Update on therapies in development

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Disclosures

- None

Outline

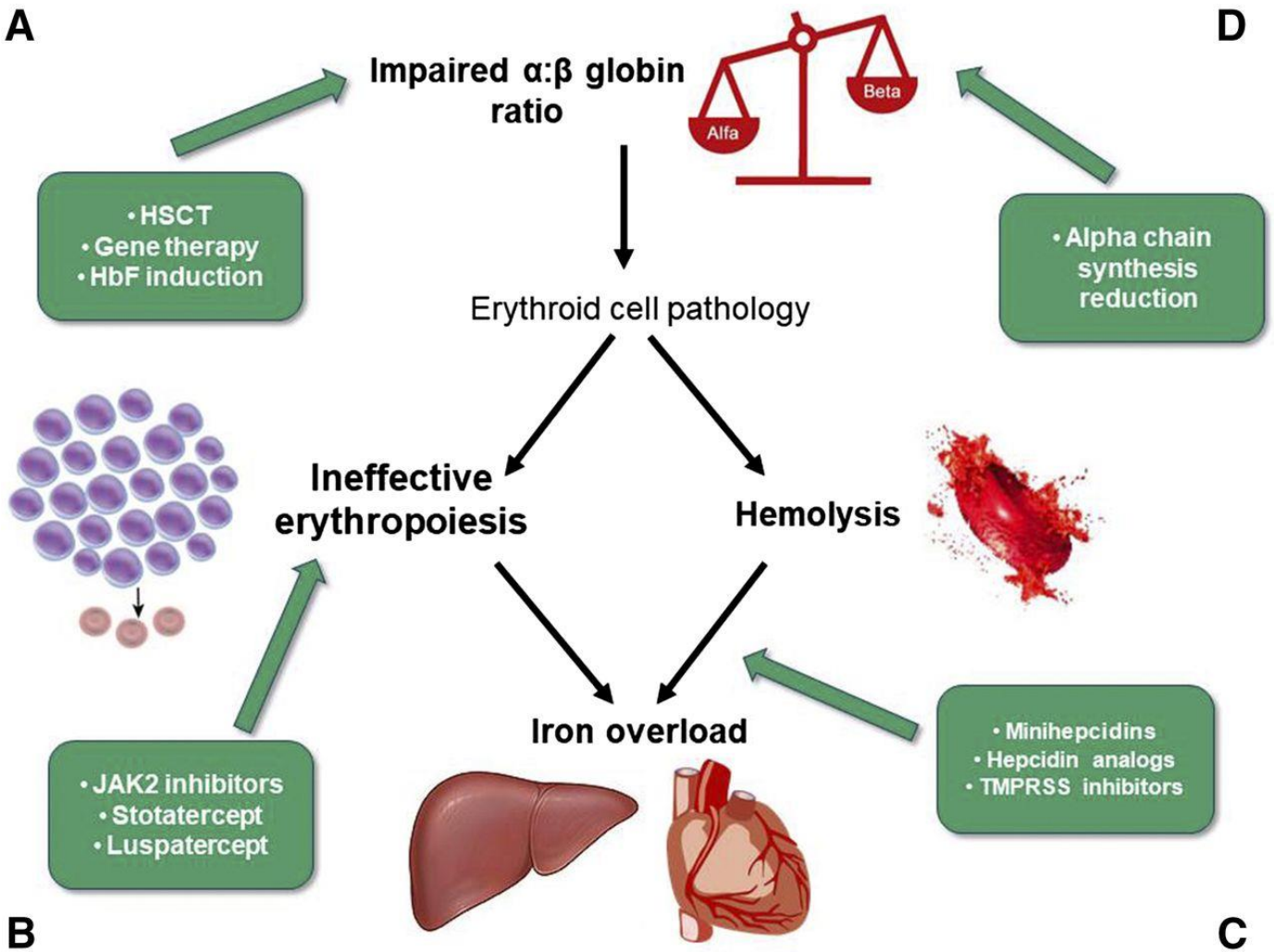
- Disease processes in thalassemia
- Gene therapy
  - Overview
  - Active Gene Therapy Trials in the US
  - Update on Bluebird Bio Gene Therapy Trial
  - Sangamo Gene therapy Trial
- Activin receptor ligand trap molecules
  - Luspatercept/Sotatercept
- Hepcidin Agonists
  - LJPC-401 (La Jolla)

Disease processes in transfusion dependent β Thalassemia

- Over 200 mutations that cause reduced (β^+) or absent (β^0) production of beta globin

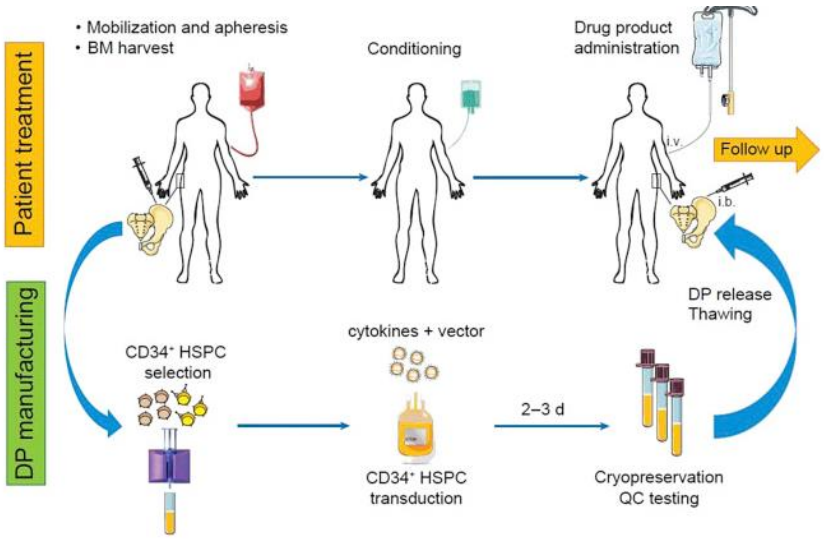
- Resultant imbalance between alpha & β chains causes
  - Impaired ability of the body to make blood efficiently (ineffective erythropoiesis)
  - Increased breakdown of manufactured red cells (excessive hemolysis)
  - Dysregulation of iron control

New therapeutic targets in β-thalassemias: (A,D) impaired α:β-globin ratio, (B) ineffective erythropoiesis, and (C) iron metabolism and hemolysis.



M. Domenica Cappellini, and Irene Motta Hematology 2017;2017:278-283

Principles of Gene Therapy



- Harvesting a patient's own stem cell (BM, cord blood, PB).
- Genetic modification of HB expression
  - Gene addition
  - Knockdown
  - Gene editing
- Transplanting cells back into the patient

Ferrari. Hematol Oncol Clin North Am. 2017 Oct;31(5):835-852

Active Gene Therapy Trials for Transfusion Dependent Beta thalassemia in the US

Study ID	Age / Tot. Number	Intervention	Sites in US	Sponsors
HGB-212 Phase 3 (β^0 / β^0)	*Up to 50Y 15 participants	Lentiglobin BB305	UCSF Beniof Lurie Children's CHOP/Penn	Bluebird Bio
HGB-207 Phase 3 (Non β^0)	*UP to 50Y 23 participants	Lentiglobin BB305	UCSF Beniof Lurie Children's CHOP/Penn	Bluebird Bio
NCT01639690 Phase I (active, not recruiting)	>/=18Y 10 participants	TNS9.3.55 Lentiviral vector	Memorial Sloan Kettering Cancer Center	Memorial Sloan Kettering Cancer Center
ST-400-01 Phase 1/II	>/= 18Y 6 participants	ST-400 Zn finger mediated genome editing	USCF Beniof Univ. of Minnesota Emory Univ	Sangamo

Gene Therapy in Transfusion Dependent Thalassemia Results from HGB-204 & HGB 205

- HGB-204 (US, Australia, Thailand) & HGB-205 (France)
- Initiated Aug 2013. Follow up to 3Y
- Age 12-35Y
- Genotypes
  - 9 β^0/β^0 , 9 β^E/β^0 , 4 other
- Product – Lentiglobin BB305
- 27 patients assessed for eligibility
  - 18 successfully mobilized & received the infusion

AA Thompson et al. N Engl J Med 2018;378:1479-1493.

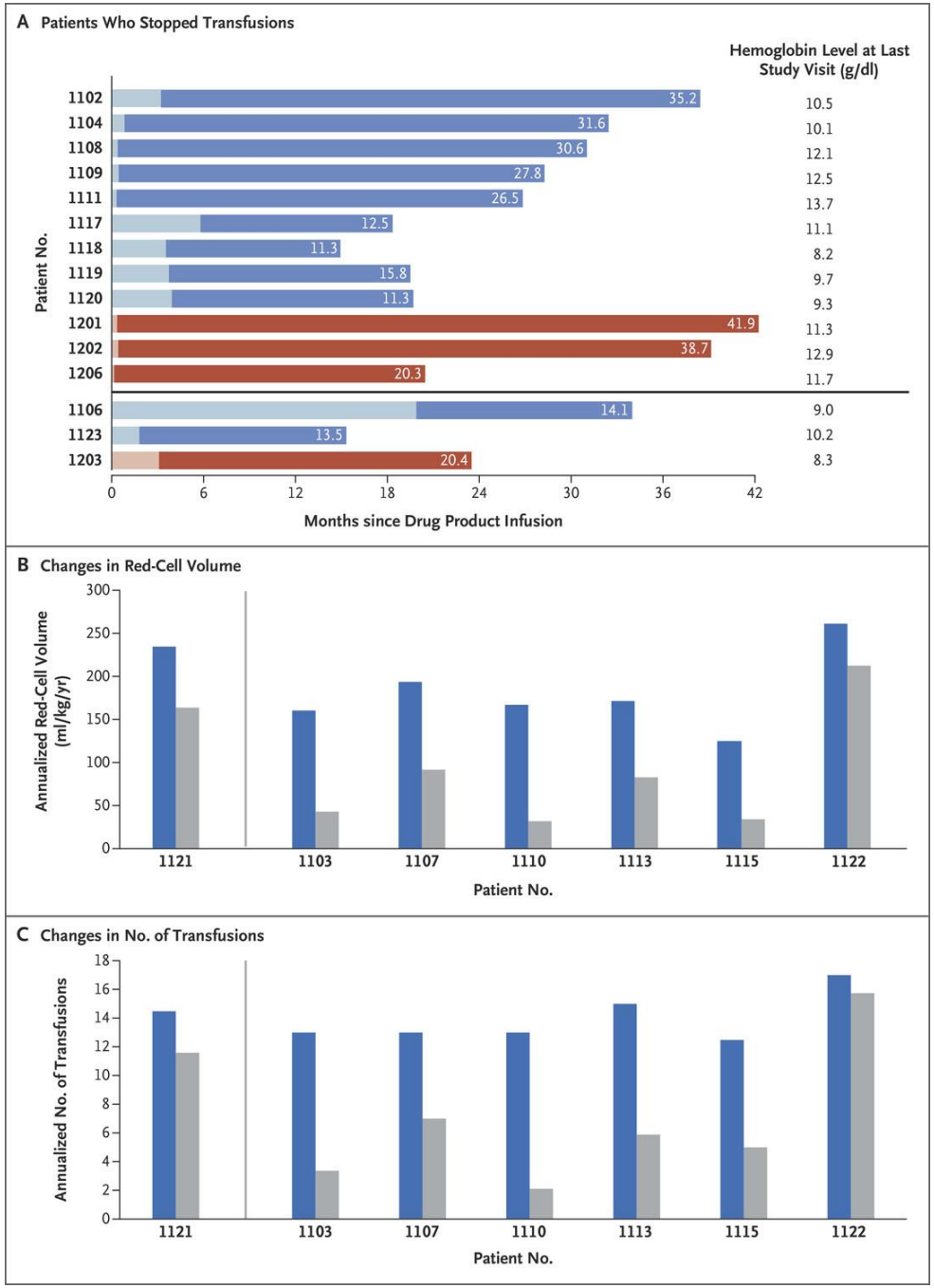
Gene Therapy in Transfusion Dependent Thalassemia Results from HGB-204 & HGB 205

- Non β^0/β^0
  - 12 of 13 patients stopped receiving transfusions at last study visit (12-36 months)
  - Hb 11.2g/dl (8.2 – 13.7)

- β^0/β^0 or IVS-110
  - 6/9 patients continued to receive transfusions
  - 73-74% reduction in annual number of transfusions & transfusion volume
  - Hb range (8.3 – 10.2g/dl)

AA Thompson et al. N Engl J Med 2018;378:1479-1493.

Changes in Transfusion Requirements after Gene Therapy.



AA Thompson et al. N Engl J Med 2018;378:1479-1493.

Gene Therapy in Transfusion Dependent Thalassemia Results from HGB-204 & HGB 205

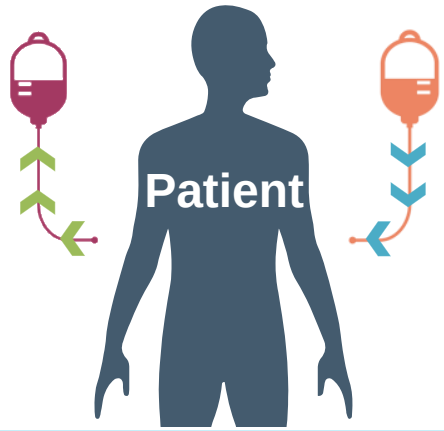
- Safety
  - No safety issues attributed to the vector
  - 9 serious adverse events recorded which were attributed the busulphan
  - No replication competent virus detected in the patients
  - Multiple vector integration sites, no dominant clones

AA Thompson et al. N Engl J Med 2018;378:1479-1493.

Autologous, gene-edited cell therapy product candidates for beta-thalassemia and sickle cell disease

Apheresis
Isolate CD34+ Hematopoietic stem cells from patient's blood

1

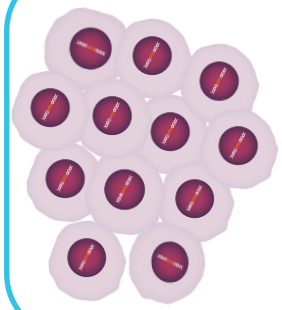


4

Infusion
ST-400 stem cells are infused back to the patient (with myeloablative pre-conditioning to promote engraftment)

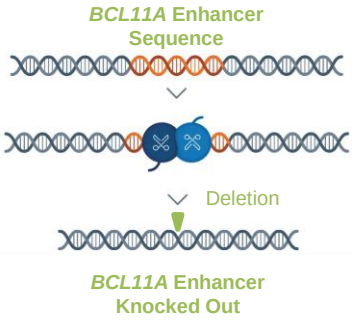
Functional RBCs with fetal hemoglobin produced from ST-400 stem cells

cGMP Manufacturing Facility



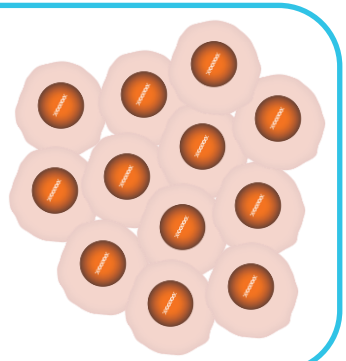
2

Gene editing
Manufacture ST-400 stem cells via transient, non-viral delivery of ZFN mRNA



3

Harvest
ST-400 stem cells are cryo-preserved and shipped to treatment center



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ST-400: Beta-thalassemia clinical program overview

Phase I/II Open Label Study

Patients

6 adults (18+) with transfusion-dependent beta-thalassemia

Cell Therapy

Autologous, ex vivo therapy of HSCs

Goals

- Increase production of fetal hemoglobin
- Reduce or eliminate blood transfusions

Clinical Trial Status
IND open
Study initiated
Patient qualification in June for early 3Q enrollment

Potential Advantages
• Leverages naturally-occurring, protective mechanism to increase fetal-hemoglobin
• Highly efficient, precise gene editing; low risk of insertional mutagenesis
• Non-viral delivery of ZFNs
• Potentially superior long-term safety profile

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Gene Therapy vs BMT

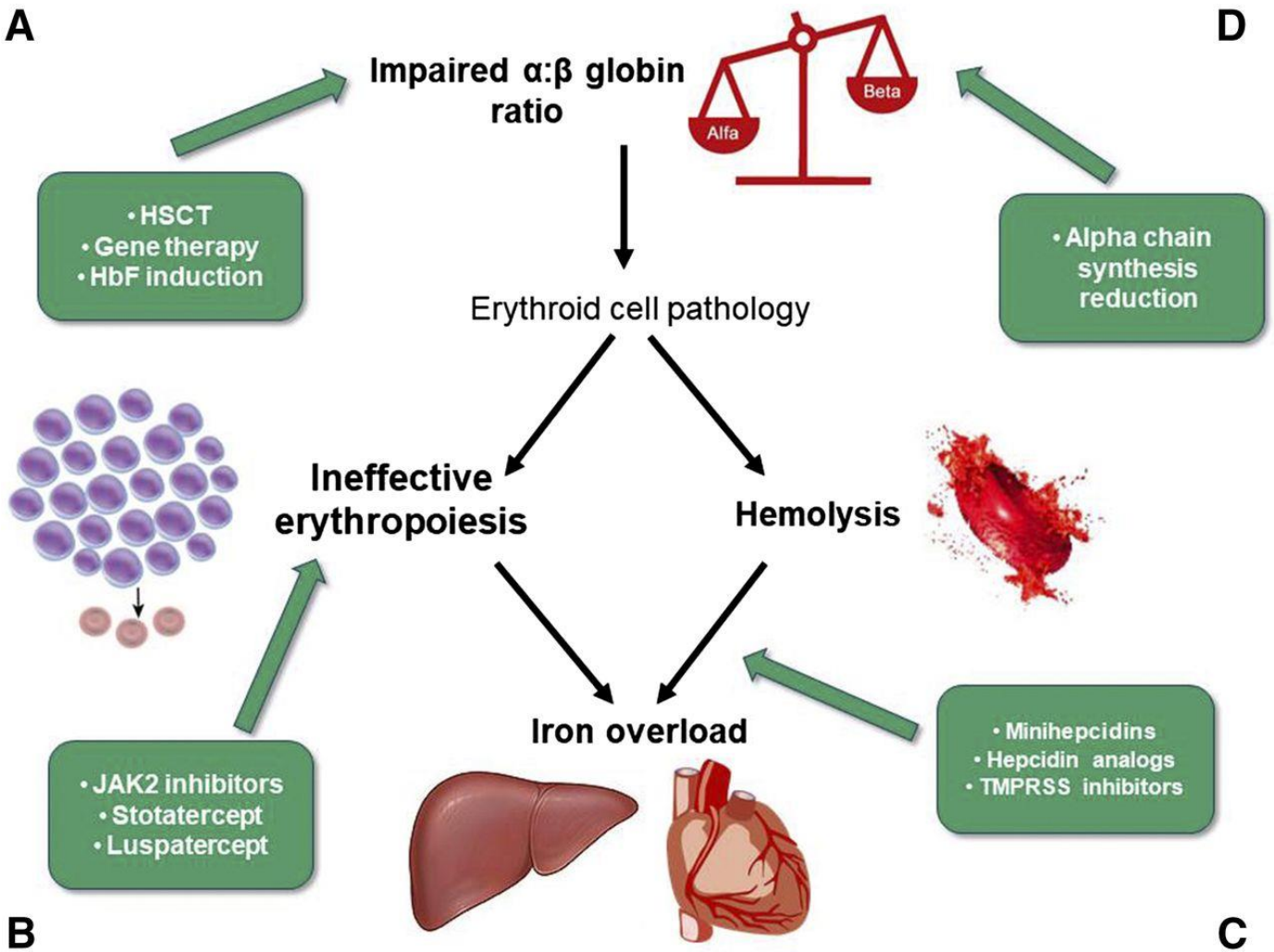
BMT

- Need for myeloablative conditioning with chemotherapy
  - End organ damage
  - Second malignancies
- Limited by lack of suitable donors
- GVHD
- Thalassemia free survival of 90% (matched sibling donors)

Gene Therapy

- Need for myeloablative conditioning with chemotherapy
  - End organ damage
  - Second malignancies
- Not limited by donor availability. No GVHD
- Mild-Mod degree of anemia and continued need for transfusion in some patients (β^0/β^0)
- Concerns for genotoxicity

New therapeutic targets in β-thalassemias: (A,D) impaired α:β-globin ratio, (B) ineffective erythropoiesis, and (C) iron metabolism and hemolysis.



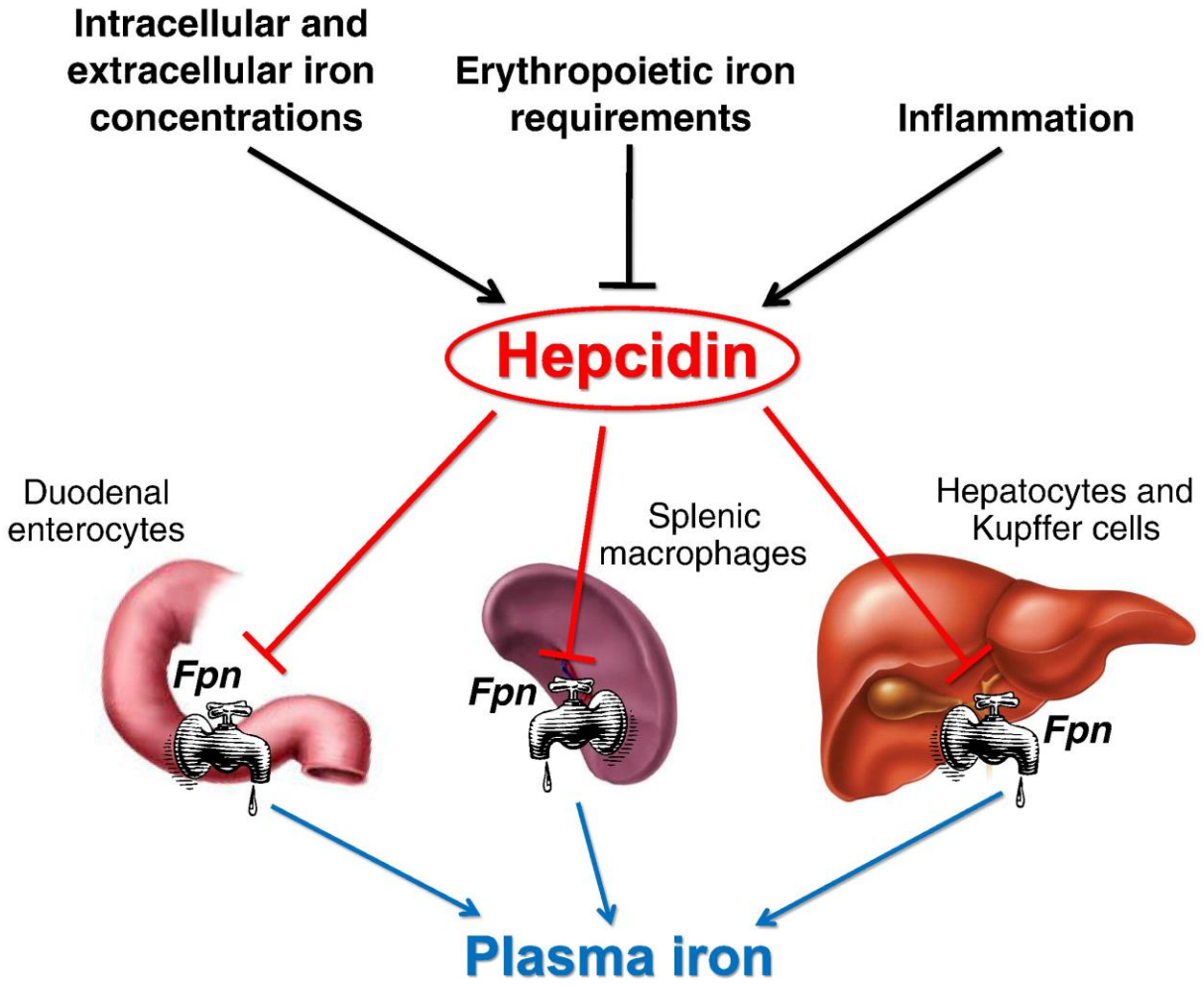
M. Domenica Cappellini, and Irene Motta Hematology 2017;2017:278-283

Activin Receptor Trap Ligands
Luspatercept & Sotatercept

- Mechanism of action
  - Improve red cell maturation and production leading to improved Hb levels
- Administered SQ every 3 weeks
- Results from initial dose finding study
  - TDT –
    - >50% reduction in transfusion needs on 67% of patients
  - NTDT
    - Increase in Hb levels by 1g/dl in 78% of patients and 1.5g/dl in 56% of patients
- Phase 2/3 studies active in the US

Cappellini. Motta. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):278-283.

Hepcidin – Key regulator of iron



Hepcidin & Iron Homeostasis. Ganz. Nemeth. Biochim Biophys Acta. 2012 Sep;1823(9):1434-43

Hepcidin Agonists

Hepcidin agonists	Company	Drug	Target	Clinical trials
Class 1: hepcidin mimetics	University of California, Los Angeles	MHs (PR65, PR73, M009, M012)	Ferroportin	Validated in preclinical studies
	La Jolla Pharmaceutical Company	LJPC-401 (hepcidin formulation)	Ferroportin	Phase 1: no toxicity reported; expected hypoferremia observed
	Protagonist Therapeutics	PTG-300	Ferroportin	Phase 1: no serious adverse events reported; expected hypoferremia observed
Class 2: stimulators of hepcidin production	Ionis Pharmaceuticals	Tmprss6-ASO	Tmprss6	Phase 1 ongoing
	Alnylam Pharmaceuticals	Tmprss6-siRNA	Tmprss6	Validated in preclinical studies
Class 3: ferroportin inhibitors	Vifor Pharma	VIT-2763	Ferroportin	Phase 1 planned in 2018

Casu et al. Hepcidin as Therapeutic Agonists. Blood. 2018 Apr 19;131(16):1790-1794

Hepcidin Agonists – LJPC-401

- LJPC-401 - Proprietary formulation of synthetic human hepcidin by La Jolla.

- Phase 1
  - 15 patients received 1-20mg of LJPC, administered subcutaneously. No dose limiting toxicities observed
  - Statistically significant reduction in serum iron

Hepcidin Agonists – LJPC-401

- Phase 2 (actively recruiting)
  - Primary outcome – myocardial iron overload (cardiac T2*)
  - 100 patients, TDT, >/=18Y, cardiac iron overload
  - Multi-institutional. Active Site – San Diego, CA
  - Comparing LJPC-401 + standard chelation for 52 weeks vs standard chelation alone for 26 weeks followed by LJPC + standard chelation for 26 weeks.

Summary

- Promising & exciting new therapies for the treatment of transfusion dependent thalassemia
- Gene therapy offers each patient the opportunity for cure when there are not favorable donor options for BMT
- Other therapies including activin receptor ligands and hepicidin agonists could significantly reduce the need for transfusions and iron burden, ultimately leading to improved QOL

Research Question

- Results of from published literature so far suggest that patients with β^0/β^0 mutations may not achieve transfusion independence after gene therapy.

Unanswered questions

- What factors influence patient/family decisions about gene therapy?
- What degree of anemia or transfusion dependence will be considered acceptable after gene therapy from a patient/caregiver perspective