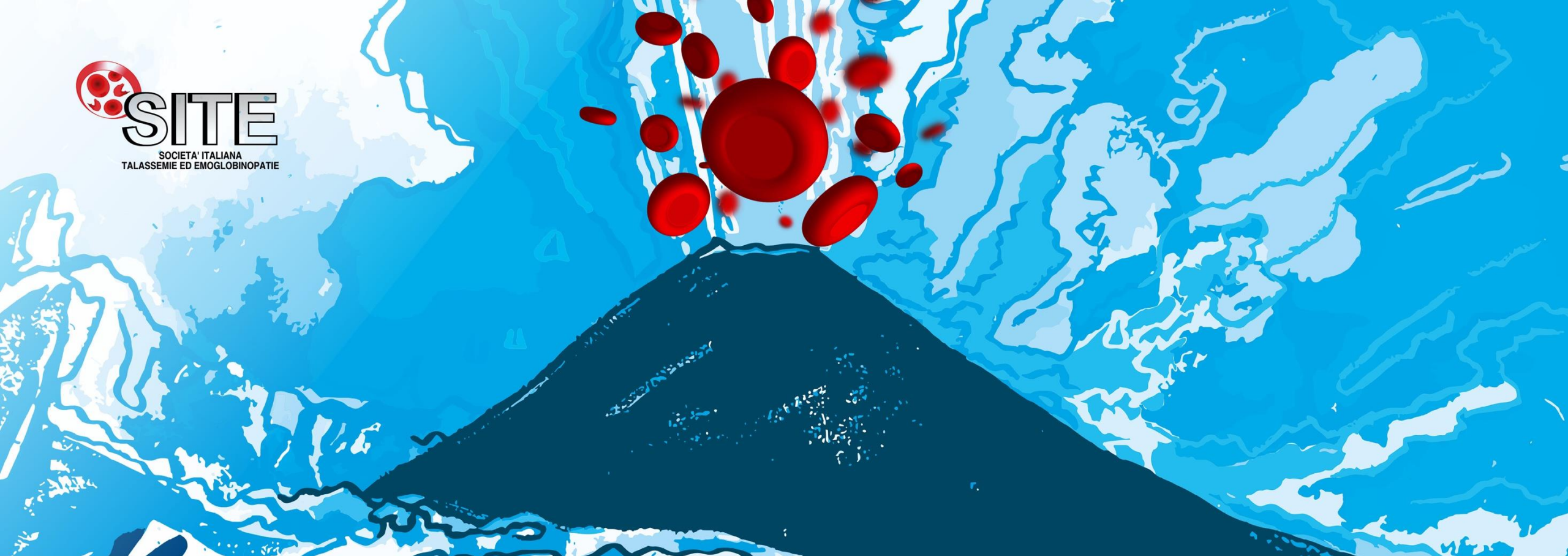




Approcci terapeutici emergenti per modulare l'epcidina

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University of Naples "Federico II"

Principal investigator and supervisor "iron defects" diagnostic unit

CEINGE Biotechnologie Avanzate Franco Salvatore

Naples – Italy

Meeting del CLUB DEL

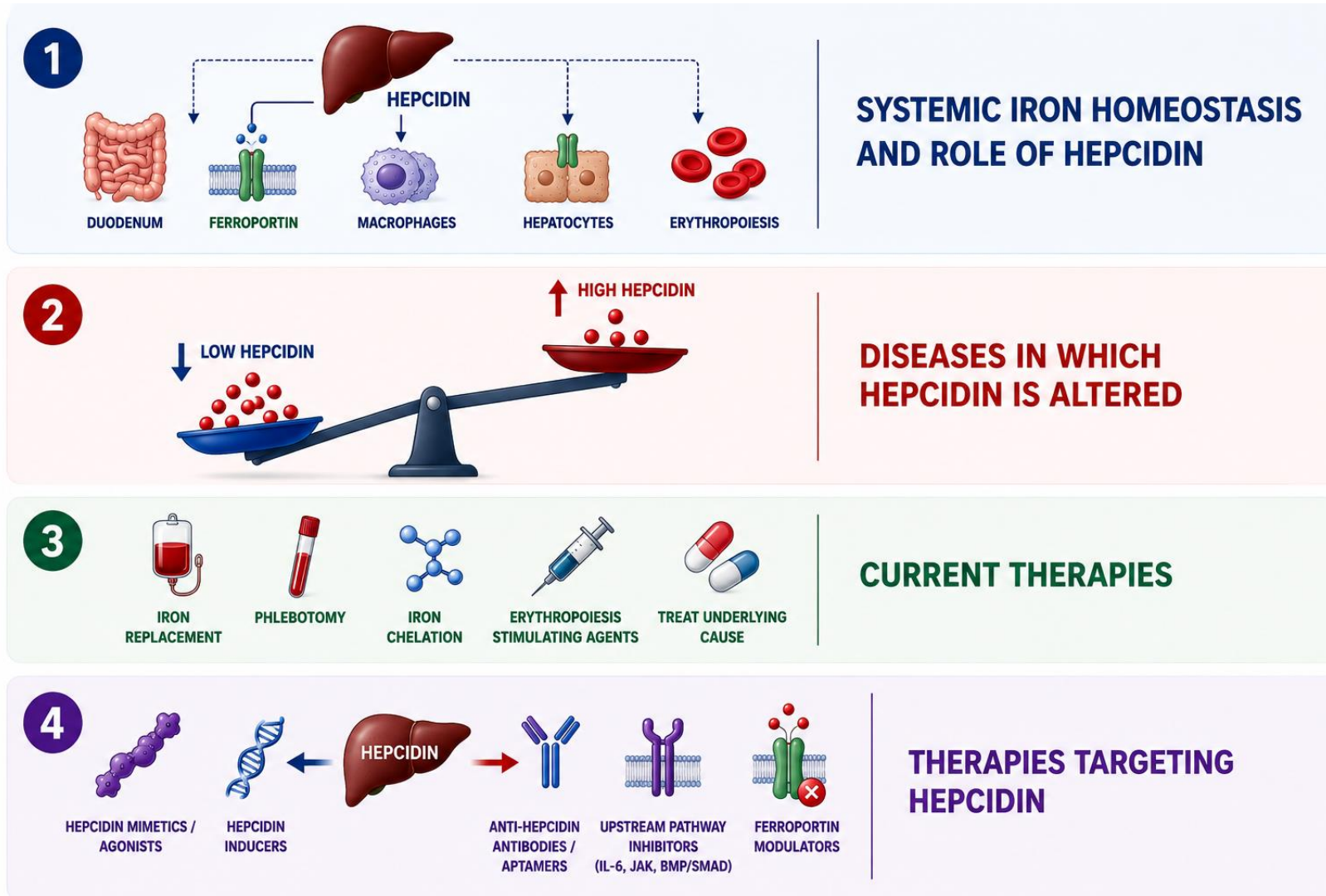
**Globulo
Rosso** 2026

NAPOLI

28-29 SETTEMBRE 2026

Complesso dei SS. Marcellino e Festo

Outline

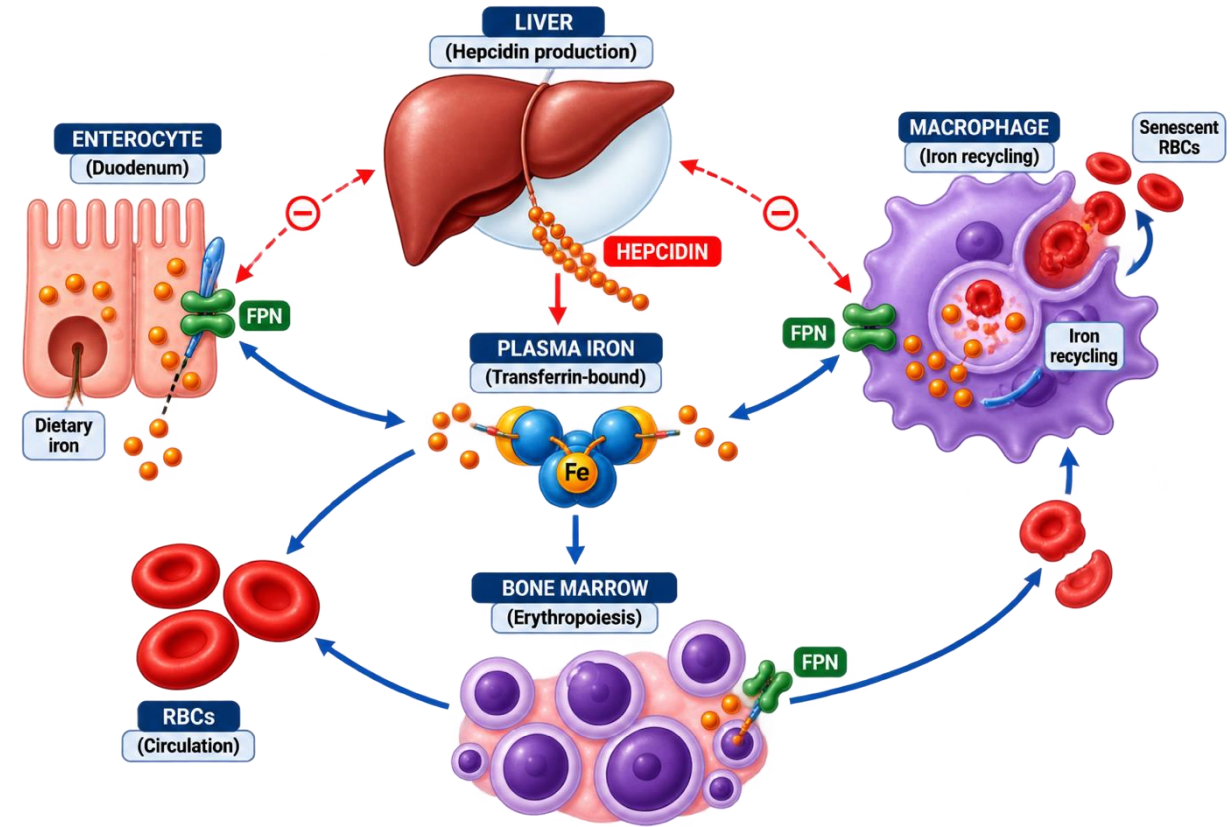


Iron metabolism and its regulation at systemic level



UNIVERSITÀ DEGLI STUDI DI NAPOLI
FEDERICO II

- ✓ The **regulation** of iron metabolism centers on providing adequate iron for cellular function while limiting iron **toxicity**.
- ✓ Mammals cannot excrete iron, mechanisms have evolved to control **iron acquisition, storage, and distribution** at both **systemic** and **cellular** levels.
- ✓ **Hepcidin** regulates absorption of iron from the **duodenum** through negative regulation of the iron-export protein **ferroportin**.
- ✓ **Increased** production of **hepcidin** in response to iron results in a reciprocal **reduction in iron absorption**.



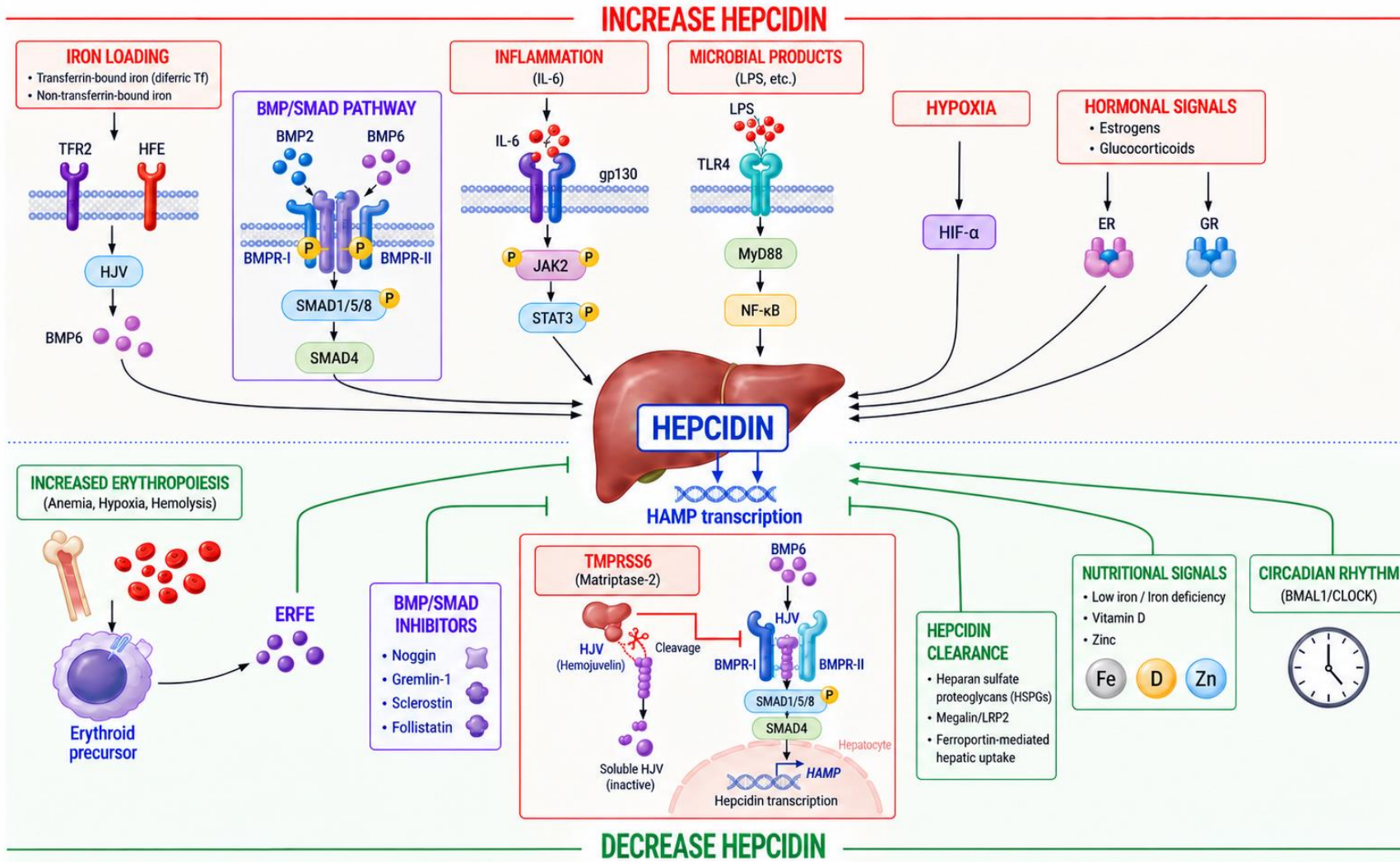
Galy B, Conrad M, Muckenthaler M. *Nat Rev Mol Cell Biol.* 2024; Olynyk JK, Ramm GA *N Engl J Med.* 2022; Muckenthaler MU, Rivella S, Hentze MW, Galy B. *Cell.* 2017; Arezes J, et al. *Blood.* 2018; Camaschella C, Nai A, Silvestri L. *Haematologica.* 2020



MEETING DEL CLUB DEL GLOBULO ROSSO 2026

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Hepcidin regulation



- ✓ Iron loading, inflammation, microbial products, and liver injury increase hepcidin expression, mainly through the BMP/SMAD, JAK2/STAT3, NF-κB, and TGF-β/SMAD pathways.
- ✓ Increased erythropoietic activity is a major suppressor of hepcidin, primarily through ERFE, thereby increasing iron availability for RBCs production.
- ✓ Hepcidin regulation is further fine-tuned by hypoxia, hormonal and nutritional signals, circadian rhythm, BMP/SMAD inhibitors, TMPRSS6, and hepcidin clearance, ensuring adaptation to changing iron requirements.

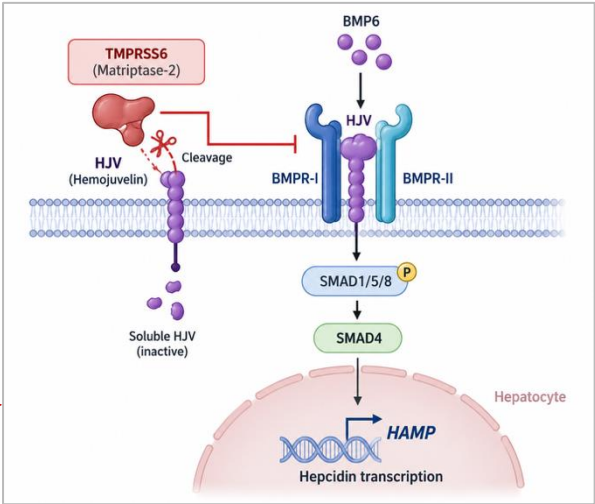
Diseases characterized by low hepcidin

Disease / Condition	Mechanism of Hepcidin Dysregulation	Key Clinical Features
 Hereditary Hemochromatosis	Genetic defects in the BMP/SMAD–hepcidin axis impair signaling or hepcidin production → ↓ hepcidin	• Iron overload • Cirrhosis • Diabetes • Cardiomyopathy • Arthropathy
 β-Thalassemia	Ineffective erythropoiesis → ↑ EPO → ↑ ERFE → ↓ BMP/SMAD signaling → ↓ hepcidin → ↑ intestinal iron absorption; Chronic RBC transfusions → additional iron loading	• Anemia • Progressive systemic iron overload • Hepatic, cardiac and endocrine complications
 Sickle Cell Disease	Ineffective erythropoiesis and chronic hemolysis → ↑ EPO and other erythroid signals (e.g., ERFE) → ↓ BMP/SMAD signaling → ↓ hepcidin → ↑ intestinal iron absorption	• Hemolytic anemia • Progressive iron overload • Organ damage (liver, heart, endocrine)
 Classical Iron-Loading Anemias (CDA II, Sideroblastic Anemias, other ineffective erythropoietic anemias)	Ineffective erythropoiesis / erythroid expansion → ↑ EPO and erythroid signals (e.g., ERFE) → ↓ BMP/SMAD signaling → ↓ hepcidin → ↑ intestinal iron absorption	• Anemia, dyserythropoiesis • Progressive iron overload • May occur even without transfusions
 PIEZO1-related DHS / HX	PIEZO1 gain-of-function → ↑ Ca ²⁺ influx → activation of ERK1/2 signaling → direct inhibition of hepatic BMP/SMAD pathway → ↓ <i>HAMP</i> transcription → ↓ hepcidin (ERFE modestly increased)	• Hemolytic anemia, RBC dehydration • Age-dependent progressive iron overload • Hemolysis
 Polycythemia Vera	JAK2 V617F mutation → constitutive JAK2/STAT activation → suppression of hepcidin transcription (direct/indirect) → ↓ hepcidin	• Elevated hemoglobin/hematocrit • Iron deficiency (functional) • Thrombosis

Camaschella C, Nai A. *Br J Haematol.* 2016; Ganz T, Nemeth E. *Hematol Oncol Clin North Am.* 2023; Taher AT, Musallam KM, Cappellini MD. *Thalassaemia International Federation*; 2023. Porter JB, Wood JC, Coates TD. *Thalassaemia International Federation*; 2025. Andolfo I, et al. *Blood* 2025; Ma S, et al. *Cell.* 2021; Bondu S, et al. *Sci Transl Med.* 2019.

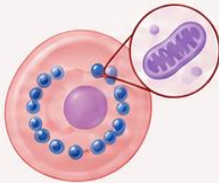
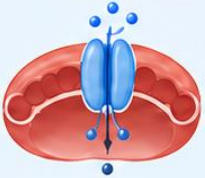
Diseases characterized by high hepcidin

Disease / Condition	Mechanism of High Hepcidin	Key Clinical Features
 Anemia of Inflammation (Chronic Diseases)	IL-6/STAT3 activation in hepatocytes → ↑ hepcidin	- Iron sequestration in macrophages - Anemia (impaired iron availability)
 Chronic Kidney Disease	Reduced hepcidin clearance due to impaired renal function; inflammation → ↑ hepcidin	- Functional iron deficiency - Anemia
 Iron-Refractory Iron Deficiency Anemia (IRIDA)	TMPRSS6 (matriptase-2) loss-of-function mutations → ↑ hepcidin	- Microcytic anemia - Low serum iron despite iron deficiency and poor response to oral iron



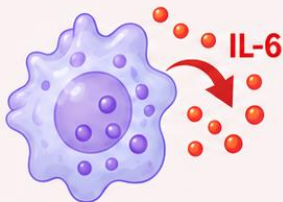
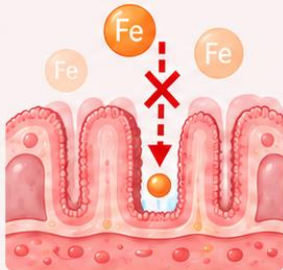
Ganz T, Nemeth E. *Nat Rev Immunol.* 2015; Babitt JL, et al. *Curr Opin Hematol.* 2016; Ganz T, Nemeth E. *Semin Nephrol.* 2016; Nemeth E, Ganz T. *Hepcidin and iron in health and disease. Annu Rev Med.* 2023; Finberg KE, et al. *Nat Genet.* 2008; De Falco L, et al. *Haematologica.* 2013.

Current treatments

Disease	Current treatments	Main adverse effects / limitations
 Hereditary Hemochromatosis	Therapeutic phlebotomy (first line); iron chelation when phlebotomy is contraindicated or not tolerated.	Phlebotomy: fatigue, dizziness, hypotension, anemia/iron deficiency if excessive. Chelators: GI toxicity, renal/hepatic toxicity; deferoxamine also injection-site reactions, auditory/ocular toxicity.
 β-Thalassemia and SCD	Hydroxyurea ; RBC transfusions , iron chelation; luspatercept ; in selected patients: HSCT or gene therapy/gene editing.	Transfusions: iron overload, alloimmunization, transfusion reactions. Chelators: renal/hepatic/GI toxicity depending on agent. Luspatercept: bone/musculoskeletal pain, headache, hypertension, thromboembolic events. HSCT/gene therapy: conditioning toxicity, infections; HSCT also GVHD.
 Classical Iron-Loading Anemias (congenital sideroblastic anemias)	Supportive RBC transfusions when needed; iron chelation; pyridoxine (B6) in responsive forms, especially ALAS2; selected severe cases: HSCT.	Transfusion-related iron overload and alloimmunization; chelator toxicity; pyridoxine: peripheral neuropathy at high or chronic doses; HSCT-related conditioning toxicity, infections, GVHD, and morbidity/mortality.
 PIEZO1-related DHS/HX	Mainly supportive care; folate ; phlebotomy or iron chelation for iron overload; transfusion when required.	Phlebotomy may worsen anemia or stimulate erythropoiesis; chelator toxicity. Splenectomy should be avoided or is contraindicated because of the high thrombotic risk.

Zoller H et al., *J Hepatol.* 2022; Cappellini MD et al., *N Engl J Med.* 2020; Iolascon A et al., *Blood.* 2020; Ducamp S et al., *Blood.* 2019; Andolfo I et al., *Am J Hematol.* 2018.

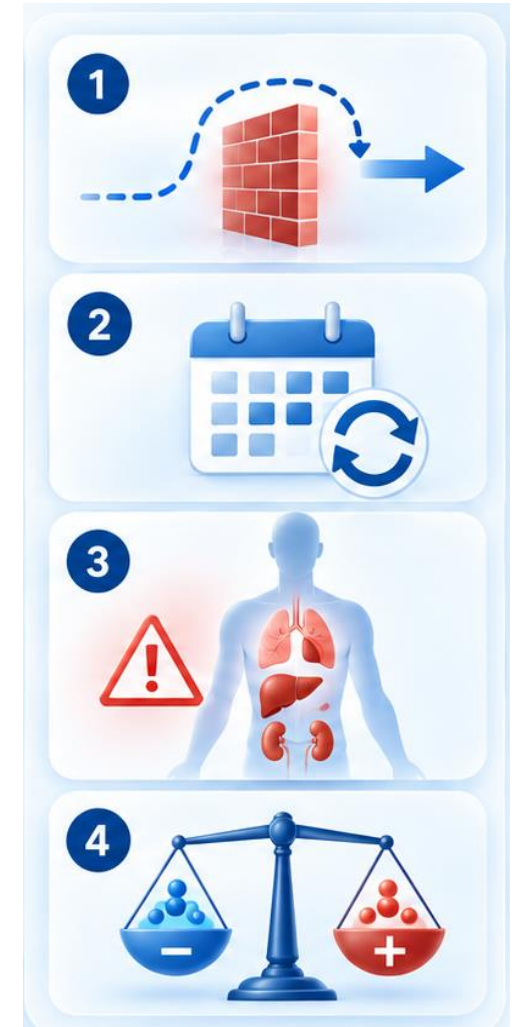
Current treatments

Disease / Condition	Current treatment	Main adverse effects / limitations
 Anemia of Inflammation (Chronic Diseases)	Treatment of the underlying inflammatory disease; IV iron in selected patients; ESAs in selected settings; RBC transfusion for severe/symptomatic anemia.	IV iron: infusion reactions, iron overload. ESAs: hypertension, thromboembolic events. Transfusions: reactions, alloimmunization, iron overload.
 Chronic Kidney Disease	Iron supplementation (oral or IV according to CKD setting/iron status); ESAs: HIF-PH inhibitors in selected patients; RBC transfusion when necessary.	Iron: GI intolerance (oral), infusion reactions $\pm$ hypophosphatemia (IV). ESAs: hypertension, thrombosis/ cardiovascular risk. HIF-PHIs: cardiovascular/thrombotic safety concerns. Transfusions: alloimmunization, iron overload.
 IRIDA (iron-refractory iron deficiency anemia)	IV iron when response is inadequate; occasionally ESAs in selected severe cases.	Oral iron: often poorly effective, GI intolerance. IV iron: infusion reactions, potential iron accumulation. ESAs: not routinely required. Complete Hb normalization may not be achievable.

Weiss G et al., *Blood*, 2019; Marques O et al., *Blood*, 2022; Babitt JL et al., *Kidney Int.*, 2026; Wang CY et al., *Curr Opin Hematol.*, 2016; Finberg KE et al., *Nat Genet.*, 2008; De Falco L et al., *Haematologica*, 2013.

Why target hepcidin?

- ✓ Current therapies mainly **bypass or compensate for hepcidin dysregulation** rather than **restoring physiological iron homeostasis**.
- ✓ Transfusions, iron supplementation, phlebotomy and chelation require **repeated or long-term treatment** and impose a substantial clinical burden.
- ✓ Available treatments are associated with **relevant adverse effects**, including iron overload or deficiency, organ toxicity, transfusion reactions, alloimmunization and thrombotic complications.
- ✓ Direct modulation of the hepcidin–ferroportin axis may **address the underlying mechanism**, improving iron availability or limiting iron overload according to the disease context.



Hepcidin modulating agents

STRATEGIES THAT INCREASE HEPCIDIN (Hepcidin Agonists / Mimetic Approaches)

HEPCIDIN MIMETICS

Mimic hepcidin action
(agonize hepcidin pathway)



Mimic the action of hepcidin by binding to ferroportin and promoting its internalization and degradation

↑ Hepcidin effect

MECHANISM

Enhance hepcidin pathway activity or replicate hepcidin's interaction with ferroportin

HEPCIDIN INDUCERS

Increase endogenous hepcidin production or transcription



Stimulate hepcidin (*HAMP*) gene expression via upstream signaling pathways

↑ Hepcidin levels

MECHANISM

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↓ Hepcidin effect

MECHANISM

Block hepcidin or prevent its binding to ferroportin, preserving ferroportin at the cell surface and enabling iron export

INDIRECT HEPCIDIN INHIBITORS

Reduce hepcidin expression by targeting upstream pathways



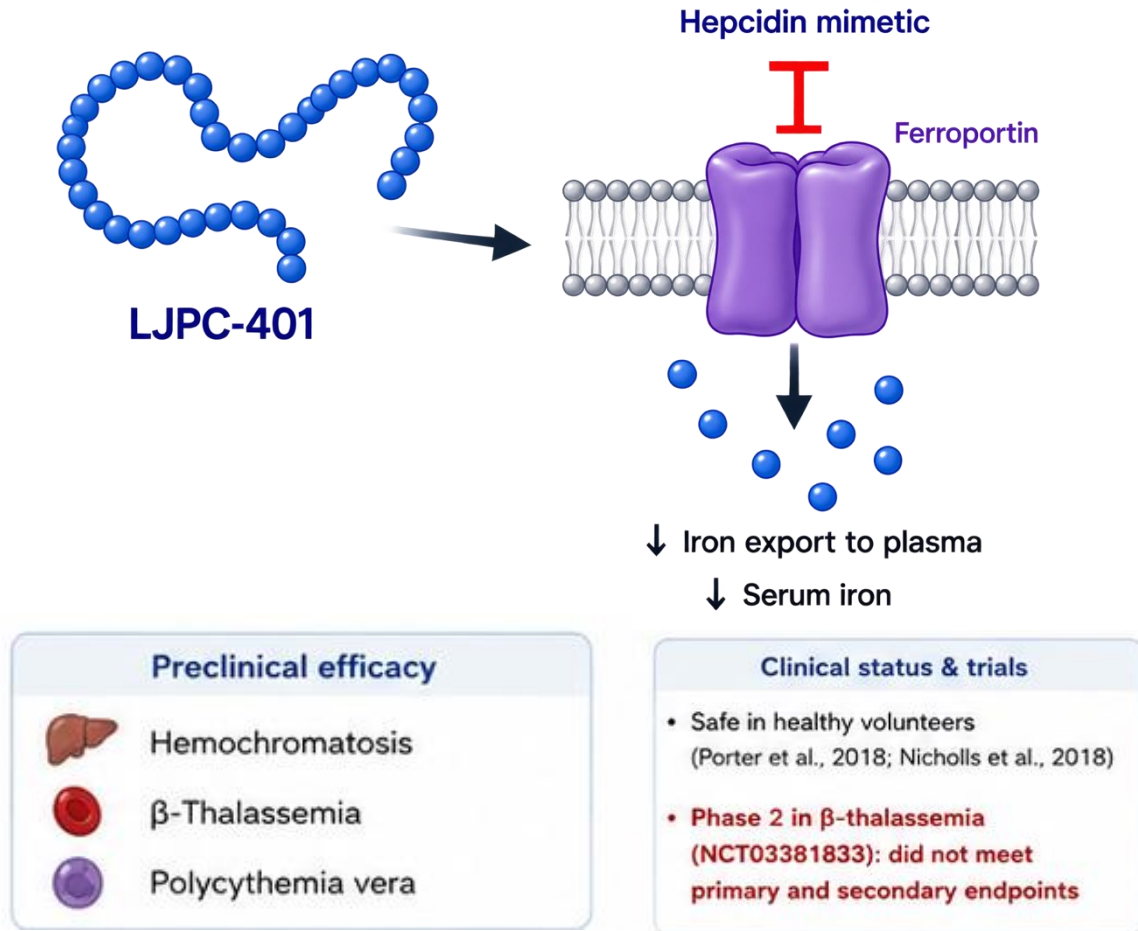
Inhibit upstream pathway(s) that drive hepcidin expression (e.g., inflammation, BMP/SMAD, IL-6/JAK/STAT3)

↓ Hepcidin levels

MECHANISM

Suppress upstream signals that increase hepcidin transcription or production

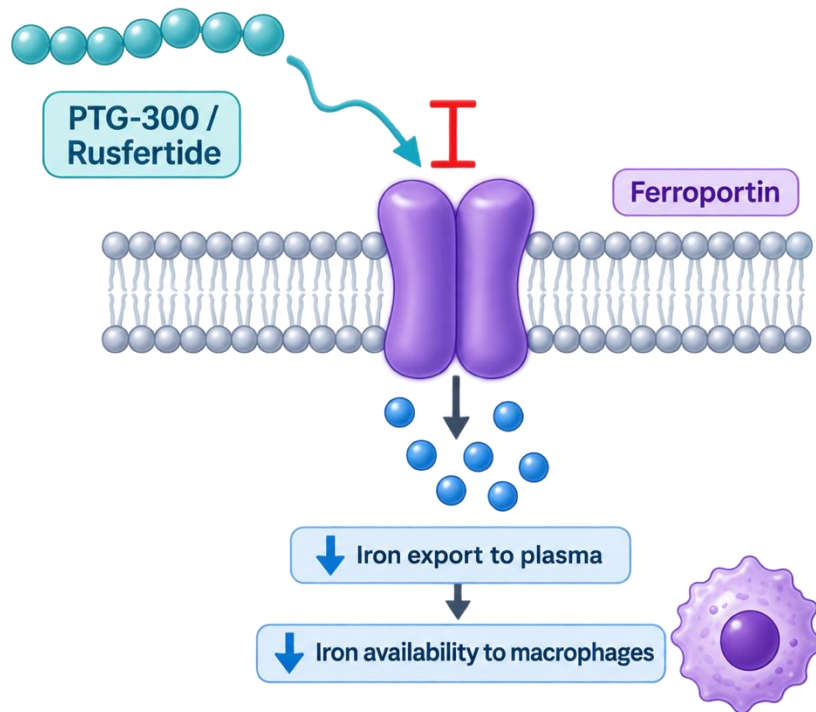
LJPC-401: full-length hepcidin mimetic



- ✓ **Mechanism:** synthetic 25-aa human hepcidin → ferroportin internalization/degradation → ↓ iron export → ↓ serum iron/TSAT.
- ✓ **Preclinical activity** was demonstrated in iron-loading disorders (HH, β-thal, and PV), but the Phase 2 β-thal study NCT03381833 was terminated early for **lack of efficacy** after interim analyses.
- ✓ The main practical limitation was subcutaneous administration with frequent injection-site reactions.

Antonella Nai, Laura Silvestri, Michela Asperti, and Francesca Vinchi. Iron Metabolism in Human Health and Disease, *Advances in Experimental Medicine and Biology*. 2025

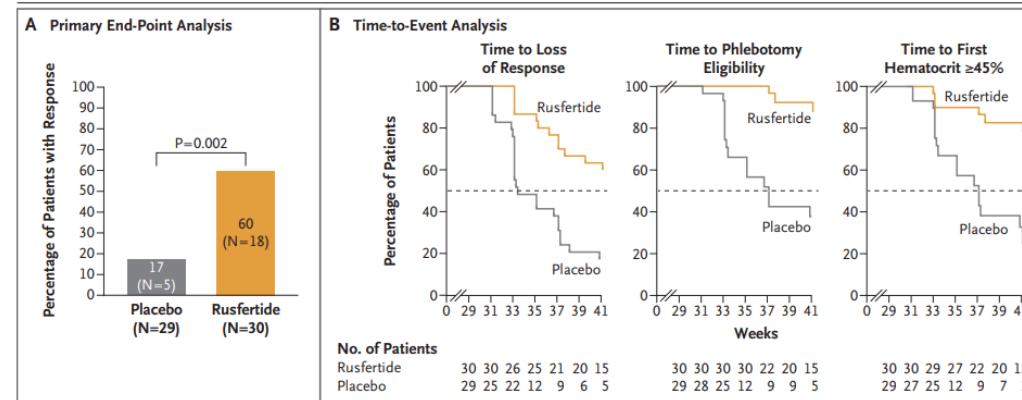
PTG-300/Rusfertide: N-terminal hepcidin mimetic



Clinical status & trials

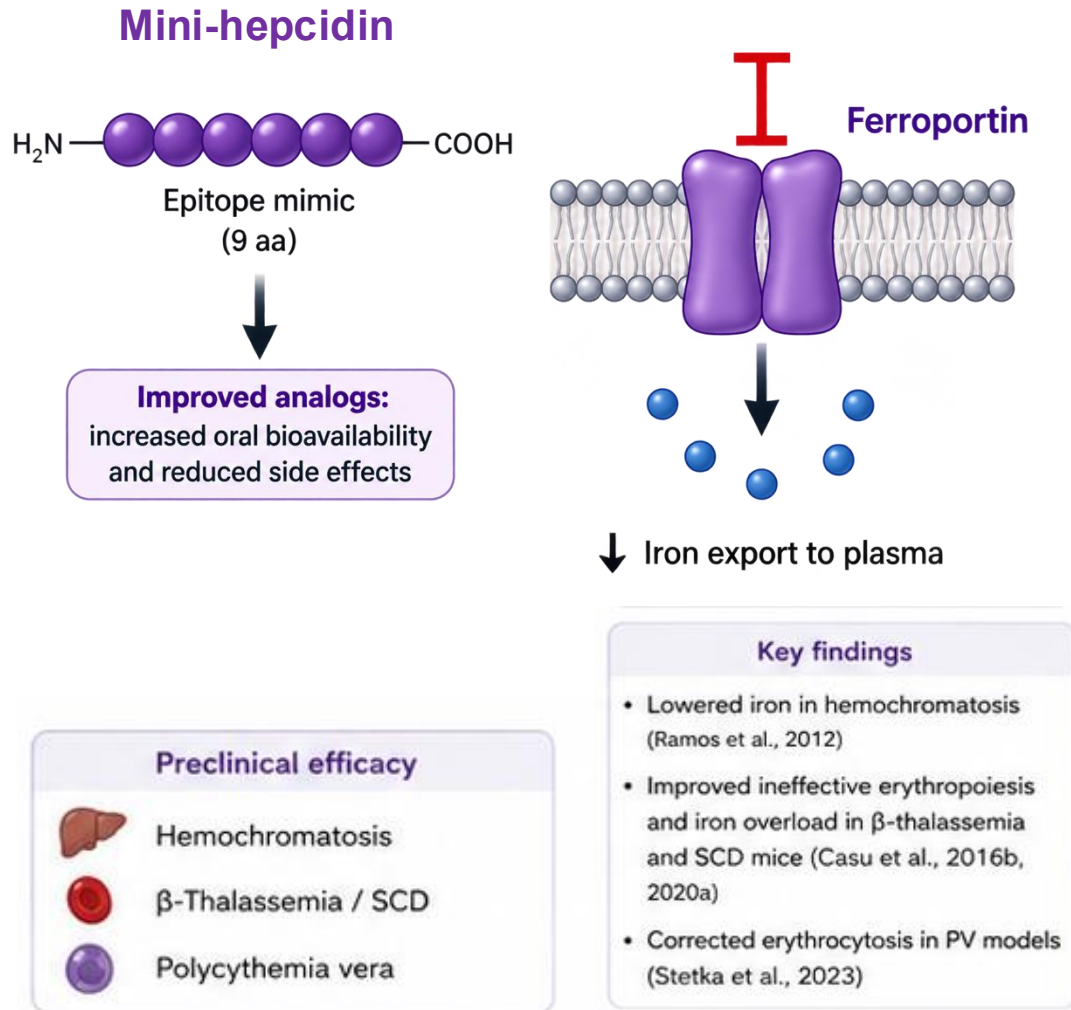
- Phase 2 in hemochromatosis: prevented further iron overload and redistributed iron to macrophages (Kowdley et al., 2023)
- Reduced Hct and phlebotomy frequency in PV (PACIFIC, REVIVE trials) (Hoffman et al., 2022; Kremyanskaya et al., 2024)
- Phase 3 VERIFY trial showed clinical response in 76.9% of patients vs 32.9% with placebo (VERIFY trial, 2025)
- On August 28, 2026, FDA approved MIMRYLO™ (rusfertide) for erythrocytosis in adults with PV

- ✓ It is an injectable peptide mimicking the **biologically active N-terminal region of hepcidin (18 aa)** → ferroportin inhibition → functional iron restriction → **reduced iron availability for erythropoiesis**.
- ✓ **Phase II REVIVE** showed marked reduction in phlebotomy requirements in PV
- ✓ **Phase III VERIFY (293 adult patients)** 76.9% of rusfertide-treated patients achieved clinical response during weeks 20–32 vs 32.9% with placebo ($P < 0.0001$); mean phlebotomies through week 32: 0.53 vs 1.82..
- ✓ **First approved hepcidin mimetic**. On August 28, 2026, FDA approved MIMRYLO (rusfertide) for erythrocytosis in adults with PV.



Kremyanskaya M, et al Rusfertide, a Hepcidin Mimetic, for Control of Erythrocytosis in Polycythemia Vera. *N Engl J Med*. 2024 Feb 22;390(8):723-735

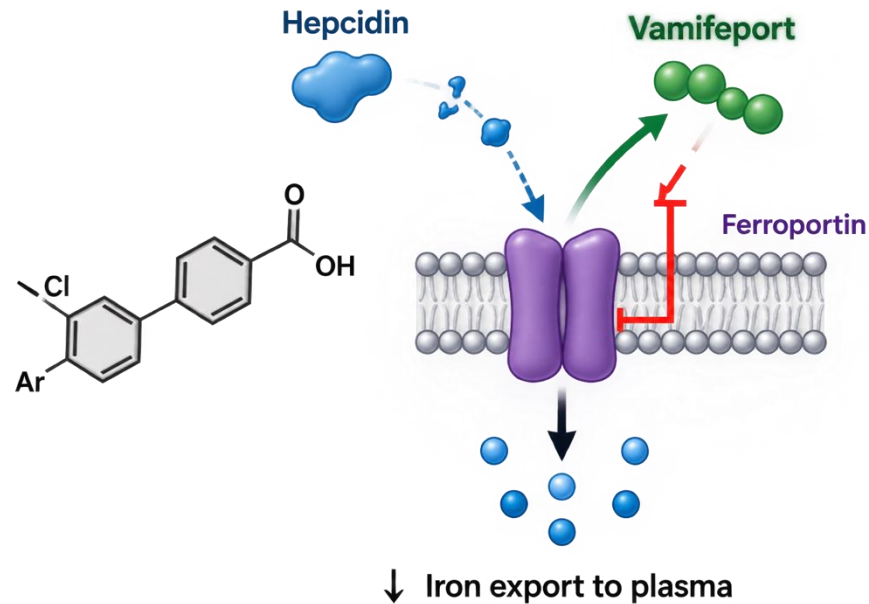
Mini-hepcidins: next-generation hepcidin mimetics



- ✓ Short peptides derived from the **N-terminal bioactive region of hepcidin** bind ferroportin and reproduce hepcidin activity. Designed on the bioactive hepcidin epitope encompassing the first 9 amino acids of the mature protein (Preza et al. 2011), whose structure was improved to **increase oral bioavailability and avoid side effects from subcutaneous administration**.
- ✓ **Preclinical studies** showed reduction of iron overload in hemochromatosis models, improvement of ineffective erythropoiesis and iron overload in **β-thalassemia**, and effects in **SCD** and **PV models**.
- ✓ However, **classical mini-hepcidins have not progressed into established clinical development in humans**. PN-8047: oral small-molecule hepcidin functional mimetic; Phase I planned for 2027

Antonella Nai, Laura Silvestri, Michela Asperti, and Francesca Vinchi. Iron Metabolism in Human Health and Disease, Advances in Experimental Medicine and Biology. 2025

Vamifeport (VIT-2763): oral ferroportin inhibitor



Preclinical efficacy

- Hemoglobinopathies (β -thalassemia, SCD)
- Hemochromatosis
- Polycythemia vera
- MDS (improves myeloid expansion and delays AML progression)

Clinical status & trials

- Phase 1 in healthy volunteers: $\downarrow$ serum iron and transferrin saturation; safe (Richard et al., 2020)
- Phase 2 in β -thalassemia (NCT04938635): terminated due to lack of efficacy on anemia
- Phase 2 ViSionSerenity in SCD (NCT04817670): completed – demonstrated reduction in hemolysis

- ✓ Oral ferroportin inhibitor; it binds ferroportin and competes with hepcidin.
- ✓ **Preclinical studies** in cellular and animal models (HH, SCD, beta thal) showed that it acts in competition with hepcidin in binding to ferroportin, and reducing cellular iron efflux by **reducing iron overload and improving anemia**.
- ✓ **Phase I**, randomized, double-blind, placebo controlled, multiple-ascending doses of vamifeport demonstrated pharmacodynamic activity and a favorable safety profile.
- ✓ **Phase II, β -thalassemia** NTD (NCT04364269), and TD (NCT04938635) NTDT Phase II: completed; no convincing improvement in anemia. TDT Phase IIb: withdrawn for strategic reasons.
- ✓ **Phase II, SCD study** (NCT04817670). In SCD, iron restriction is hypothesized to decrease intracellular HbS levels and, consequently, reduce sickling and hemolysis. Phase IIa completed: reduction in markers of hemolysis was reported.

Antonella Nai, Laura Silvestri, Michela Asperti, and Francesca Vinchi. *Iron Metabolism in Human Health and Disease, Advances in Experimental Medicine and Biology*. 2025; Pilo F, Angelucci E. *Vamifeport: Monography of the First Oral Ferroportin Inhibitor*. *J Clin Med*. 2024 Sep 18;13(18):5524.

Hepcidin modulating agents

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Inhibit upstream pathway(s) that drive hepcidin expression (e.g., inflammation, BMP/SMAD, IL-6/JAK/STAT3)

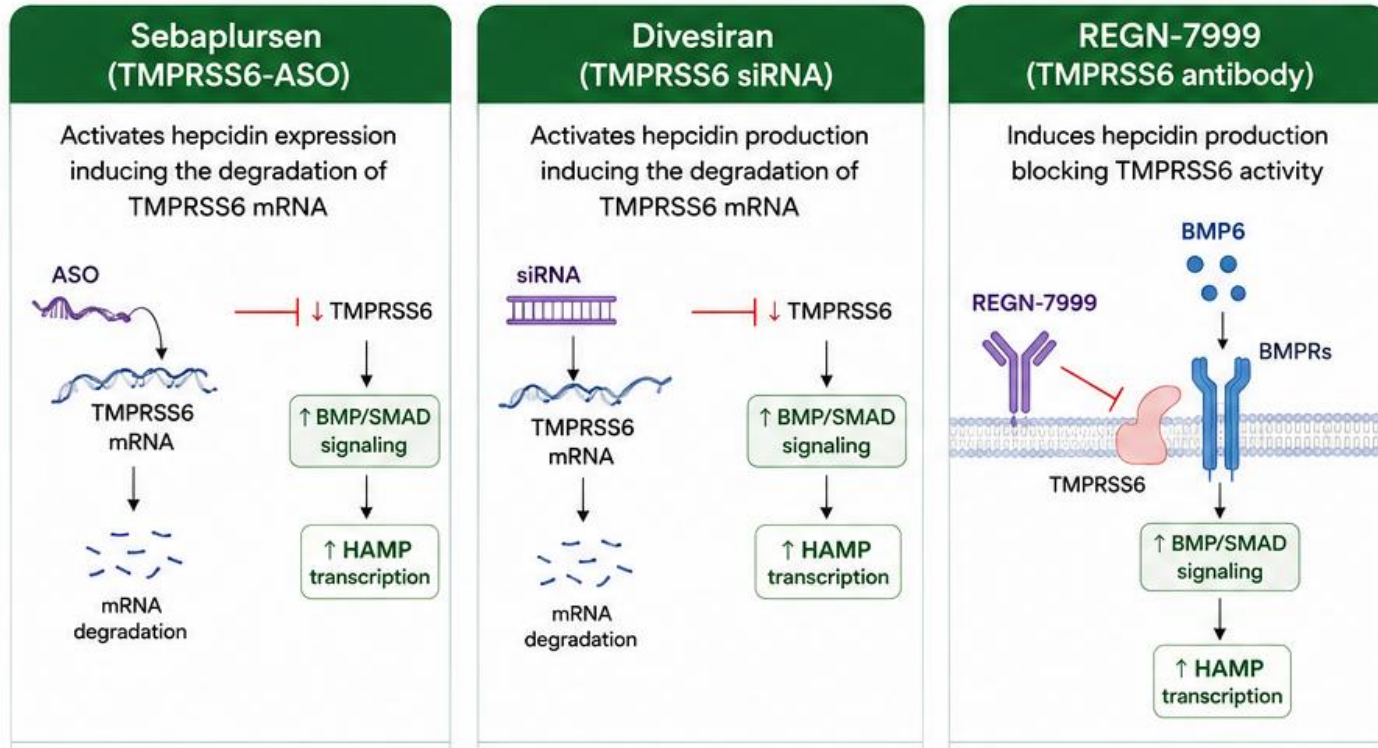
↓ Hepcidin levels

MECHANISM

Suppress upstream signals that increase hepcidin transcription or production

Hepcidin inducers

TMPRSS6/Matriptase-2 is the hepatocyte-specific serine protease inhibitor of hepcidin expression by cleaving the BMP co-receptor hemojuvelin



Sapablursen (TMPRSS6-ASO)

- ✓ Activates hepcidin expression by inducing **TMPRSS6 mRNA degradation**.
- ✓ **Hemochromatosis:** preclinical studies successful.
- ✓ **β-thalassemia:** Phase 2a completed (NCT04059406); **primary and secondary efficacy endpoints were not met**.
- ✓ **Polycythemia vera:** Phase 2 IMPRSSION (NCT05143957) showed **↑ hepcidin, ↓ phlebotomy requirement and improved symptom burden; generally, well tolerated**.
- ✓ **Results support Phase III development**

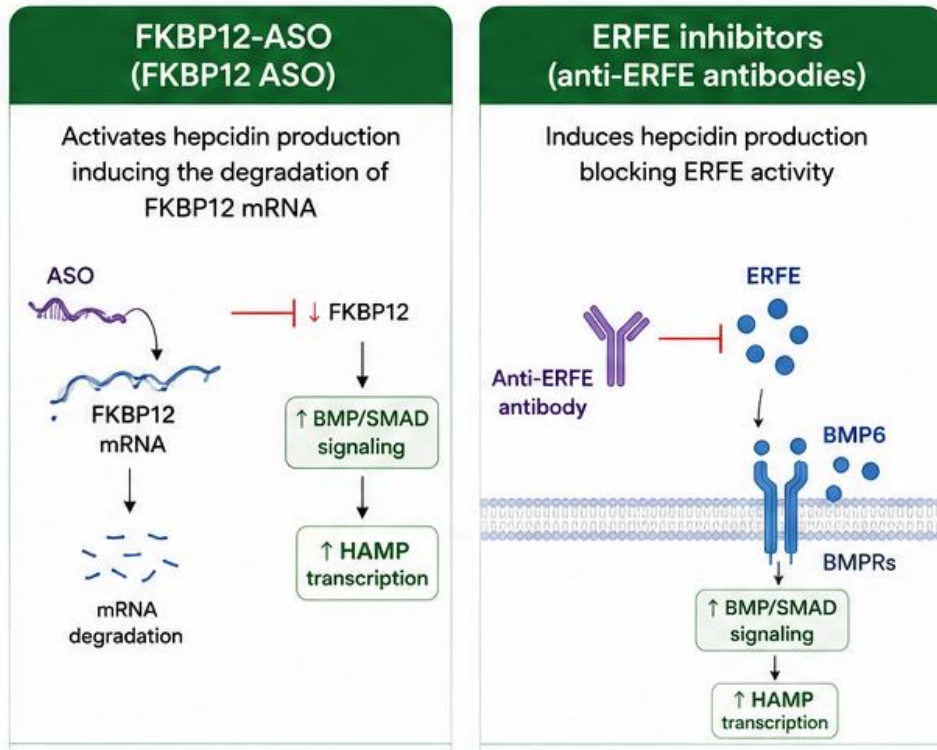
Divesiran (TMPRSS6 siRNA)

- ✓ Activates hepcidin production by inducing **TMPRSS6 mRNA degradation**.
- ✓ **Hemochromatosis:** preclinical studies successful.
- ✓ **β-thalassemia:** no established clinical efficacy data.
- ✓ **Polycythemia vera:** Phase 2 SANRECO **positive** — 88% clinical response versus 19% with placebo
- ✓ **Phase III development planned**

REGN7999 (TMPRSS6 antibody)

- ✓ Induces hepcidin by **blocking TMPRSS6 activity**.
- ✓ **β-thalassemia:** successful preclinical efficacy in Hbb^{th3/+} mice.
- ✓ **Phase 1 (NCT05481333):** completed in healthy volunteers; **↑ hepcidin and sustained ↓ serum iron**, with acceptable tolerability.
- ✓ Phase I completed in healthy volunteers; further clinical development remains to be established.

Hepcidin inducers



FKBP12-ASO

- ✓ FKBP12 is a small intracellular immunophilin that acts as a negative regulator of BMP/SMAD signaling. In hepatocytes, FKBP12 binds BMP type I receptors, particularly ALK2 (ACVR1), maintaining the receptor in an inactive state in the absence of ligand.
- ✓ **FKBP12-ASO** activates hepcidin production by inducing **FKBP12 mRNA degradation**, thereby enhancing BMP/SMAD signaling.
- ✓ **Preclinical development.**
- ✓ **No clinical trials reported (immunomodulatory properties of the drug).**

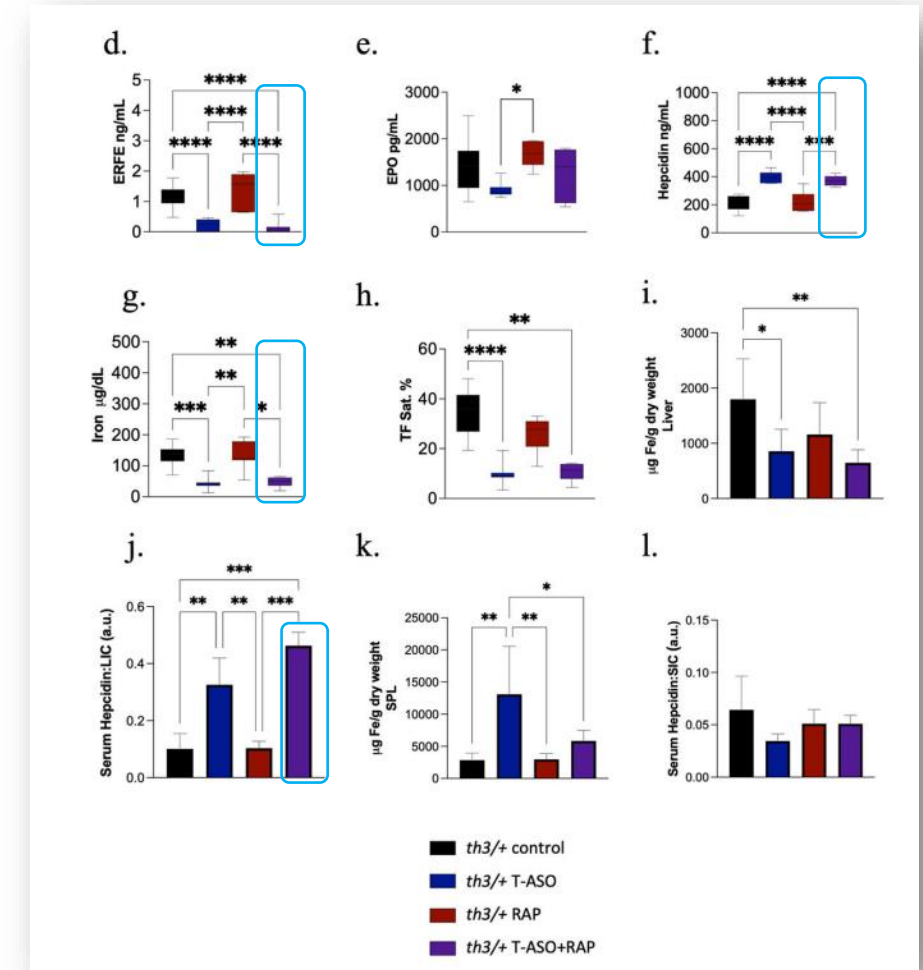
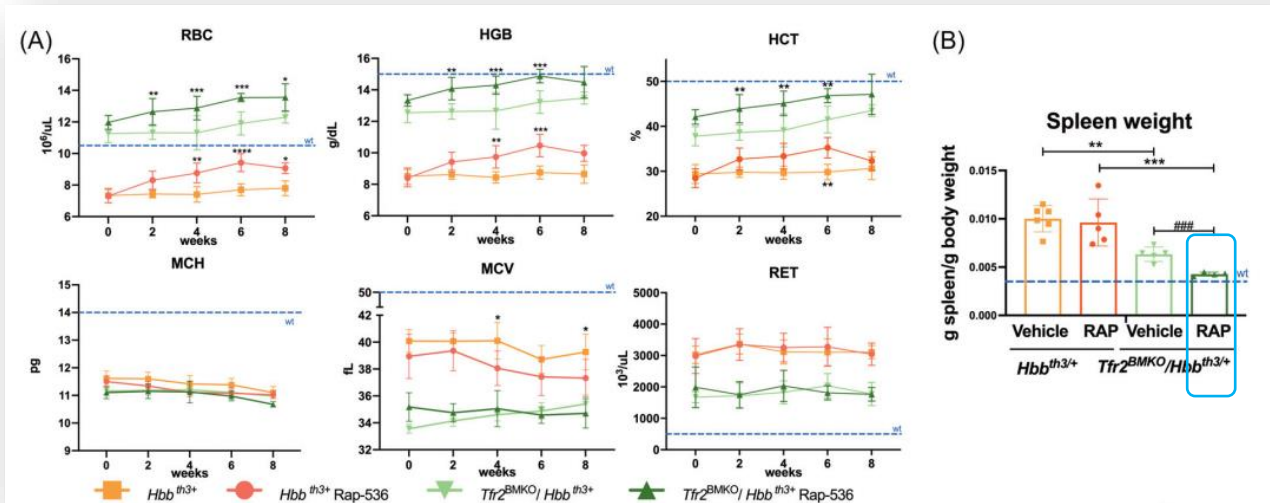
ERFE antibody

- ✓ Neutralizes erythropoietin and prevents **ERFE-mediated suppression of BMP/SMAD signaling.**
- ✓ **Antibodies against the N-terminal domain** of the protein significantly **improved anemia, ineffective erythropoiesis, and iron overload in the same model** (Arezes et al. 2020).
- ✓ **No clinical trials reported.**

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Combinatorial approaches

- ✓ Although the clinical development of **hepcidin inducers/mimetics** for single use in **β -thalassemia** was terminated, their use in combination with drugs against other targets may offer an alternative therapeutic option.
- ✓ The combinatorial administration of **Tmprss6-ASOs** with a **luspatercept-like TGF- β ligand trap**, an erythroid maturation agent or with the **erythroid deletion of Tfr2** proved to be superior in the correction of anemia and improvement of iron overload compared to the single approaches in preclinical models of β -thalassemia.
- ✓ These studies paved the way for the clinical development of more robust approaches for the treatment of β -thalassemia based **on the combinatorial application of iron-restrictive compounds**.



Tanzi et al. AJH 2024; Guerra et al. AJH 2024

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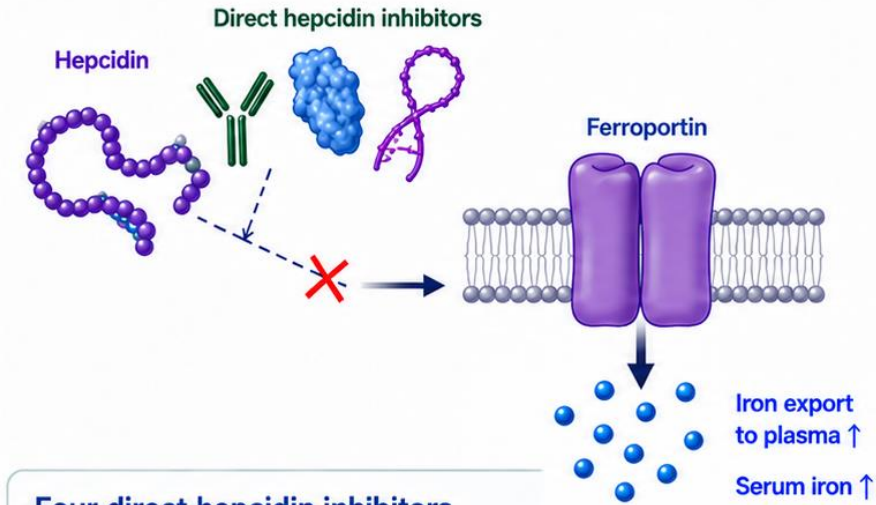
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Direct hepcidin inhibitors



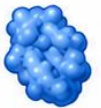
Four direct hepcidin inhibitors



Ab12B9m
Anti-hepcidin
monoclonal antibody



LY2787106
Anti-hepcidin
monoclonal antibody



PRS-080#022
Anticalin protein



NOX-H94 (Lexaptepid)
Structured mirror-image
L-oligoribonucleotide (Spiegelmer)



Ab12B9m
Anti-hepcidin monoclonal antibody

- ✓ Preclinical only
- ✓ Hepcidin neutralization
- ✓ ↑ serum iron and Hb in anemia of inflammation models
- ✓ **No further clinical development**



LY2787106
Anti-hepcidin monoclonal antibody

- ✓ Phase 1 completed
- ✓ 33 patients with cancer-associated anemia
- ✓ Well tolerated
- ✓ Dose-dependent ↑ serum iron and TSAT
- ✓ **Development discontinued**



PRS-080#022
Anticalin protein

- ✓ Binds hepcidin with high affinity
- ✓ Early clinical development
- ✓ ↑ serum iron / iron availability
- ✓ Acceptable safety
- ✓ **No advanced late-phase development**



NOX-H94 (Lexaptepid)
Structured mirror-image
L-oligoribonucleotide (Spiegelmer)

- ✓ Binds human hepcidin with high affinity
- ✓ Blocks hepcidin biological function
- ✓ L-enantiomeric oligonucleotide
- ✓ Nuclease resistant and immunologically passive
- ✓ No Toll-like receptor activation; low risk of neutralizing antibodies
- ✓ Chemically manufactured, avoiding biological contamination

- ✓ **Direct hepcidin neutralization** provides robust proof-of-mechanism through rapid iron mobilization, but continuous hepcidin production, and the multifactorial nature of inflammatory **anemia limit sustained hematologic efficacy**.
- ✓ **Clinical development not continued** / no active later-phase program identified

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Increase endogenous hepcidin production or transcription



Stimulate hepcidin (*HAMP*) gene expression via upstream signaling pathways

↑ Hepcidin levels

MECHANISM

Activate signaling pathways that upregulate *HAMP* transcription and increase hepcidin production

STRATEGIES THAT REDUCE HEPCIDIN (Hepcidin Antagonists / Lowering Approaches)

DIRECT HEPCIDIN INHIBITORS

Neutralize hepcidin activity
(block hepcidin-ferroportin interaction)



Bind hepcidin directly and prevent its interaction with ferroportin

↓ Hepcidin effect

MECHANISM

Block hepcidin or prevent its binding to ferroportin, preserving ferroportin at the cell surface and enabling iron export

INDIRECT HEPCIDIN INHIBITORS

Reduce hepcidin expression by targeting upstream pathways



Inhibit upstream pathway(s) that drive hepcidin expression (e.g., inflammation, BMP/SMAD, IL-6/JAK/STAT3)

↓ Hepcidin levels

MECHANISM

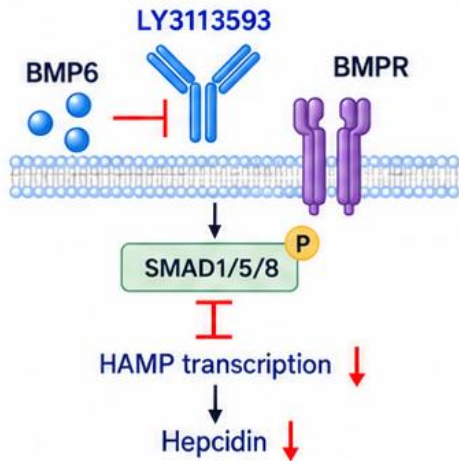
Suppress upstream signals that increase hepcidin transcription or production

Indirect hepcidin inhibitors

Indirect hepcidin inhibitors – BMP/SMAD pathway

1 LY3113593 Anti-BMP6 antibody

Prevents BMP6 from binding to BMPR

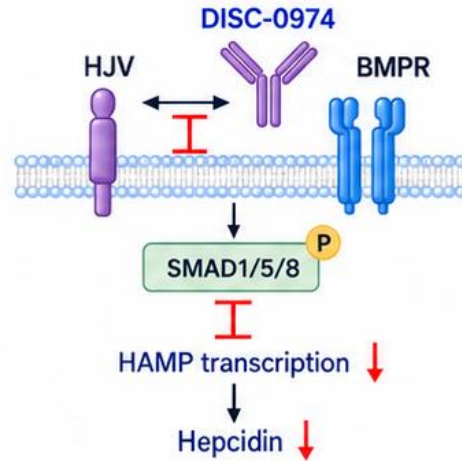


NET EFFECT:

↓ Hepcidin → ↑ Ferroportin → ↑ Iron export → ↑ Iron availability

2 DISC-0974 Anti-HJV antibody

Blocks HJV–BMPR co-receptor interaction

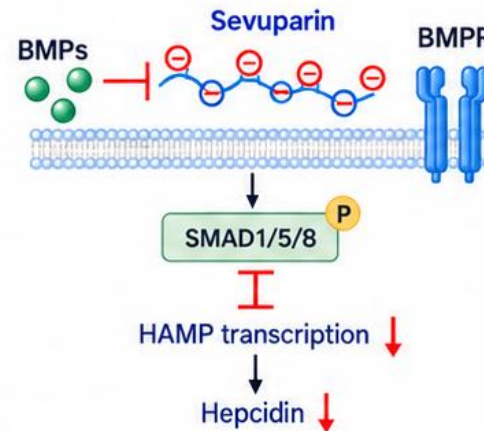


NET EFFECT:

↓ Hepcidin → ↑ Ferroportin → ↑ Iron export → ↑ Iron availability

3 Sevuparin (heparin) BMP/SMAD pathway inhibitor

Binds BMP ligands and limits receptor activation

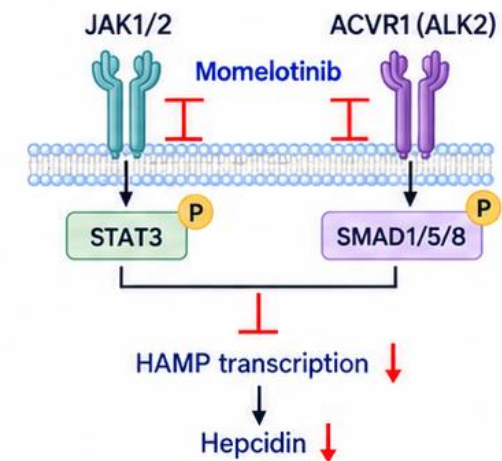


NET EFFECT:

↓ Hepcidin → ↑ Ferroportin → ↑ Iron export → ↑ Iron availability

4 Momelotinib JAK1/2 and ACVR1 (ALK2) inhibitor

Inhibits JAK1/2 and ACVR1 signaling



NET EFFECT:

↓ Hepcidin → ↑ Ferroportin → ↑ Iron export → ↑ Iron availability

LY3113593: proof-of-mechanism in **CKD**; no advanced development reported.

DISC-0974: active Phase 2 positive anemia-response data in patients with **myelofibrosis-associated anemia**. Phase 3 planned.

Sevuparin: robust hepcidin suppression in healthy volunteers; anemia efficacy still unproven.

Momelotinib: Dual suppression of IL-6/JAK/STAT3 and BMP6/ACVR1
FDA approved for myelofibrosis with anemia.

Take home messages

1 Hepcidin is the master regulator of systemic iron homeostasis

The hepcidin–ferroportin axis is a key therapeutic target in iron overload and iron-restricted erythropoiesis.

2 Therapeutic modulation can work in both directions

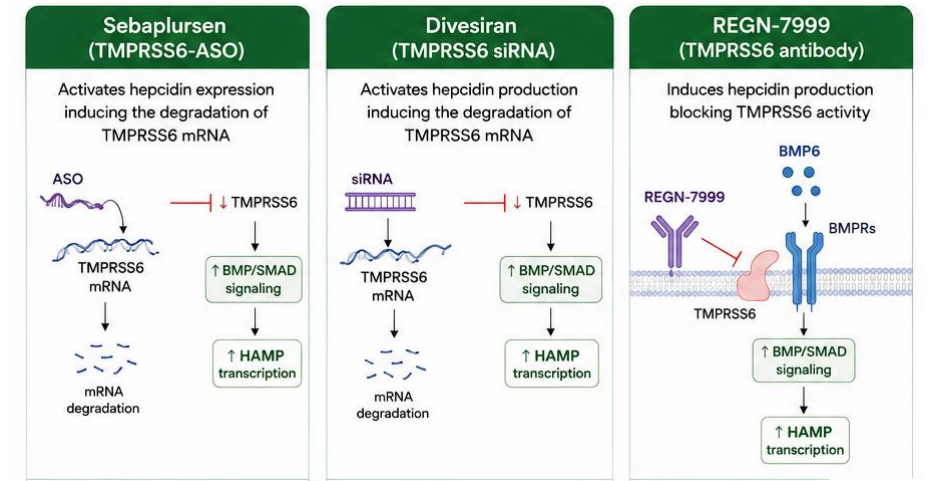
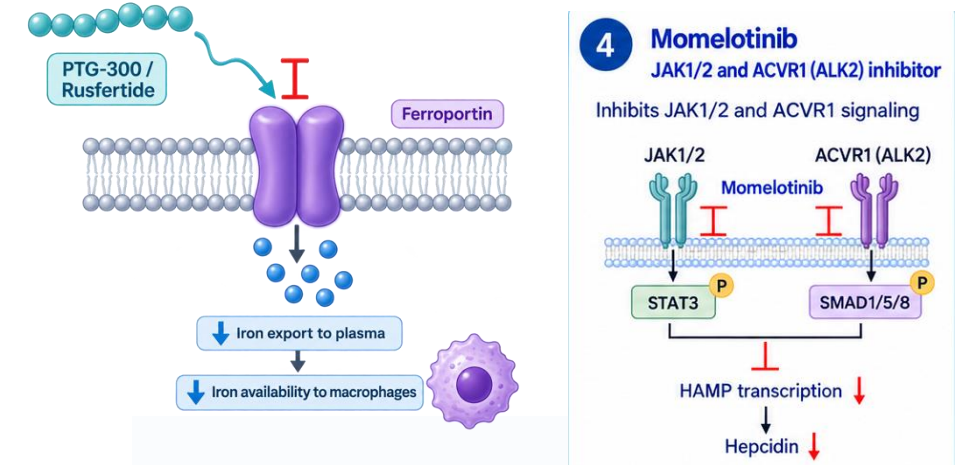
Increase hepcidin activity to restrict iron or reduce hepcidin activity to restore iron availability — according to disease mechanism.

3 Clinical translation is now a reality

Rusfertide provides clinical validation that the hepcidin–ferroportin axis is druggable; TMPRSS6-targeting strategies further broaden the landscape.

4 Biological activity does not always equal clinical benefit

Several programs showed pharmacodynamic effects but limited efficacy: disease-specific targeting, magnitude and duration of modulation matter.



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