosplenomegalia
- Eritropoiesi extramidollare

# Farmaci chelanti

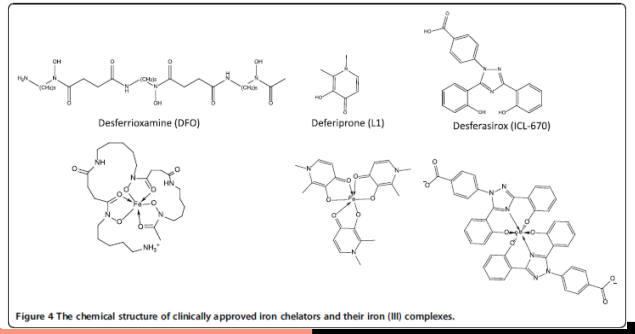


Figure 4 The chemical structure of clinically approved iron chelators and their iron (III) complexes.

| Active ingredient | DFO | DFP | DFX[a] | DFX[a] |
|---|---|---|---|---|
| Administration | Parenteral | Oral tablets or solution | Oral, tablets dispersible in liquid | Oral, film-coated tablets |
| Usual dose and frequency | 30–50 mg/kg/day over 8 h of infusion for 5 or 7 days/week | 75–100 mg/kg/day in three times divided doses daily | 10–40 mg/kg/day once daily | 7–28 mg/kg/day once daily |
| Excretion | Urinary, fecal | Mainly urinary | Fecal | Fecal |
| Adverse effects | Reactions at site of infusion | Gastrointestinal | Gastrointestinal disturbances | Rash |
| | Bone anomalies | Arthralgia | Rash | Increase in liver enzymes |
| | Auditory ophthalmologic | Increase in liver enzymes neutropenia/ agranulocytosis | Renal insufficiency | Renal insufficiency |
| | | | Increase in liver enzymes | |
| Advantages/ disadvantages | Long-standing experience/ parenteral | Robust evidence on improving cardiac siderosis/weekly monitoring of CBC | Once-daily dosing, oral / high cost | Once-daily dosing, oral / high cost |
| Licensed use | Treatment of chronic iron overload resulting from transfusion-dependent anemia | Treatment of iron overload in thalassemia major where DFO is contraindicated or inadequate | US: treatment of transfusional iron overload in patients 2 years or older. Europe: treatment of transfusional iron overload 6 years and older, and when DFO is contraindicated or inadequate, in patients 2–5 years | US: treatment of transfusional iron overload in patients 2 years or older. Europe: treatment of transfusional iron overload 6 years and older, and when DFO is contraindicated |

DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.
[a]Same active ingredient but with different peak serum concentration and bioavalability; CBC, complete blood count; TM, thalassemia major.

# Nuovi farmaci chelanti?

| drug | type | Route | Pre-clinical studies | Clinical stadies | Status |
|---|---|---|---|---|---|
| HBDE<br>90’ yrs | Hexadentate<br>MW: 388Da | SC- EV | Yes | Phase 1 | Not been further developed for clinical use |
| Starch-DFO<br>1989-2007 | Hexadentate<br>MW:260 000 Da | EV<br>weekly | yes | Phase 1-2 | Not been further developed for clinical use |
| Deferitrin<br>2003-2007 | Tridentate | Orally | yes | Phase 1<br>Phase 2 | unacceptable renal toxicity |
| FBS0701<br>(Ferrokin)<br>2007-2015 | Tridentate<br>MW: 400 Da | Orally | yes | Phase 1<br>Phase 2 | withdrawn until the evaluation of the nonclinical rat findings is complete |
| SP-420<br>2007-2015 | Tridentate | Orally | yes | Phase 1 | renal toxicity when the dose was escalated. |
| CM1<br>2012 | Bidentate<br>MW : 256 Da | Orally | Yes | / | • able to chelate iron effectively<br>• no toxicity to peripheral blood and liver cells of the mice under normal and iron overload conditions.<br>• can be transferred to the clinical phase studies |

Am J Hematol. 2017 Sep 22. doi: 10.1002/ajh.24914.

# Safety and Pharmacokinetics of the Oral Iron Chelator SP-420 in β-thalassemia.

Taher AT[1], Saliba AN[2], Kuo KH[3], Giardina PJ[4], Cohen AR[5], Neufeld EJ[6], Aydinok Y[7], Kwiatkowski JL[5], Jeglinski BI[8], Pietropaolo K[8], Berk G[8], Viprakasit V[9].

## Abstract

Our Phase I, open-label, multi-center, dose-escalation study evaluated the pharmacokinetics (PK) of SP-420, a tridentate oral iron chelating agent of the desferrithiocin class, in patients with transfusion dependent β-thalassemia. SP-420 was administered as a single dose of 1.5 (n=3), 3 (n=3), 6 (n=3), 12 (n=3), and 24 (n=6) mg/kg or as a twice-daily dose of 9 mg/kg (n=6) over 14-28 days. There was a near dose-linear increase in the mean plasma SP-420 concentrations and in the mean values for $C_{max}$ and $AUC_{0-\tau}$ over the dose range evaluated. The median $t_{max}$ ranged from 0.5 - 2.25 h and was not dose-dependent.

**The study was prematurely terminated by the sponsor due to renal adverse events including proteinuria, increase in serum creatinine, and one case of Fanconi syndrome**. Other adverse effects included hypersensitivity reactions and gastrointestinal disturbances. Based on current dose administration, the renal adverse events observed outweighed the possible benefits from chelation therapy. However, **additional studies assessing efficacy and safety of lower doses or less frequent dosing of SP-420 over longer durations with close monitoring would be necessary to better explain the findings of our study and characterize the safety of the study drug**.

# Nuova tipologia di farmaci per controllare l'accumulo di ferro : calcio-antagonisti

EUROPEAN JOURNAL OF Haematology

European Journal of Haematology 88 (535–548)

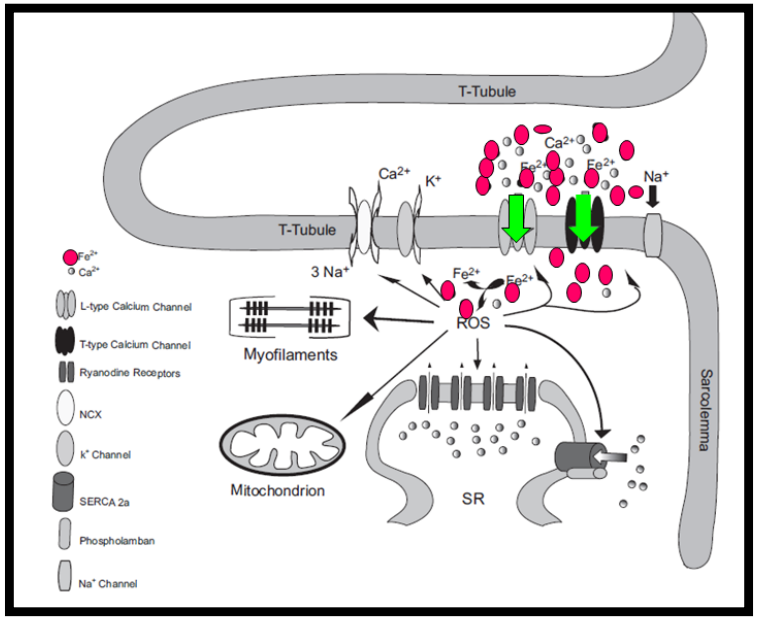
ORIGINAL ARTICLE

**T-type calcium channel blockade improves survival and cardiovascular function in thalassemic mice**

Sirinart Kumfu[1], Siriporn Chattipakorn[1,2], Kroekkiat Chinda[1], Suthat Fucharoen[3], Nipon Chattipakorn[1,4]

- iron-overloaded thalassemic murine model
- efonidine: specific blocker of TTCC

- lowered mortality
- prevented myocardial iron deposition and oxidative stress, and resulted in improved cardiac function.




## Calcium channel blockers in patients with iron-overload conditions:

- a novel therapeutic tool to prevent and treat iron-overload cardiomyopathy
- it should be studied in randomized clinical trials.

G.Y. Oudit, 2012

Am J Med. 2013 Sep;126(9):834-7 **ClinicalTrials.gov Identifier:**NCT01395199

# Amlodipine reduces cardiac iron overload in patients with thalassemia major: a pilot trial.

Fernandes JL[1], Sampaio EF, Fertrin K, Coelho OR, Loggetto S, Piga A, Verissimo M, Saad ST.

- **15 pts** with TM undergoing chelation therapy, age > 6yrs
- randomized to receive amlodipine (5 mg/day) or placebo in a 1:2 allocation for 12 months

| cardiac T2* | Baseline | 6 m | 12 m | P (b vs 12m) |
|---|---|---|---|---|
| Amlodipine group | 21.7 ± 7.2 ms | 28.2 ± 7.9 ms | 28.3 ± 8.0 ms | 0.03 |
| Control group | 25.1 ± 8.8 ms | 24.7 ± 7.8 | 26.2 ± 11.4 ms | ns |

# A randomized trial of amlodipine in addition to standard chelation therapy in patients with thalassemia major

Juliano L. Fernandes,[1] Sandra R. Loggetto,[2] Monica P. A. Veríssimo,[3] Kleber Y. Fertrin,[4] Giorgio R. Baldanzi,[5] Luciana A. B. Fioravante,[1] Doralice M. Tan,[6] Tatiana Higa,[7] Denise A. Mashima,[8] Antonio Piga,[9] Otavio R. Coelho,[4] Fernando F. Costa,[4] and Sara T. Saad[4]

[1]Jose Michel Kalaf Research Institute, Campinas, Brazil; [2]Centro de Hematologia de São Paulo, São Paulo, Brazil; [3]Centro Infantil de Investigações Hematológicas Dr Domingos A Boldrini, Campinas, Brazil; [4]University of Campinas, Campinas, Brazil; [5]Centro de Hematologia e Hemoterapia do Paraná, Curitiba, Brazil; [6]Marilia Medical School, Marilia, Brazil; [7]Maringa State University, Maringa, Brazil; [8]Londrina State University, Londrina, Brazil; and [9]University of Torino, Turin, Italy

- multicenter,
- randomized,
- placebo-controlled,
- double-blind trial, allocation rate of 1:1.
- **Amlodipine: 5 mg/day for bw> 30 kg**
  **2.5 mg/day for bw< 30 kg**

Procedures:

- MR : T2*C e LIC: 0,6,12 m
- Serum ferritin: 0,6,12 m
- FE Vs: 0,6,12 m
- adverse events: 6, 12 m.

Inclusion criteria

- TM
- Age: 6 years or older
- Receiving regular blood for at least 2 years (total lifetime red blood cell transfusions above 20 units).
- no advanced clinical heart failure or FE< 35%;

Primary Endenpoint

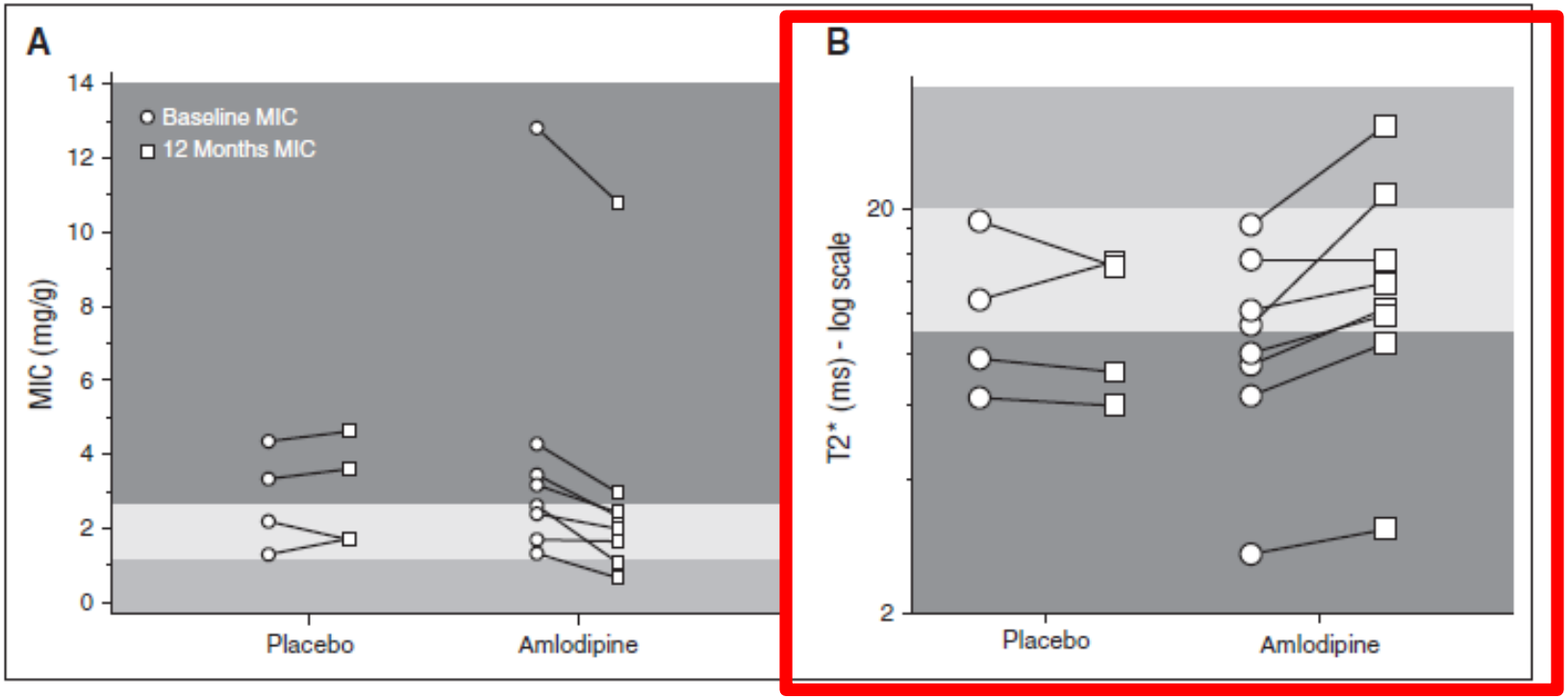
- the change in cardiac iron at 12 months from baseline in both arms (placebo and amlodipine) as defined by T2* values

# Baseline characteristics of patients (59 pts)

| Characteristic | Amlodipine (n = 30) | Placebo (n = 29) | All patients (n = 59) |
|---|---|---|---|
| **Sex, n (%)** | | | |
| Female | 17 (57) | 12 (41) | 29 (49) |
| Age, y (range) | 23.3 ± 7.7 (12-38) | 23.5 ± 10.2 (8-49) | 23.4 ± 9.0 (8-49) |
| Weight, kg | 55.8 ± 11.4 | 55.9 ± 17.5 | 55.8 ± 14.6 |
| Body mass index, kg/m$^2$ | 22.1 ± 3.3 | 22.3 ± 4.1 | 22.2 ± 3.7 |
| Hepatitis C, n (%) | 9 (30) | 6 (21) | 15 (25) |
| Splenectomy, n (%) | 5 (17) | 2 (7) | 7 (12) |
| Pretransfusional hemoglobin, g/dL | 9.4 ± 1.0 | 9.5 ± 1.0 | 9.5 ± 1.0 |
| Time since start of chelation therapy, y | 19.7 ± 6.7 | 20.3 ± 9.5 | 20.0 ± 8.1 |
| **Chelation therapy at baseline, n (%)** | | | |
| DFO | 3 (10) | 4 (14) | 7 (12) |
| DFP | 5 (16) | 6 (21) | 11 (19) |
| DFX | 17 (57) | 13 (45) | 30 (51) |
| DFO + DFP | 5 (16) | 5 (17) | 10 (16) |
| DFO + DFX | 0 | 1 (3) | 1 (2) |
| Serum ferritin, ng/mL (median [range]) | 2638 (478-7282) | 1922 (386-13 113) | 2024 (386-13 113) |
| Myocardial T2*, ms (median [range]) | 34.1 (2.8-43.8) | 34.1 (6.8-42.7) | 34.1 (2.8-43.8) |
| Myocardial iron concentration, mg/g dry weight (median [range]) | 0.61 (0.45-12.81) | 0.61 (0.46-4.34) | 0.61 (0.45-12.81) |
| Left ventricular ejection fraction, % | 67.7 ± 5.5 | 67.1 ± 6.6 | 67.4 ± 6.0 |
| **Myocardial T2* categories, n (%)** | | | |
| <10 ms | 4 (13) | 2 (7) | 6 (10) |
| 10 to ≤20 ms | 4 (13) | 2 (7) | 6 (10) |
| 20 to <35 ms | 7 (23) | 11 (38) | 18 (31) |
| ≥35 ms | 15 (50) | 14 (48) | 29 (49) |
| LIC, mg/g, median (range) | 11.3 (1.9-40.0) | 9.2 (1.5-33.3) | 9.6 (1.5-40.0) |
| **LIC categories, n (%)** | | | |
| <7 mg/g | 10 (33) | 12 (42) | 22 (37) |
| 7 to ≤15 mg/g | 8 (27) | 9 (31) | 17 (29) |
| >15 mg/g | 12 (40) | 8 (28) | 20 (34) |

Values expressed as mean ± standard deviation, unless otherwise specified.
DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

Baseline and 12-month MIC and myocardial T2* in the placebo (n= 4) and amlodipine arm (n =8) in patients with a baseline T2* <20 ms (MIC > 1.16mg/g).




- **<u>in the placebo group:</u>**
  - no patient shifted from their original risk assessment
  - no significant changes in MIC were observed (2.8 mg/g [9(2.8 mg/g [95% CI,1.7-3.8] vs 2.7 [95% CI, 1.7-4.1], P = .88).

- **<u>In the amlodipine group:</u>**
  - 4 / 8 patients changed from severe to moderate risk or from moderate to low risk.
  - All cases had reduced their baseline MIC values with a significant change at 12 months (2.9 mg/g [95% CI, 1.6-5.9] vs 2.1 [95% CI, 1.0-4.5], P = .008)

# Adverse events

**Table S3 – Adverse Events**

| Adverse Event | Amlodipine (n=30) | Placebo (n=29) | p |
|---|---|---|---|
| Any | 4 (13) | 0 (0) | 0.11 |
| Ankle edema | 2 (7) | 0 (0) | 0.49 |
| Dizziness | 1 (3) | 0 (0) | 1.0 |
| Mild cutaneous allergy | 1 (3) | 0 (0) | 1.0 |

Numbers represent n (%); Adverse events were reported according to International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice.[6]

reduction of the dose :

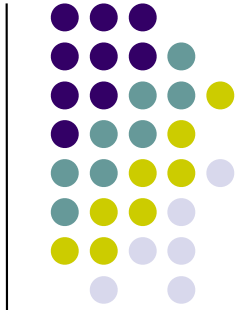
- 3 patients (10%) in the amlodipine arm had their initial dose of 5 mg/day reduced to 2.5 mg/day because of mild ankle edema (2 patients) and dizziness (1 patient).All events subsided with dose reduction.

interruption of the medication:

- 1 patient developed a mild cutaneous allergic reaction and stopped the medication after 15 days of use while continuing in the study.

No significant cases of hypotension or bradycardia occurred in either of the groups during follow-up.

# Conclusions



- Amlodipine combined with iron chelation resulted in more effective reduction of cardiac iron.
- Because this conclusion is based on subgroup analyses, **it needs to be confirmed in ad hoc clinical trials**.
- Future studies may also help investigate whether amlodipine can prevent iron overload or help iron removal **in endocrine organs** that also absorb iron through voltage-gated channels, particularly considering the close association of cardiac siderosis with endocrine complications and the correlation of pancreas and MICs

| ClinicalTrials.gov Identifier: | N CT01395199 | NCT02065492 | NNCT02474420 |
|---|---|---|---|
| site | University of Campinas, Brazil | Aga Khan University Pakistan | University Health Network, Toronto Canada |
| | Phase 3, randomized, blinded | Phase 2-3 randomized | Randomized |
| Drug | Amlodipine 5mg/die *VS* placebo<br><br>1 yr | Amlodipine 0.1 mg/kg/ day or maximum of 2.5 mg/day. *VS* no therapy<br>1 yr | Amlodipine 2.5mg/day up to 10 mg/day *VS* no therapy<br><br>1 yr |
| Patients | 62 TM<br>> 6 yrs | 20 TM<br>6 - 20 Years | 60 TM<br>>18 Years<br>Cardiac T2*10-20ms<br>DFX |
| Outcomes ( 6-12 m) | Cardiac T2* (MRI )<br>Liver T2* (MRI )<br>Serum ferritin<br>Left ventricular volume and function | Cardiac T2* (MRI )<br>Liver T2* (MRI )<br>Serum ferritin<br>Cardiac function | Cardiac T2* (MRI )<br>Cardiac function |
| status | completed<br>September 2015 | Completed<br>June 2017 | Recruiting<br>Completion Date :June 2018 |
| | Blood. 2016;128(12): 1555-1561 | No results | |

# Nuova tipologia di farmaci per controllare il sovraccarico di ferro : modulatori della epcidina

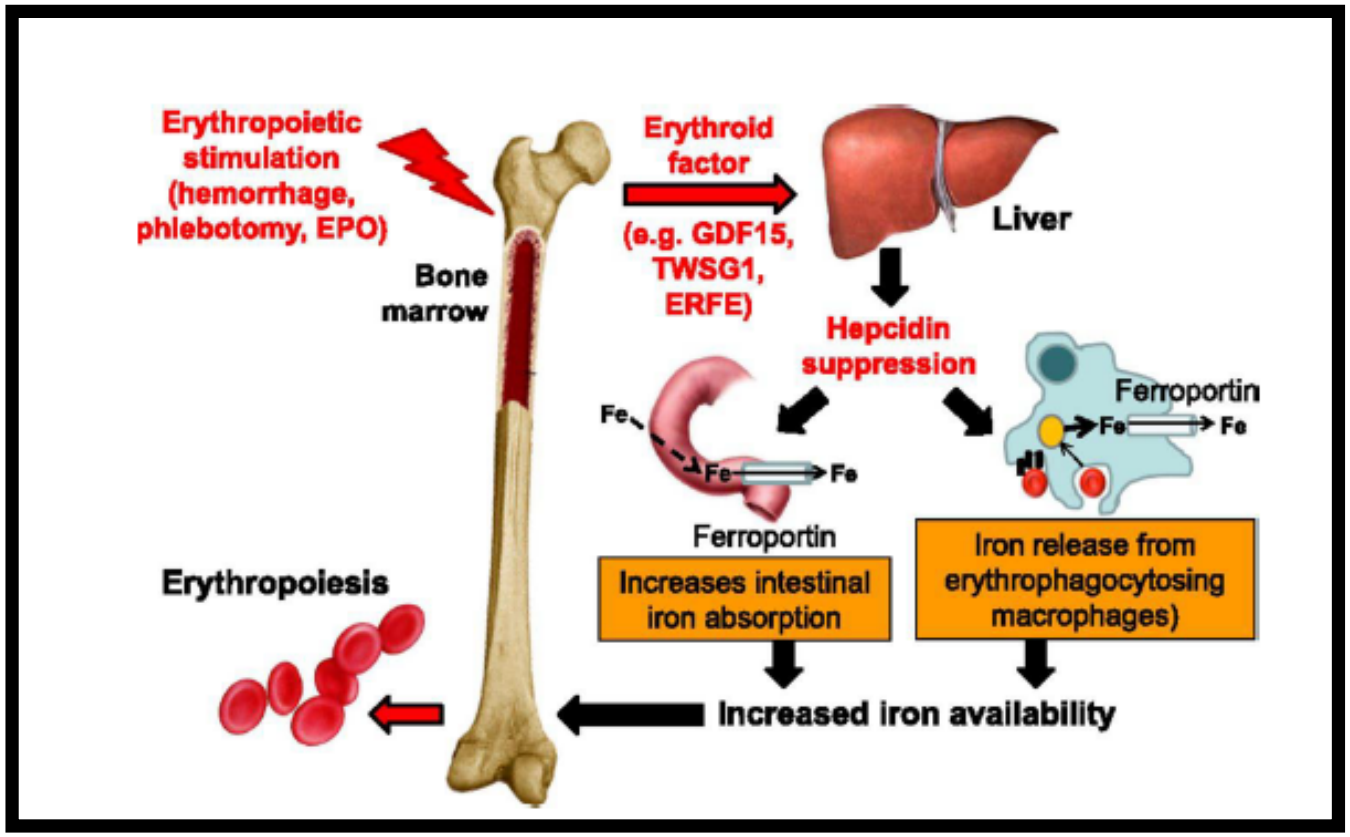
- **miniepcidine**
- **repressori della matriptasi-2 (TMPRSS6)**

# Agenda

Terapie innovative: fase di sperimentazione clinica 1-2-3

- **Terapia chelante:**
  - **nuovi chelanti**
  - **modulatori del metabolismo del ferro:**
    - **amlopidina (calcio-antagonista)**
    - **miniepcidine**
    - **repressori della Matriptase-2**
- **Modulatori della eritropoiesi:**
  - **ACE-536**
  - **Jak-inibitori**
- Induttori Hb Fetale
- Terapia genica

# Metabolismo del ferro ed epcidina




Epcidina

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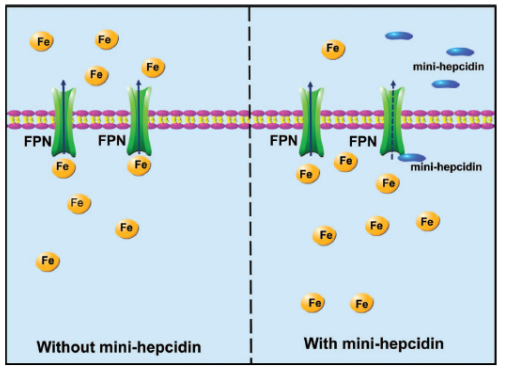
Ferroportina

**Bassi livelli di epcidina nella beta Talassemia Intermedia e Major**


Papanikolaou, et al, Hepcidin in iron overload disorders, **Blood. 2005;105:4103-4105)**
Pasricha et al. Transfusion suppresses erythropoiesis and increases hepcidin in adult patients with β-thalassemia major: a longitudinal study. Blood. 2013;122:124–33.

# Miniepcidine



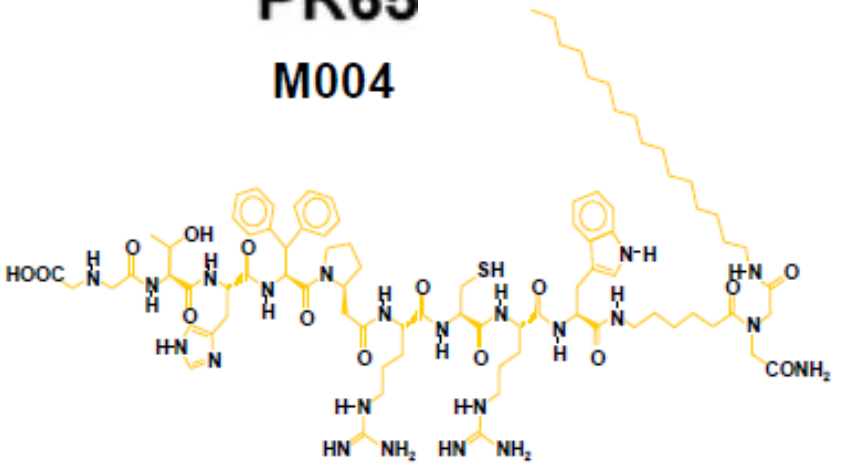

- Miniepcidine sono piccoli peptidi che mimano l'attività di epcidina
- Derivate dalla sequenza AA terminale e modificate per l'attività in vivo
- Miniepcidini riducono il sovraccarico marziale in modelli animali di emocromatosi HFE e HAMP correlata

**Minihepcidins are rationally designed small peptides that mimic hepcidin activity in mice and may be useful for the treatment of iron overload**
Preza GC, Ruchala P, Pinon R, Ramos E, Qiao B, Peralta MA, Sharma S, Waring A, Ganz T, Nemeth E.
*Journal of Clinical Investigation* 2011;121:4880-8.

**Minihepcidins prevent iron overload in a hepcidin-deficient mouse model of severe hemochromatosis**
Ramos E, Ruchala P, Goodnough JB, Kautz L, Preza GC, Nemeth E, Ganz T.
*Blood* 2012;120:3829-36.

**PR65**

**M004**

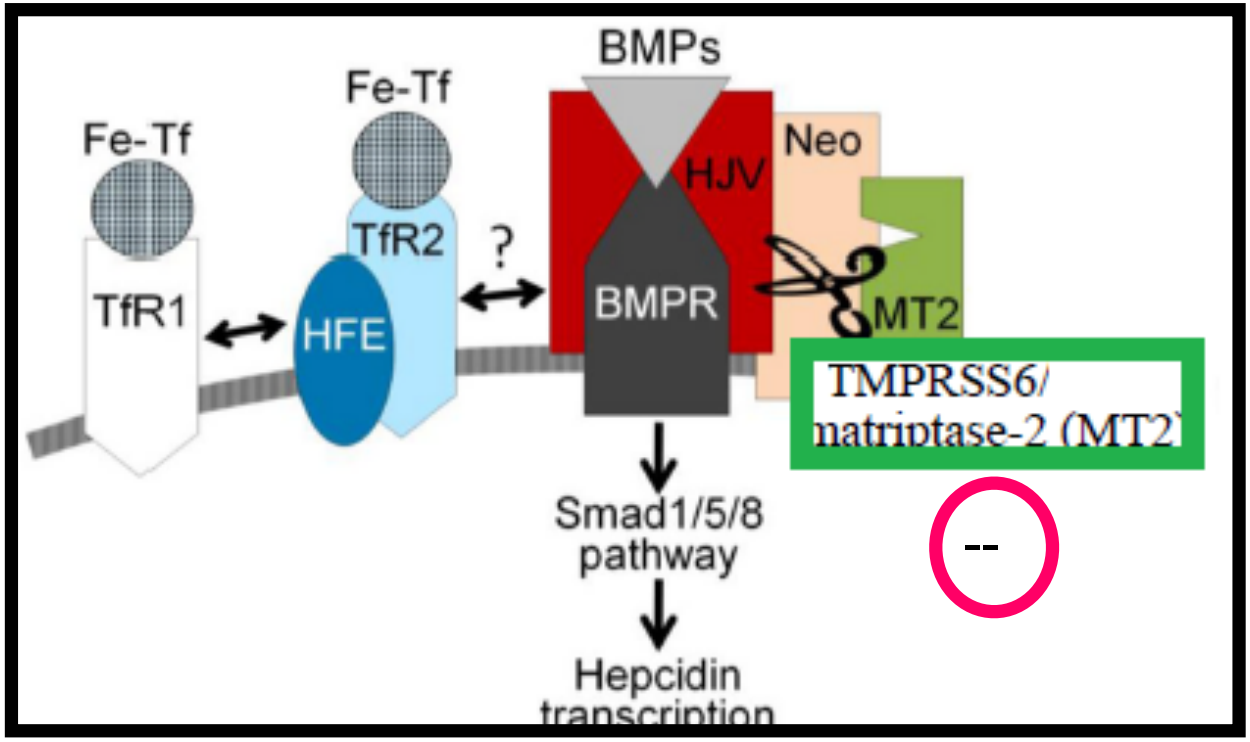


# Minihepcidins
# drug under commercial development

| Name | Company | Type | Mechanism | Indication | Development status | Trial identifiers[d] |
|---|---|---|---|---|---|---|
| M012 | Merganser Biotech Australia Pty Ltd. | Peptide | Hepcidin mimetic peptide that functions as a hepcidin agonist | β-thalassemia, low risk myelodysplastic syndrome, polycythaemia vera | Phase 1 | ACTRN12616000093482 |
| LJPC-401 | La Jolla Pharmaceutical Company | Peptide | Hepcidin mimetic peptide that functions as a hepcidin agonist | Iron overload | Phase 1 | ACTRN12616000132448 |
| PTG-300 | Protagonist Therapeutics | Peptide | Hepcidin mimetic peptide that functions as a hepcidin agonist | Iron overload | preclinical | n.a. |

(http://apps.who.int/trialsearch/Default.aspx)

## Matriptase -2 (TMPRSS6) Antagonist



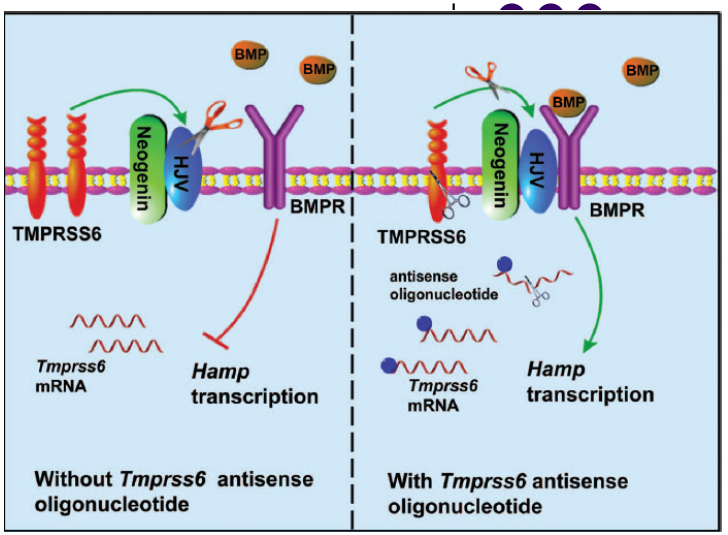

Regulation of hepcidin transcription by extracellular iron

TMPRSS6 is a transmembrane serine protease mainly produced by hepatocytes that negatively regulates hepcidin expression

TMPRSS6 inhibition to induce hepcidin transcription and syntesis

Nai A et al. Deletion of TMPRSS6 attenuates the phenotype in a mouse model of beta-thalassemia. Blood. 2012;119:5021–5029.

# TMPRSS6 Antagonist in animal model




## Molecules against Tmprss6 mRNA:

- **antisense oligonucleotides (ASO)**
- **small interfering RNA (siRNA)**

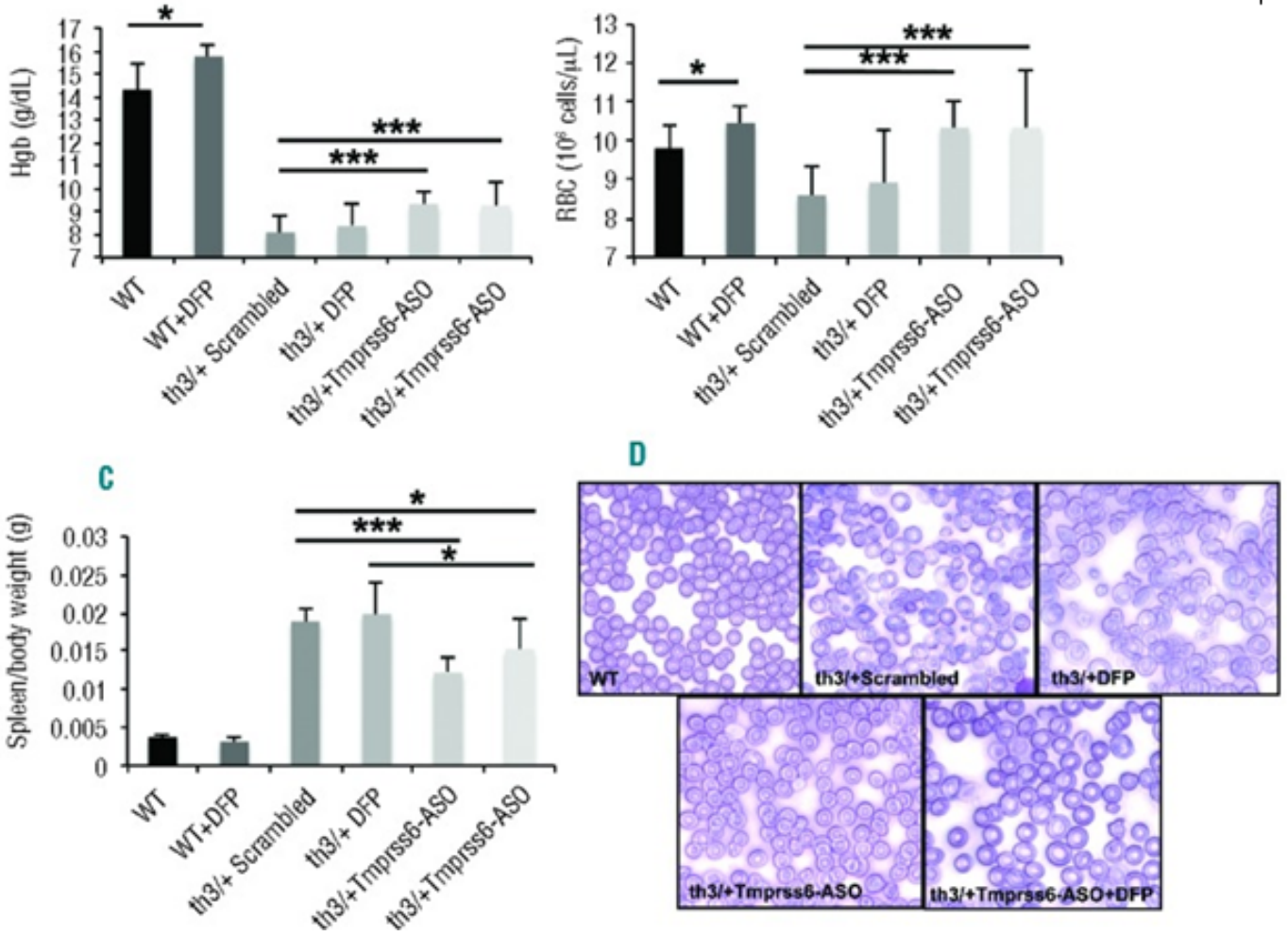

- Guo S, et al. Reducing TMPRSS6 ameliorates hemochromatosis and beta-thalassemia in mice. J Cli Invest. 2013;123:1531–1541.
- Schmidt PJ et al. An RNAi therapeutic targeting Tmprss6 decreases iron overload in Hfe(-/-) mice and ameliorates anemia and iron overload in murine betathalassemia intermedia. Blood. 2013;121:1200–1208.
- Schmidt PJ, et al. Combination therapy with a Tmprss6 RNAi-therapeutic and the oral iron chelator deferiprone additively diminishes secondary iron overload in a mouse model of beta-thalassemia intermedia. Am J Hematol. 2015;90:310–313.

**Combination of *Tmprss6*-ASO and the iron chelator deferiprone improves erythropoiesis and reduces iron overload in a mouse model of beta-thalassemia intermedia**

Casu et al.

haematologica 2016; 101:e9

Miglioramento dei livelli di Hb, e dl numero di GR circolanti , riduzione della splenomegalia, miglioramento della morfologia dei GR



# Matriptase-2 (TMPRSS6) agonist

## under commercial development

| Name | Company | Type | Mechanism | Indication | Development status | Trial identifiers[a] |
|---|---|---|---|---|---|---|
| IONIS-TMPRSS6-LRx | Ionis Pharmaceuticals | Antisense DNA oligo-nucleotide | Inhibition of MT-2 expression to promote hepcidin transcription | β-thalassemia | Phase 1 | NCT03165864 |
| ALN-TMP | Alnylam | siRNA | Inhibition of MT-2 expression to promote hepcidin transcription | β-thalassemia, iron overload | Preclinical | n.a. |

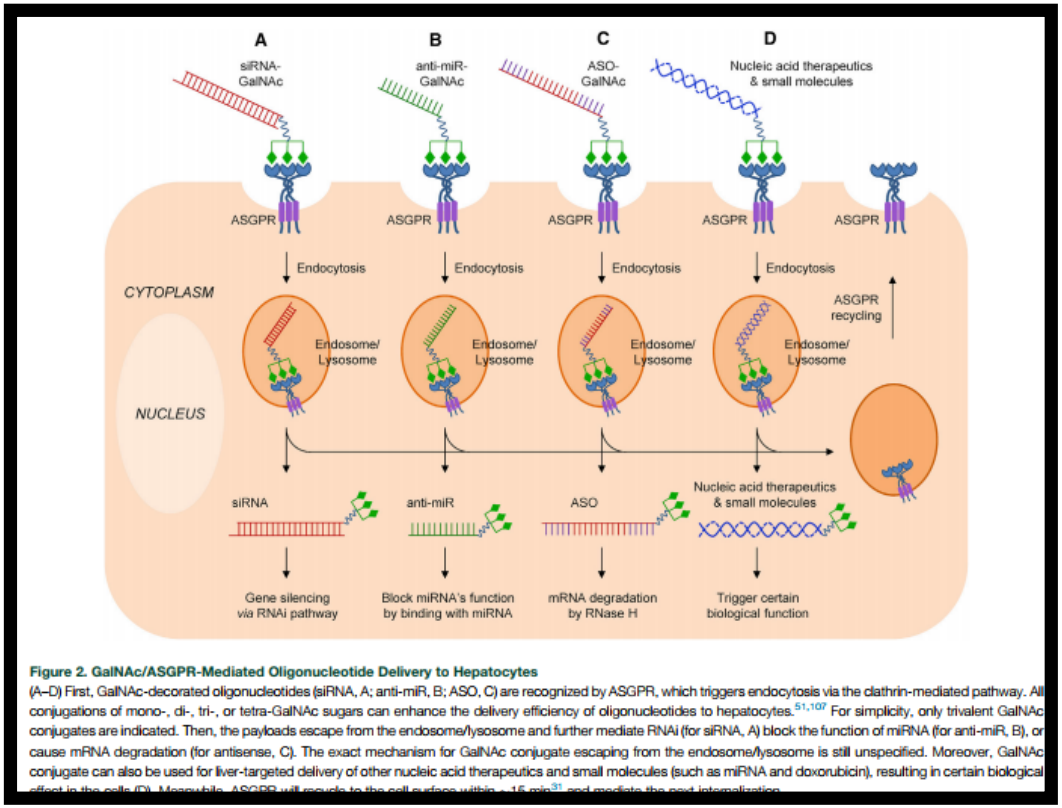


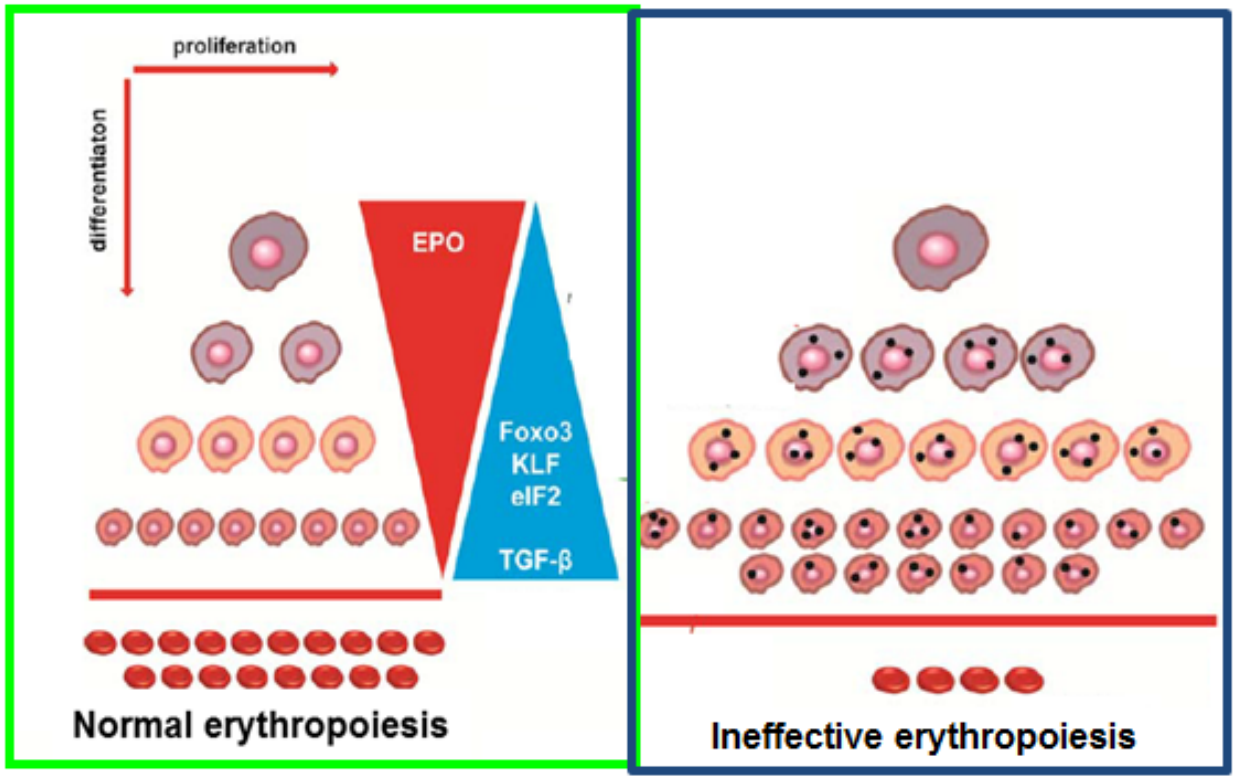

**Figure 2. GalNAc/ASGPR-Mediated Oligonucleotide Delivery to Hepatocytes**

(A–D) First, GalNAc-decorated oligonucleotides (siRNA, A; anti-miR, B; ASO, C) are recognized by ASGPR, which triggers endocytosis via the clathrin-mediated pathway. All conjugations of mono-, di-, tri-, or tetra-GalNAc sugars can enhance the delivery efficiency of oligonucleotides to hepatocytes.[51,107] For simplicity, only trivalent GalNAc conjugates are indicated. Then, the payloads escape from the endosome/lysosome and further mediate RNAi (for siRNA, A) block the function of miRNA (for anti-miR, B), or cause mRNA degradation (for antisense, C). The exact mechanism for GalNAc conjugate escaping from the endosome/lysosome is still unspecified. Moreover, GalNAc conjugate can also be used for liver-targeted delivery of other nucleic acid therapeutics and small molecules (such as miRNA and doxorubicin), resulting in certain biological

# Conclusioni (1)

- Farmaci chelanti:
  - Nuova formulazione deferasirox
  - Nuove  molecole: ?
- Calcio antagonisti: Amlopidina :
  - Ulteriori studi (siderosi cardiaca; e pancreatica?)
  - Da considerare nella pratica clinica per pazienti con accumulo cardiaco  e scarsa risposta alle terapie chelanti standard
- Per il futuro:
  - miniepecidine
  - antagonisti matriptasi-2

# Normal and Ineffective Erythropoiesis in thalassemia



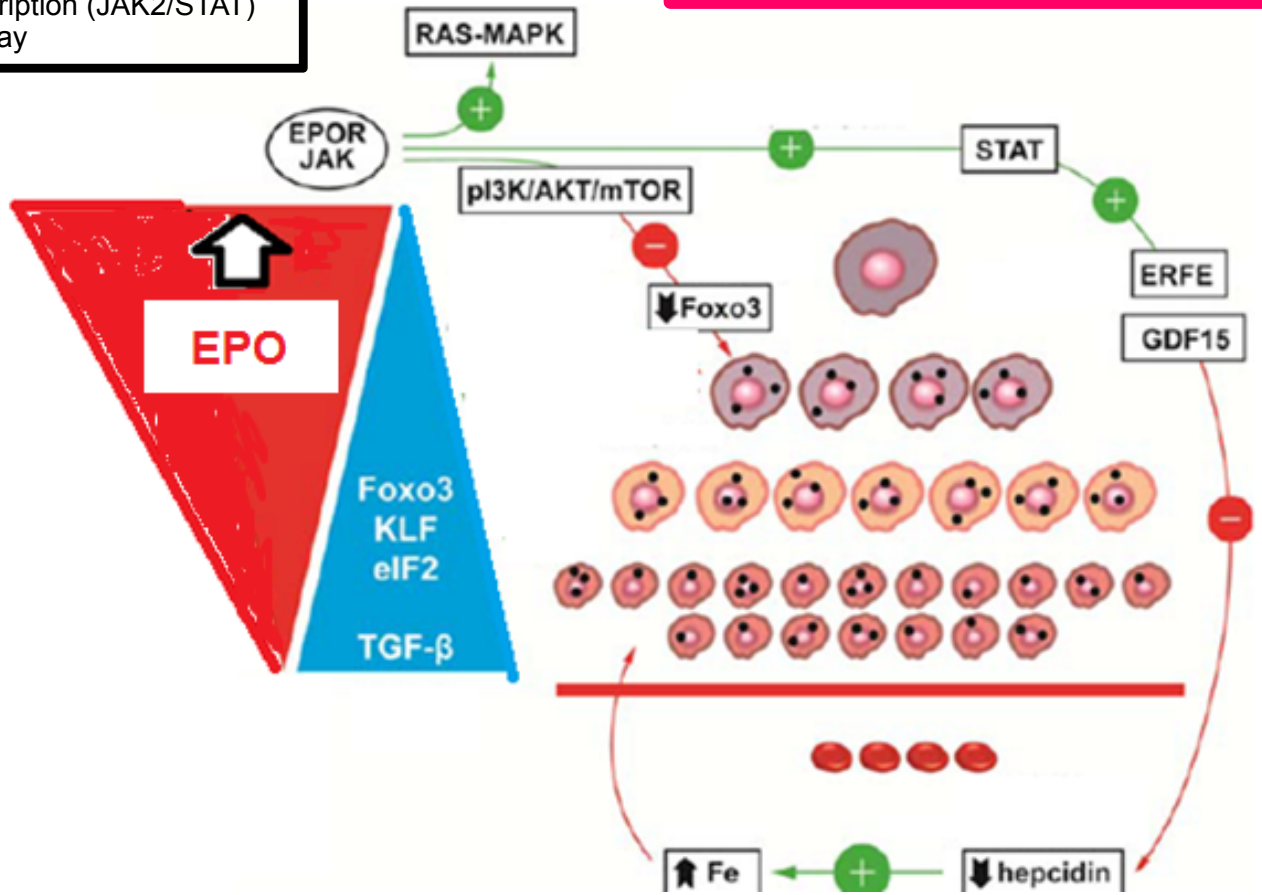

- expansion of very early erythroid precursors

- accelerated erythroid differentiation,
- maturation blockade at the polychromatophilic stage,
- death of erythroid precursors

initiation of RAS-MAPK (rat sarcoma/mitogen-activated protein kinases) which have an impact cell proliferationand differentiation

Janus kinase 2/signal transducer and activator of transcription (JAK2/STAT) pathway

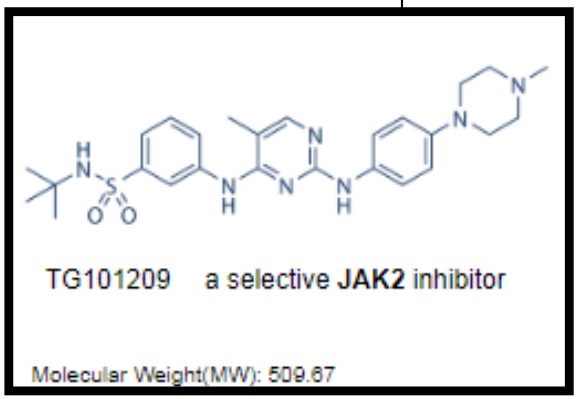
The pI3K/AKT/mTOR pathway inactivates the antioxidant factor Foxo3 contributing to oxidative damage in late erythroblasts.




expansion of early erythroid precursors and erythroid progenitors which produce factors such as growth and differentiating factor 15 (GDF15) and erythroferrone (ERFE).
These factors inhibit the production of hepcidin, the major regulator of iron hemostasis, and increase the intestinal absorption and macrophage release of iron contributing to tissue iron overload.

# JAK2 inhibitor in thalassemia

- **TG101209 :**
  - mice models with β-TI (th3/1)
  - short-term administration
  - reduced ineffective erythropoiesis and splenomegaly

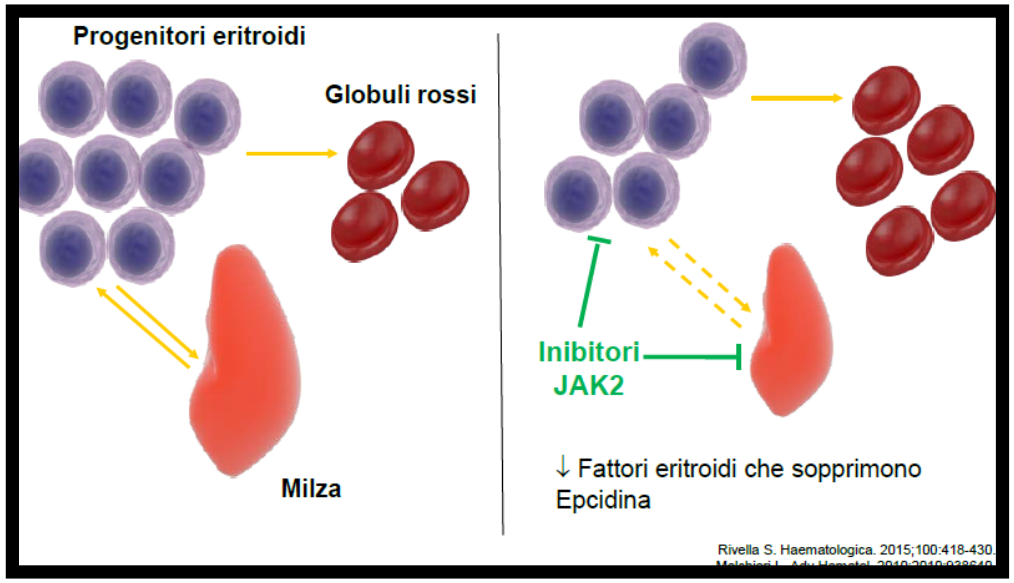



BLOOD, 1 AUGUST 2008, VOLUME 112, NUMBER 3

Decreased differentiation of erythroid cells exacerbates ineffective erythropoiesis in β-thalassemia

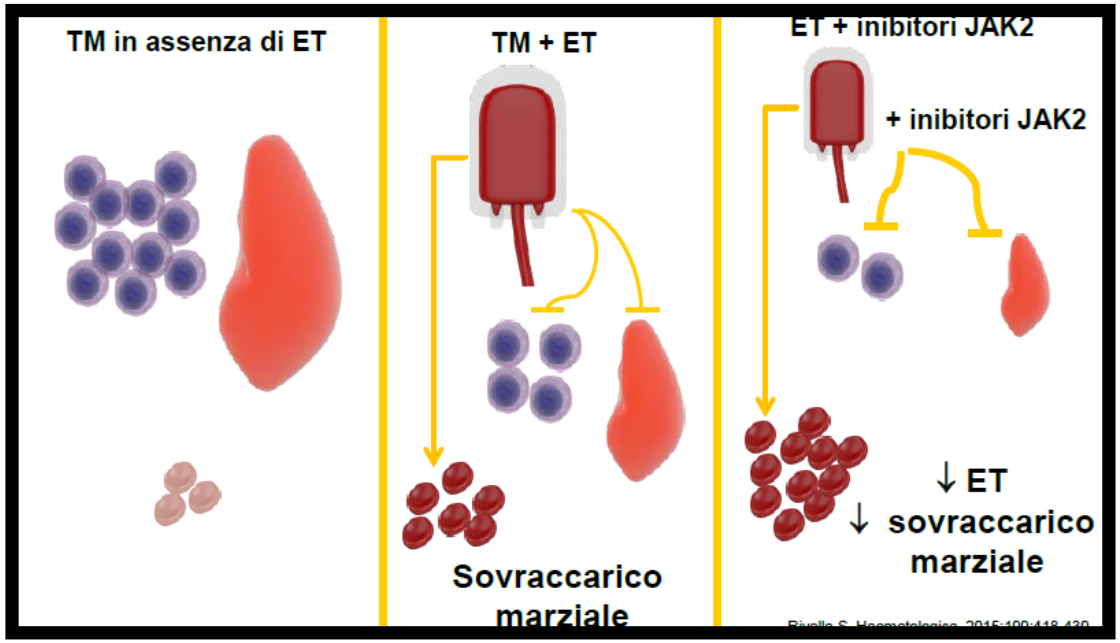
*Ilaria V. Libani,[1,2] *Ella C. Guy,[1] *Luca Melchiori,[1] *Raffaella Schiro,[1] Pedro Ramos,[1,3] Laura Breda,[1] Thomas Scholzen,[4] Amy Chadburn,[5] YiFang Liu,[5] Margrit Kernbach,[4] Bettina Baron-Lühr,[4] Matteo Porotto,[6] Maria de Sousa,[3] Eliezer A. Rachmilewitz,[7] John D. Hood,[8] M. Domenica Cappellini,[2] Patricia J. Giardina,[1] Robert W. Grady,[1] Johannes Gerdes,[4] and Stefano Rivella[1]

[1]Department of Pediatric Hematology-Oncology, Children's Cancer and Blood Foundation Laboratories, Weill Medical College of Cornell University, New York, NY; [2]Centro Anemie Congenite, Fondazione Policlinico, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS), University of Milan, Milan, Italy; [3]Iron Genes and Immune System (IRIS Lab), Instituto de Biologia Molecular e Celular (IBMC), Oporto University, Oporto, Portugal; [4]Research Center Borstel, Department of Immunology and Cell Biology, Division of Tumour Biology, Borstel, Germany; Departments of [5]Pathology and Laboratory of Medicine and [6]Pediatrics and Microbiology and Immunology, Weill Medical College of Cornell University, New York, NY; [7]E. Wolfson Medical Centre, Institute of Hematology, Holon, Israel; and [8]TargeGen, San Diego, CA




**Talassemia non Trasfusione Dipendente**

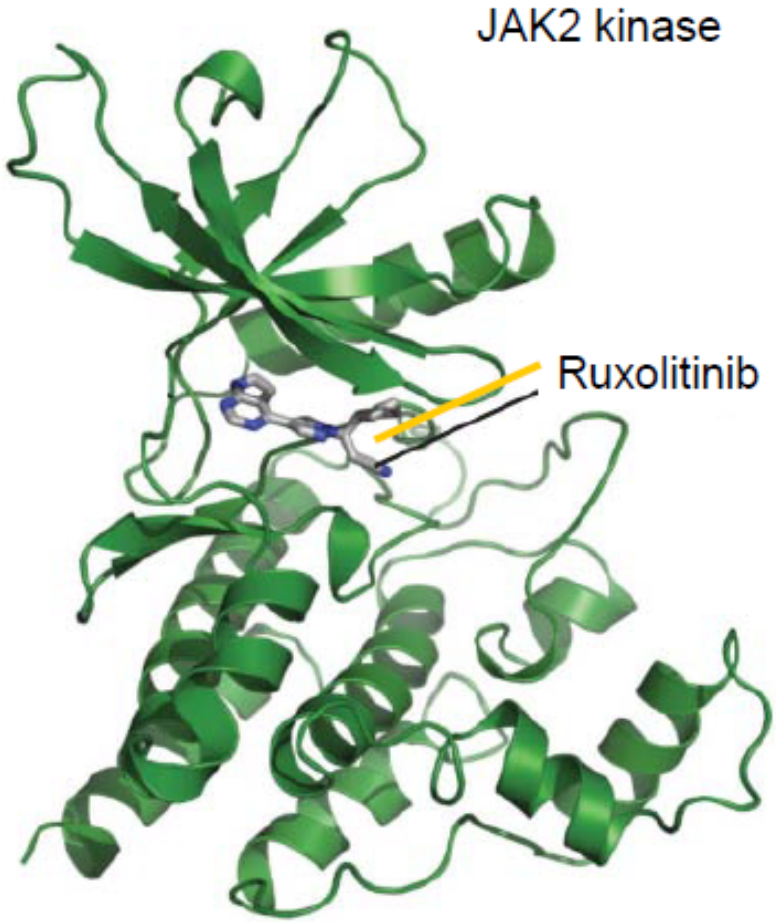
## Potenziali effetti degli inibitori di JAK2




**Talassemia Trasfusione Dipendente**

# Ruxolitinib: potente inibitore orale di JAK2

- Ruxolitinib è approvato per
  - mielofibrosi
  - pz affetti da PV resistenti o che non tollerano HU
- Ruxolitinib è associato a un significativo miglioramento della splenomegalia e dei sintomi




FDA, Food and Drug Administration.

Zhou T, et al. Leukemia. 2014;28:404-7.

28 gg

30 settimane

**30 pz adulti regolarmente trasfusi affetti da talassemia + splenomegalia**

**Screening**

(ET nelle 24 settimane prima dello screening)

**Ruxolitinib**
**Dose iniziale: 10 mg x 2 volte/dì**
**Aggiustamento dose: da 5 a 25 mg x 2 volte/dì**

- Primary end-point
  - Variazione percentuale di supporto trasfusionale tra la settimana 6 e 30 rispetto al baseline
- Secondary end-points
  - Variazione del volume della milza rispetto al baseline misurato con RMN o TC
  - Variazione dei valori di Hb pre-trasfusionali rispetto al baseline a ogni visita post baseline
  - Farmacocinetica (PK)
  - Safety

**Inclusion Criteria**:
- Terapia trasfusionale regolare.
- Splenomegalia : milza palpabile di volume ≥ 450 cm3 by MRI (or CT scan)
- Terapia chelante in atto (deferoxamine or deferasirox)

**Exclusion Criteria:**
- Gravi Infezioni in atto
- Hb <6,5 g/dl
- PLTS <75.000×ml, GN < 1.500ml.
- MDRD < 30 mL/min/1.73 m2 ,ALT (SGPT) levels >5 times ULN
- Epatopatia ( epatite B , C, cirrosi)
- HIV positivitità

# Efficacy and Safety of Ruxolitinib in Regularly Transfused Patients with Thalassemia: Results from Single-Arm, Multicenter, Phase 2a Truth Study

Yesim Aydinok, Zeynep Karakas, Elena Cassinerio, Noppadol Siritanaratkul, Antonis Kattamis, Aurelio Maggio, Norbert Hollaender, Bruyère Mahuzier, Brian Gadbaw and Ali T. Taher

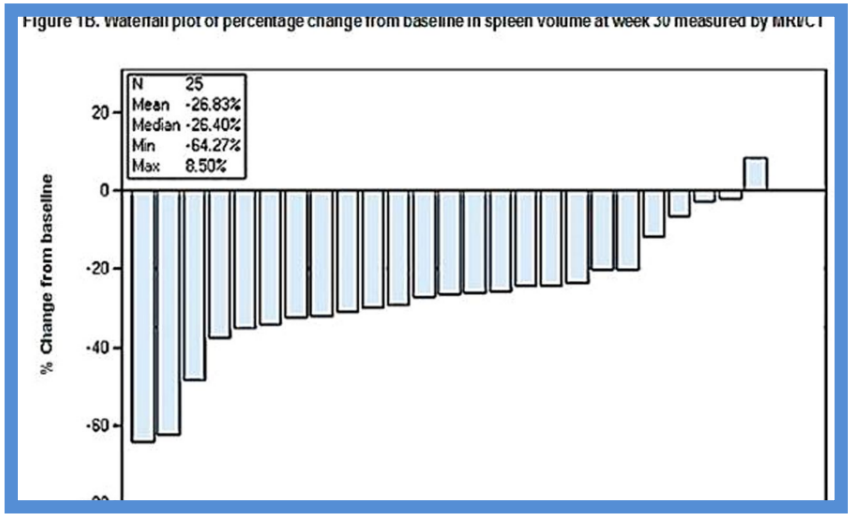
Blood 2016 128:852;

- **30 pts enrolled (median age:24 years; 60% male)**
- **26 pts completed the core phase at week 30**
- **4 pts discontinued before week 30 (adverse event , N = 2; withdrew consent, N = 2)**
- **Median duration of exposure: 30.2 weeks**
- **Median dose intensity of RUX: 27.2 mg/day (range, 13.3-39.0 mg/day).**

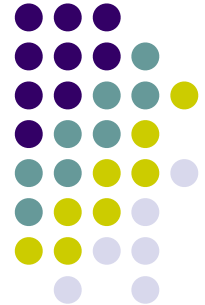
- Mean % change of transfusion rate: −5.9 (95% CI: −14.7, 2.83).
- Median pre-transfusion Hb levels:
  - pre-Tx = 8.4 g/dl;
  - end of study = 8.9 g/dl (week 24-30)
- **Mean Spleen Volume reduction from BL :**
  - at week 12 (N = 26): −19.7%
  - at week 30 (N = 25): −26.8%

**Adverse events :**

- RUX well tolerated
- **13 patients experienced adverse events associated with the study drug.**
- **3/13 patients reported serious adverse events.**



# Ruxolitinib : conclusion



- sustained decrease in Spleen Volume
- further studies could be valuable to determine if RUX Tx may be an alternative to splenectomy in pts with TDT.

# ACE-011 e ACE-536:
# human ActRIIreceptor ligand TRAP selettivi

**ACE-011**
**sotatercept**

ActRIIA receptor

Dominio Fc dell'Ab
umano $IgG_1$

**ACE-536**
**luspatercept**

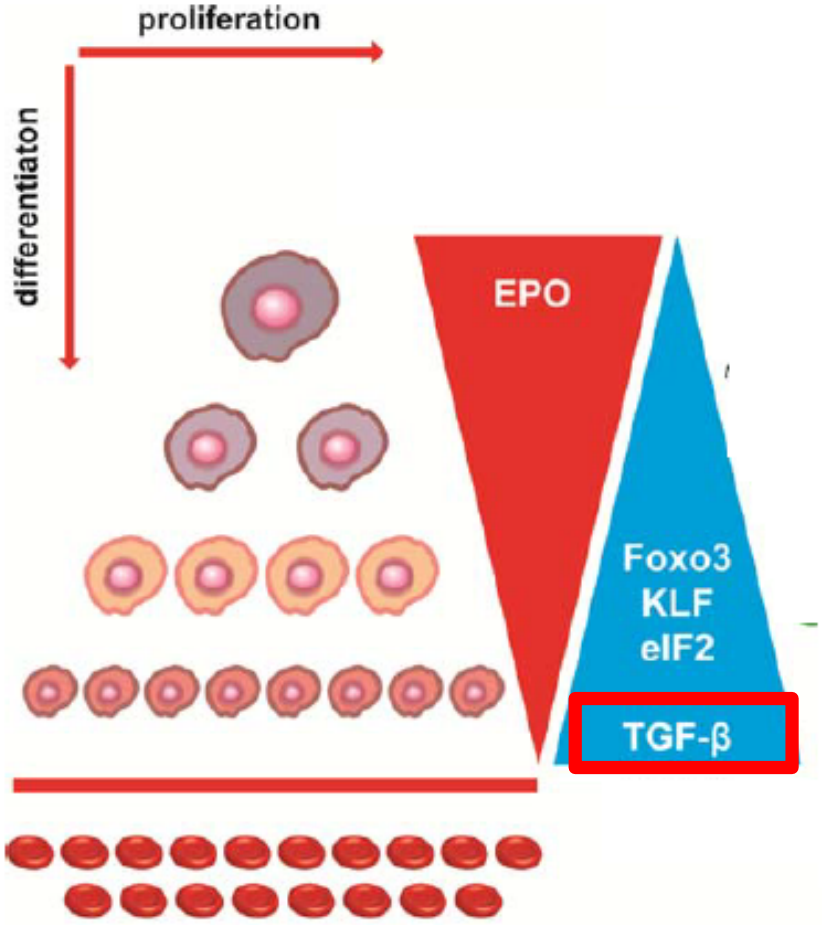
ActRIIB receptor

Dominio Fc dell'Ab
umano $IgG_1$

ACE-536 e ACE-011 legano ligandi della TGF-β superfamily

| phase 1-2 | phase 1-2-3 |
|---|---|

# The transforming growth factor-β (TGF-β)superfamily



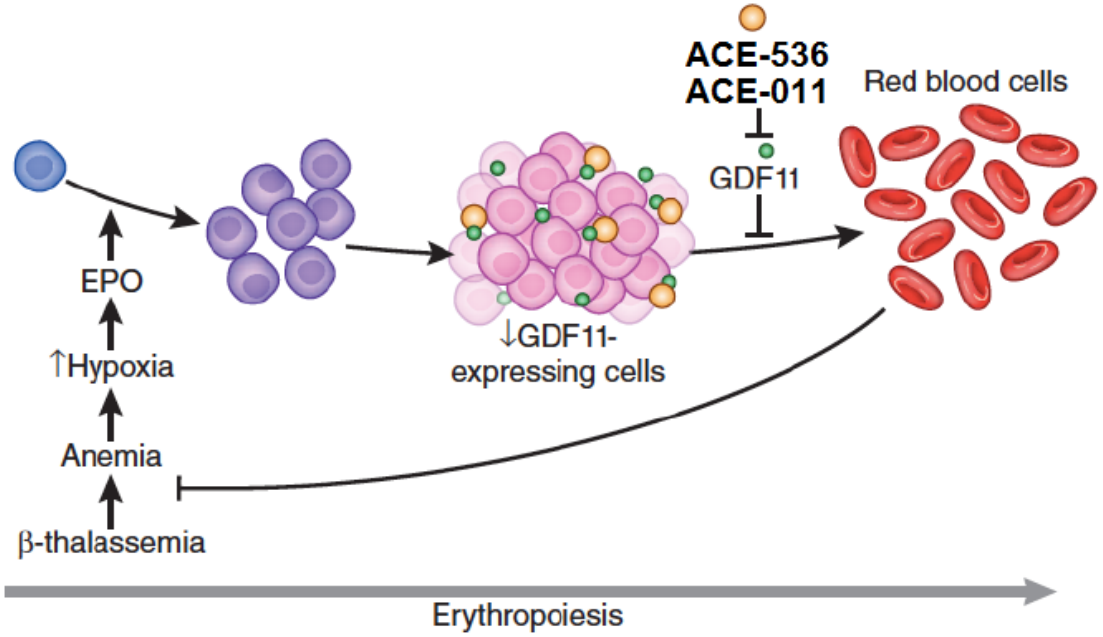

**The TGF-β superfamily consists of four groups of proteins with similar structure and regulatory activity at the cellular level:**

1. **TGF-β: +**
2. **BMP (bone morphogenetic proteins) +**
3. **GDFs (growth and differentiating factors) --**
4. **activins --**

ACE-011 e ACE-536

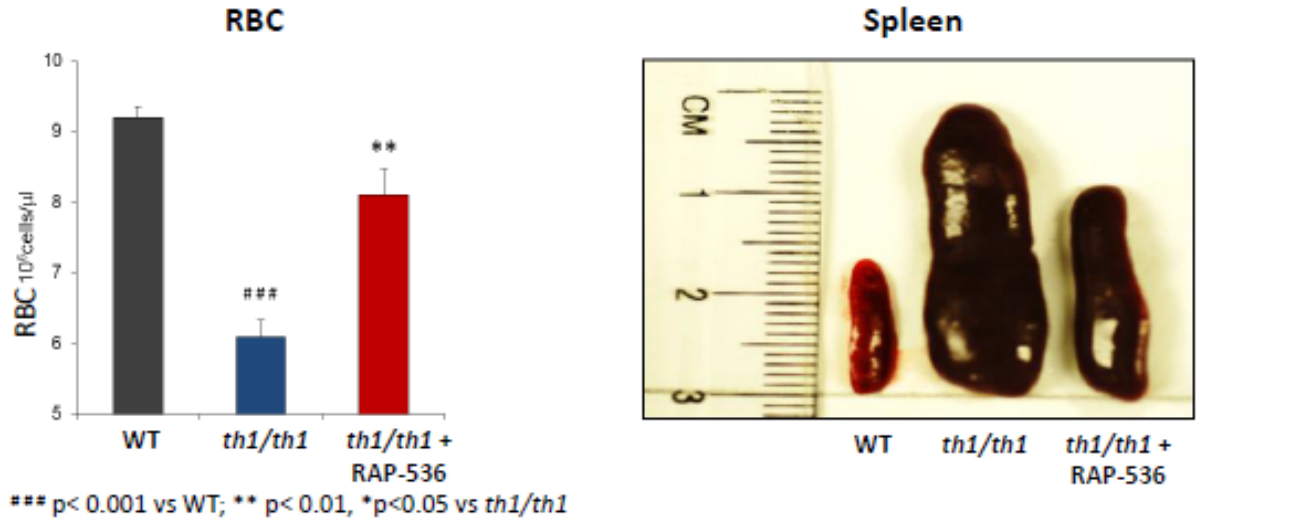
# ACE-011 e ACE-536: come funzionano?

**ACE-536 and ACE-011 promote differentiation and maturation by binding GDF11**



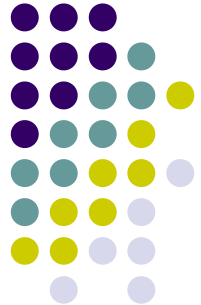
# ACE-536 for β-Thalassemia:pre-clinical studies

RAP-536 (murine luspatercept) reduces ineffective erythro-poiesis and disease burden in mouse model of β-thalassemia




Suragani R et al., Blood 2014
Martinez P et al., EHA 2016 abstract S136

# Phase 2 study ACE- 536 Eligible for Study

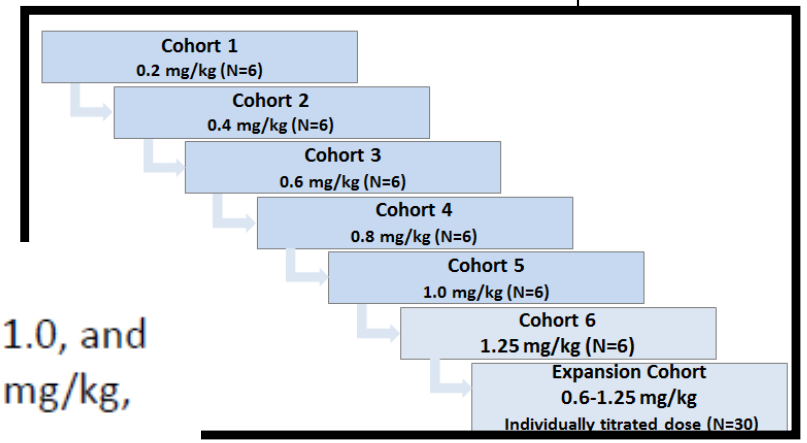


Inclusion criteria

- documented diagnosis of β-thalassemia
  - **NTD**: received <4 RBC units in the 8 weeks prior to treatment start, and mean hemoglobin concentration <10.0 g/dl
  - **TD patients** : received ≥4 RBC units every 8 weeks
- aged ≥18 years
- spleen size <18 cm in the longest diameter measured by abdominal ultrasound

Exclusion criteria

- folate deficiency,
- symptomatic splenomegaly,
- history of thromboembolic events
- any clinically significant pulmonary, cardiovascular, endocrine, neurologic, hepatic,gastrointestinal, infectious, immunologic, or genitourinary disease considered by the investigator to be not adequately controlled were also excluded




- Dose levels (SC q3 weeks)
  - **Base study** dose escalation phase (n=35): 0.2, 0.4, 0.6, 0.8, 1.0, and 1.25 mg/kg and expansion cohort (n=29): starting dose 0.8 mg/kg, titration up to 1.25 mg/kg (total n=64)
  - **Extension study** (n=51): 0.8-1.25 mg/kg
- Follow-up
  - All patients are followed for 2 months post treatment completion or early discontinuation

**Base Study (n=64)**
**3 Months**
NCT01749540

→

**Extension Study (n=51)**
**→ 2 years (ongoing)**
NCT02268409

**September 2, 2016**

Still on Extension (N=33)

# Endpoints

## Primary endpoints

- Efficacy: erythroid response
  - NTD : Hb increase ≥1.5 g/dl from baseline
  - TD: reduction in RBC transfusion burden of ≥20%, ≥33%, or ≥50% over 12 weeks versus the 12 weeks before
- Safety and tolerability

## Secondary endpoints

- evaluation of changes in liver iron concentration (LIC)
- leg ulcers
- bone mineral density by dual energy X-ray absorptiometry (DEXA) scans
- quality of life using patient-reported outcomes

# Paients enrolled in the initial stage

| | Total (N=64) |
|---|---|
| Age, median (range), years | 38.5 (20–62) |
| Female, n (%) | 31 (48.4) |
| Splenectomy, n (%) | 43 (67.2) |
| NTD patients, n (%) | 33 (51.6) |
| Hb, median (range), g/dl | 8.5 (6.5–9.8) |
| Liver iron concentration, mean ± SD, mg/g dry weight | 5.4 ± 3.8 |
| TD patients, n | 31 |
| RBC transfusion burden, median (range), units/12 weeks* | 8.0 (4–18) |
| Liver iron concentration, mean ± SD, mg/g dry weight† | 5.0 ± 5.3 |

The median total duration of treatment for 64 patients was 428 days (range 21–768)

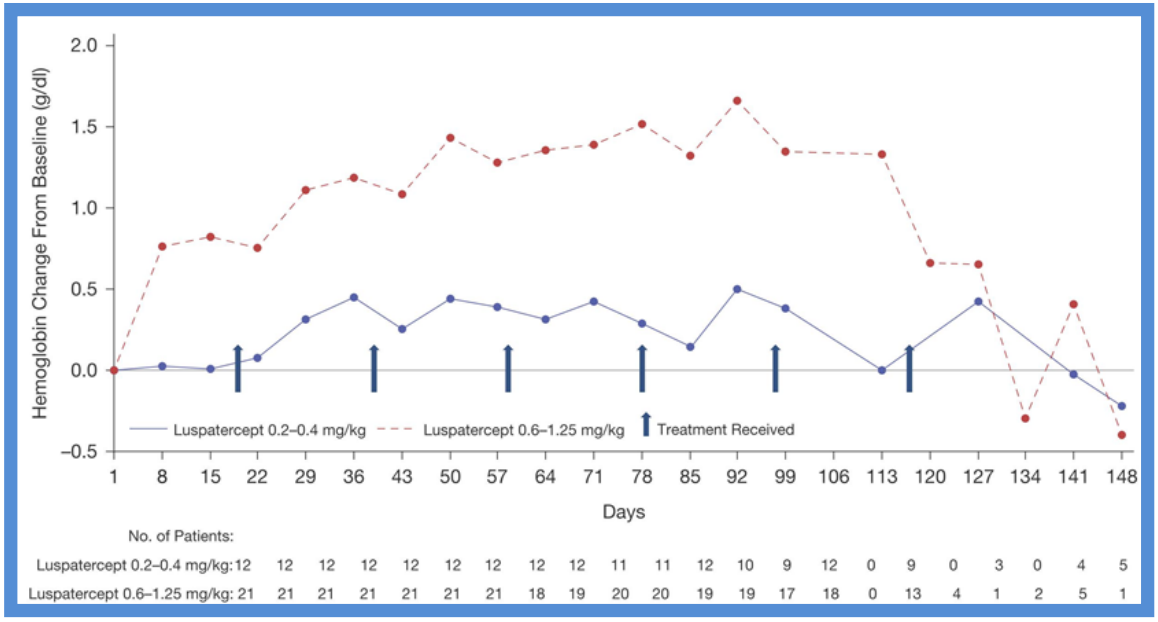
**63 received higher dose levels of luspatercept (0.6–1.25 mg/kg):**

- **31 NTD**
- **32 TD**

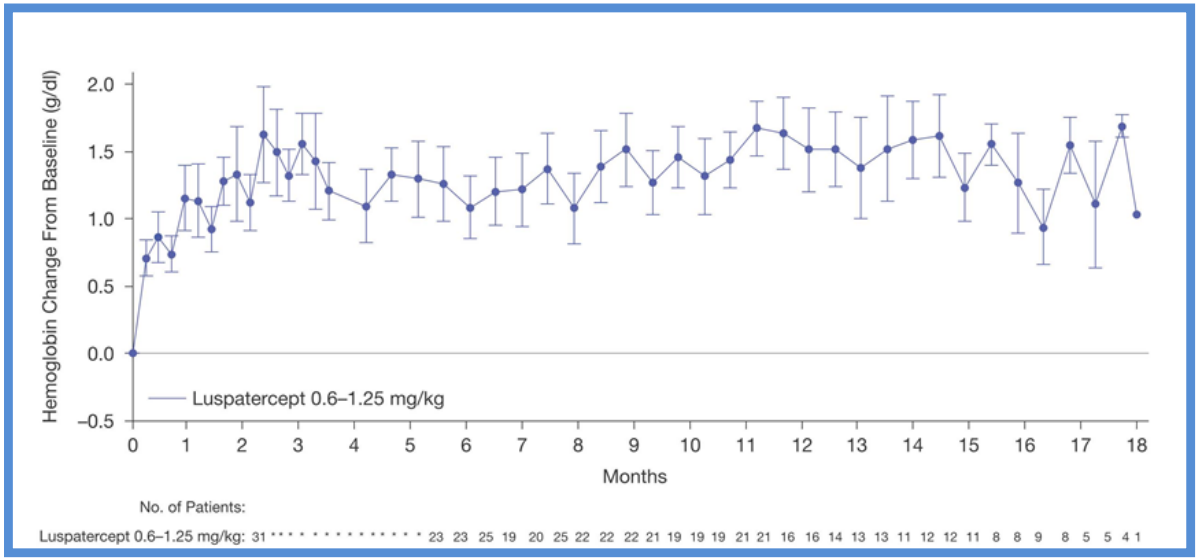
# Hemoglobin Response in Non–Transfusion-Dependent Patients

| Luspatercept 0.6–1.25 mg/kg in the Initial and Extension Stages | |
|---|---|
| **NTD patients, n/N (%)** | **31** |
| Mean Hb increase ≥1.0 g/dl | 22/31 (71.0%) |
| **Mean Hb increase ≥1.5 g/dl** | **14/31 (45.2%)** |

# Hb levels in NTD patients



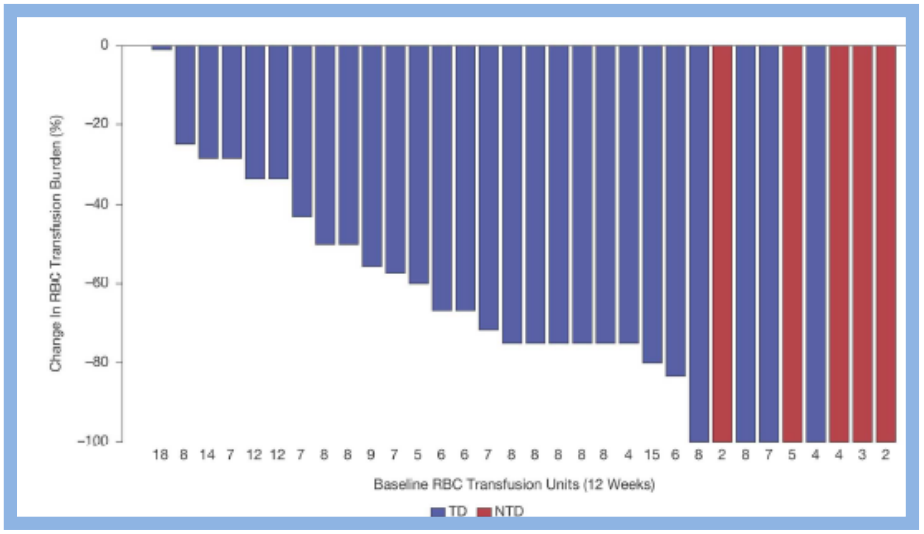

**Mean Change in Hemoglobin Level Relative to Baseline for Patients Treated With Luspatercept 0.2–0.4 mg/kg Compared With 0.6–1.25 mg/kg in the Initial Stage of the Study,.**




**Mean Change in Hemoglobin Level Relative to Baseline and for all Patients Treated With Luspatercept 0.6–1.25 mg/kg During the Study**

# Transfusion Burden Reduction in Transfusion-Dependent Patients

| Luspatercept 0.6–1.25 mg/kg in the Initial and Extension Stages | |
|---|---|
| **TD patients, n/N (%)** | **32** |
| ≥20% transfusion burden reduction | 26/32 (81.3 %) |
| ≥33% transfusion burden reduction | 23/32 (71.9%) |
| **≥50% transfusion burden reduction** | **20/32 (62.5%)** |



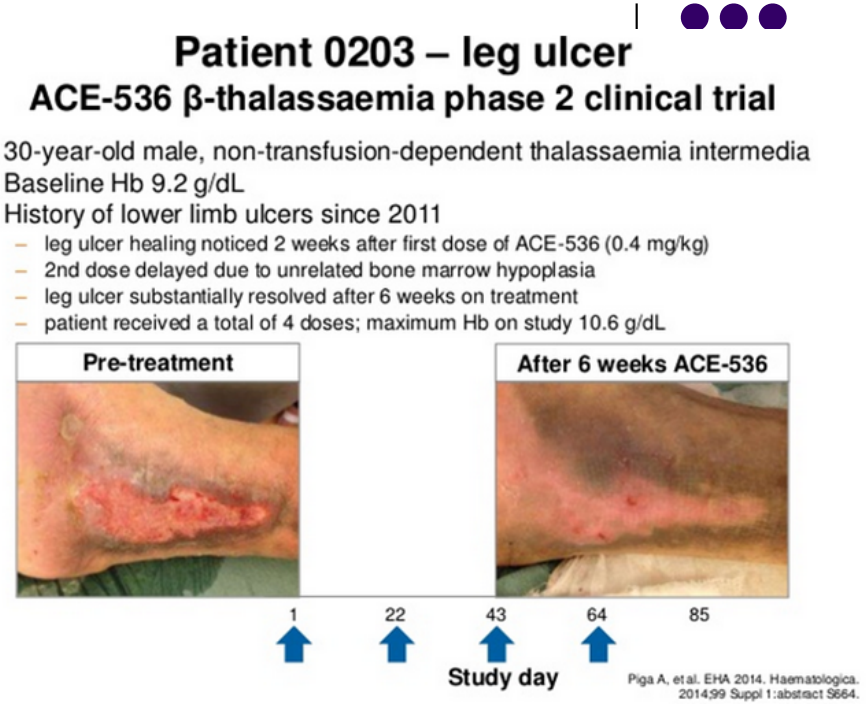

Only in the 32 patients with a baseline transfusion burden of ≥2 RBC units are shown

**BONE MINERAL DENSITY**

**After 24 weeks of treatment at dose levels ≥0.6 mg/kg**

| (DEXA) scans | Baseline Z score | mean percentage change in BMD | |
|---|---|---|---|
| total hip | −0.74 ± 1.21 (n=25) | 5.29 ± 15.84% | P=0.23 ( n=14) |
| lumbar spine | −1.61 ± 0.88 (n=27). | 3.12 ± 6.56% | P=0.068; (n=17) |

# Leg ulcers




- **Six patients**
- **total number of ulcers over the malleoli: 14**
- **9 ulcers: fully healed***
- **2 ulcers :partially healed**
- **3 ulcers improved.**

***The median time to complete healing: 10 weeks (range 6–33).**

# Quality of life:

- FACIT-F :  13-question patient-reported outcome (PRO) questionnaire (subscore of FACT-An) used to assess anemia related symptoms (e.g., fatigue)
- NTD: improvements were correlated with the mean 12-week change in hemoglobin

## Safety:
## Related TEAEs Occurring During the Study

| Preferred term*, n (%) | Grade 1–2 TEAEs in ≥2 Patients (N=64) | Grade 3–4 TEAEs (N=64) |
|---|---|---|
| | | |
| Bone pain | 21 (32.8) | 3 (4.7) |
| Headache | 16 (25.0) | 1 (1.6) |
| Myalgia | 13 (20.3) | 0 |
| Arthralgia | 12 (18.8) | 0 |
| Musculoskeletal pain | 10 (15.6) | 0 |
| Asthenia | 6 (9.4) | 2 (3.1) |
| Back pain | 7 (10.9) | 0 |
| Injection site pain | 7 (10.9) | 0 |
| Erythroblastosis | 3 (4.7) | 0 |
| Injection site erythema | 3 (4.7) | 0 |
| Musculoskeletal chest pain | 3 (4.7) | 0 |
| Neck pain | 3 (4.7) | 0 |
| Pain in jaw | 3 (4.7) | 0 |
| Pyrexia | 3 (4.7) | 0 |
| Chills | 2 (3.1) | 0 |
| Influenza | 2 (3.1) | 0 |
| Injection site pruritus | 2 (3.1) | 0 |
| Macule | 2 (3.1) | 0 |
| Muscle spasms | 2 (3.1) | 0 |
| Paresthesia | 2 (3.1) | 0 |

**No treatment-related serious AEs were reported**

One patient with a history of cardiac disease died due to cardiac arrest considered unrelated to treatment;
**no treatment-related deaths were reported.**

**4/64 (6.3%) patients discontinued treatment due to AEs**

# La nostra esperienza

| | Pts arruolati | In terapia al 1/10/2017 | Dose sc ogni 21 g |
|---|---|---|---|
| NTD | 5 pts | 3 | 2: 1mg/kg<br>1: 1,25 mg/kg |
| TD | 5 pts | 1 | 1:1,25 mg/kg |

causa della sospensione della terapia:

- 1 NTD : complicanze non correlate al farmaco in studio
- 1 NTD: decisione del paziente
- 1TD: inefficacia sul regime trasfusionale
- 3 TD: astenia marcata(1), dolori osteomuscolari (2)

| | Hb g/dl baseline | Hb g/dl attuale |
|---|---|---|
| 1-NTD | 9,2 | 10 |
| 2-NTD | 8 | 11 |
| 3-NTD | 8,5 | 9,9 |
| 1-TD | 50% riduzione delle unità trasfusione | |

# The BELIEVE Study

## Phase 3 Study of Luspatercept in β-Thalassemia: FULLY ENROLLED

BELIEVE

| | |
|---|---|
| **Patient Population / Study Design** | Randomized, double-blind, placebo-controlled study in adult β-thalassemia patients (including HbE/β-thal)<br>300 patients, randomized 2:1; luspatercept 1 mg/kg SC every 3 weeks, titration up to 1.25 mg/kg possible |
| **Key Eligibility Criteria** | Patients who receive 6-20 units of RBCs over past 24 weeks and no transfusion-free period ≥ 35 days (regularly transfused patients)<br>No current ESA or hydroxyurea |
| **Primary Efficacy Endpoint** | Proportion of patients with ≥ 33% reduction in transfusion burden from weeks 13-24 compared to the 12 weeks preceding treatment |

*Study sponsored by Celgene in collaboration with Acceleron Pharma*

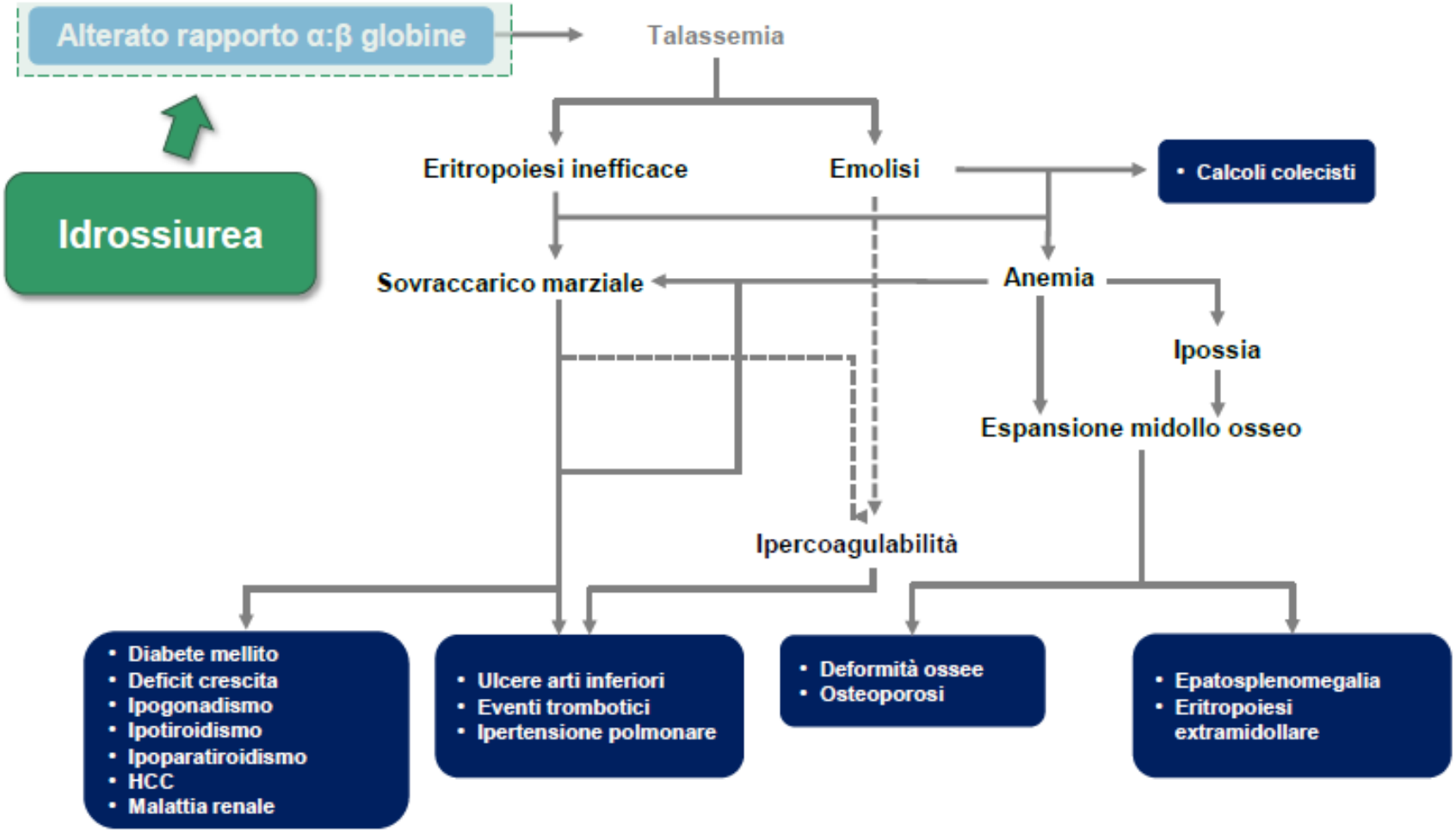
NCT02604433

# Agenda

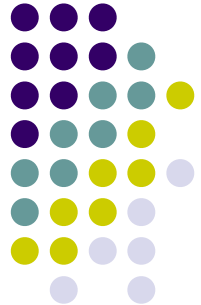
Terapie innovative : fase di sperimentazione clinica 1-2-3

- **Terapia chelante:**
  - **nuovi chelanti**
  - **modulatori del metabolismo del ferro:**
    - **amlopidina (calcio-antagonista)**
    - **miniepcidine**
    - **repressori della Matriptase-2**
- **Modulatori della eritropoiesi:**
  - **ACE-536**
  - **Jak-inibitori**
- **Induttori Hb Fetale**
- Terapia genica

# Terapia standard della talassemia: idrossiurea ?



# Hyd in NTDT ( TIF 2013)

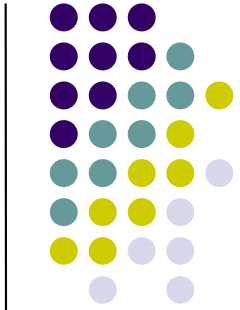


- There are no randomized clinical trials to recommend an evidence-based use of hydroxyurea in NTDT patients. However, based on data from a large body of observational cohort studies and small clinical trials, the agent may be considered in the following groups of NTDT patients:
  - > ß-Thalassemia intermedia homozygous for the XmnI polymorphism
  - > Patients with Lepore or δß-thalassemia
  - > Patients for which a transfusion course is required but are alloimmunized
  - > Patients with the following clinical morbidities
  - - Pulmonary hypertension (see Chapter 7)
  - - Extramedullary hematopoietic pseudotumors (see Chapter 11)
  - - Leg ulcers (see Chapter 12)

# HbF inducers

| Cytotoxic agents: | DNA methyl transferase (DNMT) inhibitors | Histone Deacetylase (HDAC) inhibitors | Short-chain fatty acids (SCFAs): | Inducers from naturale source | Other agents |
|---|---|---|---|---|---|
| hydroxyurea | 5-azacytidine | sodium butyrate | valproic acid | bergaptene | EPO |
| cytosine arabinoside | decitabine | trichostatin A | phenylbutyrate | angelicin | pomalidomide |
| busulfan | | adicipin | propionate | rapamycin everolimus | talidomide |
| vinblastine | | scriptaid | SCFA derivates: HQK-1001 | resveratrol | |
| | | | | mithramicin | |

# Short Chain Fatty Acid (SCFA)



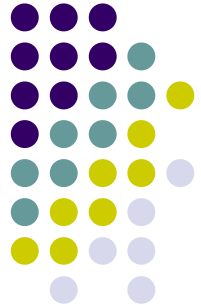
**1)Prior generation:**

- arginine butyrate and phenylbutyrate,
  - increased fetal  and total hemoglobin levels
  - high doses or intravenous infusion.

**2) seconde generation:**

- sodium 2,2 dimethylbutyrate (SDMB or HQK-1001)

# Sodium 2,2-dimethylbutyrate (SDMB or HQK-1001)



- orally bioavailable  in non-human primate models

**Preclinical studies:**

- induces fetal globin synthesis in reporter gene assays, in patients' cultured cells and in transgenic mice
- increases total hemoglobin levels in phlebotomized anemic baboons
- the compound has a favorable pharmacokinetic profile in non-human primates and is non-mutagenic

Boosalis et, al, Blood. 2001; 97:3259–3267;
Pace  et al, Blood. 2002; 100:4640–4648; Castaneda et al, Blood Cells, Molecules, & Diseases. 2005; 35:217–226)

*J Clin Pharmacol*. 2011 August ; 51(8): 1186–1194. doi:10.1177/0091270010379810.

# Evaluation of Safety and Pharmacokinetics of Sodium 2,2 Dimethylbutyrate, a Novel Short Chain Fatty Acid Derivative, in a Phase 1, Double-Blind, Placebo-Controlled, Single- and Repeat-Dose Studies in Healthy Volunteers

Susan P. Perrine[1,2], William A. Wargin[4], Michael S. Boosalis[2], Wayne J. Wallis[1], Sally Case[1], Jeffrey R. Keefer[3], Douglas V. Faller[2], William C. Welch[1], and Ronald J. Berenson[1]

## Abstract

Healthy adult human subjects were treated with a novel SCFA derivative, sodium 2,2 dimethylbutyrate (SDMB), or placebo, with one of four single dose levels (2, 5, 10 and 20 mg/kg) or daily doses (5, 10, or 15 mg/kg) over 14 days, and monitored for adverse clinical and laboratory events, drug levels, reticulocytes, and HbF assays.
SDMB was well-tolerated with no clinically significant adverse events related to study medication.
The terminal half-life ranged from 9–15 hours.
Increases in mean absolute reticulocytes were observed at all dose levels in the 14-day study.
**The favorable PK profiles and safety findings indicate that SDMB warrants further investigation for treatment of anemic subjects with beta hemoglobinopathies.**

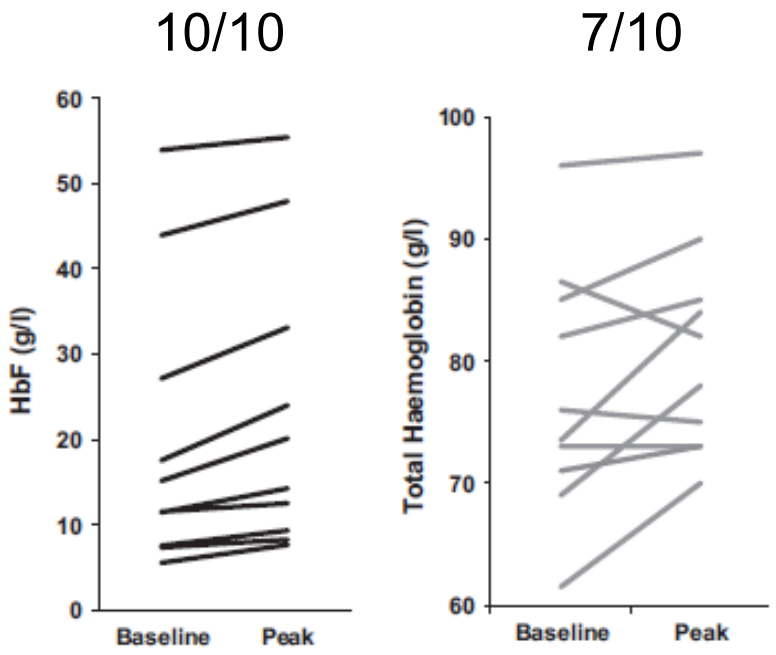
NCT 01642758

**Inati et al, British Journal of Haematology, 2014, 164, 451–464**

**A phase 2 study of HQK-1001, an oral fetal haemoglobin inducer, in β-thalassaemia intermedia**

- b-thalassaemia intermedia characterized by two b-globin mutations
- Hb: 6-9 g/dl
- 10 patients , mean age 29 yrs ( 18-52)
- HQK-1001 at 20 mg/kg per day for 6 months

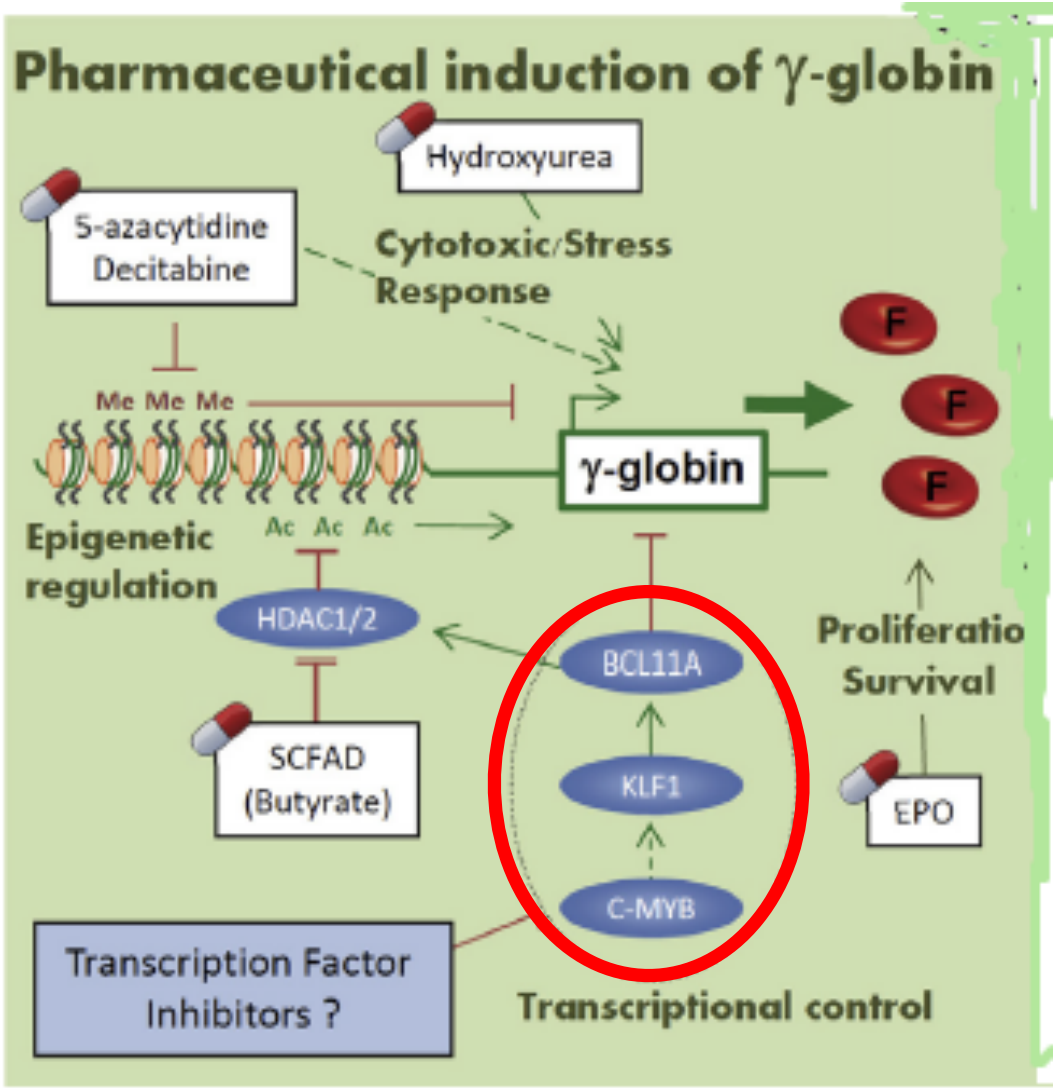
- **Significantly increased HbF**,
  - .Fetal globin increased in all subjects, with peak increase occurring after a mean of 14 weeks of therapy
- **Modestly increased total haemoglobin**
  - Total haemoglobin increased in seven subjects, with a mean increase of 47 g/l (range 10–100 g/l).




Baseline and peak values for HbF and total haemoglobin.

- **Longer and alternate regimens, such as intermittent pulsed dosing**
- **selection of patients (younger subjects with greater hematologic reserve )**

# Future treatments




**Future treatments may target the transcription factors involved in gamma-globin repression, such as BCL11a and KLF1.**

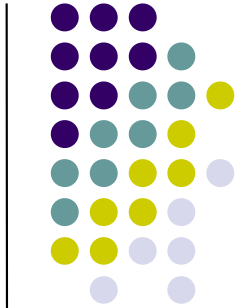
**BCL11**a is an essential transcription factor involved in g-globin downregulation. It binds to intergenic regions of the HBB locus, promoting long-range interactions with the LCR that favors b-globin expression. It recruits histone deacetylase to repress g-globin.

**KLF1** is a strong inducer of b-globin expression that also activates BCL11A transcription when produced in large amounts in adult cells. KLF1 may itself be stimulated **by c-Myb.**

# Agenda

Terapie innovative : fase di sperimentazione clinica 1-2-3

- **Terapia chelante:**
  - **nuovi chelanti**
  - **modulatori del metabolismo del ferro:**
    - **amlopidina (calcio-antagonista)**
    - **miniepcidine**
    - **repressori della Matriptase-2**
- **Modulatori della eritropoiesi:**
  - **ACE-536**
  - **Jak-inibitori**
- **Induttori Hb Fetale**
- **Terapia genica**



# Currently trials of gene therapy active worldwide

# NCT01639690,
# Memorial Sloan Kettering Cancer Center
# New York,USA

| Phase | Gene | Vector | Disease | Estimated enrollment | Conditioning regimen | Intervention | Start date |
|---|---|---|---|---|---|---|---|
| I | β-globin | TNS9.3.55 | β-TM | 10 (≥18 yrs) | Partial cyto-reduction (Bu 8 mg/kg) for 3 patients, myeloablative (Bu 14 mg/kg) for 1 patient | Transplantation of HSCs transduced ex vivo with a LV | Jul 2012 |

Estimated Study Completion Date: July 2018

**This study is ongoing, but not recruiting participants**

no published data are available and no further development has been reported

Negre et al , Hum Gene Ther. 2016;27:148–165 :

**4 patients treated (3: β0/β+ ,1:β0/β0)**

**One patient had a significant decrease in transfusion requirements.**

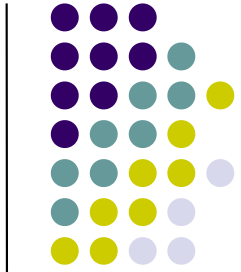
**ClinicalTrials.gov**

# TIGET-BTHAL trial (NCT02453477)
# Italy- IRCCS San Raffaele
# (Dec 3–6, 2016)

| Phase | Gene | Vector | Disease | Estimated enrollment | Conditioning regimen | Intervention | Start date |
|---|---|---|---|---|---|---|---|
| I/II | β-globin | GLOBE | β-TM | • 3 adults (≥18 yrs)<br>• 3 elderly children (8–17 yrs)<br>• 4 younger children (3–7 yrs | Myeloablative | Transplantation of HSCs transduced ex vivo with a LV (intrabone injection) | May 2015 |

**adult group enrollment (3 patients, ≥18 years) : completed**
follow-up: ranged between 271 and 400 days post-transplan
all patients are alive and are doing well, obtained an early hematological engraftment, and showed a good tolerability of the overall procedure with limited AE
patients presented a highly polyclonal engraftment, no clonal dominance, and **significant transfusion reduction** (one patient reached transfusion independence for 9 months; the other two patients had a reduction of 80% and 50%, respectively).

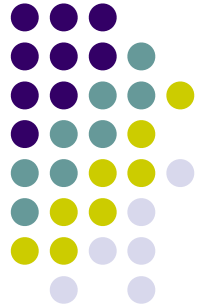
The elderly children (8–17 years) group enrollment (3 patients) is complete with promising preliminary results.
One patient of the younger children group (3–7 years) has been treated, and recruitment is still open



Bluebird bio trials

| Phase | Gene | Vector | Disease | Estimated enrollment | Conditioning regimen | Intervention | Start date |
|---|---|---|---|---|---|---|---|
| **HGB-204 trial (NCT01745120) USA, Thailand, Australia** | | | | | | | |
| I/II | βA-T87Q-globin | BB305 | β-TM | 18 (12–35 yrs) | Myeloablative | Transplantation of HSCs transduced ex vivo with a LV | Aug 2013 |
| **HGB-205 study (NCT02151526) , France** | | | | | | | |
| I/II | βA-T87Q-globin | BB305 | • β-TM<br>• severe SCD | 7 (5–35 yrs) | Myeloablative | Transplantation of HSCs transduced ex vivo with a LV | Jul 2013 |
| **NCT02906202 , France, Germany, Greece ,Italy, Thailand, USA** | | | | | | | |
| III | βA-T87Q-globin | BB305 | β-TM<br>do Not Have β0/β0 Genotype | 15 (12–50 yrs) | Myeloablative | Transplantation of HSCs transduced ex vivo with a LV | Aug 2016 |

# HGB-204 and HGB-205 trials: results



**14 patients at ≥12 months of follow-up**

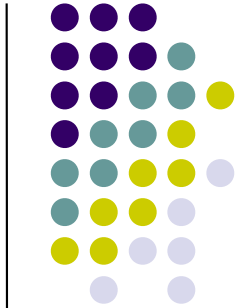
- **5 patients with β° /β° genotypes**
  - 60% reduction in annual median transfusion volumes.
- **9 patients with non-β° /β° genotypes**
  - All transfusions free, with a median total Hb of 11.6 g/dL (range: 9.0–11.9 g/dL).

**Adverse events:**

- 18 patients, aged 12–35 years (14 patients with ≥6 months of follow-up)
- no evidence of:
  - ≥Grade 3 drug product-related AE
  - clonal dominance or replication competent lentivirus.

# Conclusioni:

- Più  farmaci per controllare l'accumulo di ferro
- Farmaco (Ruxolitinib)  per la splenomegalia
- Farmaco (ACE-536/luspatercet ) per trattare l'anemia
- Terapia genica



# Grazie per l’attenzione